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Highly Stereoselective Total Synthesis of Fully Hydroxy-Protected Mycolactones A and B and Their Stereoisomerization upon Deprotection

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Abstract

Unprecedentedly efficient and highly (98%) stereoselective syntheses of mycolactones A and B sidechains relied heavily on Pd-catalyzed alkenylation (Negishi version) and were completed in 11 longest linear steps from ethyl (*S*)-3-hydroxybutyrate in 12% and 11% overall yields, respectively, roughly corresponding to an average of 82% yield per step. The synthesis of mycolactone core was realized by using Pd-catalyzed alkenyl–allyl coupling and an epoxide-opening reaction with a trialkylalkenylaluminate as key steps. Fully hydroxy-protected mycolactones A and B of 98% isomeric purity were synthesized successfully for the first time. However, unexpected 4/3-5/4 inseparable mixtures of mycolactones A and B were obtained upon deprotection.

Keywords

mycolactones A and B; total synthesis; Pd-catalyzed cross-coupling (Negishi coupling); high (98%) stereo- and regioselectivity

Introduction

Mycobacterium ulcerans infection, described by Sir Albert Cook as early as 1897 and named *Buruli ulcer* after the Buruli district in Uganda where the first large number of cases were recorded, is the third most common mycobacteriosis after *mycobacterium tuberculosis* and *mycobacterium leprae*.^[1] Despite its long history, the first successful isolation of the real determinants of *Buruli ulcer* had not been accomplished until 1999.^[2] A stereoisomeric mixture of mycolactones A and B was isolated from western African strain of *M. ulcerans*. They are the first toxins isolated from mycobacterium species and the first isolated complex polyketides from human pathogens. Since then, other congeners, i.e., mycolactones C, D, E, F, and G, have also been isolated from different strains of *M. ulcerans*.^[3] All of these mycolactones consist of a twelve membered lactone core with two sidechains attached. Notably, structural variations among them are confined to the highly unsaturated sidechain connected via an ester linkage (Figure 1).

Mycolactones A (**1A**) and B (**1B**) display potent inhibition of interleukin production. However, explorations of their biological potencies have been seriously hampered by the

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This paper is dedicated to Professor Yoshito Kishi of Harvard University in recognition of his pioneering studies on the synthesis of numerous natural products including mycolactones.

Supporting information for this article is available on the WWW under <http://www.chemeurj.org/> or from the author.

slow growth of the host mycobacterium, pointing to the desirability of their efficient chemical syntheses. The first synthesis of mycolactones A and B was reported in 2002 by Kishi's group.^[4] The synthesis of the core part involved application of Pd-catalyzed isobutyl–alkenyl coupling (Negishi version)^[5] at two critical stages, while the construction of the five C=C bonds in the sidechains was realized by successive application of carbonyl olefination reactions. The reported modest yields of Pd-catalyzed isobutyl–alkenyl coupling in their first synthesis (50 and 60%)^[4a] and the general lack of high stereoselectivity in conventional carbonyl olefinations^[4,6,7] including the Horner-Wadsworth-Emmons reaction^[4b,4c] prompted us to consider and seek alternate routes to both core and sidechains of mycolactones A and B. More specifically, our goals in this research have been multifold and as follows:

1. First and foremost, we hoped to provide one or more high-yielding, efficient, and highly (98%) selective routes to mycolactones A and B C1–C16 sidechains containing conjugated pentaenes (**2A** and **2B**), to which no highly (98%) stereoselective routes had been available until our preliminary report in 2006.^[8] This was to be further refined, as detailed later.
2. From the viewpoint of alkene synthetic methodology, the alkyne elementometalation–Pd-catalyzed alkenylation and related ancillary protocols we started developing in the mid-1970s^[9,10] may have finally reached a reasonably mature and widely applicable method,^[7] which promise to supplement and even surpass the conventional carbonyl olefination methods. From this perspective, we hoped to discuss and evaluate various currently available Pd-catalyzed alkenylation methods within the context of the syntheses of **2A** and **2B** as well as of two trisubstituted alkenes in the core-containing **3**.
3. Upon accomplishing one or more efficient and selective routes, we hoped to achieve a fully stereoselective (98%) synthesis of both mycolactone A (**1A**) and mycolactone B (**1B**), a previously unaccomplished feat.
4. Toward the above-indicated goal, we also hoped to explore a new selective (98%) and satisfactory route to the core-containing C1–C20 fragment (**3**).

Results and Discussion

Structural Analysis of Mycolactones A and B

A quick glance at the structures of mycolactones A and B (**1A** and **1B**, respectively) readily suggests that two esterification reactions, one of which is a lactonization, are to be carried out at some advanced stages of the syntheses of appropriately hydroxy-protected forms of advanced intermediates. Both may be performed under Yamaguchi's conditions^[11] including the use of $\text{Cl}_3\text{C}_6\text{H}_2\text{COCl}$, DMAP, and $i\text{Pr}_2\text{NEt}$ that have indeed been employed in the previous syntheses.^[4] Aside from these straightforward tasks, there are at least two synthetically more challenging features of mycolactones A and B that should be clearly noted for their retrosynthetic analyses. First and foremost is the presence of five Me-branched trisubstituted alkenes. All except for the one at C4 of **1A** are *E*-trisubstituted alkenes, and three of them are incorporated in the conjugated pentaene moieties (C2–C11) of the C1–C16 sidechains, posing considerable synthetic challenges. The second notable feature is the presence of ten asymmetric carbon centers, seven of which bear either an OH group or its derivative, while the other three are Me-branched. Some of their more subtle but synthetically important features include the following: (a) There are four vicinally dichiral moieties accounting for eight of the ten asymmetric carbon centers, and three of the four pairs are β -methyl alcohols, while the fourth is a vicinal diol. (b) There are two *syn* 1,3-diols. (c) Both C12–C20 and C1–C16 sidechains contain one asymmetric center adjacent to the monosubstituted end, or tail end (**T**, hereafter), of trisubstituted alkenes which influences

the direction of their construction, i.e., **H**- to-**T** or **T**-to-**H** construction, where **H** refers to the disubstituted end or “head” of a trisubstituted alkene, as defined in Scheme 1.

