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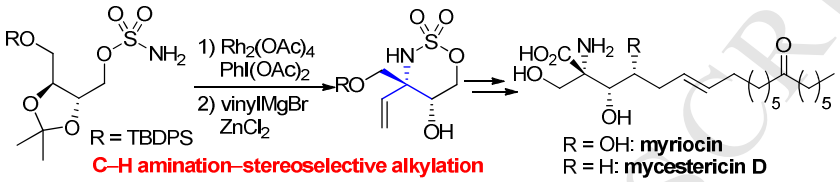
Narumi Noda[a], Hisanori Nambu[a], Kana Ubukata[a], Tomoya Fujiwara[a], Kiyoshi Tsuge[b], Takayuki Yakura[a,*]

[a] *Graduate School of Medicine and Pharmaceutical Sciences, University of Toyama, Sugitani, Toyama 930-0194, Japan*

[b] *Department of Chemistry, Graduate School of Science and Engineering, University of Toyama, Gofuku, Toyama 930-8555, Japan*



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[a] Graduate School of Medicine and Pharmaceutical Sciences, University of Toyama, Sugitani, Toyama 930-0194, Japan
[b] Department of Chemistry, Graduate School of Science and Engineering, University of Toyama, Gofuku, Toyama 930-8555, Japan

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ABSTRACT

Total synthesis of myriocin and mycestericin D was achieved using the Du Bois Rh(II)-catalyzed C–H amination of a sulfamate and subsequent alkylation as a key step. The reaction of a sulfamate with $PhI(OAc)_2$ and MgO in the presence of $Rh_2(OAc)_4$ gave oxathiazinane *N*,*O*-acetal as the sole product in high yield. Alkylation of *N*,*O*-acetal using vinylmagnesium bromide in the presence of $ZnCl_2$ proceeded stereoselectively to provide an oxathiazinane bearing a quaternary chiral center in high yield. Myriocin and mycestericin D were synthesized from a common synthetic intermediate. This route includes the first application of the Du Bois procedure for constructing a quaternary chiral center.

1. Introduction*

Myriocin and mycestericins are complex α,α-disubstituted amino acid natural products structurally related to sphingolipids. Myriocin (**1**, Figure 1) was isolated from the fermentation broth of the thermophilic fungi *Myriococcum albomyces*[1] and *Mycelia sterilia*[2] in 1972, and from the culture broth of *Isalia sinclairii* in 1994.[3] Notably, myriocin exhibits 10–100 times more potent immunosuppressive activity than cyclosporine A[3] and has been shown to have potent inhibitory activity against serine palmitoyltransferase, which is an essential enzyme in the biosynthesis of sphingolipids.[4] Mycestericins A−G were isolated from the culture broth of *M. sterilia* ATCC 20349 and exhibited immunosuppressive activity similar to that of myriocin.[5] Owing to their challenging structural motif containing a quaternary chiral center and interesting biological activity, myriocin[6] and the mycestericins[7] are attractive targets for total synthesis. The first total synthesis of myriocin (**1**) was achieved from D-fructose using a Strecker reaction to construct a quaternary chiral center, but the desired diastereoisomer was the minor component.[6a,b] Thereafter, several synthetic chemists reported total and formal syntheses of **1** by employing various methods for stereoselective introduction of the quaternary chiral center, including epoxide opening with external[6c–g] or internal[6h] nitrogen nucleophiles, aldol reactions of chiral bislactim ether[6i] or oxazoline templates,[6j] Overman rearrangement of an allylic trichloroacetimidate,[6k,l] photolytic hydroxymethylation of an α-alkoxycarboxy ketoxime ether,[6m] enzymatic kinetic resolution of racemic methyl ester,[6n] and deconjugative alkylation of a dehydroamino acid.[6o] On the contrary, there is only one example of the total synthesis of mycestericin D (**2**, Figure 1), although **2** has the same stereochemistry at C2 and C3, and an identical long side chain. Node and co-workers reported the asymmetric total synthesis of **2** by employing a stereoselective hydroxymethylation of an oxazoline derivative for the construction of a quaternary chiral center.[7d,e] Thus, there are no examples of the synthesis of **1** and **2** using the same synthetic strategy. In our laboratory, we have been exploring the synthesis of sphingosine natural products using Rh(II)-catalyzed reactions as key steps.[8] As part of this program, we herein report a novel strategy for the concise synthesis of myriocin (**1**)[9] and mycestericin D (**2**) by applying Du Bois' Rh(II)-catalyzed C–H amination–alkylation procedure[10] for construction of a quaternary chiral center.

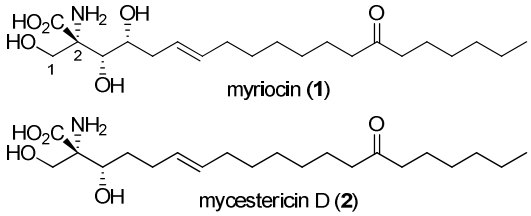
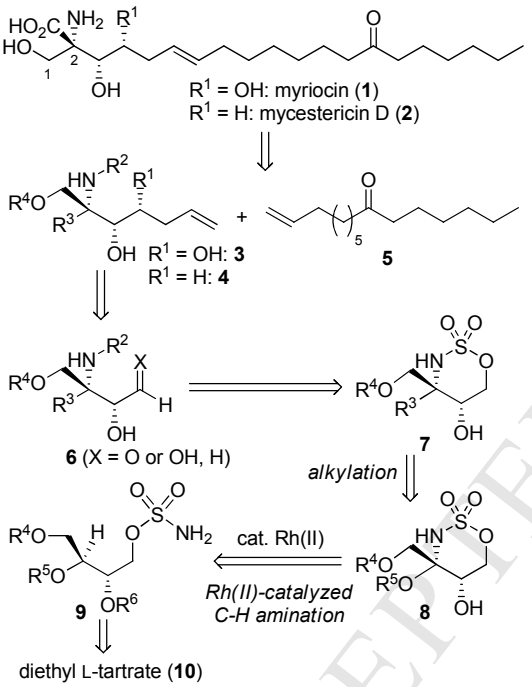


Fig. 1. Structure of myriocin (**1**) and mycestericin D (**2**).

* Corresponding author. Tel.: +81-76-434-7555; fax: +81-76-434-5053; e-mail: yakura@pha.u-toyama.ac.jp (T. Yakura).

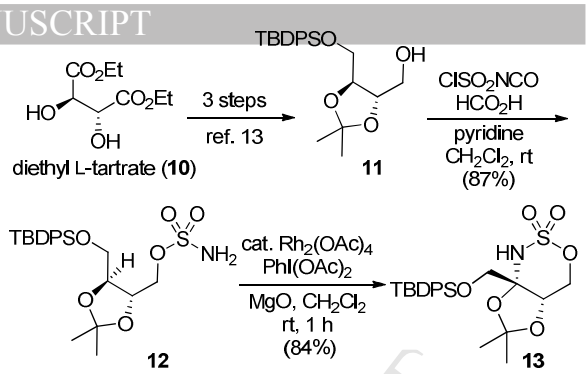
2. Results and discussion

Our retrosynthetic strategy for myriocin (**1**) and mycestericin D (**2**) is outlined in Scheme 1. Introduction of the long side chain at a later stage in the synthesis was proposed because it would provide high flexibility for analogue synthesis. The conversion would involve cross metathesis of amino alkenes **3** and **4**, which contain all asymmetric carbons of **1** and **2**, respectively, with their desired configurations, and the known alkene **5**.[11] It was anticipated that **3** and **4** would be accessible by allylation from aldehyde or alcohol **6** as a key intermediate. Alcohol **6** can be obtained from oxathiazinane **7** by a ring-opening reaction. The key steps of the stereoselective construction of the quaternary chiral center of **7** would be accomplished by applying Du Bois' Rh(II)-catalyzed C−H amination reaction[12] of sulfamate **9**, followed by stereoselective alkylation.[10] Although Du Bois' pioneering work has been applied to the synthesis of propargylic amine derivatives[10a] and (+)-saxitoxin,[10b,c] there are no reported examples of its use for the construction of quaternary chiral centers. Sulfamate ester **9** would be prepared from commercially available diethyl L-tartrate (**10**).



