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Total synthesis of mycolactones A and B

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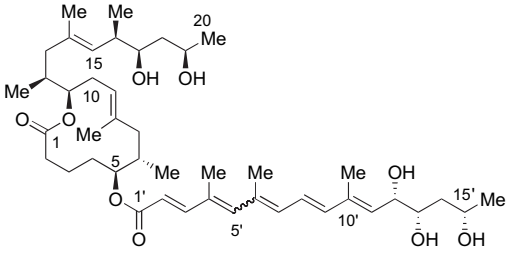
Abstract—First and second generation total syntheses of mycolactones A and B are reported. The first generation total synthesis unambiguously confirmed our earlier assignment of the relative and absolute stereochemistry of mycolactones A and B. Knowledge of the chemical properties of the mycolactones accumulated through the first generation total synthesis allowed us to implement several major improvements to the original synthesis, including: (1) optimizing the choice of protecting groups, (2) eliminating the unnecessary adjustment of protecting groups, and (3) improving the overall stereoselectivity and synthetic efficiency. The second generation total synthesis consists of 21 longest linear steps, with 6.3% overall yield.

1. Introduction

Buruli ulcer is a severe necrotizing skin disease caused by *Mycobacterium ulcerans.*[1] Among the diseases caused by mycobacteria, Buruli ulcer occurs with less frequency than tuberculosis and leprosy. However, the occurrence of the disease is increasing and spreading in tropical countries. Indeed, it is noted that the incidence of Buruli ulcer may exceed that of leprosy and tuberculosis in highly affected areas. Infection with *M. ulcerans*, probably carried by aquatic insects,[2] results in progressive necrotic lesions that, if untreated, can extend to 15% of a patient's skin surface. Unfortunately, surgical intervention is currently the only realistic therapy for Buruli ulcer.

Most pathogenic bacteria produce toxins that play an important role(s) in disease. However, there has been no evidence thus far to suggest toxin production by *Mycobacterium tuberculosis* and *Mycobacterium leprae*, the two most-recognized pathogenic members of the genus *Mycobacterium*. Interestingly, the possible presence of a toxin in *M. ulcerans* was hypothesized for a number of years prior to the isolation and characterization of two polyketide-derived macrolides from this bacteria by Small and co-workers in 1999.[3] These macrolides were designated mycolactones A and B, and it was demonstrated that intradermal inoculation of the purified mycolactones into guinea pigs produced a lesion similar to that of Buruli ulcer in humans.

The gross structure of mycolactones A and B was elucidated by Small and co-workers via spectroscopic methods, including extensive 2D NMR experiments, to be a 12-membered macrolide bearing a highly unsaturated side-chain.[4] Through the combined use of an NMR database and the preparation of model compounds, we studied and established the relative and absolute configuration of the mycolactone core,[5] and then applied the newly developed universal NMR database concept in *chiral* solvents,[6] to establish the complete structure of the mycolactones.[7] Finally, the assigned structure was confirmed by total synthesis.[8] Through these efforts, mycolactones A and B are now characterized as having the stereochemistry shown below, and as an approximately 3:2 mixture of Z-$\Delta^{4',5'}$- and E-$\Delta^{4',5'}$-geometric isomers of the unsaturated side-chain (Fig. 1).



1: Mycolactone A: $\Delta^{4',5'}$=Z
2: Mycolactone B: $\Delta^{4',5'}$=E

Figure 1. Structure of mycolactones A (**1**) and B (**2**).

Keywords: Mycolactones; Total synthesis; Buruli ulcer.
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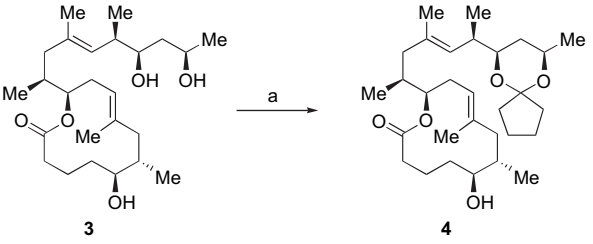
Mycolactones A and B constitute the major metabolites produced by West African strains of *M. ulcerans*. However, several mycolactone congeners, including mycolactone C,[9] mycolactone D,[10] and C2′-methyl mycolactones A and B,[11] have recently been isolated from clinical isolates of *M. ulcerans* from Africa, Malaysia, Asia, Australia, and Mexico. In this connection, it is worthwhile noting that clinical isolates from Asia, Mexico, and Australia are less virulent than clinical isolates from Africa. In addition, mycolactone congeners have also been isolated from the frog pathogen *Mycobacterium marinum*[12] and the fish pathogen *Mycobacterium liflandii*.[13]

Mycolactones have attracted considerable attention from the synthetic community not only for their highly potent biological activity, but also for being the first examples of polyketide macrolides to be isolated from a human pathogen.[14–18] In this paper, we report first and second generation total syntheses of mycolactones A and B.

2. Results and discussion

2.1. First generation total synthesis[19]

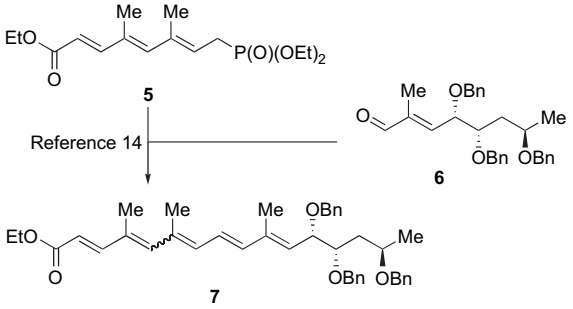
We envisioned that an obvious synthetic route to the mycolactones would proceed through esterification of the C5 hydroxyl group present in the mycolactone core with the pentaenoic acid present in the mycolactones. To demonstrate the feasibility of this approach, we decided to utilize the mycolactone core triol **3**, previously synthesized for the purposes of stereochemical assignment.[5] Selective protection of the C17/C19-1,3-diol of **3** was smoothly accomplished by treatment with dimethoxycyclopentane and *p*-TsOH, to furnish the suitably protected core **4** in good yield (Scheme 1).



Scheme 1. Reagents: (a) 1,1-dimethoxycyclopentane, *p*-TsOH, benzene, 80%.

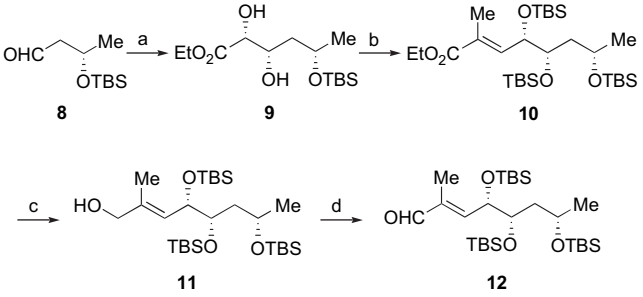
We then focused on the synthesis of a suitably protected pentaenoic acid. Considering the anticipated instability of the pentaenoate system, we chose to protect the side-chain alcohols as *tert*-butyldimethylsilyl (TBS) ethers. Gurjar and Cherian reported a synthesis of ethyl ester **7** of the pentaene fatty acid via Horner–Wadsworth–Emmons olefination at C8′–C9′ (Scheme 2).[14] Despite the differences in the stereochemistry of the triol and the protecting groups, this synthetic route appeared well suited to our needs, and we chose to adopt this route for the synthesis of tris-TBS pentaenoate **18** (see Scheme 6 for the structure **18**).

Our first task was the synthesis of the tris-TBS aldehyde **12**. In conjunction with the stereochemical assignment of the mycolactone unsaturated side-chain, we previously prepared all four diastereomers of **12** from D-glyceraldehyde



Scheme 2.

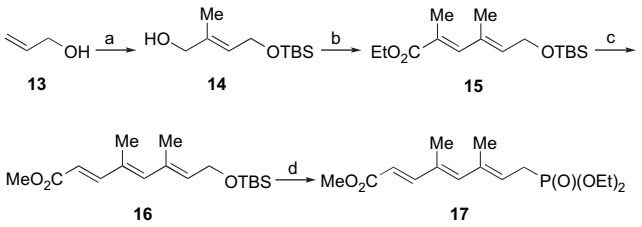
acetonide in an optically active form.[7] Worth noting is that the availability of all four diastereomers was critical for the unambiguous determination of the side-chain stereochemistry. However, once the stereochemistry was established, we could focus on the synthesis of the desired tris-TBS aldehyde **12** specifically. Although the synthetic route from D-glyceraldehyde acetonide served well for the stereochemical study, we wished to have a more efficient synthesis. For this reason, we studied an alternative synthetic route (Scheme 3). Thus, the known aldehyde **8**[20] was subjected to Horner–Wadsworth–Emmons olefination, then catalytic asymmetric dihydroxylation with AD-mix-α,[21] resulting in a 3.8:1 mixture of diastereomers,[22] with the expected and desired diol **9** as the major product. The diol was protected as its bis-TBS ether, and the resulting compound was then subjected to a sequence of reduction, oxidation, and Wittig olefination, to give the corresponding α,β-unsaturated ester **10**. Reduction of **10**, followed by chromatographic separation of the diastereomers and then oxidation, gave aldehyde **12**.



Scheme 3. Reagents: (a) (1) NaH, $(EtO)_2P(O)CH_2CO_2Et$, benzene, 64%; (2) AD-mix-α, $MeSO_2NH_2$, *t*-BuOH/H_2O (1:1), 40 h, 0 °C, 70%, d.r.=3.8:1; (b) (1) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 99%; (2) DIBAL, CH_2Cl_2, 89%; (3) SO_3·py, *i*-Pr_2NEt, CH_2Cl_2/DMSO (3:2); (4) $Ph_3P{=}C(Me)CO_2Et$, toluene, 110 °C, 83% (two steps); (c) DIBAL, CH_2Cl_2, −78 °C, followed by chromatographic separation of the diastereomers, 57%; (d) SO_3·py, *i*-Pr_2NEt, CH_2Cl_2/DMSO (3:2), quant.

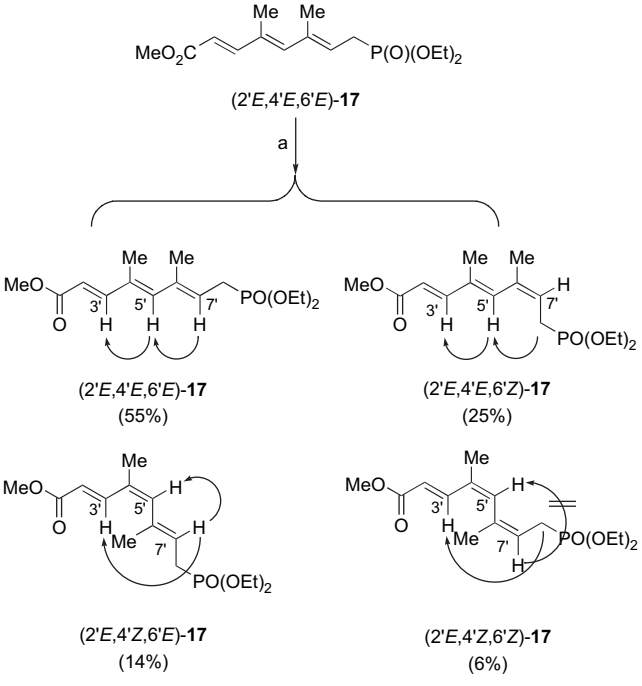
Next, phosphonate (2′*E*,4′*E*,6′*E*)-**17** was synthesized employing a minor modification of the procedure reported by Gurjar and Cherian.[14] The allylic alcohol **14** was prepared in four steps from allyl alcohol in 25% overall yield (Scheme 4). Oxidation, followed by Wittig olefination, gave diene ester **15**. Reduction, oxidation, and Wittig olefination provided triene ester **16**. Finally, a three-step sequence of deprotection, bromination, and phosphonate formation furnished (2′*E*,4′*E*,6′*E*)-**17**.

To gain insight into the chemical behavior of the anion generated from phosphonate **17**, we first studied its protonation



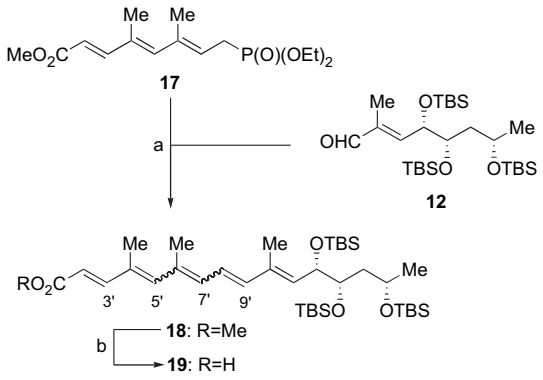
Scheme 4. Reagents: (a) (1) TBSCl, imidazole, DMF; (2) O_3, CH_2Cl_2, −78 °C, then Ph_3P; (3) $Ph_3P{=}C(Me)CO_2Et$, CH_2Cl_2; (4) DIBAL, CH_2Cl_2, −78 °C, 25% (four steps); (b) (1) $SO_3{\cdot}py$, *i*-Pr_2NEt, CH_2Cl_2/DMSO (3:2); (2) $Ph_3P{=}C(Me)CO_2Et$, benzene, 90 °C, 80% (two steps); (c) (1) DIBAL, CH_2Cl_2, −78 °C; (2) $SO_3{\cdot}py$, *i*-Pr_2NEt, CH_2Cl_2/DMSO (3:2); (3) $Ph_3P{=}CHCO_2Me$, benzene, 90 °C, 89% (three steps); (d) (1) TBAF, THF, 87%; (2) PBr_3, Et_2O, 77%; (3) $(EtO)_3P$, 90 °C, 96%.