Synthetic Strategy for Construction of the Trisubstituted Alkenes and Vicinally Chiral Centers in Mycolactones A and B

The highly (98%) selective alkyne elementometalation–Pd-catalyzed alkenylation route to trisubstituted alkenes was first realized in 1978^[9d] with the discovery of Zr-catalyzed alkyne methylalumination (ZMA hereafter)^[12] permitting a **H**-to-**T** construction of Me-branched *E*-trisubstituted alkenes. In principle, Normant alkyne carbocupration^[13] might also be applicable to the **H**-to-**T** synthesis of either *E* or *Z* trisubstituted alkenes, but such possibilities remain to be further developed. More recently, alkyne bromoboration-based **H**-to-**T** construction of trisubstituted alkenes introduced by Suzuki^[14] has been substantially further developed by the authors' group.^[15] Notably, this is now applicable to highly selective syntheses of either *E* or *Z* Me-branched trisubstituted alkenes.^[15b] For **T**-to-**H** construction of *E* or *Z* Me-branched trisubstituted alkenes, highly selective Pd-catalyzed stepwise alkenylation of 1,1-dibromo-1-alkenes has been recently developed.^[16] For the **T**-to-**H** synthesis of the *E* isomers, a Peterson-type olefination modified by Corey, Schlessinger, and Mills (CSM-modified Peterson olefination, hereafter)^[17] is also highly satisfactory. These **T**-to-**H** construction routes are especially useful in those cases where the desired trisubstituted alkenes possess an α -asymmetric carbon atom on the tail side,^[18] such as those at C14 and C10 of mycolactones A and B. With these several mutually complementary routes to various trisubstituted alkenes at our disposal, we are now in a position to choose the best-suited option for a given synthetic task. Thus, those *E* trisubstituted alkenes at C14 and C10 may be most satisfactorily prepared by **T**-to-**H** construction via carbonyl olefination, while those *E* trisubstituted alkenes at C8, C4, and C6 may conveniently be prepared by **H**-to-**T** construction via ZMA reaction for convergent assembly of the entire carbon frameworks of both C1-C20 core-sidechain and C1-C16 sidechains of mycolactone B. Construction of the 4 *Z*-trisubstituted alkene was prepared earlier by **T**-to-**H** construction using Pd-catalyzed selective stepwise alkenylation of a 1,1-dibromo-1-alkene derivative.^[8] In this study, however, we planned to use a more efficient and satisfactory **H**-to-**T** route via recently developed propyne bromoboration–Pd-catalyzed tandem alkenylation.^[15b] Finally, preparation of two *E*-disubstituted alkenes at C2 and C8 may reliably be carried out by alkyne hydrozirconation–Pd-catalyzed tandem alkenylation with the use of a highly convenient procedure for generation of HZrCp₂Cl from ZrCp₂Cl₂ and *t*Bu₂AlH in THF.^[19]

For asymmetric generation of the vicinally dichiral C5-C6, C16-C17, and C12-C13 fragments, the use of Brown allylboration^[20] appeared most efficient and reasonably economical despite its stoichiometric use of a chiral reagent, i.e., *B*-methoxydiisopinocampheylborane, Ipc₂BOMe hereafter. As is well known, one of its outstanding features is its ability to introduce two vicinal asymmetric carbon centers leading to statistical asymmetric amplification and facile diastereomeric purification, while minimizing enantiomeric separation. For preparing the C11-C12 fragment, however, we planned to resort to Sharpless epoxidation.^[21] Finally, commercially available methyl 3-hydroxybutyrate (98% ee) was chosen for the C16-C20 and C13-C16 fragments. Despite its relatively high current cost, it is preparable by catalytic asymmetric hydrogenation, e.g., Noyori version,^[22] of an acetoacetic ester.

Retrosynthetic Plan of Mycolactones A and B

As we have mentioned earlier, the synthesis of mycolactone can be divided into (a) the synthesis of a twelve-membered lactone core **3** linked to a nine-carbon sidechain (C12-C20 moiety) and (b) a highly unsaturated conjugated pentaene sidechain linked to the core

through an ester bond, the only structural difference between mycolactone A (**1A**) and mycolactone B (**1B**) being the alkene configuration at C4 position in the C5-bound sidechains. Both mycolactone A sidechain (**2A**) and mycolactone B sidechain (**2B**) shown in Scheme 2 may be prepared through the common intermediate **4**. A priori, it is generally desirable to synthesize α -chirally substituted alkenes by completing the construction of the chirally substituted end of the alkenes (**T-to-H** construction), even though some gallant efforts to prepare them in the opposite direction are known.^[18] Accordingly, our synthesis of **4** was to begin with the preparation of **5**. After Ramirez dibromomethylenation^[23] of **5**, our recently developed Pd-catalyzed highly (>98%) *trans*-selective ethynylation–methylation tandem cross-coupling with highly catalytically active Pd(*t*Bu₃P)₂^[16d] used in the second methylation step was expected to give the desired enyne, which would then be hydrozirconated by using an operationally simpler and convenient hydrozirconation procedure we developed in 2006.^[19] The preparation of trienes **6A** and **6B** will showcase our alkyne elementometalation–Pd-catalyzed cross-coupling methodology. In addition to the convenient hydrozirconation procedure mentioned above^[19] and the highly dependable and selective Zr-catalyzed methylalumination (ZMA),^[12] we have just added the previously difficult and selective propyne bromoboration–Pd-catalyzed Negishi–Suzuki tandem alkenylation^[15b] for efficiently and selectively preparing the *E, Z, E*- triene (**6A**).

As shown in Scheme 3, the retrosynthetic strategy for the synthesis of the mycolactone core **3** involves (a) highly selective assembly of C10–C20 intermediate **7** via Pd-catalyzed alkenyl–allyl coupling (using alkenylmetals and allyl halides),^[24] (b) highly efficient construction of C1–C9 intermediate **8** by using Brown's crotylboration^[20] and ZMA reaction,^[12] and (c) union of two key intermediates **7** and **8** via epoxide opening with alkenyltrialkylaluminate.^[25]

Synthesis of the C1–C20 Core-containing Fragment 3

(a) C10–C20 Fragment (7)—Commercially available (TCI) (*R*)-3-hydroxy-butyric acid methyl ester (>98% ee) was reduced with *t*Bu₂AlH after OH protection with *t*BuMe₂SiCl (TBSCl) in 96% yield and subjected to Brown crotylboration with (–)-Ipc₂B[(*Z*)-crotyl], where Ipc is isopinocampheyl.^[20a] Analysis of the crudely isolated product revealed a set of signals corresponding to one isomer (presumably one enantiomeric pair of diastereomers) present to the extent of 5% of the desired product **13**. Since the starting 3-hydroxybutyric ester was >98% pure, the observed diastereomeric ratio reliably suggests that **13** is of >99% enantiomeric purity. After conversion of **13** to the corresponding aldehyde **14** (>98% pure by ¹³C NMR), the CSM-modified Peterson olefination with CyN=CHC(Me)Li(SiEt₃) followed by treatment with CF₃CO₂H gave **15** (>98% *E*) in 91% yield based on **14**, which was then reduced with NaBH₄ and brominated with CBr₄, PPh₃, and 2,6-lutidine to give **10** (>98% pure) in 91% yield or 66% from methyl 3-hydroxybutyrate in five isolation steps (Scheme 4).