Scheme 1. Retrosynthetic analysis of myriocin (**1**) and mycestericin D (**2**).

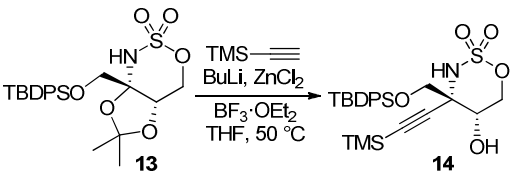
The starting diethyl L-tartrate (**10**) was converted into the known mono-*tert*-butyldiphenylsilyl (TBDPS) ether **11** according to the literature[13] (Scheme 2). Reaction of alcohol **11** with chlorosulfonyl isocyanate, formic acid, and pyridine in dichloromethane provided sulfamate ester **12** in 87% yield.[12b,14] Rhodium(II)-catalyzed C–H amination of **12** using Du Bois' conditions[12] proceeded stereospecifically to yield oxathiazinane *N*,*O*-acetal **13**. Thus, treatment of **12** with 4 mol% of dirhodium(II) tetraacetate, 1.1 equivalents of phenyliodine(III) diacetate, and 2.3 equivalents of magnesium oxide in dichloromethane at room temperature for 1 h gave the corresponding C–H amination product **13** in 84% yield.



Scheme 2. Rh(II)-catalyzed C–H amination of sulfamate ester **12**.

To construct the quaternary chiral centers in **1** and **2**, we investigated alkylation of oxathiazinane *N*,*O*-acetal **13**. Since ethynylation gave better results than vinylation in Du Bois' original report on the construction of tertiary centers,[10] we first examined ethynylation of **13** using the Du Bois' conditions[10a] (Table 1). When *N*,*O*-acetal **13** was reacted with trimethylsilylethynylzinc chloride generated from 2.1 equivalents of trimethylsilylacetylene, butyllithium (2.0 equiv), and zinc chloride (2.1 equiv) in the presence of boron trifluoride diethyl etherate ($BF_3 \cdot OEt_2$, 3.0 equiv) in tetrahydrofuran (THF) at 50 °C for 2 h, ethynylation product **14** was obtained in only 42% yield as the sole product (entry 1). The use of twice the amounts of all reagents increased the yield of **14** to 62% (entry 2). We then screened the amount of the Lewis acid $BF_3 \cdot OEt_2$. Reaction of **13** with 4.0 equivalents of *in situ* generated zinc acetylide and 4.2 equivalents of $BF_3 \cdot OEt_2$ afforded **14** in 71% yield (entry 3). When the amount of $BF_3 \cdot OEt_2$ was decreased to 3.0 and 2.1 equivalents, these product yields slightly decreased to 69% and 65%, respectively (entries 4 and 5). Reaction of **13** with a large amount of zinc acetylide (10.0 equiv) in the presence of $BF_3 \cdot OEt_2$ (4.2 equiv) furnished **14** in 81% yield (entry 6). These results demonstrate that Du Bois' C−H amination–alkylation procedure was effective for the stereoselective construction of the quaternary chiral center.

Table 1
Ethynylation of sulfamate ester **13** with zinc acetylide and $BF_3 \cdot OEt_2$

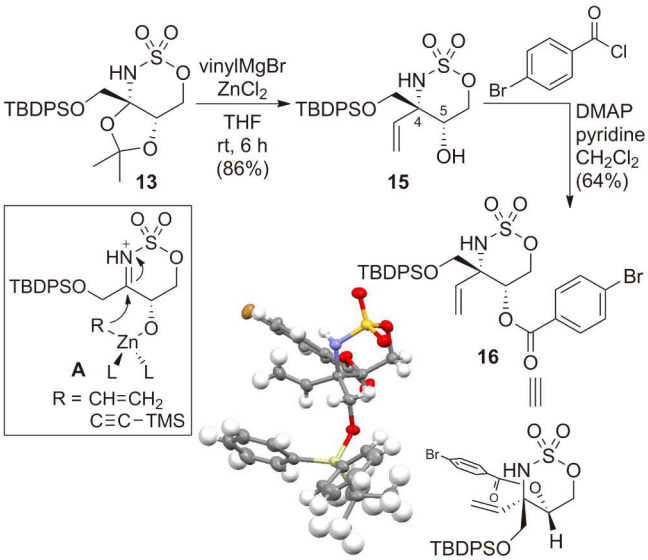


Entry	Zinc Acetylide[a] (equiv)	$BF_3 \cdot OEt_2$ (equiv)	Time (h)	Yield (%)
1	2.0	3.0	2	42
2	4.0	6.0	3.5	62
3	4.0	4.2	1	71
4	4.0	3.0	5	69
5	4.0	2.1	5	65
6	10.0	4.2	2	81

[a] Zinc acetylide was prepared *in situ* with trimethylsilylacetylene (1.05 × X equiv), butyl lithium (X equiv) and zinc chloride (1.05 × X equiv).

Next, we examined the vinylation of **13**, which was accomplished according to Du Bois' original conditions[10c] (Scheme 3). Thus, reaction of **13** with 4.2 equivalents of vinylmagnesium bromide in the presence of zinc chloride (2.2 equiv) in THF at room temperature for 6 h produced **15** as the sole product in 86% yield. The stereochemistry of **15** was determined to be (4*R*,5*R*) via single-crystal X-ray analysis of the

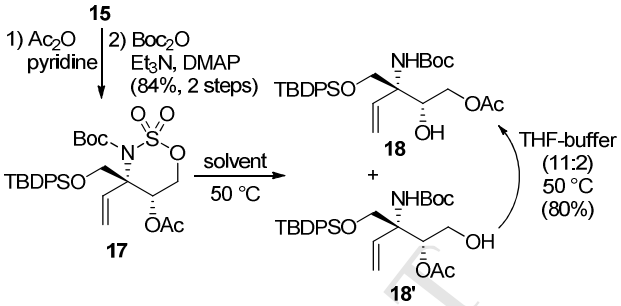
p-bromobenzoyl derivative **16**.[15] The stereoselectivity of the C−H amination–alkylation reaction was observed in a manner similar to those reported by Du Bois.[10] Thus, the alkylation would proceed through intermediate **A**,[10c] which may be intramolecularly coupled to nucleophiles. Considering the yields of **14** and **15** and the necessary further conversions into a common synthetic intermediate for **1** and **2**, vinyl compound **15** was selected.



Scheme 3. Vinylation of sulfamate ester **13** and determination of the stereochemistry of **15**.

With the stereoselective construction of the quaternary chiral center in **1** and **2** accomplished, we next examined opening of the oxathiazinane ring of **15** after protection of OH and NH groups (Table 2). Acetylation of the hydroxy group in **15** followed by *tert*-butoxycarbonylation of the amino group gave protected oxathiazinane **17** in high yield. We initially investigated the opening of **17** using Du Bois' conditions.[10c,12b] When **17** was warmed in acetonitrile–water (11:2) at 75 °C, decomposition was observed (Table 2, entry 1). Use of 0.1 M phosphate buffer instead of water at 50 °C led to ring opening and an interesting 1,2-acetyl group shift to give secondary alcohol **18** as the major product in 31% yield, and the initially expected primary alcohol **18′** in 7% yield (entry 2). After screening of organic solvents such as dichloromethane, acetone, and THF, we found that THF was the most effective solvent (entries 3–5). Warming of **17** in a THF–buffer solution (11:2) at 50 °C for 24 h was found to afford **18** and **18′** in 73% and 23% yields, respectively. Increasing the ratio of buffer (THF/buffer = 5:1 and 3:1) resulted in a decrease in the combined product yield of **18** and **18′** (entries 6 and 7). Longer reaction times led to low yields of the desired products due to decomposition; however, treatment of purified **18′** under the same reaction conditions gave **18** in 80% yield.