(Scheme 5). On quenching with 2,4,6-trimethylphenol, the anion generated from (2′*E*,4′*E*,6′*E*)-**17** with LDA at −78 °C yielded a 55:25:14:6 mixture[23] of the geometric isomers of **17**. An NOE experiment was conducted on this mixture, yielding the results shown for the structures in Scheme 5. Based on this NOE experiment, the geometric isomers obtained from the protonation were established as (2′*E*,4′*E*,6′*E*)-**17** (55%), (2′*E*,4′*E*,6′*Z*)-**17** (25%), (2′*E*,4′*Z*,6′*E*)-**17** (14%), and (2′*E*,4′*Z*,6′*Z*)-**17** (6%). This experiment suggested that the stereochemical integrity of (2′*E*,4′*E*,6′*E*)-**17** would likely be lost during the subsequent Horner–Wadsworth–Emmons olefination.



Scheme 5. Reagents: (a) LDA, THF, −78 °C, then 2,4,6-trimethylphenol. An arrow indicates a detected, or not detected, NOE.

In the event, aldehyde **12** smoothly reacted with the anion generated from (2′*E*,4′*E*,6′*E*)-**17**, to furnish the expected product as a 73:17:7:3 mixture (Scheme 6).[23] Once again, based on NOE experiments, the stereochemistry was assigned as (2′*E*,4′*E*,6′*E*,8′*E*,10′*E*)-**18** (73%), (2′*E*,4′*Z*,6′*E*,8′*E*,10′*E*)-**18** (17%), (2′*E*,4′*E*,6′*Z*,8′*E*,10′*E*)-**18** (7%), and (2′*E*,4′*Z*,6′*Z*,8′*E*,10′*E*)-**18** (3%).



Scheme 6. Reagents: (a) LDA, **12**, THF, −78 °C to rt, 94%; (b) LiOH, THF/MeOH/H_2O (4:1:1), quant.

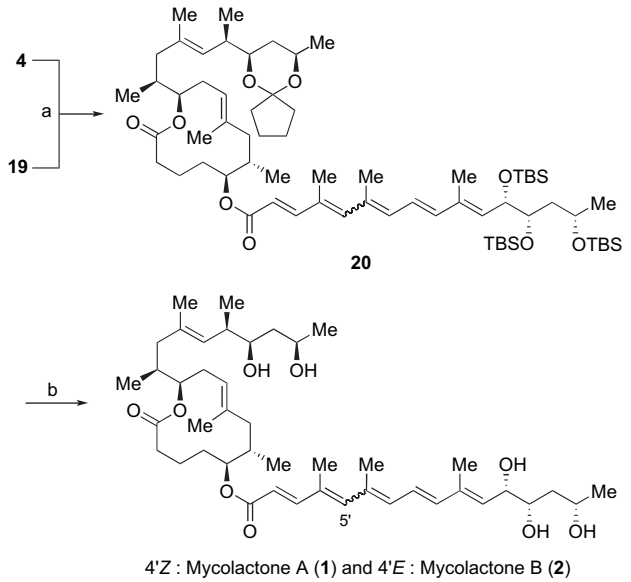
Worth noting, in reference to the ^1H NMR characteristics established for the four geometric isomers of **18**, we examined the ^1H NMR data reported for natural mycolactones A and B, thereby revealing that the sample of natural mycolactones contains a small amount (<5%) of a third geometric isomer whose spectroscopic characteristics match well those of the (2′*E*,4′*Z*,6′*Z*,8′*E*,10′*E*)-isomer of **18**.

The pentaenoate system present in the product **18** was expected to be prone to cis/trans-isomerization. Indeed, on photolysis (acetone-d_6, tungsten lamp), the 73:17:7:3 mixture yielded a new mixture consisting of (2′*E*,4′*E*,6′*E*,8′*E*,10′*E*)-**18** (36%), (2′*E*,4′*Z*,6′*E*,8′*E*,10′*E*)-**18** (52%), (2′*E*,4′*E*,6′*Z*,8′*E*,10′*E*)-**18** (4%), (2′*E*,4′*Z*,6′*Z*,8′*E*,10′*E*)-**18** (5%), and two minor isomers (3% combined).[23] The two minor isomers appeared to be (2′*E*,4′*E*,6′*E*,8′*E*,10′*Z*)-**18** and (2′*E*,4′*Z*,6′*E*,8′*E*,10′*Z*)-**18**. The two major isomers were found to be readily interconvertible, and the 3:2 ratio appeared to represent the steady-state ratio for this system.[4,14]

The product methyl pentaenoates were found to be chromatographically inseparable. However, upon hydrolysis to the corresponding acids, (2′*E*,4′*E*,6′*E*,8′*E*,10′*E*)-**19** could be separated from (2′*E*,4′*Z*,6′*E*,8′*E*,10′*E*)-**19** by silica gel column chromatography. Thus, it was possible to obtain the mycolactones A and B enriched with the C4′ *Z* geometrical isomer (vide infra).

To complete the total synthesis, **4** was coupled with **19** under Yamaguchi esterification conditions,[24] to furnish the protected mycolactones **20** in excellent yield (Scheme 7). Interestingly, attempted esterification under the conditions of EDCI/DMAP or BOP/DMAP did not give the desired product **20**.

Attempted global deprotection of **20** with HF·py in MeCN did give synthetic mycolactones A and B in 5–10% yield, but the product was accompanied by a complex mixture of side-products. ^1H NMR analysis suggested that these by-products might be formed via sequential oxy-Michael additions of the alcohol moieties to the pentaenoate system. To suppress these putative side-reaction(s), stepwise deprotection was then tested. In the event, treatment with tetra-*n*-butylammonium fluoride (TBAF) removed the three TBS groups, to furnish the corresponding triol in 81% yield. The cyclopentylidene ketal was then hydrolyzed with aqueous acetic acid in THF. Through extensive studies, the optimal



Scheme 7. Reagents: (a) $Cl_3C_6H_2COCl$, *i*-Pr_2NEt, DMAP, benzene, 90%; (b) (1) TBAF, THF, 81%; (2) AcOH/H_2O/THF (2:1:2), 67% with one recycle.

ratio of AcOH/H_2O/THF was found to be 2:1:2. However, even under the optimized conditions, by-product formation became significant when the reaction was allowed to go to completion. For this reason, the deprotection was quenched at approximately 60% completion, and the recovered triol was recycled. After one recycle, synthetic mycolactones A and B were isolated in 67% yield as an approximately 3:2 mixture of 4′-*Z* (mycolactone A) and 4′-*E* (mycolactone B) isomers.

On comparison of ^{1}H NMR (Fig. 2), ^{13}C NMR (Table 1), and TLC [silica gel, $CHCl_3$/MeOH/H_2O (90:10:1)], the synthetic mycolactones A and B were found to be superimposable on the natural mycolactones A and B, respectively. Rigorously speaking, however, these comparisons could not eliminate the possibility that the synthetic mycolactones A and B might be the remote diastereomers[25] of the natural products. In order to exclude this possibility, the ^{1}H NMR characteristics in a chiral NMR solvent were studied. As shown in Graph 1, both the synthetic and natural mycolactones A and B exhibited the identical $\Delta\delta$ profile in (*R*)- and (*S*)-*N*,α-dimethylbenzylamines (DMBAs).[6] Through these comparisons, we concluded that the synthetic mycolactones A and B are indeed identical to the natural mycolactones A and B. In addition, the synthetic mycolactones A and B exhibited biological properties identical to those of the natural products.[26]

2.2. Second generation total synthesis

Based on the knowledge accumulated through our first generation total synthesis of the mycolactones, we recognized that improvements could be made in two major areas. First, the acid-promoted deprotection of the cyclopentylidene ketal proved to be more problematic than originally anticipated. In contrast, mycolactones A and B appeared to be stable to TBAF-promoted TBS-deprotection conditions. These observations immediately suggested that the cyclopentylidene protecting group present in the C17/C19-diol **20** should be replaced by TBS ethers. Thus, TBAF-promoted desilylation should allow us to accomplish a more efficient global deprotection.

We were interested in demonstrating the effectiveness of this approach experimentally. For this purpose, we utilized the cyclopentylidene protected core **4** employed in the first synthesis. Thus, the protecting groups of **4** were adjusted in four steps to obtain the requisite TBS-protected core **21** (Scheme 8). Yamaguchi esterification of **21** with **19** proceeded to pentakis-TBS protected mycolactone. As anticipated, global deprotection conditions (TBAF, THF, rt) furnished mycolactones A and B in excellent yield.

As was previously mentioned, we decided to utilize the core triol **4** for our first generation total synthesis of the

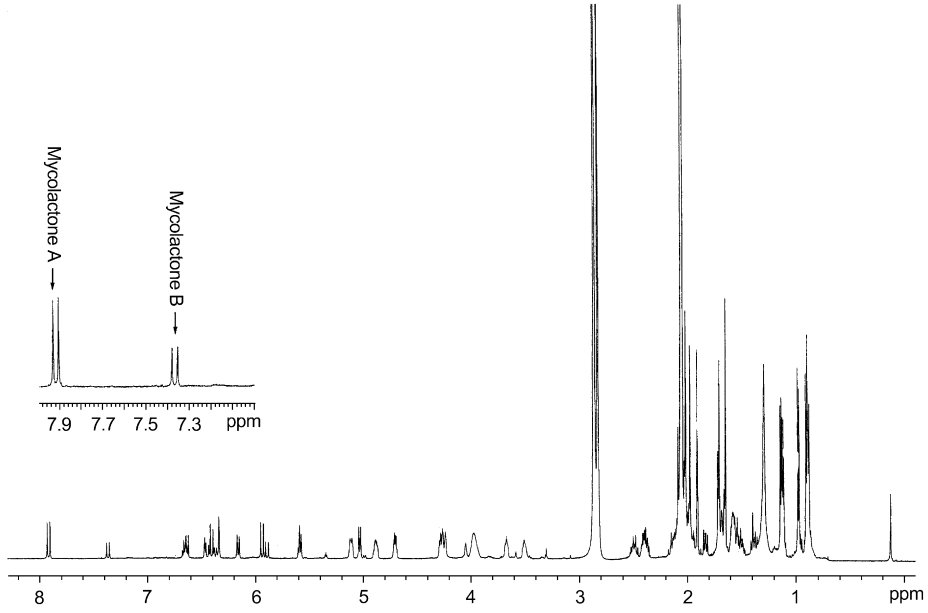


Figure 2. ^{1}H NMR spectrum (600 MHz, acetone-d_6) of synthetic mycolactones A and B.

Table 1. ^{13}C NMR chemical shifts observed for natural[4] and synthetic mycolactones A and B (125 MHz, acetone-d_6)

Carbon	Mycolactone A		Mycolactone B	
	Natural	Synthetic	Natural	Synthetic
1	173.3	173.3	173.3	173.3
2	35.9	35.9	35.9	35.9
3	20.8	20.7	20.8	20.7
4	31.4	31.5	31.4	31.5
5	79.3	79.3	79.3	79.3
6	32.8	32.7	32.8	32.7
7	46.4	46.3	46.4	46.3
8	137.2	137.3	137.2	137.3
9	123.8	123.8	123.8	123.8
10	29.3	[a]	29.3	[a]
11	76.3	76.2	76.3	76.2
12	35.4	35.3	35.4	35.3
13	44.3	44.3	44.3	44.3
14	133.9	133.4	133.9	133.4
15	131.2	131.2	131.2	131.2
16	40.5	40.4	40.5	40.4
17	76.9	76.9	76.9	76.9
18	43.8	43.8	43.8	43.8
19	68.9	68.9	68.9	68.9
20	24.6	24.6	24.6	24.6
21	20.5	20.5	20.5	20.5
22	15.9	15.9	15.9	15.9
23	15.0	14.9	15.0	14.9
24	16.2	16.2	16.2	16.2
25	17.1	17.1	17.1	17.1
1′	166.9	166.9	166.9	166.9
2′	119.6	119.6	117.4	117.4
3′	143.1	143.1	151.1	151.1
4′	132.1	132.1	133.2	133.2
5′	141.8	141.8	144.3	144.3
6′	134.7	134.8	135.3	135.3
7′	134.8	134.9	136.1	136.1
8′	125.1	125.1	125.1	125.1
9′	139.9	139.9	139.9	140.3
10′	137.2	137.2	137.2	137.2
11′	134.6	134.6	134.6	134.6
12′	72.4	72.3	72.4	72.3
13′	75.7	75.7	75.7	75.7
14′	41.9	41.8	41.9	41.8
15′	67.7	67.6	67.7	67.6
16′	24.2	24.2	24.2	24.2
17′	21.0	21.0	14.3	14.3
18′	17.6	17.6	17.1	17.1
19′	13.3	13.4	13.3	13.3

[a] Overlapped with the solvent signals.

mycolactones, since **4** was already in hand from our previous work on the stereochemistry assignment. However, having identified suitable protecting groups for the alcohols at C17 and C19, we were in a position to implement specific improvements for the synthesis of the mycolactone core; in particular, we were anxious to develop a shorter synthetic route with a greater degree of selectivity and efficiency.

Having demonstrated the feasibility of global TBAF-promoted TBS-deprotection, we wished to implement the TBS protecting groups from the very beginning of the synthesis, thereby improving the overall efficiency of the synthesis (Scheme 9). Thus, olefin **23** was prepared from the known aldehyde **22**[20] via Brown crotylboration[27] and subsequent protection of the alcohol as the TBS ether. Olefin **23** was then oxidatively cleaved, followed by treatment with dimethyl (diazomethyl)phosphonate (DAMP) and *t*-BuOK,[28] to provide the terminal alkyne **24** in good yield. The alkyne was then methylated using *n*-BuLi and MeI. Hydrozirconation,[29] followed by iodine quench, furnished the bis-TBS protected vinyl iodide **25**.