For the conversion of **10** into epoxide **7**, which was to be combined with alkenylaluminate containing the C1–C9 fragment, conversion of **10** to **9** via Pd-catalyzed alkenyl–allyl coupling developed by us in 1981^[26] was considered. We were then reminded that, whereas this Pd-catalyzed alkenyl–allyl coupling proceeded in >98% stereo- and regioselectivity with α , β -disubstituted allylic halides, the use of α -monosubstituted allylic bromides led to both stereo- and regioisomerization to the extents of ca. 5–15% each (Eqs. 2 and 3 in Scheme 5). Gratifyingly, however, the use of β -Me-branched α -monosubstituted allylic bromides led to >98% regio- and stereoselective alkenyl–allyl coupling in good yields (Eqs. 4–6). Prompted by these findings summarized in Scheme 5, THP-protected (*Z*)-3-zinco-2-buten-1-ol, prepared via reduction of 2-butyne-1-ol with LiAlH₄, iodinolysis, and zincation, was cross-coupled with **10** in the presence of 2.5 mol% of Pd₂(dba)₃ and tris(2-

furyl)phosphine^[27] (10 mol%) to give **9** (98% pure) in 89% yield or 59% from methyl (*R*)-3-hydroxybutyrate in 6 steps.

The final functional modifications for converting **9** into **7** critically relied on Sharpless epoxidation.^[21] After deprotection of the THP group with MgBr₂,^[28] Sharpless epoxidation with *t*BuO₂H and Ti(O*i*Pr)₄ in the presence of (-)-DIPT, where DIPT stands for diisopropyl tartrate, converted **9** to **16** (98% pure) in 76% yield. Successive treatment of **16** with LiBH₄ and BF₃•OEt₂²⁹ followed by selective monomesylation and base-induced epoxidation provided 98% isomerically pure **7** in 65% over two steps. Thus, the C10-C20 fragment of 98% isomeric purity was prepared in 29% overall yield from methyl (*R*)-3-hydroxybutyrate in 9 longest linear steps.

(b) Synthesis of the C1-C9 Fragment **11** and Its Conversion to the C1-C20 Fragment **3**—

Synthesis of the first key intermediate **18** was achieved by Brown crotylboration of **17**, which, in turn, was prepared in two steps from 1,5-pentanediol via selective monoprotection with TBSCl and imidazole followed by Swern oxidation^[30] in 75% yield over two steps. After flash chromatography, **18** of 98% isomeric purity was obtained in 84% yield from **17** (63% from 1,5-pentanediol). Conversion of **18** into **11** was performed via a straightforward but less than stellar sequence consisting of protection, hydroboration–oxidation, Swern oxidation,^[30] and Corey-Fuchs acetylenation.^[23] The yield of **11** over 7 steps from 1,5-pentanediol was 35%.

With the C1-C9 fragment **11** and the C10-C20 fragment **7** in hand, the stage is set for the crucial union of these two fragments to produce the entire C1-C20 skeleton for its further conversion to the C1-C20 core-sidechain **3**. To this end, we chose the epoxide-opening reaction with alkenylaluminates developed by us in 1980.^[25] Accordingly, the C1-C9 fragment **11** was treated with Me₃Al (4 equiv) and 7 mol% of ZrCp₂Cl₂ in CH₂Cl₂. When the ZMA reaction^[12] was complete, the volatiles including Me₃Al and CH₂Cl₂ were removed by evaporation at reduced pressure and transferred to another flask containing *n*BuLi in hexane to generate alkenylaluminate **20**. To this was added the C10-C20 fragment **7** to give the desired C1-C20 intermediate **21** in 83% yield as an isomerically 98% pure compound. After selective desilylation at C1 with TBAF, a selective two stage oxidation with TEMPO and BAIB,^[31] where TEMPO and BAIB are 2,2,6,6-tetramethylpiperidiny-1-oxyl and [bis(acetoxy)iodo]benzene, respectively, gave **22** in 66% yield over 2 steps. Finally, Yamaguchi lactonization^[11] followed by desilylation with HF•pyridine afforded the fully assembled C1-C20 core-sidechain fragment **3** of 98% isomeric purity in 67% yield over 2 steps. The overall yield of **3** synthesized in 14 longest linear steps from methyl (*R*)-3-hydroxybutyrate is 11%. Although not performed, CH₂OH-to-CO₂H oxidation at C1 at an earlier stage might have further improved the synthesis of **3** (Scheme 6).

Synthesis of C1'-C16' sidechains of mycolactones **A** and **B**

In our preliminary communication in 2006,^[8] we reported a highly (>98%) stereoselective synthesis of the C1 -C16 sidechains of both mycolactones **A** and **B** (**2A** and **2B**, respectively) in nearly identical 16% yield from methyl (*S*)-3-hydroxybutyrate in 15 steps in the longest linear sequence. For the eventual total synthesis of mycolactones **A** and **B** discussed herein, however, a few modifications were made, as detailed below.

(a) C8'-C16' fragment (**4**)—

This fragment was prepared first as previously reported.^[8] The use of the MOM (methoxymethyl) group for protection of the OH group at C12 was mandated in Brown allylboration^[20c] with (*Z*)-MOMOCH=CHCH₂B(Ipc)₂. However, selective removal of MOM group at the end of total synthesis, while avoiding unwanted side-reactions, turned out to be difficult. Luckily, however, replacement of the MOM group

with a TBS group in an advanced intermediate **26** was readily feasible, and the triply TBS protected C8–C16 fragment **4** was obtained as a 98% pure compound in 24% yield in 9 steps, as shown in Scheme 7.

(b) C1'–C7' fragment (6B) of the sidechain (2B) of mycolactone B—The C1–C7 fragment (**6B**) of 98% purity was prepared as reported earlier^[8] (Scheme 8). Although it is efficient and highly selective, the observed yield of 23% over 6 steps leaves some room for improvement, and further yield optimization in our investigation of related Pd-catalyzed cross-coupling projects is ongoing.