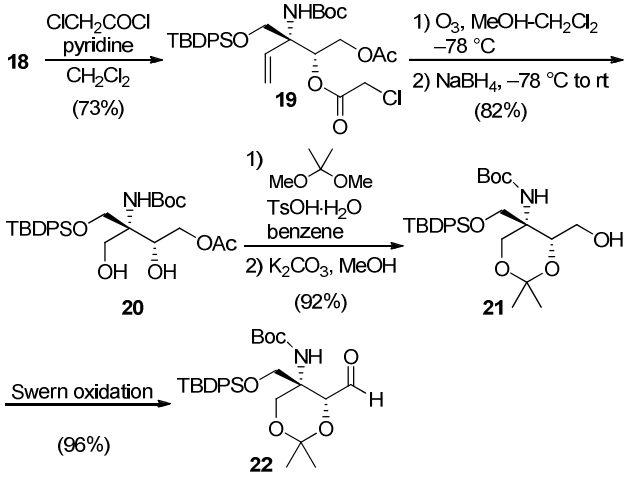
Table 2
Ring opening of oxathiazinane **17**



Entry	Solvent	time (h)	yield (%) 18	18′
1[a]	CH_3CN/H_2O (11:2)	2	Decomposition	
2	CH_3CN/buffer[b] (11:2)	4	31	7
3	CH_2Cl_2/buffer[b] (11:2)	8	No reaction	
4	acetone/buffer[b] (11:2)	7	67	9
5	THF/buffer[b] (11:2)	24	73	23
6	THF /buffer[b] (5:1)	23	72	19
7	THF/buffer[b] (3:1)	27	50	16

[a] The reaction was conducted at 75 °C.
[b] Buffer: 0.1 M phosphate buffer.

We focused on the synthesis of alcohol **21** and aldehyde **22** as key intermediates for **1** and **2** (Scheme 4). Protection of the secondary OH group in **18** with chloroacetyl chloride and pyridine yielded chloroacetate **19**. Reductive ozonolysis of **19** resulted in conversion of the vinyl group to a hydroxymethyl substituent and chloroacetyl deprotection to form diol **20** in 82% yield. After protection of the diol as an acetonide, methanolysis of the acetoxy group provided alcohol **21** in 92% yield. Swern oxidation of **21** afforded aldehyde **22** in 96% yield.

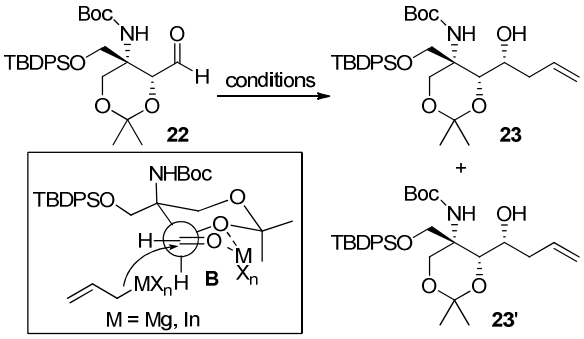


Scheme 4. Synthesis of key intermediates **21** and **22**.

With the key intermediate **22** in hand, we investigated the formation of the third stereocenter using chelation-controlled allylation for synthesis of myriocin (**1**, Table 3). Reaction of **22** with allylmagnesium bromide in THF afforded a 1:3.5 mixture of desired **23** and undesired **23′** in 36% combined yield (entry 1). Switching the solvent to diethyl ether greatly improved the product yield and diastereoselectivity, providing a 1.6:1 mixture of **23** and **23′** in 69% combined yield (entry 2). We next examined the use of magnesium iodide as a chelating agent. As expected, the reaction of **22** with magnesium iodide increased diastereoselectivity from 1.6:1 to 4.2:1 (entry 3). The allylation

would proceed through chelated complex **B**. To further enhance the product yield and diastereoselectivity, we directed our efforts to allylation using stannane[7a,b] and indium reagents.[16] The reaction of **22** with allyltributylstannane and magnesium bromide in dichloromethane afforded **23** as the major product (**23**:**23′** = 2.8:1) in 42% yield (entry 4). Gratifyingly, the treatment of **22** with allylbromide and indium metal in the presence of tetrabutylammonium iodide in *N*,*N*-dimethylformamide gave **23** as the major product (**23**:**23′** = 5.1:1) in 80% yield (entry 5). Furthermore, the addition of magnesium iodide under the conditions of entry 4 improved the product yield and diastereoselectivity (80% yield, **23**:**23′** = 6.6:1, entry 6). The two diastereomers were then readily separated by column chromatography.[17]

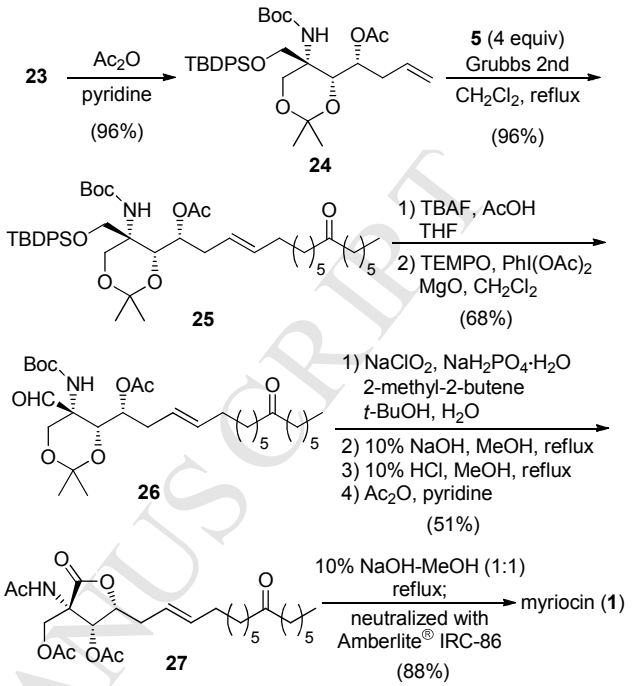
Table 3
Allylation of aldehyde **22** with allylmagnesium bromide, allyltributylstannane, and allylindium reagents



Entry	Conditions	Time (h)	Yield (%)[a]	**23**:**23′**
1	Allyl-MgBr, THF, –80 °C to rt	1.5	36	1:3.5
2	Allyl-MgBr, Et_2O, –80 °C to rt	overnight	69	1.6:1
3	Allyl-MgBr, MgI_2, Et_2O, 0 °C to rt	7	73	4.2:1
4	Allyl-$SnBu_3$, $MgBr_2$, CH_2Cl_2, –78 °C to rt	6	42	2.8:1
5	Allyl-Br, In, TBAI, DMF, rt	overnight	80	5.1:1
6	Allyl-Br, In, MgI_2, TBAI, DMF, rt	overnight	84	6.6:1

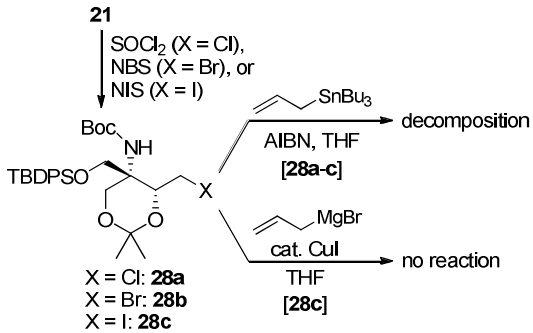
[a] The combined yield of **23** and **23′**.