In the interest of the overall efficiency of the synthesis, we sought to protect the alcohol at C5 with a protecting group orthogonal to the TBS group, and therefore employed a *p*-methoxybenzyl (PMB) group. Thus, the C1–C7 alkyl iodide with the carboxylate group at C1 was synthesized from aldehyde **26** using Brown crotylboration[27,30] to install the C5 and C6 stereocenters (Scheme 10).

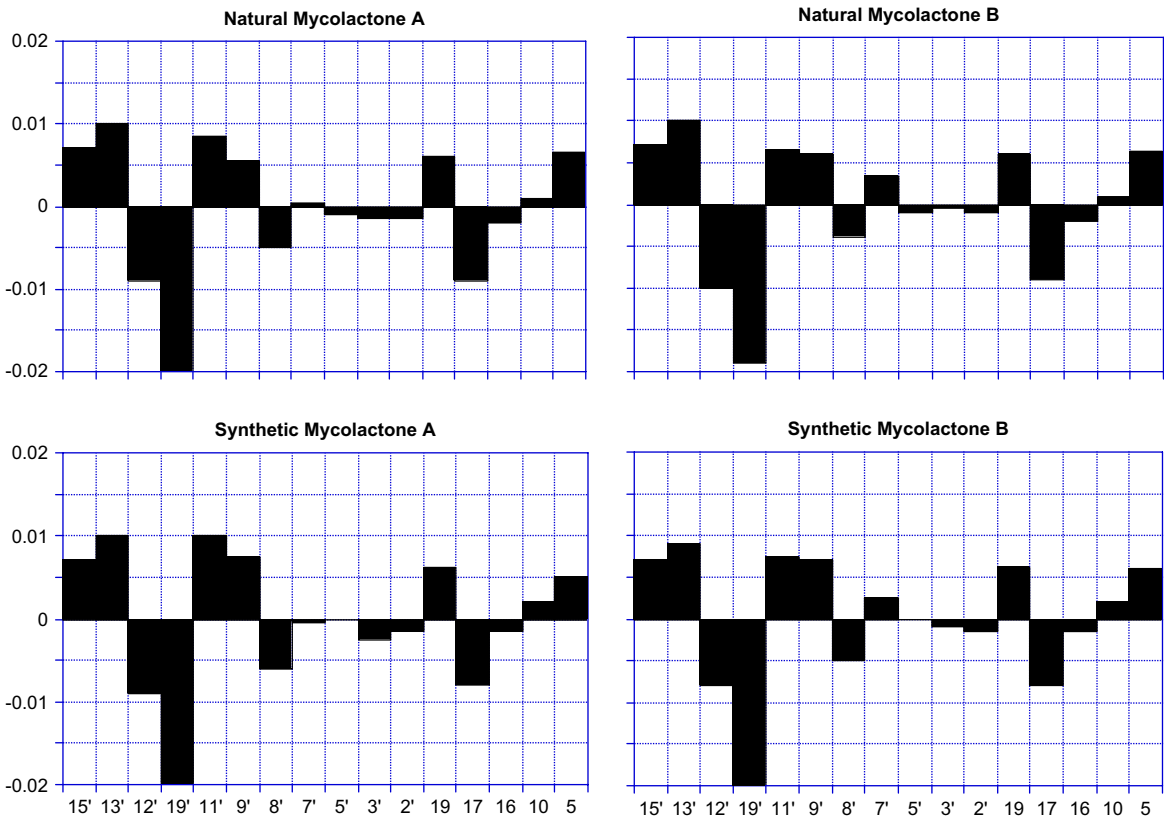
The synthesis of the C8–C13 building block is outlined in Scheme 11. Using the procedure reported by Seebach, (*S*)-diethyl malate (**31**) was alkylated with MeI and LDA in THF, to give alcohol **32**, along with its *syn* diastereomer (stereoselectivity=8:1).[31] Reduction of **32** using $LiAlH_4$ provided the known triol **33**[32] in excellent yield. The triol **33** was selectively protected to give TBS ether **34** via a dibutyltin ketal intermediate.[33] The resulting diol **34** was first converted to epoxide **35** and then coupled with propyne under Yamaguchi conditions.[34] Cleavage of the TBS ether and subsequent protection of the resulting 1,3-diol gave cyclopentylidene ketal **36**. The alkyne moiety of **36** was then converted to vinyl iodide **37** by hydrozirconation, followed by iodine quench. The vinyl iodide thus obtained was found to be identical to a sample synthesized by the previous route.[5]

With the three building blocks **25**, **30**, and **37** in hand, we next focused on the coupling reactions. Negishi coupling[35] was used to form the C7–C8 bond, i.e., **30**+**37**→**38**. Considering the presence of an electrophilic ester group in **30**, we chose to prepare the alkylzinc iodide species via zinc insertion by an active Zn–Cu couple,[36] instead of via transmetalation from Li to Zn. Additionally, $Pd(PPh_3)_4$ (10 mol %) was found the most effective catalyst for this case. In the event, the coupling of **30** (1.4 equiv) and **37** proceeded smoothly in the presence of 6–8 equiv of LiCl in *N*-methylpyrrolidinone (NMP),[37] to furnish **38** in 83% yield (Scheme 12).

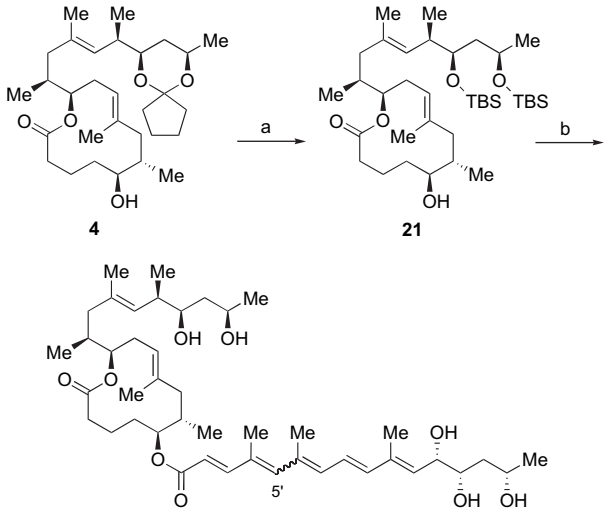
The coupled product **38** was transformed to the *seco*-acid **39** in better than 70% overall yield for three steps: (1) acid-promoted deprotection of the cyclopentylidene group, (2) selective protection of the resultant primary alcohol as the triisopropylsilyl (TIPS) ether, and (3) base-promoted hydrolysis of the methyl ester. Yamaguchi macrolactonization of **39** then furnished the desired macrolactone **40** in 96% yield. It is worthwhile noting that the lactone was designed to serve as a protecting group for the C11 alcohol during the following steps.

Deprotection of the silyl ether in **40**, followed by iodination, gave alkyl iodide **41**. Under the Negishi coupling conditions optimized for the case of the coupling of **30** with **37**, alkyl iodide **41** was coupled with **25** (1.5 equiv), to give **42** in 80% yield. The PMB group was then cleaved with DDQ, to furnish the bis-TBS protected core **21**.

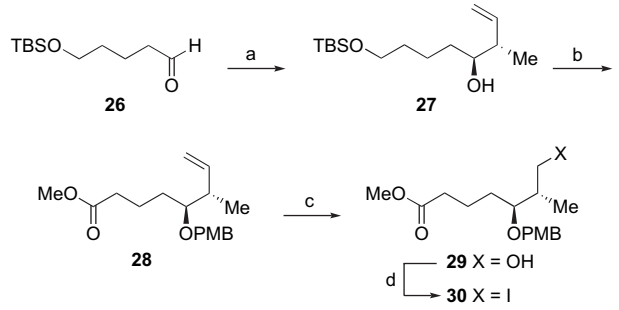
As demonstrated in Scheme 8, **21** was coupled with **19** and then subjected to the TBAF promoted global deprotection, to furnish a 3:2 mixture of the mycolactones A and B in 72% overall yield. Upon comparison of spectroscopic data and



Graph 1. $\Delta\delta$-Values of ^{1}H NMR chemical shifts in (*R*)- and (*S*)-DMBAs-d_{13}. Each graph shows the $\Delta\delta$ in chemical shift for natural and synthetic mycolactones A and B, with $\Delta\delta$ being [δ(*R*-DMBA)−δ(*S*-DMBA)].

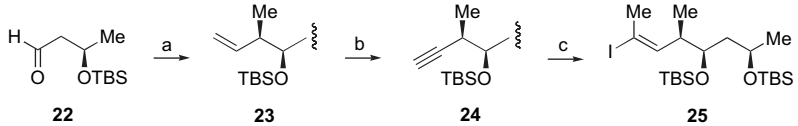


Scheme 8. Reagents: (a) (1) $MeOCH_2COCl$, *i*-Pr_2NEt, DMAP, CH_2Cl_2, 91%; (2) CH_2Cl_2/H_2O/TFA (16:4:1), 92%; (3) TBSOTf, 2,6-lutidine, CH_2Cl_2, quant.; (4) K_2CO_3, MeOH, 0 °C, 84%; (b) (1) **19**, $Cl_3C_6H_2COCl$, *i*-Pr_2NEt, DMAP, benzene, 90%; (2) TBAF, THF, 80%.

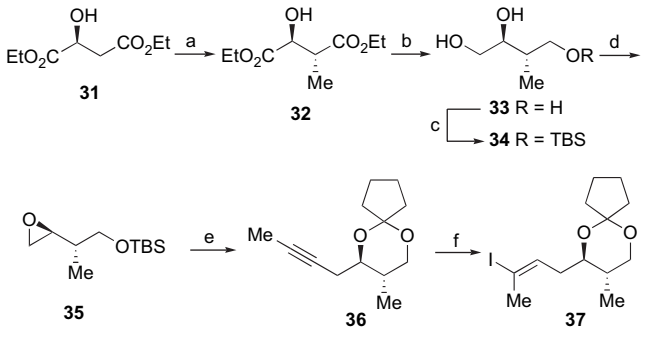


Scheme 10. Reagents: (a) *Z*-2-butene, *t*-BuOK, *n*-BuLi, (+)-Ipc_2BOMe, $BF_3{\cdot}OEt_2$, THF, −78 °C, then H_2O_2, NaOH, 80%; (b) (1) NaH, PMBBr, DMF, 89%; (2) TBAF, THF, 96%; (3) $SO_3{\cdot}$py, *i*-Pr_2NEt, CH_2Cl_2/DMSO (3:2), 94%; (4) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, *t*-BuOH/H_2O; (5) MeI, DBU, CH_3CN, 84% for two steps; (c) (1) OsO_4, NMO, acetone/H_2O (1:1), 80%; (2) $Pb(OAc)_4$, benzene; (3) $NaBH_4$, MeOH, 0 °C, 83% (two steps); (d) Ph_3P, imidazole, I_2, CH_2Cl_2, 92%.

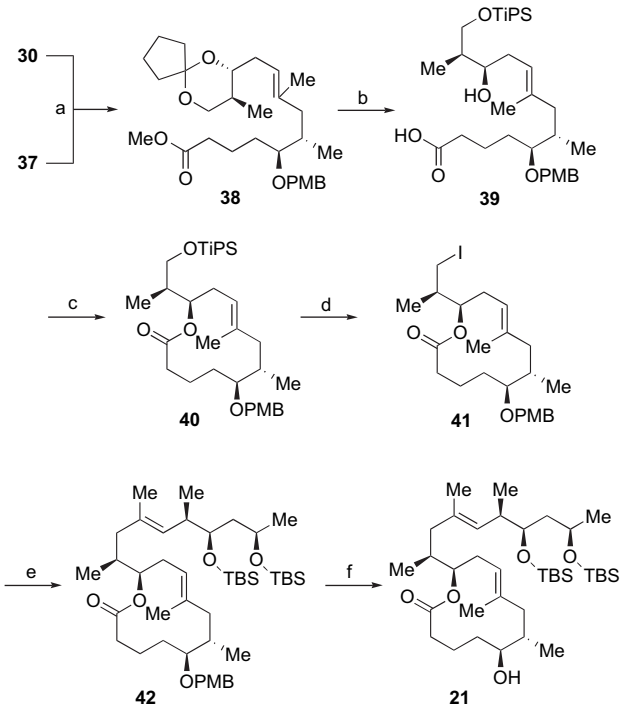
TLC, the mycolactones A and B thus synthesized were found to be identical to the synthetic mycolactones A and B obtained via the first route as well as to the authentic natural products.



Scheme 9. Reagents: (a) (1) *Z*-2-butene, *t*-BuOK, *n*-BuLi, (−)-Ipc_2BOMe, $BF_3{\cdot}OEt_2$, THF, −78 °C, then H_2O_2, NaOH, 78%; (2) TBSCl, imidazole, DMF, quant.; (b) (1) O_3, CH_2Cl_2, −78 °C, then Ph_3P, 94%; (2) *t*-BuOK, DAMP, THF, 84%; (c) (1) *n*-BuLi, MeI, THF, −78 °C to rt, 93%; (2) Cp_2ZrHCl, THF, 50 °C, then I_2, THF, 65%.