(c) C1'–C7' fragment (6A) of the sidechain (2A) of mycolactone A—In our earlier synthesis of the C1–C7 fragment (**6A**), construction of the (4 *Z*)-trisubstituted alkenyl group was achieved through application of Pd-catalyzed selective two-stage methylation–alkenylation of 1,1-dibromoene **27**, as shown in Scheme 8. It is noteworthy that the methylation with Me₂Zn in the first stage in DMF-THF (1:1) proceeded in an unprecedentedly selective manner, providing **28** (98% *Z*) in 70% yield and that the second alkenylation was achieved without using highly active catalysts, such as Pd(*t*Bu₃P)₂ or PEPPSI.^[16b] After desilylation, **29** (98% *Z*) was obtained in 66% from **28** (42% in 6 steps from propargyl alcohol). Although highly satisfactory, this synthesis of **29** has just been supplanted by a three-step synthesis of **29** (98% *Z*) in 72% yield from propyne via its bromoboration followed by two-stage Pd-catalyzed alkenylation–ethynylation^[15b] (Scheme 9).

(d) Assembly of the sidechains 2A and 2B of mycolactones A and B—With the three fragments **4**, **6A**, and **6B** in hand, the final assembly of the sidechains **2A** and **2B** was performed, as detailed below. Construction of pentaene **30A** or **30B** by Pd-catalyzed alkenyl–alkenyl coupling of **6A** or **6B** with the metal-containing precursor of **4** proved to be highly demanding.^[8] However, the Pd-catalyzed cross-coupling between the alkenylzinc derivative generated *in situ* by treating **6B** with 2 equiv of *t*BuLi followed by 1 molar equiv of dry ZnBr₂ and **4** in a 1.4:1 ratio in the presence of 5% of Pd(DPEphos)Cl₂, where DPEphos is bis[2-(diphenylphosphino)phenyl]ether, in 2:1 THF-DMF at 23 °C for 8 h proceeded smoothly to give the desired fully hydroxy-protected pentaene, which was directly subjected to selective removal of only one TBS group of the primary hydroxyl group at C 1 with TBAF in THF at 0 °C to give **30B** in 61% yield and 98% stereoselectivity (Scheme 10). The alcohol **30B** was oxidized first with Dess–Martin periodinane^[32] and then with NaClO₂–NaH₂PO₄ in a 2:1:1 mixture of *t*BuOH, H₂O, and H₂C=C(Me)Et^[33] to provide, after chromatographic purification (silica gel, EtOAc/hexanes), **2B** in 73% isolated yield. In summary, **2B** was synthesized as a 98% isomerically pure compound in 11% overall yield over 11 steps with 98% isomeric purity from ethyl (*S*)-3-hydroxybutyrate.

The Pd-catalyzed cross-coupling of the *in situ* zincated derivative of **6A** with **4** was performed under the same conditions as those for the reaction of the zinc derivative of **6B** with **4**. This reaction also proceeded smoothly and selectively to provide **30A** in 65% yield, which was converted to **2A** in 76% isolated yield (Scheme 10). Overall, **2A** was synthesized as 98% pure compound in 12% yield over 11 steps from ethyl (*S*)-3-hydroxybutyrate.

Assembly of mycolactones A and B through union of the core 3 and sidechains 2A and 2B

In order to selectively esterify the hydroxyl group at C5 of **3**, the other two hydroxyl groups at C17 and C19 were selectively protected by treatment of **3** with 1,1-dimethoxycyclopentane in the presence of *p*-TsOH, following the protocol used by Kishi.^[4c] Esterification of **31** thus obtained with **2A** and **2B** was achieved by using Yamaguchi's reagent for lactonization

consisting of $\text{Cl}_3\text{C}_6\text{H}_2\text{COCl}$, DMAP, and $i\text{Pr}_2\text{NEt}^{[11]}$ to afford fully hydroxy-protected mycolactones A (**32A**) and its 4 *E* isomer, which is mycolactone B (**32B**), in 67 and 73% yields, respectively, as 98% isomerically pure compounds (Scheme 11). Neither ^1H nor ^{13}C NMR spectra of the two compounds revealed any sign of contamination by the other.

One final remaining task was to unprotected all five hydroxyl groups at C12, C13, C15, C17 and C19. Upon treatment of **32A** with TBAF in THF at 23 °C, all three TBS groups were removed, as judged by ^1H NMR spectroscopy. To our surprise, however, it also revealed an unexpected *Z* to *E* isomerization to give a ca. 80:20 mixture of the 4*Z* and 4*E* isomer of **33** (Figure 2). Under the same conditions for deprotection with TBAF, the 4*E* isomer **32B** was converted to ca. 30:70 mixture of the 4*Z* and 4*E* isomers of **33** (Figure 3). Without further monitoring of the unexpected isomerization processes, the crudely isolated mixtures of **33A** and **33B** obtained and examined by ^1H NMR spectroscopy were subjected next to treatment with HOAc in a THF- H_2O mixture at 23 °C for 12 h to produce ca. 60:40 to 55:45 mixtures of mycolactones A (**1A**) and B (**1B**) (Scheme 12).

Conclusion

In summary, unprecedentedly efficient and highly (98%) selective syntheses of mycolactone A sidechain (**2A**) and mycolactone B sidechain (**2B**) have been achieved mainly by repetitive application of Negishi coupling in 11 longest linear steps from commercially available ethyl (*S*)-3-hydroxybutyrate in 12% and 11% overall yield, respectively. The synthesis of mycolactone core (**3**) has been realized in 11% overall yield in 14 longest linear steps by using Pd-catalyzed alkenyl-allyl coupling and trialkylalkenylaluminate-mediated epoxide-opening reaction as key steps. Also reported are syntheses of fully protected mycolactones A (**32A**) and B (**32B**) of 98% isomeric purity as well as their deprotection to give what appear to be thermodynamically equilibrated 4/3-5/4 mixtures of mycolactones A (**1A**) and B (**1B**).

Experimental Section

General information

All experiments were conducted under argon atmosphere. THF and diethyl ether were dried and distilled by the standard methods. ZnBr_2 was flame-dried under vacuum prior to use. $\text{Pd}(\text{PPh}_3)_4$ and $\text{Pd}(\text{DPEphos})\text{Cl}_2$ were prepared according to the literature procedures. Other reagents were purchased from commercial sources and used as received. Flash chromatographic separations were carried out on 230–400 mesh silica gel 60. Gas chromatography was performed on an HP 6890 Gas Chromatography using a HP-5 capillary column (30 m $\times$ 0.32 mm, 0.5 μm film) with appropriate hydrocarbons as internal standards. ^1H and ^{13}C NMR spectra were recorded in CDCl_3 on a Varian Inova-300 or a Bruker ARX-400 spectrometer. LRMS and HRMS were obtained on Hewlett Packed 5995 GC-MS and Finnigan MATL 95 mass spectrometers, respectively. Optical rotations were measured on an Autopol III automatic polarimeter.