The stage was now set for completion of the synthesis of myriocin (**1**, Scheme 5). After protection of the secondary hydroxy substituent in **23** as an acetoxy group, introduction of the long alkyl chain using Grubbs' cross metathesis chemistry was examined. According to the procedure reported by Shibasaki, Kumagai, and co-workers,[7h] alkenes **24** was treated with 4 equivalents of the known alkene **5**[11] in the presence of a catalytic amount of Grubbs' 1st generation catalyst in dichloromethane at reflux for 6 h. Unfortunately, the reaction did not occur at all and the starting **24** was recovered in 96% yield. To our delight, using more reactive Grubbs' 2nd generation catalyst in refluxing dichloromethane gave the good result and coupling product **25**, which has all carbons of the myriocin skeleton, was obtained in 96% yield after 5.5 h. Deprotection of TBDPS protecting group in **25** and subsequent oxidation of the resulting hydroxyl group with 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO), $PhI(OAc)_2$ and MgO afforded aldehyde **26**. Oxidation of **26** to the corresponding carboxylic acid and global deprotection by sequential alkaline and acidic hydrolyses produced crude myriocin (**1**). Since it was difficult to directly obtain **1** in high purity, the crude product was acetylated with acetic anhydride in pyridine to afford the known γ-lactone **27**: $[\alpha]_D^{18}$ +55.6 (*c* 1.0, $CHCl_3$) {lit.[6h] $[\alpha]_D^{23}$ +52.5 (*c* 0.85, $CHCl_3$)}. Finally, saponification of **27** followed by neutralization with Amberlite® IRC-86 furnished pure **1**. The synthetic material **1** exhibited spectroscopic data (^1H and ^{13}C NMR, and IR) consistent with those reported for natural product **1** and had its melting point (165–168 °C) and an optical rotation {$[\alpha]_D^{23}$ +5.6 (*c* 0.30, DMSO)} in good agreement with literature values {mp 164–168 °C,[3] $[\alpha]_D^{20}$ +6.1 (*c* 0.26, DMSO)[6h]}.



Scheme 5. Synthesis of myriocin (**1**).

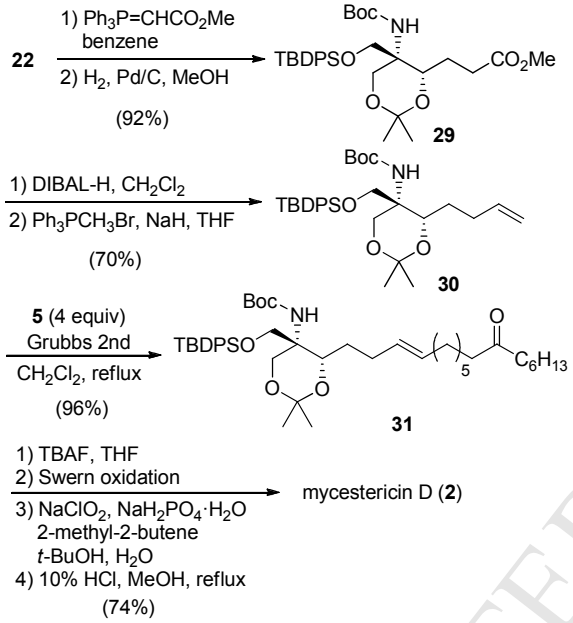
Next, the synthesis of mycestericin D (**2**) from the key intermediate alcohol **21** was investigated (Scheme 6). Initially, we examined a direct coupling of **21** with the allyl component. After conversion of **21** to halides **28a**–**c** by treatment with thionyl chloride (R = Cl: **28a**), *N*-bromosuccinimide (NBS, R = Br: **28b**), and *N*-iodosuccinimide (NIS, R = I: **28c**), their reaction with allyltributylstannane in the presence of azobisisobutyronitrile (AIBN) in THF gave decomposition products. Furthermore, we examined the copper-catalyzed cross-coupling reaction of alkyl iodide with allylmagnesium bromide.[18] However, the allylation did not proceed at all.



Scheme 6. Attempts to introduce an allyl group to alcohol **21**.

As cross-coupling reactions between alkyl halides and allylmetal reagents were difficult, we examined introduction of the C3 unit using a Wittig reaction with a key intermediate aldehyde **22** (Scheme 7). Wittig reaction of **22** using a stable ylide reagent followed by hydrogenation provided ester **29** in 92% yield. After reduction of the methyl ester to an aldehyde with diisobutylaluminum hydride (DIBAL-H), synthesis of

alkene **30** was achieved by conversion of the resulting aldehyde with an unstable ylide Wittig reagent. As we obtained the amino alkene component for mycestericin D (**2**), we finally investigated the completion of the total synthesis of **2**. The cross metathesis for the long side chain extension was conducted. The reaction between **30** and 4 equivalents of the alkene **5**[11] in the presence of Grubbs' 2nd generation catalyst in dichloromethane at reflux proceeded smoothly to afford coupling product **31** in 96% yield. Desilylation of the primary silyl ether in **31**, Swern oxidation of the resulting hydroxyl group, oxidation of the resulting aldehyde to the corresponding carboxylic acid, and global deprotection by acidic hydrolysis furnished pure mycestericin D (**2**). The synthetic compound **2** was spectroscopically (^{1}H and ^{13}C NMR, and IR) identical to natural **2**, and its melting point (164–166 °C) and optical rotation {$[\alpha]_D^{23}$ –7.48 (*c* 0.39, MeOH)} were in good agreement with literature values for the natural product {mp 162–167 °C,[5a] $[\alpha]_D$ –7.5 (*c* 0.16, MeOH)[5a]}.



Scheme 7. Synthesis of mycestericin D (**2**).

3. Conclusion

In summary, the total synthesis of myriocin and mycestericin D was achieved using Rh(II)-catalyzed C−H amination of a sulfamate followed by stereoselective alkylation as a key step. This synthesis is the first example of the construction of a quaternary chiral center using sequential Rh(II)-catalyzed C−H amination/alkylation reactions. As the quaternary chiral center can be easily and stereoselectively constructed and the long side chain can be introduced at a later stage in the synthesis, the present method would provide high flexibility for analogue synthesis. Thus, the synthesis of myriocin analogues, including sphingofungins, is currently in progress.

4. Experimental section

4.1. General

Melting points were determined using a Yanaco micro melting point apparatus and are uncorrected. Optical rotations were determined using a JASCO P-2100 polarimeter. Infrared (IR) spectra were recorded on a JASCO FT/IR-460 Plus spectrophotometer and absorbance bands are reported in wavenumber (cm^{-1}). ^{1}H NMR spectra were recorded on JEOL JNM-ECX400P (400 MHz) spectrometer. Chemical shifts are reported relative to internal standard (tetramethylsilane at δ_H 0.00 or $CDCl_3$ at δ_H 7.26). Data are presented as follows: chemical shift (δ, ppm), multiplicity (s = singlet, d = doublet, t = triplet, m = multiplet, br = broad), coupling constant and integration. ^{13}C NMR spectra were recorded on JEOL JNM-ECX400P (100 MHz) spectrometer. The following internal reference was used ($CDCl_3$ at δ 77.0). All ^{13}C NMR spectra were determined with complete proton decoupling. High-resolution mass spectra (HRMS) were determined with JEOL JMS-GCmate II and JEOL JMS-AX505HAD instruments. Column chromatography was performed on Silica Gel 60 PF_{254} (Nacalai Tesque) and Kanto silica gel 60 N (63–210 mesh) under pressure. Analytical thin layer chromatography (TLC) was carried out on Merck Kieselgel 60 F_{254} plates. Visualization was accomplished with UV light and phosphomolybdic acid stain solution followed by heating.

All reagents such as diethyl L-tartrate (**10**), chlorosulfonyl isocyanate and trimethylsilylacetylene are commercially available and were purchased from suppliers such as Sigma-Aldrich Co.; Wako Pure Chemical Industries, Ltd.; Tokyo Chemical Industry Co., Ltd.; Nacalai Tesque, INC. Dehydrated CH_2Cl_2, THF, MeOH, benzene, DMF, DMSO and pyridine were purchased from Wako Pure Chemical Industries, Ltd. (4*S*,5*S*)-[5-(*tert*-butyldiphenylsilyloxy)methyl-2,2-dimethyl-1,3-dioxolan-4-yl]methanol (**11**)[13] and petadec-1-en-9-one (**5**)[11] were prepared according to literature procedures.