Scheme 11. Reagents: (a) LDA, MeI, THF, −78 °C, 80%, d.r.=8:1; (b) $LiAlH_4$, THF, reflux; (c) (1) *n*-Bu_2SnO, MeOH, reflux; (2) TBSCl, $CHCl_3$, 70% for three steps; (d) 1-(*p*-toluenesulfonyl)imidazole, NaH, THF, 88%; (e) (1) *n*-BuLi, propyne, $BF_3{\cdot}OEt_2$, THF, −78 °C, 96%; (2) TBAF, THF; (3) cyclopentanone, *p*-TsOH, benzene, 76%; (f) Cp_2ZrHCl, THF, 50 °C, then I_2, 62%.



Scheme 12. Reagents: (a) Zn, $Cu(OAc)_2$, $Pd(PPh_3)_4$, LiCl, NMP, 60 °C, 83%; (b) (1) CH_2Cl_2/H_2O/TFA (16:4:1), 90%; (2) TIPSCl, imidazole, DMF, quant.; (3) LiOH, 4:1:1 THF/MeOH/H_2O, 81%; (c) $Cl_3C_6H_2COCl$, *i*-Pr_2NEt, benzene, then DMAP, benzene, 96%; (d) (1) HF·py/py/CH_3CN, 90%; (2) Ph_3P, imidazole, I_2, CH_2Cl_2, 98%; (e) Zn, $Cu(OAc)_2$, **25**, $Pd(PPh_3)_4$, LiCl, NMP, 60 °C, 80%; (f) DDQ, CH_2Cl_2/H_2O, 91%.

As was previously discussed, the pentaenoate system present in the mycolactones is readily prone to cis/trans-isomerization. This isomerization appeared to be facile under the acidic conditions used for deprotection of the cyclopentylidene ketal in the first generation total synthesis (Scheme 7). Interestingly, under the conditions of TBAF-promoted global deprotection used in the second generation total synthesis (Scheme 12), the cis/trans-isomerization seemed to be controllably slow in the dark, thereby suggesting the possibility that either mycolactone A free of mycolactone B, or mycolactone B free of mycolactone A, could be obtained, if pure Z-$\Delta^{4',5'}$ or E-$\Delta^{4',5'}$ pentaenoic acid was used. In order to test this possibility, a 10:1 mixture of Z-$\Delta^{4',5'}$ and E-$\Delta^{4',5'}$ pentaenoic acids, obtained by silica gel column chromatography (vide ante), was coupled with **21** and then subjected to TBAF-deprotection in the dark, to furnish a 6:1 mixture of mycolactone A and mycolactone B (Fig. 3). Apparently, during this synthetic operation, the stereochemical integrity of the pentaenoic acid was compromised to some extent. We would attribute, at least partly, the observed cis/trans-isomerization to the exposure of these substrates to light. If this is the case, this experiment indicates the possibility of obtaining pure mycolactone A and/or B through this route. In this connection, we specifically reference the recent work by Negishi and co-workers, disclosing a stereoselective synthesis of both protected (2′*E*,4′*E*,6′*E*,8′*E*,10′*E*)- and (2′*E*,4′*Z*,6′*E*,8′*E*,10′*E*)-pentaenoic acids.[17,38]

3. Conclusion

Mycolactones A and B have been synthesized through two different routes. Our first generation total synthesis unambiguously confirmed the relative and absolute stereochemistry predicted via an NMR database approach. Knowledge regarding the chemical properties of the mycolactones accumulated through the first generation total synthesis allowed us to implement several major improvements to the original synthesis, including: (1) optimizing the choice of protecting groups, (2) eliminating the unnecessary adjustment of protecting groups, and (3) improving the overall stereoselectivity and synthetic efficiency. The second generation of total synthesis consists of 21 steps in the longest linear sequence, with 6.3% overall yield.

As was previously noted, several mycolactone congeners have been isolated from various clinical isolates of *M. ulcerans* and also from the frog pathogen *M. marinum* and the fish pathogen *M. liflandii*. Structurally, all of these congeners appear to contain the same core structure of mycolactones A and B, but different unsaturated side-chains. However, given the fact that these congeners were obtained in very minute amounts, an unambiguous structural determination is challenging. In this connection, we should specifically emphasize that our second generation total synthesis offers an appealing opportunity to study their structure as well as their biological profile, particularly because of its overall efficiency and flexibility. Indeed, the effectiveness of this approach has recently been demonstrated in the case of mycolactone C.[39]

4. Experimental section

4.1. General procedures and methods

NMR spectra were recorded on Varian Inova spectrometers (400, 500, and 600 MHz). Chemical shifts are reported in parts per million (ppm) and coupling constants in hertz. For ^1H and ^{13}C spectra, the central residual solvent peak (methanol, acetone, benzene) was used as the internal reference (3.30, 2.05, 7.15 ppm, and 49.0, 29.8, 128.0 ppm, respectively). Analytical thin layer chromatography (TLC) was performed with E. Merck pre-coated TLC plates, silica gel 60 F_{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

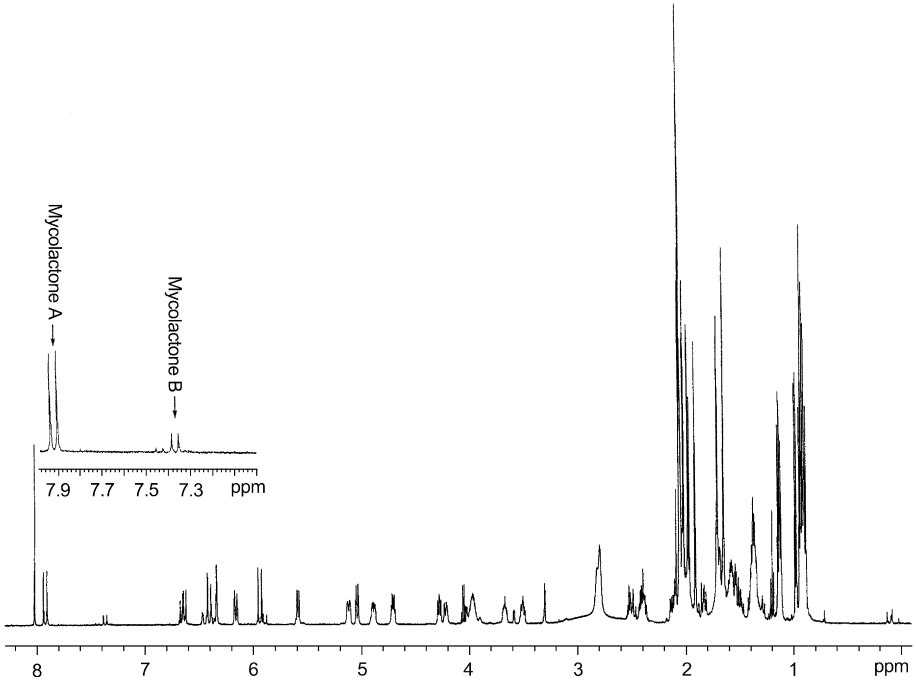


Figure 3. ^{1}H NMR spectrum (500 MHz, acetone-d_6) of the synthetic mycolactones enriched with mycolactone A.

commercial grade and were used as supplied, with the following exceptions: benzene, ether, and THF were distilled from sodium benzophenone ketyl, dichloromethane was distilled from calcium hydride, and toluene was distilled from sodium. All reactions were conducted under an argon atmosphere unless otherwise noted. Reaction vessels and apparatus were flame-dried or oven-dried and allowed to cool under an inert atmosphere.

4.2. First generation total synthesis

Experimental details outlined in Schemes 1–7 are given in the Supplementary data of Refs. 5, 7, and 8.

4.3. Second generation total synthesis

4.3.1. Synthesis outlined in Scheme 8. To a stirred solution of alcohol **4** (23.2 mg, 0.047 mmol) in CH_2Cl_2 (3.0 mL) at 0 °C was added *i*-Pr_2NEt (25 μL, 0.142 mmol), DMAP (11.5 mg, 0.095 mmol), and methoxyacetyl chloride (13 μL, 0.142 mmol). The resulting solution was stirred at 0 °C for 1 h, then diluted with CH_2Cl_2 (10 mL) and water (10 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3×10 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. Flash chromatography (4:1 hexanes/EtOAc) provided the methoxyacetate (24.2 mg, 91%).

Dichloromethane saturated with aqueous TFA was prepared by shaking CH_2Cl_2, TFA (8 mL), and H_2O (2 mL) in a separatory funnel. The layers were allowed to separate for 30 s, and the organic layer was used. The organic layer (5 mL) was added to the above ester (57.2 mg, 0.102 mmol), and the resulting solution stirred for 3.5 h. CH_2Cl_2 (10 mL) and saturated aqueous sodium bicarbonate (15 mL) were then added. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3×10 mL). The combined organic layers were washed with water (30 mL) and brine (30 mL), dried over Na_2SO_4, and concentrated in vacuo. Flash chromatography (4:1 hexanes/EtOAc, then 2:1 EtOAc/hexanes) provided the corresponding diol (46.0 mg, 92%).

To a stirred solution of the above diol (46.0 mg, 0.093 mmol) in CH_2Cl_2 (6.0 mL) at 0 °C were added 2,6-lutidine (44 μL, 0.372 mmol) and TBSOTf (87 μL, 0.372 mmol). The resulting solution was stirred for 90 min, then saturated aqueous ammonium chloride (10 mL) was added. The layers were separated, and the aqueous layer was extracted with EtOAc (3×10 mL). The combined organic layers were washed with water and brine, dried over Na_2SO_4, and concentrated in vacuo. Flash chromatography (4:1 hexanes/EtOAc) afforded the methoxyacetate (67.1 mg, quant.).

To a stirred solution of the methoxyacetate (70.0 mg, 0.096 mmol) in MeOH (7.0 mL) at 0 °C was added K_2CO_3 (35.0 mg, 0.25 mmol). The resulting solution was stirred at 0 °C for 2 h, then at room temperature for 5 h. The reaction mixture was then diluted with CH_2Cl_2 (15 mL) and saturated aqueous ammonium chloride (15 mL). The layers were separated, and the aqueous layer extracted with CH_2Cl_2 (3×15 mL). The combined organic layers were washed with brine (2×30 mL), dried over Na_2SO_4, and concentrated in vacuo. Flash chromatography (8:1 hexanes/EtOAc) provided **21** (52.9 mg, 84%). ^{1}H NMR (CD_3COCD_3, 500 MHz,) δ 5.23 (d, J=9.0, 1H), 5.04 (d, J=11.5, 1H), 4.91 (ddd, J=12.5, 5.5, 2.5, 1H), 3.98 (q, J=6.5, 1H), 3.74 (td, J=5.5, 4.5, 1H), 3.36 (m, 1H), 2.59 (m, 1H), 2.49 (dt, J=14.0, 11.5, 1H), 2.31 (ddd, J=13.5, 8.0, 3.0, 1H), 2.08–2.18 (m, 3H), 1.91 (m, 3H), 1.76 (dd, J=13.0, 10.0, 1H), 1.65 (s, 6H), 1.42–1.62 (m, 7H), 1.16 (d, J=6.0, 3H), 0.96 (d, J=6.5, 3H), 0.92 (s, 9H), 0.91 (m, 3H), 0.90 (s, 9H), 0.87 (d, J=6.5, 3H), 0.091 (s, 3H), 0.086 (s, 3H), 0.08 (s, 6H).

4.3.1.1. Mycolactones A and B via penta-TBS protection (1 and 2). To a stirred solution of pentaene acid **19** (89.6 mg, 0.132 mmol) in benzene (1 mL) were added *i*-Pr_2NEt (92 μL, 0.53 mmol), $Cl_3C_6H_2COCl$ (42.6 μL, 0.26 mmol), and DMAP (80.8 mg, 0.66 mmol). Alcohol **21** (43.1 mg, 0.066 mmol) was then added in benzene (1.5 mL, 0.5 mL wash). The resulting solution was stirred for 20 h. Benzene (5 mL) and saturated aqueous sodium bicarbonate (5 mL) were then added. The layers were separated, and the aqueous layer was extracted with benzene (3×5 mL). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, and concentrated in vacuo. Flash chromatography (20:1 hexanes/EtOAc, followed by 4:1 hexanes/EtOAc) gave the protected mycolactones (78.0 mg, 90%). These protected mycolactones exist as a 3:2 mixture of *Z*:*E* isomers at $\Delta^{4',5'}$ (mycolactone numbering). ^{1}H NMR (CD_3COCD_3, 600 MHz, *Z*-$\Delta^{4',5'}$ isomer) δ 7.93 (d, *J*=15.6, 1H), 6.66 (dd, *J*=15.0, 11.4, 1H), 6.44 (d, *J*=15.0, 1H), 6.34 (s, 1H), 6.19 (d, *J*=11.4, 1H), 5.94 (d, *J*=15.6, 1H), 5.66 (d, *J*=9.0, 1H), 5.23 (d, *J*=9.0, 1H), 5.15 (br d, *J*=10.2, 1H), 4.88 (m, 1H), 4.71 (sextet, *J*=4.2, 1H), 4.58 (dd, *J*=9.0, 3.6, 1H), 3.96–4.06 (m, 2H), 3.76–3.80 (m, 1H), 3.72–3.76 (m, 1H), 2.55–2.62 (m, 1H), 2.47–2.55 (m, 1H), 2.37–2.45 (m, 1H), 2.14–2.19 (m, 1H), 2.08–2.13 (m, 1H), 2.09 (s, 3H), 1.92–2.05 (m, 5H), 1.98 (s, 3H), 1.95 (s, 3H), 1.84–1.92 (m, 2H), 1.76–1.82 (m, 1H), 1.71 (s, 3H), 1.56–1.72 (m, 6H), 1.66 (s, 3H), 1.17 (d, *J*=6.0, 3H), 1.16 (d, *J*=6.6, 3H), 0.92 (s, 9H), 0.91 (s, 9H), 0.86–0.91 (overlapped three singlets and three doublets, 36H), 0.08–0.10 (overlapped eight singlets, 24H), 0.04 (s, 3H), 0.03 (s, 3H). ^{1}H NMR (CD_3COCD_3, 600 MHz, *E*-$\Delta^{4',5'}$ isomer) δ 7.37 (d, *J*=15.0, 1H), 6.68 (dd, *J*=15.0, 11.4, 1H), 6.49 (d, *J*=15.0, 1H), 6.48 (s, 1H), 6.40 (d, *J*=11.4, 1H), 5.89 (d, *J*=15.0, 1H), 5.67 (d, *J*=9.0, 1H), 5.23 (d, *J*=9.0, 1H), 5.15 (br d, *J*=10.2, 1H), 4.88 (m, 1H), 4.71 (sextet, *J*=4.2, 1H), 4.58 (dd, *J*=9.0, 3.6, 1H), 3.96–4.06 (m, 2H), 3.76–3.80 (m, 1H), 3.72–3.76 (m, 1H), 2.55–2.62 (m, 1H), 2.47–2.55 (m, 1H), 2.37–2.45 (m, 1H), 2.14–2.19 (m, 1H), 2.08–2.13 (m, 1H), 2.09 (s, 3H), 1.92–2.05 (m, 5H), 1.98 (s, 3H), 1.94 (s, 3H), 1.84–1.92 (m, 2H), 1.76–1.82 (m, 1H), 1.72 (s, 3H), 1.56–1.72 (m, 6H), 1.66 (s, 3H), 1.17 (d, *J*=6.0, 3H), 1.16 (d, *J*=6.6, 3H), 0.92 (s, 9H), 0.91 (s, 9H), 0.86–0.91 (overlapped three singlets and three doublets, 36H), 0.08–0.10 (overlapped eight singlets, 24H), 0.04 (s, 3H), 0.03 (s, 3H). MS (ES) *m*/*z* 1332 ($M+NH_4^+$).