(2*Z*,5*E*,7*R*,8*R*,10*R*)-8,10-Bis-(*tert*-butyldimethylsilyloxy)-1-(tetrahydropyran-2-yloxy)-3,5,7-trimethyl-undeca-2,5-diene (**9**)

To a solution of (2*Z*)-2-iodo-4-(tetrahydropyran-2-yloxy)-2-butene (1.13 g, 4.00 mmol) in Et_2O (6 mL) was added $t\text{BuLi}$ (4.47 mL, 1.7 M in pentane, 7.60 mmol) slowly (20 min) at -78 °C. The resultant solution was stirred for 30 min at -78 °C. To this was added via cannula a solution of dry ZnBr_2 (901 mg, 4.00 mmol) in THF (10 mL). The mixture thus obtained was stirred for 15 min at -78 °C and then warmed to 23 °C over 30 min. In another

flask containing Pd₂(dba)₃ (92 mg, 0.10 mmol) and tri-2-furylphosphine (92 mg, 0.4 mmol) was added DMF (6.0 mL) and the resultant dark green solution was stirred at 23 °C for 15 min. A solution of (2*E*,4*R*,5*R*,7*R*)-1-bromo-5,7-bis-(*tert*-butyldimethylsiloxy)-2,4-dimethyl-oct-2-ene (**10**) (1.28 g, 2.68 mmol) in DMF (4 mL) and zinc reagent generated above was then introduced via cannula at 23 °C. The reaction mixture was stirred for 1 h, and then quenched with water, extracted with ether, washed with brine, dried over MgSO₄, filtered, and concentrated. Flash chromatography (silica gel, pure hexanes – 99: 1 hexanes/ethyl acetate) afforded the title compound **9** (1.31 g, 89 %) as oil. [α]_D²³ -6° (c 3.6, CH₂Cl₂); IR: 2931, 1611, 1462, 1254 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) -0.01 (s, 6 H), -0.02 (s, 6 H), 0.82-0.88 (m, 21 H), 1.09 (d, *J* = 5.7 Hz, 3 H), 1.48 (s, 3H), 1.50-1.59 (m, 4 H), 1.62 (s, 3 H), 1.66-1.82 (m, 4 H), 2.38-2.49 (m, 1 H), 2.64-2.77 (m, 2 H), 3.44-3.50 (m, 1 H), 3.51-3.59 (m, 1 H), 3.81-3.89 (m, 2 H), 3.93-4.01 (m, 1 H), 4.15-4.24 (m, 1H), 4.58-4.60 (m, 1H), 5.12 (d, *J* = 9.9 Hz, 1 H), 5.44 (t, *J* = 6.9 Hz, 1H); ¹³C NMR (75.4 MHz, C₆D₆) -4.55, -4.21, -4.07, -3.85, 15.64, 16.25, 18.28, 19.74, 23.44, 24.20, 25.68, 26.08, 26.14, 30.88, 37.62, 42.45, 45.03, 62.41, 63.70, 66.20, 73.24, 98.09, 122.93, 130.04, 131.38, 138.77; HRESI-MS *m/z* ([M+Na]⁺) 577.4080; calcd. 577.4084.

(2*R*,4*R*,5*R*,6*E*,9*S*,10*R*,12*E*,15*S*,16*S*)-2,4,16,20-Tetra(*tert*-butyldimethyl-siloxy)-5,7,9,13,15-pentamethyl-icosa-6,12-dien-10-ol (21**)**

To a solution of Cp₂ZrCl₂ (28 mg, 0.10 mmol) in CH₂Cl₂ (7 mL) was added AlMe₃ (0.54 mL, 5.7 mmol) at 23 °C. This reaction mixture was then cooled to -40 °C, and water (33 μL, 1.86 mmol) was then slowly dropped in. After 15 min, (4*S*,5*S*)-5,9-bis-(*tert*-butyldimethylsiloxy)-4-methyl-1-nonyne (**11**) (569 mg, 1.43 mmol) in CH₂Cl₂ (4.3 mL) was introduced. The resultant solution was stirred at -40 °C until TLC indicated the fully consumption of starting material (~ 3 h). The solvent was removed and the remaining slurry was distilled at 50 °C under reduced pressure (0.5 mmHg) for 2 h. The residue was then extracted with anhydrous hexane (3 times). The extracts was transferred to another dry reaction vessel under argon and then cooled to -78 °C. *n*BuLi (0.69 mL, 1.72 mmol) was slowly dropped in. The reaction mixture was stirred at -78 °C for 0.5 h and then warmed to -40 °C. (2*S*)-2-[(1*S*,3*E*,5*R*,6*R*,8*R*)-6,8-Bis(*tert*-butyldimethylsiloxy)-1,3,5-trimethyl-non-3-enyl]-oxirane (**7**) (443 mg, 0.94 mmol) in Et₂O (2.8 mL) was added to above solution. The resultant mixture was slowly warm to 23 °C (~ 4 h) and stirred at 23 °C for another 6 h. The reaction was quenched with water, extracted with Et₂O. The combined organic phase was washed with brine, dried over MgSO₄ and concentrated. Flash chromatography (silica gel, 99:1-50:1 hexanes/ethyl acetate) afforded the title compound **21** (690 mg, 83 %) as oil. ¹H NMR (300 MHz, CDCl₃) 0.0-0.01 (m, 24 H), 0.70 (d, *J* = 6.3 Hz, 3 H), 0.78 (d, *J* = 6.3 Hz, 3 H), 0.84 (s, 9 H), 0.85 (s, 9 H), 0.86 (s, 18 H), 1.10 (d, *J* = 6.0 Hz, 3 H), 1.18-1.26 (m, 2 H), 1.30-1.41 (m, 3 H), 1.42-1.78 (m, 18 H), 2.10-2.27 (m, 4 H), 2.40-2.47 (m, 1 H), 3.36-3.43 (m, 1 H), 3.44-3.53 (m, 1 H), 3.55-3.59 (m, 2 H), 3.83-3.89 (m, 1 H), 5.08-5.16 (m, 2 H); ¹³C NMR (75.4 MHz, CDCl₃) -5.08, -4.49, -4.18, -4.10, -3.95, -3.82, 14.15, 15.13, 15.86, 16.37, 18.33, 18.56, 22.54, 24.26, 26.11, 26.19, 32.76, 33.32, 35.77, 36.22, 37.76, 43.01, 43.15, 45.31, 63.36, 66.25, 73.32, 75.88, 76.14, 122.04, 130.46, 132.45, 138.07; HRESI-MS *m/z* ([M+Na]⁺) 907.6861; calcd. 907.6858.