4.2. Rh(II)-catalyzed C−H amination followed by alkylation

*4.2.1 (4S,5S)-5-(tert-Butyldiphenylsilyloxy)methyl-2,2-dimethyl-4-sulfamoyloxymethyl-1,3-dioxolane (**12**).* Formic acid (1.3 mL, 34.5 mmol) was added dropwise to neat chlorosulfonyl isocyanate (3.0 mL, 34.5 mmol) at 0 °C with rapid stirring. The resulting viscous suspension was stirred at 0 °C for 5 min. CH_2Cl_2 (20 mL) was added to the mixture and the solution was stirred at 0 °C for 20 minutes and then at room temperature overnight. The reaction mixture was cooled to 0 °C, and a solution of the known alcohol **11**[13] (7.0 g, 17.5 mmol) and pyridine (3.5 mL, 43.8 mmol) in CH_2Cl_2 (6 mL) was added via cannula. The reaction mixture was warmed to room temperature and stirred for 1 h. The reaction was quenched with EtOAc and H_2O. The organic phase was collected and the aqueous layer was extracted with EtOAc (2 x 30 mL). The combined organic extracts were washed with brine (20 mL), dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, 10% EtOAc in hexane) to provide **12** (7.29 g, 87%) as a colorless oil: $[\alpha]_D^{22}$ –9.3 (*c* 1.00, $CHCl_3$); IR (film, cm^{-1}) ν 3366, 3279, 1559, 1428, 1374, 1219, 1187; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68–7.64 (m, 4H), 7.47–7.38 (m, 6H), 4.92 (br s, 2H), 4.39 (m, 1H), 4.32–4.26 (m, 2H), 3,93 (ddd, *J* = 7.0, 5.4, 4.4 Hz, 1H), 3.85 (dd, *J* = 10.6, 4.4 Hz, 1H), 3.76 (dd, *J* = 10.6, 6.0 Hz, 1H), 1.43 (s, 3H), 1.40 (s, 3H), 1.07 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.50, 135.49, 132.72, 132.70, 129.88, 129.85, 127.79, 127.77, 110.2, 77.2, 76.6, 70.5, 63.7, 26.9, 26.8, 26.7, 19.1; HRMS (FAB) *m/z* calcd for $C_{23}H_{34}NO_6SSi$ $(M+H)^+$ 480.1876, found 480.1889.

*4.2.2. (4S,5S)-4-(tert-Butyldiphenylsilyloxy)methyl-(2,2-dimethyl-1,3-dioxolo)[4,5-d]tetrahydro-1,2,3-oxathiazine-2,2-dioxide (**13**).* $Rh_2(OAc)_4$ (270 mg, 0.611 mmol), $PhI(OAc)_2$ (5.39 g, 16.7 mmol) and MgO (1.41 g, 35.0 mmol) were added to a solution of sulfamate **12** (7.29 g, 15.2 mmol) in CH_2Cl_2 (96 mL). After stirring at room temperature for 1 h, the reaction mixture was filtered through a pad of Celite. The filter cake was rinsed with CH_2Cl_2, and the combined filtrates were concentrated in vacuo. The residue was purified by column chromatography (silica gel,

10% EtOAc in hexane) to provide **13** (6.11 g, 84%) as a white solid: mp 86–88 °C; $[\alpha]_D^{21}$ +12.9 (*c* 1.00, $CHCl_3$); IR (KBr, cm^{-1}) ν 3281, 1590, 1429, 1422, 1199, 1186; ^1H NMR (400 MHz, $CDCl_3$) δ 7.65 (d, *J* = 6.4 Hz, 4H), 7.47–7.39 (m, 6H), 4.62 (dd, *J* = 13.2, 1.2 Hz, 1H), 4.38 (s, 1H), 4.37 (dd, *J* = 13.2, 2.0 Hz, 1H), 4.29 (br s, 1H), 4.06 (d, *J* = 12.0 Hz, 1H), 3.90 (d, *J* = 12.0 Hz, 1H), 1.59 (s, 3H), 1.45 (s, 3H), 1.08 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.6, 132.21, 132.18, 130.2, 130.1, 128.0, 127.9, 110.8, 94.5, 69.0, 68.8, 63.5, 27.8, 26.9, 26.1, 19.2; HRMS (EI) *m/z* calcd for $C_{23}H_{31}NO_6SSi$ $(M)^+$ 477.1641, found 477.1627.

*4.2.3. (4R,5R)-4-(tert-Butyldiphenylsilyloxy)methyl-5-hydroxy-4-[2-(trimethylsilyl)ethynyl]tetrahydro-1,2,3-oxathiazin-2,2-dioxide (**14**).* *n*-butyllithium solution (1.05 mL, 1.6 M in hexane, 1.68 mmol) was added dropwise to a solution of trimethylsilylacetylene (0.25 mL, 1.76 mmol) in THF (0.55 mL) at –78 °C under nitrogen. After stirring for 20 minute, $ZnCl_2$ in THF (1.76 mL, 1.76 mmol) was added dropwise to the reaction mixture, and the resulting mixture was warmed to room temperature and stirred for 30 minutes. A solution of oxathiazinane *N*,*O*-acetal **13** (200 mg, 0.42 mmol) in THF (1.0 mL) was added to the reaction mixture via cannula at 0 °C. After addition of $BF_3 \cdot OEt_2$ (0.22 mL, 1.76 mmol), the reaction mixture was warmed to 50 °C and stirred for 2 h. The reaction was quenched with saturated $NaHCO_3$ and the whole mixture was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with water (10 mL) and brine (10 mL), and dried over anhydrous $MgSO_4$. Filtrate was concentrated in vacuo, and the residue was purified by column chromatography (silica gel, 10% EtOAc in hexane) to provide **14** (155 mg, 71%) as a white solid: mp 100–101 °C; $[\alpha]_D^{18}$ –28.9 (*c* 1.00, $CHCl_3$); IR (KBr, cm^{-1}) ν 3493, 3202, 2175; ^1H NMR (400 MHz, $CDCl_3$) δ 7.66–7.62 (m, 4H), 7.50–7.42 (m, 6H), 5.11 (s, 1H), 4.58 (t, *J* = 11.2 Hz, 1H), 4.37 (dd, *J* = 11.2, 4.4 Hz, 1H), 4.16 (ddd, *J* = 11.2, 10.6, 4.4 Hz, 1H), 3.95 (d, *J* = 10.2 Hz, 1H), 3.71 (d, *J* = 10.2 Hz, 1H), 1.63 (d, *J* = 10.6 Hz, 1H), 1.09 (s, 9H), 0.18 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.9, 135.8, 132.04, 132.02, 130.81, 130.80, 128.6, 128.5, 97.0, 77.2, 70.0, 65.0, 62.9, 62.2, 27.3, 19.7, 0.0; HRMS (FAB) *m/z* calcd for $C_{25}H_{36}NO_5SSi_2$ $(M+H)^+$ 518.1853, found 518.1881.