To a stirred solution of the pentakis-TBS protected mycolactone precursor (6.6 mg, 5.03 μmol) in THF (1 mL) was added TBAF (1 M solution in THF, 75 μL, 75 μmol). The solution was stirred at room temperature for 8 h. The reaction mixture was concentrated. Flash chromatography (100:1 EtOAc/MeOH, followed by 90:10:1 $CHCl_3$/MeOH/H_2O) gave mycolactones (3.0 mg, 80%).

4.3.2. Synthesis outlined in Scheme 9.

4.3.2.1. Preparation of vinyl iodide 25. To a solution of *t*-BuOK (6.56 g, 58.5 mmol) in THF (400 mL) at −78 °C was added *Z*-2-butene (8.2 g, 146 mmol) followed by *n*-BuLi in hexanes (2.16 M, 27.1 mL, 58.5 mmol). The bright yellow suspension was stirred at −78 °C for 5 min, −45 °C for 10 min, and then −78 °C for 15 min. A solution of (−)-Ipc_2BOMe (21.58 g, 68.2 mmol) in Et_2O (50 mL) was then added via cannula. The colorless solution was allowed to stir at −78 °C for 30 min, and then $BF_3\cdot Et_2O$ (9.5 mL, 75 mmol) was added followed immediately by a solution of the known aldehyde **22**[20] (9.86 g, 48.7 mmol) in THF (50 mL, 10 mL wash). The solution was stirred at −78 °C for 3 h and then quenched by addition of 3 N NaOH (130 mL). H_2O_2 (30%, 65 mL) was then added carefully with stirring, and the resulting mixture was stirred vigorously at room temperature for 12 h. The mixture was then diluted with EtOAc and washed with H_2O and brine. The organic phase was then dried over anhydrous $MgSO_4$ and concentrated in vacuo. Flash chromatography (39:5 hexanes/EtOAc) gave alcohol (9.87 g, 78% yield). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.78 (ddd, *J*=17.6, 10.4, 7.6, 1H), 5.02 (br d, *J*=17.6, 1H), 5.01 (br d, *J*=10.4, 1H), 4.03 (ddq, *J*=9.6, 4.0, 5.6, 1H), 3.60 (dddd, *J*=9.6, 5.6, 2.0, 1.2, 1H), 3.41 (d, *J*=1.2, *OH*), 2.21 (apparent sextet, *J*=7.0, 1H), 1.59 (ddd, *J*=14.4, 4.0, 2.0, 1H), 1.43 (dd, *J*=14.4, 9.6, 1H), 1.16 (d, *J*=6.0, 1H), 1.01 (d, *J*=6.8, 1H), 0.88 (s, 9H), 0.10 (s, 3H), 0.08 (s, 3H); ^{13}C NMR ($CDCl_3$, 400 MHz) δ 141.0, 114.6, 74.6, 70.3, 43.7, 42.6, 25.8 (3C), 24.5, 17.8, 14.9, −4.0, −4.8.

To a solution of the alcohol (5.069 g, 19.65 mmol) in DMF (100 mL) were added imidazole (3.345 g, 49.13 mmol) and TBSCl (5.924 g, 39.30 mmol). The solution was stirred for 15 h. Then water was added and the mixture was extracted with Et_2O twice. The combined extracts were washed with H_2O, brine, dried over anhydrous $MgSO_4$, and concentrated in vacuo. Flash chromatography (49:1 hexanes/EtOAc) gave the silyl ether **23** (7.318 g, 19.67 mmol, quant.). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.90 (ddd, *J*=17.5, 10.5, 6.5, 1H), 5.00 (br d, *J*=10.5, 1H), 4.99 (br d, *J*=17.5, 1H), 3.90 (apparent sextet, *J*=6.5, 1H), 3.68 (dddd, *J*=6.5, 6.0, 4.0, 1H), 2.29–2.36 (m, 1H), 1.60 (ddd, *J*=13.5, 6.5, 6.5, 1H), 1.48 (ddd, *J*=13.5, 6.5, 6.5, 1H), 1.13 (d, *J*=6.5, 1H), 0.94 (d, *J*=7.0, 1H), 0.89 (s, 9H), 0.88 (s, 9H), 0.05 (s, 3H), 0.044 (s, 3H), 0.039 (s, 3H), 0.035 (s, 3H); ^{13}C NMR ($CDCl_3$, 400 MHz) δ 141.4, 113.8, 72.9, 76.9, 43.8, 42.2, 25.9 (6C), 23.7, 18.11, 18.08, 13.7, −4.31, −4.33, −4.4, −4.7.

A solution of **23** (7.318 g, 19.67 mmol) at −78 °C in CH_2Cl_2 (190 mL) was saturated with ozone until a blue color persisted. The solution was then purged with argon until the blue color dissipated, and Ph_3P (5.419 g, 20.66 mmol) was added. The solution was warmed to room temperature and stirred for 12 h, then concentrated in vacuo. Flash chromatography (39:1 hexanes/Et_2O) gave the aldehyde (6.910 g, 94% yield) as a colorless oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.74 (br s, 1H), 4.37 (ddd, *J*=8.4, 6.0, 3.0, 1H), 3.83 (apparent sextet, *J*=6.5, 1H), 2.48 (dq, *J*=3.0, 6.0, 1H), 1.59–1.71 (m, 2H), 1.16 (d, *J*=6.0, 3H), 1.05 (d, *J*=6.5, 3H), 0.89 (s, 9H), 0.85 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H), 0.04 (s, 3H), 0.02 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 205.0, 68.7, 65.6, 50.5, 44.2, 25.8 (3C), 25.7 (3C), 24.0, 18.0, 17.9, 6.9, −4.1, −4.2, −4.7, −4.8.

To a solution of DAMP (2.451 g, 16.34 mmol) in THF (90 mL) at −78 °C was added *t*-BuOK (95%, 1.930 g, 16.34 mmol). To the resulting yellow solution was added a solution of the aldehyde (6.112 g, 16.34 mmol) in THF (20 mL, 5 mL wash), and the resulting solution was stirred

at −78 °C for 1 h and then warmed to 0 °C for 1 h. The mixture was then diluted with saturated aqueous $NaHCO_3$ and EtOAc. The organic phase was washed with saturated aqueous $NaHCO_3$, dried over $MgSO_4$, and concentrated in vacuo. Flash chromatography (40:1 hexanes/EtOAc) gave the alkyne **24** (5.083 g, 84% yield). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.98 (apparent sextet, J=6.5, 1H), 3.72 (apparent q, J=5.5, 1H), 2.56–2.64 (m, 1H), 2.20 (d, J=2.5, 1H), 1.83 (ddd, J=13.0, 6.5, 5.5, 1H), 1.56 (ddd, J=13.0, 6.5, 5.5, 1H), 1.13 (d, J=5.5, 3H), 1.12 (d, J=6.5, 3H), 0.90 (s, 9H), 0.89 (s, 9H), 0.09 (s, 3H), 0.06 (three overlapped singlets, 9H).

To a solution of the alkyne **24** (3.653 g, 9.87 mmol) in THF (100 mL) at −78 °C were added *n*-BuLi (2.38 M in hexanes, 4.98 mL, 11.84 mmol) and MeI (1.0 mL, 15.99 mmol). The solution was stirred and warmed to room temperature for 1 h. The solution was then diluted with saturated aqueous $NaHCO_3$ and EtOAc. The organic phase was washed with saturated aqueous $NaHCO_3$, brine, dried over $MgSO_4$, and concentrated in vacuo. Flash chromatography (20:1 hexanes/EtOAc) gave the methyl alkyne (3.541 g, 93% yield). $[\alpha]_D^{23}$ +10.8 (*c* 1.28, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.98 (apparent sextet, J=6.0, 1H), 3.68 (apparent q, J=6.0, 1H), 2.46–2.54 (m, 1H), 1.82 (ddd, J=13.5, 6.0, 6.0, 1H), 1.77 (d, J=2.5, 3H), 1.54 (ddd, J=13.5, 6.0, 6.0, 1H), 1.14 (d, J=6.0, 3H), 1.07 (J=6.0, 3H), 0.90 (overlapped two singlets, 18H), 0.08 (s, 3H), 0.07 (s, 3H), 0.061 (s, 3H), 0.057 (s, 3H). HRMS (ES) 385.2954 (M+H$^+$), calcd 385.2958.

A solution of the methyl alkyne (1.627 g, 4.24 mmol) in THF (10.5 mL) was added to Cp_2ZrHCl (2.189 g, 8.49 mmol) via cannula. The mixture was protected from light and stirred at 50 °C for 2 h. The resulting dark red suspension was cooled to room temperature. A solution of I_2 (2.150 g, 8.47 mmol) in THF (7 mL) was added via cannula. The dark brown mixture was stirred at room temperature for 30 min and then poured into a 1:1 mixture of saturated aqueous $Na_2S_2O_3$ and saturated aqueous $NaHCO_3$. The mixture was diluted with EtOAc and the organic phase was separated and washed with saturated aqueous $Na_2S_2O_3$, saturated aqueous $NaHCO_3$, and brine. The organic solution was dried over anhydrous $MgSO_4$ and concentrated in vacuo. Flash chromatography (100:1 hexanes/EtOAc) gave the vinyl iodide **25** (1.413 g, 65% yield). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.13 (br d, J=9.5, 1H), 3.87 (apparent sextet, J=6.0, 1H), 3.66 (ddd, J=7.0, 5.5, 4.0, 1H), 2.52 (ddq, J=9.5, 4.0, 6.5, 1H), 2.38 (d, J=1.5, 3H), 1.53–1.64 (m, 2H), 1.13 (d, J=6.0, 3H), 0.91 (d, J=7.0, 3H), 0.89 (s, 9H), 0.88 (s, 9H), 0.056 (s, 3H), 0.054 (s, 3H), 0.04 (two overlapped singlets, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 145.0, 93.1, 71.9, 65.8, 44.9, 40.3, 27.9, 25.90 (3C), 25.86 (3C), 24.1, 18.1 (2C), 14.1, −4.20 (2C), −4.6, −4.7.

4.3.3. Synthesis outlined in Scheme 10. To a solution of *t*-BuOK (6.56 g, 58.5 mmol) in THF (400 mL) at −78 °C was added *Z*-2-butene (8.2 g, 146 mmol) followed by *n*-BuLi in hexanes (2.16 M, 27.1 mL, 58.5 mmol). The bright yellow suspension was stirred at −78 °C for 5 min, −45 °C for 10 min, and then −78 °C for 15 min. A solution of (+)-Ipc_2BOMe (21.58 g, 68.2 mmol) in Et_2O (50 mL) was then added via cannula. The colorless solution was allowed to stir at −78 °C for 30 min, and then $BF_3\cdot Et_2O$ (9.5 mL, 75 mmol) was added followed immediately by a solution of aldehyde **26** (9.86 g, 45.6 mmol) in THF (50 mL, 10 mL wash). The solution was stirred at −78 °C for 3 h and then quenched by addition of 3 N NaOH (130 mL). Then, H_2O_2 (30%, 65 mL) was added carefully with stirring, and the resulting mixture was stirred vigorously at room temperature for 12 h. The mixture was then diluted with EtOAc (1 L) and washed with H_2O (500 mL) and brine (500 mL). The organic phase was then dried over anhydrous $MgSO_4$ and concentrated in vacuo. Flash chromatography (39:1 hexanes/EtOAc) gave alcohol **27** (9.87 g, 80% yield) as colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.79 (m, 1H), 5.05–5.11 (m, 2H), 3.61 (t, J=5.6, 2H), 3.49 (m, 1H), 2.27 (apparent sextet, J=6.8, 1H), 1.46–1.58 (m, 4H), 1.33–1.41 (m, 2H), 1.02 (d, J=6.8, 3H), 0.89 (s, 9H), 0.04 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 141.3, 115.4, 74.9, 63.4, 43.7, 33.9, 33.0, 26.2 (3C), 22.6, 18.6, 14.3, −5.0 (2C).