Protected mycolactone Core

To a solution of (5*S*,6*S*,8*E*,11*R*,12*S*,14*E*,16*R*, 17*R*,19*R*)-5,17,19-tri(*tert*-butyldimethylsiloxy)-11-hydroxy-6,8,12,14,16-pentamethyl-icosa-8,14-dienoic acid (**22**) (90 mg, 0.115 mmol) in PhH (2.5 mL) was added *i*Pr₂NEt (159 μL, 0.91 mmol) and Cl₃C₆H₂COCl (87 μL, 0.46 mmol). The solution was stirred at 23 °C for 1 h and was added to a solution of DMAP (57 mg, 0.044 mmol) in PhH (52 mL) via syringe pump over 12 h. The mixture was stirred for 6 h, washed with NaHCO₃ (sat.) and brine, dried and concentrated. Flash chromatography (silica gel, 2:98 EtOAc/hexanes) afforded the title

compound (69 mg, 78 %) as oil. $[\alpha]_D^{23}$ -8.8° (c 0.9, CH₂Cl₂); IR (neat) 3081, 2957, 2929, 2856, 1822, 1744, 1579, 1549, 1472, 1370, 1268, 1208, 1117, 1083, 987, 836, 773 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) 0.11 (s, 18 H), 0.91 (d, *J* = 7.0 Hz, 3 H), 0.96 (s, 30 H), 1.03 (d, *J* = 6.4 Hz, 3 H), 1.20 (d, *J* = 5.9 Hz, 3 H), 1.46-1.52 (m, 2 H), 1.66 (s, 3 H), 1.69-1.80 (m, 9 H), 1.90-2.00 (m, 3 H), 2.03-2.13 (m, 2 H), 2.20 (dd, *J* = 4.1, 13.6 Hz, 1 H), 2.43-2.59 (m, 3 H), 3.44 (d, *J* = 7.6 Hz, 1 H), 3.66 (q, *J* = 5.2 Hz, 1 H), 3.82-3.95 (m, 1 H), 4.87-4.95 (m, 1 H), 5.08 (d, *J* = 9.4 Hz, 1 H), 5.20 (d, *J* = 9.4 Hz, 1 H); ¹³C NMR (75.4 MHz, CDCl₃) -4.5, -4.5, -4.2 (2C), -4.0, -3.8, 14.6, 15.9, 16.0, 16.2, 18.3, 18.8, 22.0, 24.2, 26.2 (9C), 29.9, 30.4 (2C), 33.6 (3C), 35.3, 36.2, 37.8, 43.3, 45.3, 45.6, 66.2, 73.4, 76.0, 121.7, 130.6, 131.9, 137.4, 173.7; HRESI-MS *m/z* ([M+Na]⁺) 789.5686; calcd. 789.5681.

Mycolactone core (2)

Protected mycolactone core (66 mg, 0.086 mmol) was dissolved in THF (2.2 mL) followed by the addition of HF•pyridine (0.66 mL). After 6 h, TLC indicated that the reaction is completed. The mixture was quenched with NaHCO₃ (sat.) extracted with EtOAc. The combined organic phase was dried over MgSO₄ and concentrated. Flash chromatography (silica gel, 1:99-1:25 CH₃OH/CH₂Cl₂) afforded the title compound **2** (31 mg, 86 %) as oil. ¹H NMR (500 MHz, CD₃OD) 0.92 (d, *J* = 6.7 Hz, 3 H), 1.00 (d, *J* = 6.7 Hz, 3 H), 1.01 (d, *J* = 6.7 Hz, 3 H), 1.19 (d, *J* = 6.1 Hz, 3 H), 1.51 (ddd, *J* = 7.3, 10.3, 13.7 Hz, 1 H), 1.58-1.61 (m, 3 H), 1.61-1.66 (m, 3 H), 1.67 (s, 3 H), 1.69 (s, 3 H), 1.76-1.77 (m, 1 H), 1.83-1.88 (m, 1 H), 1.92-2.00 (m, 2 H), 2.10 (br, d, *J* = 14.3 Hz, 1 H), 2.12-2.19 (m, 2 H), 2.34-2.39 (m, 1 H), 2.40-2.45 (m, 1 H), 2.52 (ddd, *J* = 11.6, 11.7, 14.1 Hz, 1 H), 3.34-3.37 (m, 1 H), 3.44 (ddd, *J* = 2.4, 7.7, 10.1 Hz, 1 H), 3.98 (sextet, *J* = 6.1 Hz, 1 H), 4.95 (ddd, *J* = 2.3, 5.0, 11.8 Hz, 1 H), 5.02 (d, *J* = 9.9 Hz, 1 H), 5.05 (d, *J* = 11.4 Hz, 1 H); ¹³C NMR (125 MHz, CD₃OD) 13.9, 14.9, 15.1, 16.1, 18.2, 20.2, 22.3, 28.9, 34.2, 34.4, 34.8, 35.3, 39.6, 43.2, 43.5, 46.0, 67.1, 74.5, 75.2, 76.5, 122.6, 130.0, 133.1, 137.3, 174.9 ppm; HRESI-MS *m/z* ([M+H]⁺) 425.3263; calcd. 425.3267.

Fully protected mycolactone B (32B)