*4.2.4. (4R,5R)-4-(tert-Butyldiphenylsilyloxy)methyl-5-hydroxy-4-vinyltetrahydro-1,2,3-oxathiazin-2,2-dioxide (**15**).* $ZnCl_2$ (0.92 mL, 1.0 M in THF, 0.92 mmol) was added dropwise to a solution of vinylmagnesium bromide (1.76 mL, 1.0 M in THF, 1.76 mmol) at –78 °C under nitrogen, and the resulting mixture was warmed to room temperature and stirred for 0.5 h. The reaction mixture was then cooled to 0 °C, and a solution of **13** (200 mg, 0.42 mmol) in THF (1.0 mL) was added dropwise via cannula. After completion of the addition, the reaction mixture was allowed to warm to room temperature and stirred for 6 h, after which time it was quenched with saturated NH_4Cl and the whole mixture was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with water (10 mL) and brine (10 mL), and dried over anhydrous $MgSO_4$. Filtrate was concentrated in vacuo, and the residue was purified by column chromatography (silica gel, 10% EtOAc in hexane) to provide **15** (163 mg, 86%) as a white solid: mp 105–106 °C; $[\alpha]_D^{18}$ –17.2 (*c* 1.00, $CHCl_3$); IR (KBr, cm^{-1}) ν 3570, 3516, 3251, 1472, 1449, 1429, 1390, 1348, 1190, 1170, 1079, 986, 912; ^1H NMR (400 MHz, $CDCl_3$) δ 7.68–7.60 (m, 4H), 7.49–7.41 (m, 6H), 6.07 (dd, *J* = 17.8, 11.6 Hz, 1H), 5.50 (d, *J* = 17.8 Hz, 1H), 5.44 (d, *J* = 11.6 Hz, 1H), 5.07 (s, 1H), 4.40 (dd, *J* = 11.2, 9.6 Hz, 1H), 4.24 (dd, *J* = 11.2, 4.0 Hz, 1H), 4.15 (m, 1H), 3.80 (d, *J* = 10.8 Hz, 1H), 3.56 (d, *J* = 10.8 Hz, 1H), 1.11 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.6, 135.6, 132.1, 131.9, 131.1, 130.5, 130.4, 128.2, 128.1, 120.6, 70.1, 65.5, 65.4, 62.7, 27.0, 19.2; HRMS (EI) *m/z* calcd for $C_{22}H_{29}NO_5SSi$ $(M)^+$ 447.1536, found 447.1525.

*4.2.5. (4R,5R)-4-(tert-Butyldiphenylsilyloxy)methyl-5-(4-bromobenzoyloxy)-4-vinyltetrahydro-1,2,3-oxathiazin-2,2-dioxide (**16**).* *p*-Bromobenzoyl chloride (29 mg, 0.134 mmol), *N*,*N*-dimethyl-4-aminopyridine (DMAP, 1.6 mg, 0.0134 mmol) and pyridine (0.4 mL) were added to a solution of the alcohol **15** (30 mg, 0.067 mmol) in CH_2Cl_2 (0.5 mL) at 0 °C. After stirring for overnight at room temperature, the reaction was quenched with saturated NH_4Cl and the whole mixture was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with water (10 mL) and brine (10 mL), and dried over anhydrous $MgSO_4$. Filtrate was concentrated in vacuo, and the residue was purified by column chromatography (silica gel, 10% EtOAc in hexane) to provide **16** (27 mg, 64%) as a white solid: mp 175–176 °C (EtOAc/hexane); $[\alpha]_D^{26}$ –2.88 (*c* 0.5, $CHCl_3$); IR (KBr, cm^{-1}) ν 3238, 1725, 1591, 1426, 1353, 1263, 1201, 1012, 986; ^1H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, *J* = 8.8 Hz, 2H), 7.61 (d, *J* = 8.4 Hz, 4H), 7.52 (d, *J* = 8.4 Hz, 2H), 7.46-7.38 (m, 3H), 7.29 (m, 1H), 7.72 (t, *J* = 7.2 Hz, 2H), 6.12 (dd, *J* = 17.6, 11.6 Hz, 1H), 5.64 (dd, *J* = 6.0, 3.8 Hz, 1H), 5.53 (d, *J* = 17.6 Hz, 1H), 5.45 (d, *J* = 11.6 Hz, 1H), 5.10 (s, 1H), 4.50 (dd, *J* = 6.0, 3.8 Hz, 1H), 3.79 (d, *J* = 10.6 Hz, 1H), 3.69 (d, *J* = 10.6 Hz, 1H), 1.10 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.4, 135.51, 135.50, 132.6, 132.1, 131.8, 131.5, 131.2, 130.3, 130.1, 128.1, 127.8, 119.4, 68.0, 65.7, 65.1, 64.6, 26.9, 19.2; HRMS (FAB) *m/z* calcd for $C_{29}H_{32}BrNO_6SSi$ $(M+H)^+$ 630.0981, found 630.0934.

4.3. Synthesis of a common intermediate aldehyde 22

*4.3.1. (4R,5R)-5-Acetoxy-4-(tert-butyldiphenylsilyloxy)methyl-3-(1,1-dimethylethoxycarbonyl)-4-vinyltetrahydro-1,2,3-oxathiazin-2,2-dioxide (**17**).* Ac_2O (7.6 mL) was added to a solution of alcohol **15** (1.12 g, 2.50 mmol) in pyridine (7.6 mL) at room temperature. After stirring for 1 h, the solvent was removed in vacuo. The resulting residue was solved in EtOAc (50 mL) and washed with water (20 mL) and brine (20 mL), and dried over anhydrous $MgSO_4$. Filtration and evaporation in vacuo furnished the crude product (1.20 g), which was used in the next step without further purification.

Boc_2O (1.1 mL, 4.88 mmol), Et_3N (1.2 mL, 8.54 mmol) and DMAP (60 mg, 0.49 mmol) were added to a solution of the crude product in THF (23 mL) at room temperature. After stirring for 1 h, the reaction was quenched with saturated NH_4Cl and the whole mixture was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with water (20 mL) and brine (20 mL), and dried over anhydrous $MgSO_4$. Filtrate was concentrated in vacuo, and the residue was purified by column chromatography (silica gel, 10% EtOAc in hexane) to provide **17** (1.26 g, 84% for 2 steps) as a white solid: mp 123–124 °C; $[\alpha]_D^{18}$ +41.4 (*c* 1.00, $CHCl_3$); IR (KBr, cm^{-1}) ν 1762, 1739, 1389, 1370, 1227, 1181, 978, 935; ^1H NMR (400 MHz, $CDCl_3$) δ 7.63–7.58 (m, 4H), 7.44–7.34 (m, 6H), 5.75 (dd, *J* = 17.2, 10.6 Hz, 1H), 5.71 (dd, *J* = 8.0, 6.8 Hz, 1H), 5.59 (d, *J* = 17.2 Hz, 1H), 5.43 (d, *J* = 10.6 Hz 1H), 4.95 (dd, *J* = 10.8, 6.8 Hz, 1H), 4.54 (d, *J* = 10.8 Hz, 1H), 3.98 (dd, *J* = 10.8, 8.0 Hz, 1H), 3.72 (d, *J* = 10.8 Hz, 1H), 1.64 (s, 3H), 1.53 (s, 9H), 1.11 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.9, 149.5, 136.0, 135.7, 132.9, 132.4, 130.3, 130.0, 129.8, 127.8, 127.6, 119.3, 85.2, 71.9, 69.9, 65.5, 60.5, 27.8, 26.8, 20.1, 19.2; HRMS (EI) *m/z* calcd for $C_{29}H_{39}NO_8SSi$ $(M)^+$ 589.2166, found 589.2143.