To a solution of alcohol **27** (2.985 g, 10.97 mmol) in DMF (80 mL) at 0 °C was added NaH (1.317 g, 60%, 32.92 mmol). The mixture was stirred at 0 °C for 30 min. Then PMBBr (3.308 g, 16.46 mmol) was added and the mixture was stirred at room temperature for 14 h. The mixture was diluted with EtOAc and washed with saturated aqueous NH_4Cl. The aqueous phase was extracted with EtOAc twice. The combined organic phase was washed with H_2O, brine, dried over anhydrous $MgSO_4$, and concentrated in vacuo. Flash chromatography (20:1 hexanes/EtOAc) gave the PMB ether (3.818 g, 89% yield). $[\alpha]_D^{23}$ −32.9 (*c* 1.70, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.27 (d, J=8.4, 2H), 6.87 (d, J=8.4, 2H), 5.85 (ddd, J=17.2, 10.4, 7.2, 1H), 5.04 (br d, J=17.2, 1H), 5.01 (br d, J=10.4, 1H), 4.49 (d, J=10.8, 1H), 4.44 (d, J=10.8, 1H), 3.80 (s, 3H), 3.60 (t, J=6.4, 2H), 3.21–3.27 (m, 1H), 2.47 (apparent sextet, J=7.2, 1H), 1.46–1.55 (m, 4H), 1.28–1.38 (m, 2H), 1.04 (d, J=7.2, 3H), 0.90 (s, 9H), 0.05 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 159.0, 141.1, 131.1, 129.3 (2C), 114.2, 113.7 (2C), 82.6, 71.4, 63.2, 55.2, 40.8, 33.0, 30.9, 26.0 (3H), 21.9, 18.3, 15.6, −5.3 (2C). MS (ES) 394 (M+H$^+$).

To a solution of the PMB ether (3.019 g, 7.70 mmol) in THF (70 mL) was added TBAF (1 M in THF, 11.5 mL, 11.5 mmol). The solution was stirred at room temperature for 1.5 h. The solution was concentrated in vacuo. Flash chromatography (2:1 hexanes/EtOAc) gave the alcohol (2.045 g, 96% yield). $[\alpha]_D^{23}$ −43.8 (*c* 0.55, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.27 (d, J=8.5, 2H), 6.87 (d, J=8.5, 2H), 5.85 (ddd, J=17.5, 11.0, 8.0, 1H), 5.05 (br d, J=17.5, 1H), 5.02 (br d, J=11.0, 1H), 4.50 (d, J=11.0, 1H), 4.43 (d, J=11.0, 1H), 3.80 (s, 3H), 3.61 (t, J=6.0, 2H), 3.22–3.27 (m, 1H), 2.49 (apparent sextet, J=6.5, 1H), 1.44–1.58 (m, 4H), 1.32–1.42 (m, 2H), 1.04 (d, J=6.5, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 159.1, 140.9, 131.0, 129.4 (2C), 114.3, 113.7 (2C), 82.5, 71.5, 62.9, 55.3, 40.7, 32.8, 30.7, 21.7, 15.6. MS (ES) *m*/*z* 279 (M+H$^+$).

To a solution of the alcohol (1.539 g, 5.53 mmol) in CH_2Cl_2 (78 mL) and DMSO (39 mL) were added *i*-PrN_2Et (6.3 mL, 36.17 mmol) and sulfur trioxide pyridine complex (3.940 g, 24.75 mmol). The solution was stirred at room temperature for 1 h. The solution was diluted with Et_2O and washed

with water, brine, dried over $MgSO_4$, and concentrated in vacuo. Flash chromatography (4:1 hexanes/EtOAc) gave the aldehyde (1.436 g, 94% yield). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.73 (d, J=2.0, 1H), 7.27 (d, J=8.5, 2H), 6.87 (d, J=8.5, 2H), 5.83 (ddd, J=17.5, 10.5, 6.7, 1H), 5.04 (br d, J=17.5, 1H), 5.03 (br d, J=10.5, 1H), 4.52 (d, J=11.0, 1H), 4.42 (d, J=11.0, 1H), 3.80 (s, 3H), 3.25 (ddd, J=8.7, 6.7, 4.7, 1H), 2.51 (apparent sextet, J=6.7, 1H), 2.39 (t, J=7.5, 2H), 1.74–1.84 (m, 1H), 1.58–1.68 (m, 1H), 1.42–1.55 (m, 2H), 1.04 (d, J=6.7, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 202.6, 159.1, 140.5, 130.8, 129.4 (2C), 114.6, 113.7 (2C), 82.1, 71.4, 55.2, 43.9, 40.5, 30.3, 18.2, 15.7. MS (ES) m/z 277 (M+H$^+$).

To a solution of the aldehyde (1.044 g, 3.78 mmol) in *t*-BuOH (80 mL) was added 2-methyl-2-butene (19 mL). Then $NaClO_2$ (3.152 g) and NaH_2PO_4 (3.152 g) in H_2O (32 mL) were added during 10 min. The mixture was stirred at room temperature for 30 min. The volatile component was evaporated under vacuum. The residue was diluted with H_2O and extracted with EtOAc twice. The aqueous phase was acidified to pH=3 with 1 N HCl. The acidified aqueous phase was extracted with EtOAc three times. The combined organic phase was washed with water, brine, dried over $MgSO_4$, and concentrated. The residue was used directly for the next step without further purification.

To a solution of the crude acid in CH_3CN (10 mL) was added DBU (0.57 mL, 3.81 mmol) with good stirring. Then MeI (0.26 mL, 4.18 mmol) was added and the solution was stirred at room temperature for 14 h. Water was added and the mixture was extracted with Et_2O. The combined extracts were washed with saturated aqueous $Na_2S_2O_3$, H_2O, and brine. The organic phase was dried over $MgSO_4$ and concentrated in vacuo. Flash chromatography (10:1 hexanes/EtOAc) gave the methyl ester **28** (0.967 g, 84% yield for two steps). $[\alpha]_D^{23}$ −26.3 (c 0.40, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.27 (d, J=9.0, 2H), 6.87 (d, J=9.0, 2H), 5.83 (ddd, J=17.5, 11.0, 8.0, 1H), 5.04 (br d, J=17.5, 1H), 5.02 (br d, J=11.0, 1H), 4.50 (d, J=11.5, 1H), 4.43 (d, J=11.5, 1H), 3.80 (s, 3H), 3.66 (s, 3H), 3.24 (ddd, J=7.2, 5.6, 4.4, 1H), 2.49 (apparent sextet, J=7.2, 1H), 2.22–2.32 (m, 2H), 1.71–1.83 (m, 1H), 1.59–1.70 (m, 1H), 1.44–1.58 (m, 2H), 1.04 (d, J=7.2, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 174.1, 159.1, 140.7, 130.9, 129.4 (2C), 114.5, 113.7 (2C), 82.1, 71.4, 55.3, 51.4, 40.6, 34.1, 30.4, 21.0, 15.7. MS (ES) m/z 324 (M+NH$_4^+$).

To a solution of the methyl ester **28** in 1:1 mixture of acetone/water (24 mL) was added NMO (1.133 g, 9.67 mmol) and OsO_4 (0.3 M in toluene, 1.09 mL, 3.27 mmol). The solution was stirred at room temperature for 2 h. Saturated aqueous $Na_2S_2O_3$ and EtOAc were added. The mixture was stirred for 1 h. The aqueous phase was separated and extracted with EtOAc three times. The combined organic phase was washed with brine, dried over Na_2SO_4, and concentrated in vacuo. Flash chromatography (1:1 hexanes/EtOAc) gave the diastereomeric mixture of diol (0.881 g, 80% yield).

To a solution of the diol (0.881 g, 2.59 mmol) in benzene (16 mL) was added $Pb(OAc)_4$ (1.814 g, 4.09 mmol). The mixture was stirred at room temperature for 3 h. Saturated aqueous $NaHCO_3$ was added and the mixture was extracted with EtOAc three times. The combined organic phase was washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The crude aldehyde was reduced directly without further purification.

To a solution of the crude aldehyde in MeOH (15 mL) at 0 °C was added $NaBH_4$ (0.147 g, 3.89 mmol). The solution was stirred at 0 °C for 1 h. Saturated aqueous NH_4Cl was added and the mixture was extracted with EtOAc three times. The combined organic phase was washed with brine, dried over Na_2SO_4, and concentrated in vacuo. Flash chromatography (3:1 hexanes/EtOAc) gave the alcohol **29** (0.662 g, 83% yield for two steps). $[\alpha]_D^{23}$ +0.8 (c 1.77, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.26 (d, J=9.0, 2H), 6.87 (d, J=9.0, 2H), 4.52 (d, J=11.0, 1H), 4.47 (d, J=11.0, 1H), 3.79 (s, 3H), 3.66 (s, 3H), 3.63–3.67 (m, 1H), 3.57 (dd, J=10.5, 5.0, 1H), 3.49 (ddd, J=7.0, 5.0, 4.0, 1H), 2.24–2.37 (m, 2H), 2.04–2.12 (m, 1H), 1.71–1.80 (m, 1H), 1.57–1.67 (m, 2H), 1.47–1.55 (m, 1H), 0.87 (d, J=7.0, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) 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. MS (ES) m/z 311 (M+H$^+$).

To a solution of the alcohol **29** (1.999 g, 6.448 mmol) in CH_2Cl_2 (70 mL) were added imidazole (1.317 g, 19.35 mmol), Ph_3P (3.551 g, 13.54 mmol), and I_2 (3.436 g, 13.54 mmol). The solution was stirred at room temperature for 2 h. The solution was diluted with EtOAc and washed with saturated aqueous $Na_2S_2O_3$, saturated aqueous $NaHCO_3$, and brine. The organic phase was dried over $MgSO_4$ and concentrated in vacuo. Flash chromatography (9:1 hexanes/EtOAc) gave the alkyl iodide **30** (2.481 g, 92% yield). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.25 (d, J=8.8, 2H), 6.87 (d, J=8.8, 2H), 4.49 (d, J=11.2, 1H), 4.44 (d, J=11.2, 1H), 3.79 (s, 3H), 3.67 (s, 3H), 3.43 (ddd, J=6.8, 5.2, 4.0, 1H), 3.35 (dd, J=9.6, 6.0, 1H), 3.06 (dd, J=9.6, 7.6, 1H), 2.28–2.34 (m, 2H), 1.87–1.97 (m, 1H), 1.43–1.77 (m, 4H), 1.02 (d, J=6.8, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 173.8, 159.1, 130.6, 129.3 (2C), 113.8 (2C), 80.7, 71.9, 55.2, 51.5, 39.0, 33.9, 30.1, 21.0, 15.5, 12.3.

4.3.4. Synthesis outlined in Scheme 11. To a suspension of $LiAlH_4$ (2.765 g, 72.86 mmol) in THF (65 mL) was added slowly a solution of an 8:1 diastereomeric mixture of methylated diethyl (*S*)-malate **32**[31] (3.770 g, 18.48 mmol) in THF (35 mL). The mixture was refluxed for 2 h and was cooled to room temperature. Water (2.77 mL), 15% aqueous NaOH (2.77 mL), and water (8.31 mL) were added slowly with care sequentially. The mixture was filtered through Celite and washed with Et_2O (300 mL). The filtrate was concentrated in vacuo to give an 8:1 diastereomeric mixture of triols **33** (2.101 g). ^{1}H NMR (CD_3OD, 500 MHz) δ 3.61–3.69 (m, 2H), 3.50–3.55 (m, 3H), 1.74–1.82 (m, 1H), 0.95 (d, J=6.0, 3H).

A solution of the crude triol **33** in MeOH (100 mL) was treated with *n*-Bu_2SnO (4.358 g, 17.51 mmol). The mixture was refluxed overnight to give a clear solution. The solution was concentrated in high vacuum to give white solid. The solid in $CHCl_3$ (100 mL) was treated with TBSCl (3.167 g, 21.01 mmol) for 20 min. Acetonitrile (100 mL) was added and the solution was concentrated to about 30 mL. Hexanes (100 mL) was added and then was extracted with CH_3CN

(100 mL×3). The combined acetonitrile extracts were concentrated. Flash chromatography (2:1 hexanes/EtOAc) gave an 8:1 diastereomeric mixture of 1,2-diols **34** (3.431 g, 79% yield from the diethyl ester). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.10 (br s, *OH*), 3.74 (dd, *J*=10.5, 4.0, 1H), 3.68 (br dd, *J*=11.0, 2.0, 1H), 3.61 (dd, *J*=10.5, 9.0, 1H), 3.54–3.64 (m, 2H), 2.49 (br s, *OH*), 1.82–1.92 (m, 1H), 0.90 (s, 9H), 0.85 (d, *J*=7.0, 3H), 0.09 (two overlapped singlets, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 76.7, 68.1, 64.9, 36.9, 25.8 (3C), 18.1, 13.3, −5.6, −5.7. MS (ES) *m*/*z* 235 (M+H$^+$).