To a solution of (2*E*,4*E*,6*E*,8*E*,10*E*,12*S*,13*S*,15*S*)-12,13,15-tri(*tert*-butyldimethylsiloxy)-4,6,10-trimethyl-2,4,6,8,10-hexadecapentaenoic acid (**2B**) (22 mg, 0.033 mmol) in benzene (0.2 mL) were added *i*-Pr₂NEt (17 μL, 0.098 mmol), Cl₃C₆H₂COCl (8 μL, 0.05 mmol), and DMAP (6.0 mg, 0.05 mmol). Partial protected mycolactone core **31** (8.3 mg, 0.017 mmol) in benzene (0.3 mL) was then introduced. The resultant suspension was stirred avoiding of light for 6 h, and then quenched with NaHCO₃ (sat.), extracted with EtOAc, washed with brine, dried over Na₂SO₄, filtered, and concentrated. Flash chromatography (silica gel, 20:1-15:1 hexanes/ethyl acetate) afford the title compound **32B** (14.3 mg, 73% yield) as a yellow oil. $[\alpha]_D^{23}$ -20° (c 0.7, MeOH); IR (neat) 2957, 2857, 1732, 1709, 1611, 1456, 1381, 1250, 1155, 835, 774 cm⁻¹; ¹H NMR (500 MHz, CD₃COCD₃) 0.03 (s, 3 H), 0.09 (s, 6 H), 0.10 (s, 6 H), 0.11 (s, 3 H), 0.91 (s, 18 H), 0.96 (d, *J* = 6.6 Hz, 3 H), 1.11 (d, *J* = 6.1 Hz, 3 H), 1.18 (d, *J* = 6.0 Hz, 3 H), 1.57-1.59 (m, 4 H), 1.62-1.65 (m, 4 H), 1.66 (s, 3 H), 1.72 (s, 3 H), 1.75-1.79 (m, 3 H), 1.78-1.84 (m, 3 H), 1.84-1.90 (m, 5 H), 1.95 (s, 3 H), 1.98-1.99 (m, 1 H), 2.01-2.02 (m, 2 H), 2.04-2.05 (m, 3 H), 2.07 (s, 3 H), 2.09 (s, 3 H), 2.11-2.12 (m, 1 H), 2.38-2.44 (m, 2 H), 2.51-2.52 (m, 1 H), 3.46 (ddd, *J* = 2.0, 8.2, 10.5 Hz, 1 H), 3.77-3.80 (m, 1 H), 3.82-3.86 (m, 1 H), 4.02 (sextet, *J* = 6.1 Hz, 1 H), 4.59 (dd, *J* = 3.4, 9.2 Hz, 1 H), 4.70-4.74 (m, 1 H), 4.88-4.92 (m, 1 H), 5.00 (d, *J* = 9.8 Hz, 1 H), 5.14 (d, *J* = 10.6 Hz, 1 H), 5.68 (d, *J* = 9.0 Hz, 1 H), 5.90 (d, *J* = 15.6 Hz, 1 H), 6.40 (d, *J* = 11.2 Hz, 1 H), 6.48 (s, 1 H), 6.50 (d, *J* = 14.7 Hz, 1 H), 6.69 (dd, *J* = 15.1, 11.2 Hz, 1 H), 7.37 (d, *J* = 15.5 Hz, 1 H); ¹³C NMR (125 MHz, CD₃COCD₃) -4.5, -4.4, -4.2, -4.1, -4.0, -3.9, 13.8, 14.3, 14.9, 15.8, 16.1, 17.1, 17.2, 18.5 (2 C), 18.6, 20.5, 20.7, 22.5, 23.0 (2 C), 24.1, 24.9, 26.2 (9 C), 31.8, 32.7, 35.1, 35.9, 37.8, 39.0, 41.0, 43.9, 44.4, 46.3, 66.6, 67.6, 72.0, 74.2, 75.3, 76.0, 79.1, 110.6, 117.3, 123.8, 125.2, 129.7, 133.1,

134.3, 134.9, 135.3, 135.6, 136.1, 137.2, 140.2, 144.3, 151.1, 166.7, 173.0; LRESI-MS m/z ($[M + Na]^+$) 1173; calcd. 1173.

33B from 32B

To a stirred solution of fully protected mycolactone B (**32B**) (15 mg, 0.013 mmol) in THF (5.4 mL) was added TBAF (0.13 mL, 1.0 M in THF, 0.13 mmol). The resulting yellow mixture was stirred at room temperature for 1 h and then quenched with NH_4Cl (sat.), extracted with EtOAc, washed with brine, dried over Na_2SO_4 and concentrated. Flash chromatography (silica gel, EtOAc/ CH_3OH 98:2) afforded the title compound (7.4 mg, 71 %) as yellow oil. This triol ester existed as a 0.42:1 mixture 4 *Z*:4 *E* isomers. 4 *E* isomer: $[\alpha]_D^{23} -31^\circ$ (c 0.3, MeOH); 1H NMR (500 MHz, CD_3COCD_3) 0.93 (d, $J = 6.7$ Hz, 3 H), 0.94 (d, $J = 6.4$ Hz, 3 H), 0.98 (d, $J = 6.6$ Hz, 3 H), 1.13 (d, $J = 6.4$ Hz, 3 H), 1.15 (d, $J = 6.0$ Hz, 3 H), 1.51-1.53 (m, 2 H), 1.61-1.63 (m, 7 H), 1.69 (s, 3 H), 1.69-1.74 (m, 2 H), 1.75 (s, 3 H), 1.77-1.79 (m, 2 H), 1.88-1.90 (m, 7 H), 1.94 (s, 3 H), 1.97-1.99 (m, 2 H), 2.05 (s, 3 H), 2.07 (s, 3 H), 2.08 (s, 3 H), 2.12-2.15 (m, 1 H), 2.40-2.45 (m, 2 H), 2.50-2.56 (m, 1 H), 3.49 (t, $J = 8.6$ Hz, 1 H), 3.70-3.71 (m, 1 H), 3.84-3.88 (m, 1 H), 3.95 (brs, 1 H), 4.02 (brs, 1 H), 4.05-4.07 (m, 1 H), 4.25 (brs, 1 H), 4.29-4.32 (m, 1 H), 4.72-4.75 (m, 1 H), 4.91-4.94 (m, 1 H), 5.02 (d, $J = 9.9$ Hz, 1 H), 5.16 (d, $J = 8.3$ Hz, 1 H), 5.63 (d, $J = 8.1$ Hz, 1 H), 5.92 (d, $J = 15.6$ Hz, 1 H), 6.46 (d, $J = 15.0$ Hz, 1 H), 6.50 (s, 1 H), 6.65-6.71 (m, 1 H), 7.39 (d, $J = 15.5$ Hz, 1 H); ^{13}C NMR (75.4 MHz, CD_3COCD_3) 13.4, 14.4, 15.0, 15.9, 16.3, 17.2, 17.4, 20.6, 20.8, 21.3, 22.7, 23.1, 24.3, 25.1, 31.5, 32.0, 32.9, 35.3, 36.0, 37.9, 39.2, 41.2, 41.9, 44.6, 46.5, 67.8 (2 C), 72.4, 75.5, 75.8, 76.2, 79.3, 110.7, 117.5, 124.0, 125.2, 129.9, 133.3, 134.5, 134.7, 135.4, 136.3, 137.4 (2 C), 140.5, 144.5, 151.3, 166.9, 173.3; HRESI-MS m/z ($[M + Na]^+$) 831.5379; calcd. 831.5387.