*4.3.2. (2R,3R)-1-Acetoxy-3-(tert-butyldiphenylsilyloxy)methyl-3-(1,1-dimethylethoxycarbonyl)amino-4-penten-2-ol (**18**) and (2R,3R)-2-Acetoxy-3-(tert-butyldiphenylsilyloxy)methyl-3-(1,1-*

*dimethylethoxycarbonyl)amino-4-penten-1-ol (**18'**).* 0.1 M phosphate buffer (8.0 mL) was added to a solution of **17** (1.50 g, 2.5 mmol) in THF (39 mL). After stirring at 50 °C for 24 h, the reaction was quenched with 5% $NaHCO_3$ and the whole mixture was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with water (20 mL) and brine (20 mL), and dried over anhydrous $MgSO_4$. Filtrate was concentrated in vacuo, and the residue was purified by column chromatography (silica gel, 10% EtOAc in hexane) to provide **18** (982 mg, 73%) as a colorless oil and **18'** (313 mg, 23%) as a colorless oil. **18**: $[\alpha]_D^{16}$ –31.6 (*c* 1.00, $CHCl_3$); IR (film, cm^{-1}) ν 3410, 1740, 1731, 1697, 999, 920; ^1H NMR (400 MHz, $CDCl_3$) δ 7.62 (t, *J* = 6.0 Hz, 4H), 7.45–7.37 (m, 6H), 5.87 (dd, *J* = 17.2, 11.0 Hz, 1H), 5.32 (s, 1H), 5.30 (d, *J* = 11.0 Hz, 1H), 5.18 (d, *J* = 17.2 Hz, 1H), 4.80 (br s, 1H), 4.03 (dd, *J* =11.8, 7.8 Hz, 1H), 4.27 (dd, *J* = 11.8, 2.8 Hz, 1H), 3.86 (t, *J* = 7.8 Hz, 1H), 3.77 (d, *J* = 10.0 Hz, 1H) 3.70 (d, *J* = 10.0 Hz, 1H), 2.02 (s, 3H), 1.45 (s, 9H), 1.07 (s, 9H) ; ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.9, 156.3, 136.7, 135.5, 135.4, 132.3, 132.1, 129.9, 127.8, 127.7, 80.3, 72.5, 66.2, 65.9, 63.4, 60.2, 28.1, 26.7, 20.9, 20.8, 19.1; HRMS (EI) *m/z* calcd for $C_{29}H_{41}NO_6SSi$ $(M)^+$ 527.2703, found 527.2705. **18'**: $[\alpha]_D^{26}$ +22.1 (*c* 0.5, $CHCl_3$); IR (film, cm^{-1}) ν 3425, 3361, 1739, 1724, 1495, 1042, 925; ^1H NMR (400 MHz, $CDCl_3$) δ 7.64–7.60 (m, 4H), 7.45–7.37 (m, 6H), 6.04 (dd, *J* = 17.7, 11.0 Hz, 1H), 5.39 (s, 1H), 5.40 (d, *J* = 11.0 Hz, 1H), 5.180 (t, *J* = 3.2 Hz, 1H), 5.177 (d, *J* = 17.7 Hz, 1H), 3.87 (m, 1H), 3.80 (d, *J* = 10.2 Hz, 1H), 3.78 (m, 1H), 3.62 (d, *J* = 10.2 Hz, 1H), 1.96 (s, 3H), 1.44 (s, 9H), 1.09 (s, 9H) ; ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.3, 155.0, 135.7, 135.6, 132.6, 132.5, 129.94, 129.90, 127.9, 127.8, 116.0, 80.0, 77.2, 74.7, 65.8, 61.9, 61.5, 28.3, 26.8, 21.0, 19.2; HRMS (FAB) *m/z* calcd for $C_{29}H_{41}NO_6SSi$ $(M+H)^+$ 527.2781, found 527.2748.

*4.3.3. (2R,3R)-3-(tert-Butyldiphenylsilyloxy)methyl-2-(2-chloro)acetoxy-3-(1,1-dimethylethoxycarbonyl)amino-4-pentenyl acetate (**19**).* A solution of chloroacetyl chloride (122 mg, 1.08 mmol) in CH_2Cl_2 (1.0 mL) and pyridine (0.77 mL) were added to a solution of alcohol **18** (284 mg, 0.538 mmol) in CH_2Cl_2 (1.6 mL) at 0 °C. After stirring at room temperature for 1 h, the reaction was quenched with 5% $NaHCO_3$ and the whole mixture was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with water (10 mL) and brine (10 mL), and dried over anhydrous $MgSO_4$. Filtrate was concentrated in vacuo, and the residue was purified by column chromatography (silica gel, 10% EtOAc in hexane) to provide **19** (239 mg, 73%) as a colorless oil: $[\alpha]_D^{25}$ –1.0 (*c* 1.00, $CHCl_3$); IR (film, cm^{-1}) ν 3430, 1772, 1747, 1729, 1699, 1008, 956; ^1H NMR (400 MHz, $CDCl_3$) δ 7.62 (d, *J* = 6.4 Hz, 4H), 7.44–7.36 (m, 6H), 5.93 (dd, *J* = 17.8, 11.2 Hz, 1H), 5.75 (dd, *J* = 8.2, 2.2 Hz, 1H), 5.30 (d, *J* = 11.2 Hz, 1H), 5.25 (d, *J* = 17.8 Hz, 1H), 5.06 (s, 1H), 4.53 (dd, *J* = 12.4, 2.2 Hz, 1H), 4.11 (dd, *J* = 12.4, 8.2 Hz, 1H), 3.97 (d, *J* = 10.0 Hz, 1H), 3.87 (d, *J* = 14.4 Hz, 1H), 3.84 (d, *J* = 10.0 Hz, 1H), 3.80 (d, *J* = 14.4 Hz, 1H), 2.01 (s, 3H), 1.43 (s, 9H), 1.08 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.6 165.9, 154.3, 135.6, 134.9, 132.5, 129.79, 129.76, 127.7, 127.6, 116.5, 79.8, 76.7, 73.4, 63.8, 63.0, 61.6, 40.4, 28.2, 26.7, 20.6, 19.1; HRMS (FAB) *m/z* calcd for $C_{31}H_{43}NO_7SSi$ $(M+H)^+$ 604.2497, found 604.2521.

*4.3.4. (2R,3R)-4-Acetoxy-2-(tert-butyldiphenylsilyloxy)methyl-2-(1,1-dimethylethoxycarbonyl)aminobutane-1,3-diol (**20**).* Ozone was bubbling to a solution of **19** (1.13 g, 1.86 mmol) in CH_2Cl_2 (25 mL) and MeOH (25 mL) at –78 °C. After stirring for 15 min, $NaBH_4$ (105 mg, 2.79 mmol) was added to the reaction mixture at –78 °C. After stirring at room temperature for 1 h, the reaction was quenched with acetone, and the solvent was removed in vacuo. The resulting residue was solved with EtOAc (40 mL), and washed with water (15 mL) and brine (15 mL), and dried over anhydrous $MgSO_4$. Filtrate was concentrated in vacuo, and the residue was purified by column chromatography (silica gel, 10% EtOAc in hexane) to provide **20** (817 mg, 82%) as a white solid: mp 100–101 °C; $[\alpha]_D^{21}$ –21.9 (*c* 1.00, $CHCl_3$); IR (KBr, cm^{-1}) ν 3450, 3320, 1719, 1677; ^1H NMR (400 MHz, $CDCl_3$) δ 7.64 (d, *J* = 7.2 Hz, 4H), 7.48–7.39 (m, 6H), 5.30 (s, 1H), 4.88 (d, *J* = 8.2 Hz, 1H), 4.20 (dd, *J* = 12.0, 2.8 Hz, 1H), 4.07 (dd, *J* = 12.0, 8.2 Hz, 1H), 3.99 (dd, *J* = 11.6, 4.8 Hz, 1H), 3.88 (d, *J* = 9.8 Hz, 1H), 3.80 (m, 1H), 3.74 (t, *J* = 11.6 Hz, 1H), 3.65 (d, *J* = 9.8 Hz, 1H), 2.94 (m, 1H), 2.01 (s, 3H), 1.44 (s, 9H), 1.09 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.0, 157.0, 135.53, 135.51, 132.3, 132.2, 130.1, 128.0, 127.9, 80.9, 71.1, 66.1, 63.4, 61.6, 61.5, 28.2, 26.8, 20.9, 19.3; HRMS (EI) *m/z* calcd for $C_{28}H_{41}NO_7SSi$ $(M)^+$ 531.2652, found 531.2666.