To a solution of the 8:1 diastereomeric mixture of 1,2-diols **34** (8.009 g, 34.23 mmol) in THF (200 mL) at 0 °C was added NaH (60% in mineral oil, 0.904 g, 37.65 mmol). The mixture was stirred at 0 °C for 20 min. Then 1-(*p*-toluenesulfonyl)imidazole (8.453 g, 37.65 mmol) was added slowly with caution. The cooling bath was removed and the mixture was stirred at room temperature for 14 h. The reaction was quenched by addition of saturated aqueous NH_4Cl. The mixture was extracted with Et_2O three times. The combined organic extracts were washed with water, brine, dried over $MgSO_4$, and concentrated. Flash chromatography (20:1 hexanes/EtOAc) gave an 8:1 diastereomeric mixture of epoxides **35** (6.501 g, 88% yield). ^{1}H NMR (C_6D_6, 500 MHz) δ 3.55 (d, *J*=6.0, 2H), 2.67 (ddd, *J*=7.0, 4.0, 3.0, 1H), 2.35 (dd, *J*=5.5, 4.0, 1H), 2.15 (dd, *J*=5.5, 3.0, 1H), 1.28–1.40 (m, 1H), 0.95 (s, 9H), 0.84 (d, *J*=7.0, 3H), 0.03 (s, 3H), 0.02 (s, 3H).

To a solution of propyne (4.397 g, 109.73 mmol) in THF (290 mL) at −78 °C was added *n*-BuLi (2.38 M in hexanes, 39.51 mL, 94.04 mmol). The solution was stirred for 10 min. A solution of the 8:1 diastereomeric mixture of epoxides **35** (6.771 g, 31.35 mmol) in THF (20 mL, 6 mL wash) was added, followed by $BF_3\cdot OEt_2$ (11.92 mL, 94.04 mmol). The solution was stirred at −78 °C for 2 h. The reaction was quenched by addition of saturated NH_4Cl and the mixture was extracted with EtOAc three times. The combined organic phase was washed with saturated $NaHCO_3$, brine, dried over $MgSO_4$, and concentrated. Flash chromatography (8:1 hexanes/EtOAc) gave an 8:1 diastereomeric mixture of homopropargylic alcohols (7.712 g, 96% yield). ^{1}H NMR (C_6D_6, 500 MHz) δ 3.69 (dd, *J*=10.0, 5.0, 1H), 3.62–3.66 (m, 1H), 3.51–3.57 (m, 1H), 2.90 (d, *J*=4.5, *OH*), 2.41–2.47 (m, 1H), 2.33–2.41 (m, 1H), 1.85–1.91 (m, 1H), 1.48 (t, *J*=2.5, 3H), 0.91 (s, 9H), 0.85 (d, *J*=7.0, 3H), −0.00 (s, 3H), −0.01 (s, 3H).

To a solution of the 8:1 diastereomeric mixture of homopropargylic alcohols (7.712 g, 30.12 mmol) in THF (150 mL) was added TBAF (1.0 M in THF, 36.15 mL, 36.15 mmol). Brine was added and the mixture was extracted with Et_2O three times. The combined organic phase was washed with brine, dried over Na_2SO_4, and concentrated. Flash chromatography (1:2 hexanes/EtOAc) gave an 8:1 diastereomeric mixture of diols (4.107 g, 96% yield). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.66–3.74 (m, 1H), 3.56–3.65 (m, 2H), 3.25 (br s, *OH*), 3.20 (br d, *J*=4.0, *OH*), 2.42–2.48 (m, 1H), 2.28–2.35 (m, 1H), 1.83 (dq, *J*=4.0, 6.0, 1H), 1.79 (t, *J*=2.5, 3H), 0.86 (d, *J*=7.0, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 78.6, 75.3, 74.8, 67.3, 39.1, 25.9, 13.6, 3.5.

To a solution of the 8:1 diastereomeric mixture of diols (4.300 g, 30.28 mmol) in benzene (160 mL) were added cyclopentanone (40 mL, 452 mmol), *p*-TsOH (576 mg, 3.03 mmol), and $MgSO_4$ (10 g). The mixture was stirred for 72 h, filtered, and concentrated in vacuo. Flash chromatography using EtOAc/hexanes (1:9) as eluent provided cyclopentylidene protected diol **36** (5.150 g, 76% yield). $[\alpha]_D^{23}$ −5.2 (*c* 1.95, $CHCl_3$). ^{1}H NMR (400 MHz, C_6D_6) δ 3.62 (dd, *J*=5.1, 11.4, 1H), 3.30 (ddd, *J*=4.4, 5.9, 9.9, 1H), 3.20 (t, *J*=11.4, 1H), 2.31–2.46 (m, 2H), 2.05–2.16 (m, 2H), 1.88–1.98 (m, 1H), 1.73–1.84 (m, 2H), 1.52–1.64 (m, 4H), 1.54 (t, *J*=2.6, 3H), 0.45 (d, *J*=6.6, 3H); ^{13}C NMR (100 MHz, C_6D_6) δ 110.4, 77.0, 75.9, 75.9, 67.2, 40.4, 33.6, 30.8, 24.7, 24.2, 22.8, 12.3, 3.4. HRMS (ES) *m*/*z* 209.1544 (M+H$^+$), calcd 209.1541.

A solution of alkyne **36** (588.0 mg, 2.87 mmol) in THF (7.2 mL) was added to Cp_2ZrHCl (1.480 g, 5.74 mmol) via cannula. The mixture was protected from light and stirred at 50 °C for 1 h. The resulting dark red suspension was cooled to room temperature, and a solution of I_2 (1.454 g, 5.73 mmol) in THF (5 mL) was added via cannula. The dark brown mixture was stirred for 30 min and quenched with 10% aqueous $Na_2S_2O_3$ and saturated aqueous $NaHCO_3$ (30 mL each). The mixture was diluted with EtOAc and separated. The organic phase was washed with 10% aqueous $Na_2S_2O_3$, saturated aqueous $NaHCO_3$, and brine. The organic phase was then dried over anhydrous $MgSO_4$ and concentrated in vacuo. Flash chromatography (19:1 hexanes/EtOAc) gave vinyl iodide **37** (596.2 mg, 62% yield). ^{1}H NMR (500 MHz, C_6D_6) δ 6.41 (ddq, *J*=7.5, 7.0, 1.5, 1H), 3.56 (dd, *J*=11.5, 5.0, 1H), 3.11 (apparent t, *J*=11.5), 3.07 (ddd, *J*=11.0, 8.0, 3.5), 2.14 (d, *J*=1.5, 3H), 1.90–2.06 (m, 4H), 1.70–1.77 (m, 1H), 1.60–1.66 (m, 1H), 1.48–1.58 (m, 3H), 0.26 (d, *J*=6.0, 3H).

4.3.5. Synthesis outlined in Scheme 12. Active Zn–Cu couple was prepared from Zn (1.396 g, 21.34 mmol) and $Cu(OAc)_2\cdot H_2O$ (85.2 mg, 0.43 mmol) following literature procedure[36] and was dried under vacuum for 30 min. Alkyl iodide **30** (1.794 g, 4.27 mmol) in a 15:1 mixture of benzene/DMF (15.0 mL) was added to the Zn–Cu couple. The mixture was heated in a 55 °C oil bath for 1 h with stirring to give the alkylzinc iodide. Anhydrous LiCl (1.09 mg, 25.61 mmol) (dried with flame) and $Pd(PPh_3)_4$ (352.3 mg, 0.30 mmol) in a 50 mL flask were degassed for four times. NMP (12.0 mL) was added, followed by addition of the vinyl iodide **37** (1.025 g, 3.05 mmol) in NMP (4.0 mL). Then the colorless alkylzinc iodide solution (the excess Zn was removed as much as possible) was added via cannula. The reaction mixture was degassed once and was stirred at room temperature for 15 min and then at 55 °C overnight. The cooled reaction mixture was poured into a mixture of saturated aqueous $NaHCO_3$ and EtOAc. The mixture was extracted with EtOAc four times. The combined extracts were washed with H_2O, brine, dried over Na_2SO_4, and concentrated. Flash chromatography (10:1 hexanes/EtOAc) afforded the coupled product **38** (1.265 g, 83% yield). $[\alpha]_D^{23}$ +4.9 (*c* 0.73, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.27 (d, *J*=9.0, 2H), 6.87 (d, *J*=9.0, 2H), 5.26 (dd, *J*=7.0, 6.0, 1H), 4.47 (d, *J*=11.5, 1H), 4.42 (d, *J*=11.5, 1H), 3.79 (s, 3H), 3.71 (dd, *J*=11.0, 4.5, 1H), 3.66 (s, 3H), 3.39 (t, *J*=11.0, 1H), 3.32–3.40 (m, 1H), 3.25 (ddd, *J*=7.0, 3.5,

3.5, 1H), 2.28–2.36 (m, 3H), 2.20–2.25 (m, 1H), 2.08–2.16 (m, 1H), 1.86–1.94 (m, 2H), 1.70–1.85 (m, 6H), 1.57–1.68 (m, 5H), 1.57 (s, 3H), 1.46–1.54 (m, 2H), 0.82 (d, J=6.8, 3H), 0.74 (d, J=6.8, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 174.0, 159.0, 135.0, 131.2, 129.2 (2C), 122.2, 113.7 (2C), 110.1, 82.0, 77.2, 71.4, 67.5, 55.2, 51.4, 42.7, 40.2, 34.1, 33.9, 33.3, 31.6, 30.6, 30.1, 24.3, 22.5, 21.5, 16.1, 14.5, 12.7. HRMS (ES) m/z 503.3361 (M+H$^+$), calcd 503.3372.

A mixture of CH_2Cl_2 (200 mL), H_2O (50 mL), and TFA (12.5 mL) was shaken vigorously. The CH_2Cl_2 layer (150 mL) was used to dissolve **38** (1.437 g, 2.86 mmol), which was stirred for 5.5 h at room temperature. The solution was poured into saturated aqueous $NaHCO_3$ and diluted with EtOAc. The mixture was extracted with EtOAc four times. The combined extracts were washed with brine, dried over Na_2SO_4, and concentrated. Flash chromatography (1:1 hexanes/EtOAc) gave the diol (1.119 g, 90% yield). $[\alpha]_D^{23}$ +2.6 (c 1.08, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.25 (d, J=9.0, 2H), 6.87 (d, J=9.0, 2H), 5.13 (apparent t, J=7.2, 1H), 4.46 (d, J=11.4, 1H), 4.40 (d, J=11.4, 1H), 3.80 (s, 3H), 3.70 (dd, J=11.4, 3.6, 1H), 3.67 (s, 3H), 3.63 (dd, J=11.4, 7.2, 1H), 3.50 (apparent dt, J=3.0, 8.4, 1H), 3.23 (ddd, J=7.4, 3.7, 3.7, 1H), 2.18–2.32 (m, 5H), 1.97–2.03 (m, 1H), 1.84 (dd, J=13.2, 9.0, 1H), 1.69–1.77 (m, 1H), 1.63 (s, 3H), 1.43–1.62 (m, 4H), 0.89 (d, J=6.6, 3H), 0.82 (d, J=6.6, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 174.0, 159.0, 137.9, 130.8, 129.3 (2C), 121.4, 113.6 (2C), 82.2, 77.0, 71.4, 67.6, 55.1, 51.4, 42.9, 39.6, 34.2, 33.9, 32.8, 29.4, 21.5, 16.0, 15.3, 13.8. HRMS (ES) m/z 437.2879 (M+H$^+$), calcd 437.2903.

To a solution of the diol (1.119 g, 2.56 mmol) in DMF (25 mL) were added imidazole (0.384 g, 5.64 mmol) and TIPSCl (0.70 mL, 3.27 mmol). The solution was stirred at room temperature for 5 h and then at 0 °C for 26 h. The mixture was diluted with water and was extracted with Et_2O three times. The combined extracts were washed with brine, dried over Na_2SO_4, and concentrated. Flash chromatography (3:1 hexanes/EtOAc) gave the silyl ether quantitatively. $[\alpha]_D^{23}$ +5.5 (c 1.09, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.27 (d, J=8.5, 2H), 6.87 (d, J=8.5, 2H), 5.27 (apparent t, J=7.0, 1H), 4.47 (d, J=11.0, 1H), 4.43 (d, J=11.0, 1H), 3.88 (dd, J=9.5, 4.0, 1H), 3.80 (s, 3H), 3.69 (dd, J=9.5, 7.5, 1H), 3.67 (s, 3H), 3.60 (apparent dt, J=4.5, 7.0, 1H), 3.24 (apparent dt, J=7.0, 3.5, 1H), 2.19–2.33 (m, 5H), 1.88–1.96 (m, 1H), 1.80 (dd, J=12.5, 9.5, 1H), 1.70–1.82 (m, 1H), 1.57–1.67 (m, 1H), 1.60 (s, 3H), 1.44–1.57 (m, 3H), 1.06–1.16 (m, 3H), 1.05–1.09 (m, 18H), 0.90 (d, J=6.5, 3H), 0.82 (d, J=6.5, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 174.0, 159.0, 135.6, 131.2, 129.2 (2C), 122.3, 113.7 (2C), 82.1, 76.3, 71.4, 68.4, 55.2, 51.4, 42.8, 39.3, 34.1, 33.8, 33.3, 30.0, 21.6, 17.9 (6C), 16.1, 14.7, 13.7, 11.7 (3C). HRMS (ES) m/z 593.4230 (M+H$^+$), calcd 593.4237.