Mycolactones A and B (1A + 1 B) from 32B

The triol ester (4 *Z*:4 *E* = 0.42:1) (5.4 mg, 0.0067 mmol) was dissolved in a 2:2:1 mixture of THF:AcOH:H₂O (1.2 mL). The resulting yellow solution was stirred at room temperature for 11 h, then quenched with $NaHCO_3$ (sat.), extracted with EtOAc, washed with brine, dried over Na_2SO_4 and concentrated. Flash chromatography (silica gel, EtOAc/ CH_3OH = 98:2) afforded the final as yellow oil, and the recovered triol ester. The recovered triol ester was subjected to the same condition described above and afforded a second batch of the final product (3.2 mg in total, 64% overall yield). The final products existed as a 1:0.82 mixture of 4 *Z*:4 *E* isomers (**1A** + **1B**). $[\alpha]_D^{23} -23^\circ$ (c 0.3, MeOH); 1H NMR (500 MHz, CD_3COCD_3) 4 *Z* isomer: 0.89 (d, $J = 6.7$ Hz, 3 H), 0.90 (d, $J = 6.6$ Hz, 3 H), 0.98 (d, $J = 6.6$ Hz, 3 H), 1.12 (d, $J = 6.0$ Hz, 3 H), 1.14 (d, $J = 6.1$ Hz, 3 H), 1.37-1.40 (m, 1 H), 1.53-1.55 (m, 2 H), 1.58-1.59 (m, 2H), 1.65 (s, 3 H), 1.66-1.67 (m, 1 H), 1.71 (s, 3 H), 1.81-1.88 (m, 1 H), 1.91 (s, 3 H), 1.98 (s, 3 H), 2.02 (s, 3 H), 2.02-2.03 (m, 6 H), 2.35-2.43 (m, 2 H), 2.46-2.54 (m, 1 H), 3.50-3.52 (m, 1 H), 3.65-3.69 (m, 1 H), 3.93-3.94 (m, 1 H), 3.97-3.99 (m, 1 H), 4.02-4.04 (m, 1 H), 4.22 (brs, 2 H), 4.24 (brs, 1 H), 4.26-4.29 (m, 1 H), 4.69-4.72 (m, 1 H), 4.88-4.90 (m, 1 H), 5.04 (d, $J = 9.6$ Hz, 1 H), 5.12 (d, $J = 10.4$ Hz, 1 H), 5.60 (t, $J = 7.4$ Hz, 1 H), 5.94 (d, $J = 15.7$ Hz, 1 H), 6.16 (d, $J = 11.3$ Hz, 1 H), 6.34 (s, 1 H), 6.41 (d, $J = 15.5$ Hz, 1 H), 6.65 (dd, $J = 10.6, 16.0$ Hz, 1 H), 7.92 (d, $J = 15.6$ Hz, 1 H); ^{13}C NMR (100 MHz, CD_3COCD_3 , 4 *Z* isomer) 13.4, 14.9, 15.9, 16.2, 17.1, 17.6, 20.5, 20.7, 21.0, 24.2, 24.6, 31.5, 32.7, 35.3, 35.9, 40.5, 41.8, 43.8, 44.3, 46.3, 67.7, 69.0, 72.3, 75.7, 76.2, 76.9, 79.2, 119.6, 123.8, 125.1, 131.2, 132.1, 133.4, 134.6, 134.8 (2 C), 137.3 (2 C), 139.9, 141.8, 143.1, 166.8, 173.2; 1H NMR (500 MHz, acetone- d_6) 4 *E* isomer: 0.89 (d, $J = 6.7$ Hz, 3 H), 0.90 (d, $J = 6.6$ Hz, 3 H), 0.98 (d, $J = 6.6$ Hz, 3 H), 1.12 (d, $J = 6.0$ Hz, 3 H), 1.14 (d, $J = 6.1$ Hz, 3 H), 1.37-1.40 (m, 1 H), 1.53-1.55 (m, 2 H), 1.58-1.59 (m, 2 H), 1.65 (s, 3 H), 1.66-1.67 (m, 1 H), 1.71-1.72 (m, 2 H), 1.72 (s, 3 H), 1.81-1.88 (m, 1 H), 1.91 (s, 3 H), 2.02-2.03 (m, 6 H), 2.05 (s, 3 H), 2.09 (s, 3 H), 2.13-2.14 (m, 1 H), 2.35-2.43 (m, 2 H), 2.46-2.54 (m, 1 H), 3.50-3.52 (m, 1 H), 3.65-3.69 (m, 1 H), 3.93-3.94 (m, 1 H), 3.97-3.99

(m, 1 H), 4.02–4.04 (m, 1 H), 4.22 (brs, 2 H), 4.24 (brs, 1 H), 4.26–4.29 (m, 1 H), 4.69–4.72 (m, 1 H), 4.88–4.90 (m, 1 H), 5.04 (d, $J = 9.6$ Hz, 1 H), 5.12 (d, $J = 10.4$ Hz, 1 H), 5.60 (t, $J = 7.4$ Hz, 1 H), 5.89 (d, $J = 15.7$ Hz, 1 H), 6.37 (d, $J = 11.3$ Hz, 1 H), 6.45 (d, $J = 15.5$ Hz, 1 H), 6.47 (s, 1 H), 6.66 (dd, $J = 10.6, 16.0$ Hz, 1 H), 7.36 (d, $J = 15.6$ Hz, 1 H); ^{13}C NMR (100 MHz, CD_3COCD_3 , 4 *E* isomer) 13.4, 14.3, 14.9, 15.9, 16.2, 17.1 (2 C), 17.6, 20.5, 20.7, 24.2, 24.6, 31.5, 32.7, 35.3, 36.0, 40.5, 41.8, 43.8, 44.3, 46.3, 67.7, 69.0, 72.3, 75.7, 76.2, 76.9, 79.2, 117.4, 123.8, 125.1, 131.2, 133.2, 133.4, 134.6, 135.3, 136.1, 137.2, 137.3, 140.3, 144.3, 151.1, 166.8, 173.2; HRESI-MS m/z ($[\text{M}+\text{Na}]^+$) 765.4907; calcd. 765.4918.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Figure 1. Structures of mycolactones A-G

Figure 2. ^1H NMR spectra of stepwise deprotection of fully hydroxy-protected mycolactone A (32A)

Figure 3. ^1H NMR spectra of stepwise deprotection of fully protected hydroxy-mycolactone B (32B)

Scheme 1. Definition of H-to-T and T-to-H construction of trisubstituted alkenes via alkenylation

Scheme 2. Retrosynthetic analysis of mycolactones A and B sidechains

Scheme 3. Retrosynthetic analysis of mycolactones A and B core

Scheme 4. Synthesis of C10-C20 fragment 7 of mycolactone core

Chemistry. Author manuscript; available in PMC 2013 November 11.

Chemistry. Author manuscript; available in PMC 2013 November 11.

Scheme 7. Synthesis of the C8 -C16 fragment of 4

Scheme 8. Synthesis of the C1 -C7 segment of the mycolactone B sidechain (**6B**)

Scheme 9. Synthesis of the C1 -C7 segment of the mycolactone A sidechain (6A)

Scheme 10. Syntheses of fully protected sidechains 2B and 2A

Scheme 11. Syntheses of fully hydroxy-protected mycolactones A (32A) and B (32B)

Scheme 12. Syntheses of mycolactones A (1A) and B (1B)