To a solution of the silyl ether (1.6297 g, 2.75 mmol) in a 4:1:1 mixture of THF/MeOH/H_2O (144 mL) was added aqueous solution of LiOH (1.0 M, 24 mL). The solution was stirred at room temperature for 5 h. Saturated aqueous NH_4Cl was added and the mixture was extracted with EtOAc three times. The combined extracts were washed with brine, dried over Na_2SO_4, and concentrated. Flash chromatography (1:1 hexanes/EtOAc) gave the *seco*-acid **39** (1.205 g, 81% yield). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.27 (d, J=8.5, 2H), 6.87 (d, J=8.5, 2H), 5.25 (apparent t, J=7.0, 1H), 4.48 (d, J=11.5, 1H), 4.43 (d, J=11.5, 1H), 3.89 (dd, J=10.0, 4.0, 1H), 3.79 (s, 3H), 3.69 (dd, J=10.0, 7.0, 1H), 3.62 (apparent dt, J=4.5, 7.0, 1H), 3.26 (apparent dt, J=6.5, 4.5, 1H), 2.30–2.37 (m, 2H), 2.21–2.30 (m, 3H), 1.88–1.96 (m, 1H), 1.80 (dd, J=12.5, 9.5, 1H), 1.71–1.82 (m, 1H), 1.47–1.68 (m, 4H), 1.60 (s, 3H), 1.06–1.16 (m, 3H), 1.05–1.09 (m, 18H), 0.90 (d, J=7.5, 3H), 0.82 (d, J=7.0, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 178.7, 159.0, 135.7, 131.1, 129.3 (2C), 122.3, 113.7 (2C), 81.9, 76.5, 71.4, 68.4, 55.2, 42.9, 39.2, 34.0, 33.7, 33.3, 30.0, 21.3, 17.9 (6C), 16.1, 14.8, 13.7, 11.7 (3C).

To a solution of the *seco*-acid **39** (1.078 g, 1.86 mmol) in benzene (19 mL) were added i-Pr_2NEt (1.95 mL, 11.18 mmol) and $Cl_3C_6H_2COCl$ (0.90 mL, 5.59 mmol). The solution was stirred for 50 min at room temperature and then was added to a solution of DMAP (0.683 g, 5.59 mmol) in benzene (660 mL) via syringe pump over 10 h. The resulting solution was stirred at room temperature for 8 h. The solution was washed with saturated aqueous $NaHCO_3$, brine, dried over Na_2SO_4, and concentrated. Flash chromatography (10:1 hexanes/EtOAc) gave the macrolactone **40** (0.999 g, 96% yield). $[\alpha]_D^{23}$ −19.8 (c 1.06, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.27 (d, J=9.0, 2H), 6.87 (d, J=9.0, 2H), 5.07 (ddd, J=12.0, 6.0, 3.0, 1H), 5.00 (br d, J=10.2), 4.50 (d, J=11.4, 1H), 4.31 (d, J=11.4, 1H), 3.80 (s, 3H), 3.66 (dd, J=9.9, 5.1, 1H), 3.54 (dd, J=9.9, 6.3, 1H), 3.12 (ddd, J=8.4, 4.2, 4.2, 1H), 2.43–2.51 (m, 2H), 2.03–2.11 (m, 2H), 1.90–1.95 (m, 1H), 1.85–1.91 (m, 3H), 1.67–1.81 (m, 2H), 1.65 (s, 3H), 1.58–1.64 (m, 1H), 1.40–1.48 (m, 1H), 1.03–1.13 (m, 21H), 1.03(d. J=7.2, 3H), 0.98 (d, J=7.2, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 173.4, 159.0, 137.1, 131.1, 129.4 (2C), 121.9, 113.6 (2C), 83.1, 73.6, 70.8, 65.2, 55.2, 45.7, 40.4, 35.9, 32.6, 30.6, 29.0, 20.5, 19.3, 18.0 (6C), 15.7, 12.8, 11.9 (3C). HRMS (ES) m/z 561.3985 (M+H$^+$), calcd 561.3975.

To a solution of **40** (0.460 g, 0.82 mmol) in CH_3CN (48 mL) was added a mixture of CH_3CN (48 mL), HF·pyridine (2.3 mL), and pyridine (2.3 mL). The solution was stirred at 0 °C for 120 h. The solution was poured into saturated aqueous $NaHCO_3$ and the mixture was extracted with EtOAc three times. The combined extracts were washed with brine, dried over Na_2SO_4, and concentrated. Flash chromatography (10:1 hexanes/EtOAc followed by 1:1 hexanes/EtOAc) gave the alcohol (0.300 g, 90% yield). $[\alpha]_D^{23}$ −32.9 (c 1.48, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.27 (d, J=9.0, 2H), 6.88 (d, J=9.0, 2H), 4.99 (br d, J=10.0, 1H), 4.86 (ddd, J=12.0, 9.5, 3.0, 1H), 4.50 (d, J=11.0, 1H), 4.30 (d, J=11.0, 1H), 3.80 (s, 3H), 3.56 (dd, J=12.0, 4.0, 1H), 3.46 (br dd, J=12.0, 2.8, 1H), 2.99–3.14 (m, 1H), 2.54 (ddd, J=13.0, 5.0, 3.5, 1H), 2.42 (ddd, J=14.0, 11.5, 11.5, 1H), 2.19 (br d, J=11.5, 1H), 2.11 (ddd, J=13.0, 13.0, 3.5, 1H), 1.68–1.96 (m, 6H), 1.67 (s, 3H), 1.56–1.65 (m, 1H), 1.44–1.53 (m, 1H), 1.06 (d. J=7.3, 3H), 1.04 (d, J=7.3, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 175.0, 159.0, 137.4, 130.9, 129.3 (2C), 121.7, 113.6 (2C), 83.1, 74.3, 70.7, 63.9, 55.2, 45.6, 40.2, 35.9, 32.4, 31.5, 28.8, 20.6, 19.0, 15.7, 13.6. HRMS (ES) m/z 405.2640 (M+H$^+$), calcd 405.2641.

To a solution of the alcohol (0.605 g, 1.50 mmol) in CH_2Cl_2 (30 mL) were added imidazole (0.305 g, 4.49 mmol), Ph_3P (0.824 g, 3.14 mmol), and I_2 (0.797 g, 3.14 mmol). The solution was stirred at room temperature for 30 min and diluted with saturated aqueous $Na_2S_2O_3$ solution. The mixture was extracted with EtOAc three times. The combined extracts were washed with brine, dried over Na_2SO_4, and concentrated. Flash chromatography (10:1 hexanes/EtOAc) gave the alkyl iodide **41** (0.753 g, 98% yield). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.26 (d, J=8.5, 2H), 6.87 (d, J=8.5, 2H), 4.97 (br d, J=10.5, 1H), 4.93 (ddd, J=12.0, 7.0, 3.0, 1H), 4.50 (d, J=11.0, 1H), 4.30 (d, J=11.0, 1H), 3.80 (s, 3H), 3.29 (dd, J=10.0, 4.0, 1H), 3.11 (ddd, J=8.0, 4.0, 4.0, 1H), 3.00 (dd, J=10.0, 8.5, 1H), 2.48 (ddd, J=12.0, 5.0, 3.5, 1H), 2.41 (ddd, J=14.0, 11.5, 11.5, 1H), 2.12 (br d, J=11.5, 1H), 2.08 (ddd, J=12.0, 12.0, 3.5, 1H), 1.84–1.93 (m, 3H), 1.68–1.81 (m, 3H), 1.63 (s, 3H), 1.56–1.63 (m, 1H), 1.37–1.46 (m, 1H), 1.09 (d, J=7.0, 3H), 1.02 (d, J=7.0, 3H).

Active Zn–Cu couple was prepared from Zn (0.462 g, 7.07 mmol) and $Cu(OAc)_2\cdot H_2O$ (0.028 g, 0.14 mmol) following literature procedure[36] and was dried under vacuum for 30 min. The alkyl iodide **41** (0.727 g, 1.41 mmol) in a 15:1 mixture of benzene/DMF (5.0 mL) was added to the Zn–Cu couple. The mixture was heated in a 55 °C oil bath for 1 h with stirring to give the alkylzinc iodide. Anhydrous LiCl (0.360 g, 8.48 mmol) (dried with flame) and $Pd(PPh_3)_4$ (0.245 g, 0.21 mmol) in a 25 mL flask were degassed for four times. NMP (8.0 mL) was added, followed by addition of the vinyl iodide **25** (1.085 g, 2.12 mmol). The colorless alkylzinc iodide solution (the excess Zn was removed as much as possible) was added via cannula. The reaction mixture was degassed once and was stirred at room temperature for 1 h 20 min and then at 50 °C for 15 h. The cooled reaction mixture was poured into a mixture of saturated aqueous $NaHCO_3$ and EtOAc. The mixture was extracted with EtOAc three times. The combined extracts were washed with H_2O, brine, dried over Na_2SO_4, and concentrated. Medium-pressure chromatography (50:1 hexanes/EtOAc, Biotage) gave the protected core structure **42** (0.876 g, 80% yield). $[\alpha]_D^{23}$ −9.2 (c 1.08, $CHCl_3$). ^{1}H NMR (CD_3COCD_3, 600 MHz) δ 7.28 (d, J=9.0, 2H), 6.89 (d, J=9.0, 2H), 5.23 (br d, J=9.0, 1H), 5.01 (br d, J=8.4, 1H), 4.87 (ddd, J=11.4, 5.4, 3.0, 1H), 4.52 (d, J=10.8, 1H), 4.30 (d, J=10.8, 1H), 3.98 (apparent sextet, J=6.0, 1H), 3.78 (s, 3H), 3.74 (ddd, J=6.0, 6.0, 4.2, 1H), 3.15 (ddd, J=7.8, 4.2, 3.0, 1H), 2.55–2.62 (m, 1H), 2.44–2.50 (m, 2H), 2.17 (dd, J=13.8, 5.4, 1H), 1.99–2.10 (m, 2H), 1.92–1.98 (m, 1H), 1.87–1.92 (m, 2H), 1.60–1.80 (m, 7H), 1.67 (s, 3H), 1.66 (s, 3H), 1.41–1.49 (m, 1H), 1.16 (d, J=6.0, 3H), 1.00 (d, J=6.6, 3H), 0.92 (s, 9H), 0.92 (d, J=6.0, 3H), 0.90 (s, 9H), 0.88 (d. J=6.6, 3H), 0.091 (s, 3H), 0.086 (s, 3H), 0.08 (s, 6H); ^{13}C NMR (CD_3COCD_3, 100 MHz) δ 173.1, 159.7, 137.2, 132.3, 132.2, 131.0, 129.7, 122.9, 114.0, 82.9, 75.9, 73.5, 70.9, 66.4, 55.2, 46.1, 45.7, 43.7, 37.6, 36.1, 35.6, 33.2, 30.1, 29.8, 26.1(3C), 26.0 (3C), 24.3, 20.2, 19.7, 18.4, 18.3, 16.0, 15.6, 15.4, 14.7, −4.0, −4.3, −4.4, −4.7. HRMS (ES) m/z 773.5577 ($M+H^+$), calcd 773.5572.

To a solution of the protected core structure **42** (60.1 mg, 0.078 mmol) in an 18:1 mixture of CH_2Cl_2/H_2O (19 mL) at 0 °C was added DDQ (26.5 mg, 0.117 mmol). The solution was stirred at 0 °C for 2 h. Saturated aqueous $NaHCO_3$ was added and the mixture was extracted with CH_2Cl_2 three times. The combined extracts were washed with saturated aqueous $NaHCO_3$, H_2O, brine and dried over Na_2SO_4. The solution was concentrated. Flash chromatography (15:1 hexanes/EtOAc) gave the core structure alcohol **21** (46.1 mg, 91% yield). $[\alpha]_D^{23}$ −29.2 (c 0.92, $CHCl_3$). ^{1}H NMR (CD_3COCD_3, 600 MHz) δ 5.23 (br d, J=9.0, 1H), 5.04 (br d, J=10.8, 1H), 4.90 (ddd, J=11.4, 3.6, 2.4, 1H), 3.98 (apparent sextet, J=6.0, 1H), 3.74 (ddd, J=6.0, 6.0, 4.2, 1H), 3.34–3.38 (m, 1H), 3.15 (d, J=5.4, *OH*), 2.55–2.61 (m, 1H), 2.49 (ddd, J=14.4, 11.7, 11.7, 1H), 2.31 (ddd, J=13.2, 6.8, 3.0, 1H), 2.16 (dd, J=13.2, 4.8, 1H), 2.06–2.14 (m, 2H), 1.88–1.97 (m, 3H), 1.76–1.82 (m, 2H), 1.65 (s, 6H), 1.51–1.66 (m, 5H), 1.42–1.48 (m, 1H), 1.16 (d, J=6.0, 3H), 0.96 (d, J=7.2, 3H), 0.92 (s, 9H), 0.90 (d, J=6.0, 3H), 0.896 (s, 9H), 0.87 (d, J=6.6, 3H), 0.089 (s, 3H), 0.083 (s, 3H), 0.08 (s, 6H); ^{13}C NMR (CD_3COCD_3, 100 MHz) δ 173.9, 137.3, 132.3, 131.0, 123.1, 76.4, 73.5, 73.4, 66.4, 46.4, 45.7, 43.6, 37.6, 35.7, 35.6, 35.0, 34.9, 30.2, 26.1 (3C), 26.0 (3C), 24.3, 20.4, 18.7, 18.4, 18.2, 16.0, 15.7, 15.3, 14.8, −4.0, −4.3, −4.5, −4.7. MS (ES) m/z 671 ($M+NH_4^+$).

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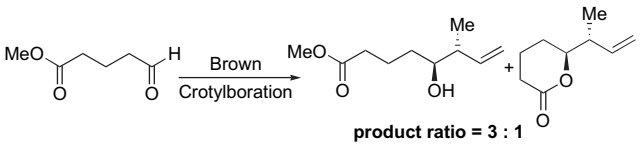

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