*4.3.5. (4R,5R)-4-Acetoxymethyl-5-(tert-butyldiphenylsilyloxy)methyl-2,2-dimethyl-5-(1,1-dimethylethoxycarbonyl)amino-1,3-dioxane (**32**).* 2,2-Dimethoxypropane (0.82 mL, 6.7 mmol) and $TsOH{\cdot}H_2O$ (13 mg, 0.067 mmol) were added to a solution of diol **20** (358 mg, 0.67 mmol) in benzene (20 mL) at room temperature. After stirring for 1 h, the reaction was quenched with 5% $NaHCO_3$ and the whole mixture was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with water (10 mL) and brine (10 mL), and dried over anhydrous $MgSO_4$. Filtrate was concentrated in vacuo, and the residue was purified by column chromatography (silica gel, 10% EtOAc in hexane) to provide **32** (359 mg, 94%) as a colorless oil: $[\alpha]_D^{18}$ +10.6 (*c* 1.00, $CHCl_3$); IR (film, cm^{-1}) ν 3430, 1745, 1723; ^1H NMR (400 MHz, $CDCl_3$) δ 7.63 (d, *J* = 7.2 Hz, 4H), 7.45–7.37 (m, 6H), 5.12 (s, 1H), 4.46 (dd, *J* = 7.2, 2.4 Hz, 1H), 4.30 (dd, *J* = 12.4, 2.4 Hz, 1H), 4.21 (br s, 1H), 4.06 (dd, *J* = 12.4, 7.2 Hz, 1H), 4.05 (d, *J* = 10.4 Hz, 1H), 3.95 (m, 1H), 3.89 (d, *J* = 10.4 Hz, 1H), 1.48 (s, 3H), 1.37 (s, 9H), 1.08 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.6, 155.0, 135.6, 135.5, 132.62, 132.60, 130.0, 129.9, 127.8, 99.2, 79.4, 70.9, 64.0, 63.5, 63.2, 54.9, 28.8, 28.2, 26.8, 20.8, 19.2, 19.1; HRMS (EI) *m/z* calcd for $C_{31}H_{45}NO_7SSi$ $(M)^+$ 571.2965, found 571.2923.

*4.3.6. (4R,5R)-5-(tert-Butyldiphenylsilyloxy)methyl-2,2-dimethyl-5-(1,1-dimethylethoxycarbonyl)amino-4-hydroxymethyl-1,3-dioxane (**21**).* K_2CO_3 (179 mg, 1.3 mmol) was added to a solution of **32** (620 mg, 1.08 mmol) in MeOH (7.7 mL) at room temperature. After stirring for 1 h, the reaction was quenched with water and the whole mixture was extracted with EtOAc (3 x 15 mL). The combined organic layers were washed with brine (15 mL), and dried over anhydrous $MgSO_4$. Filtrate was concentrated in vacuo, and the residue was purified by column chromatography (silica gel, 10% EtOAc in hexane) to provide **21** (565 mg, 98%) as a colorless oil: $[\alpha]_D^{18}$ +2.5 (*c* 1.00, $CHCl_3$); IR (film, cm^{-1}) ν 3430, 3373, 1712, 1506; ^1H NMR (400 MHz, $CDCl_3$) δ 7.65–7.62 (m. 4H), 7.45–7.36 (m, 6H), 5.54 (s, 1H), 4.21 (d, *J* = 10.0 Hz, 1H), 4.12 (d, *J* = 6.8 Hz, 1H), 4.01 (br s, 2H), 3.83 (d, *J* = 11.2 Hz, 1H), 3.70–3.63 (m, 2H), 2.67 (br s, 1H), 1.44 (s, 3H), 1.43 (s, 3H), 1.39 (s, 9H), 1.07 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.5, 135.61, 135.57, 132.8, 129.9, 129.8, 127.8, 99.1, 79.4, 72.0, 64.3, 63.0, 61.6, 55.8, 28.4, 28.3, 26.9, 19.6, 19.3; HRMS (EI) *m/z* calcd for $C_{29}H_{43}NO_6SSi$ $(M)^+$ 529.2860, found 529.2805.

*4.3.7. (4R,5R)-5-(tert-Butyldiphenylsilyloxy)methyl-2,2-dimethyl-5-(1,1-dimethylethoxycarbonyl)amino-4-formyl-1,3-dioxane (**22**).* A solution of DMSO (0.15 mL, 2.13 mmol) in CH_2Cl_2 (1.5 mL) was added dropwise to a solution of oxalyl chloride (0.12 mL, 1.42 mmol) in CH_2Cl_2 (1.5 mL) at –78 °C and stirred for 5 min. A solution of alcohol **21** (376 mg, 0.71 mmol) in CH_2Cl_2 (4.4 mL) was added dropwise to the reaction mixture and stirred for

20 min. Et_3N (0.50 mL, 3.55 mmol) was added dropwise to the reaction mixture and stirred at –78 °C for 2.5 h, and the reaction mixture was allowed to warm to room temperature and stirred for 30 min. The reaction was quenched with saturated NH_4Cl and the whole mixture was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were washed with water (10 mL) and brine (10 mL), and dried over anhydrous $MgSO_4$. Filtrate was concentrated in vacuo, and the residue was purified by column chromatography (silica gel, 10% EtOAc in hexane) to provide **22** (361 mg, 96%) as a colorless oil: $[\alpha]_D^{19}$ –6.3 (*c* 1.00, $CHCl_3$); IR (film, cm^{-1}) ν 3422, 1733, 1714, 1502; ^1H NMR (400 MHz, $CDCl_3$) δ 9.52 (s, 1H), 7.68–7.63 (m, 4H), 7.47–7.38 (m, 6H), 5.12 (s, 1H), 4.56 (s, 1H), 4.20 (d, *J* = 11.0 Hz, 1H), 4.09 (d, *J* = 12.0 Hz, 1H), 4.04 (d, *J* = 10.4 Hz, 1H), 3.84 (d, *J* = 11.0 Hz, 1H), 1.52 (s, 3H), 1.44 (s, 3H), 1.36 (s, 9H), 1.09 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.1, 154.9, 135.6, 135.5, 132.5, 132.4, 130.02, 129.97, 127.9, 99.7, 76.4, 63.9, 62.9, 60.3, 56.1, 28.3, 28.2, 26.8, 21.0, 19.2; HRMS (EI) *m/z* calcd for $C_{29}H_{41}NO_6SSi$ $(M)^+$ 527.2703, found 527.2692.

4.4. Total synthesis of myriocin (1)

4.4.1. [1R,1(4R,5R)]-1-[5-(tert-Butyldiphenylsilyloxy)methyl-2,2-dimethyl-5-(1,1-dimethylethoxycarbonyl)amino-1,3-dioxane-4-yl]-3-butene-1-ol ***(23)*** *[1S,1(4R,5R)]-1-[5-(tert-Butyldiphenylsilyloxy)methyl-2,2-dimethyl-5-(1,1-dimethylethoxycarbonyl)amino-1,3-dioxane-4-yl]-3-butene-1-ol* ***(23')***. MgI_2 (37 mg, 0.13 mmol) was added to a solution of aldehyde **22** (35 mg, 0.066 mmol) in DMF (1.0 mL) at room temperature and stirred for 30 min. Indium (11 mg, 0.099 mmol), a solution of allyl bromide (16 mg, 0.13 mmol) in DMF (1.0 mL), and tetrabutylammonium iodide (TBAI, 24 mg, 0.066 mmol) were added to the reaction mixture. After stirring overnight, the reaction was quenched with saturated NH_4Cl and the whole mixture was extracted with Et_2O (3 x 10 mL). The combined organic layers were washed with water (10 mL) and brine (10 mL), and dried over anhydrous $MgSO_4$. Filtrate was concentrated in vacuo, and the residue was purified by column chromatography (silica gel, 10% EtOAc in hexane) to provide **23** (27 mg, 73%) and **23'** (4 mg, 11%) as a colorless oil. **23**: $[\alpha]_D^{15}$ +17.5 (*c* 1.00, $CHCl_3$); IR (film, cm^{-1}) ν 3553, 3377, 3073, 1710, 1511; ^1H NMR (400 MHz, $CDCl_3$) δ 7.64–7.61 (m, 4H), 7.43–7.36 (m, 6H), 6.66 (s, 1H), 5.71 (m, 1H), 5.09 (d, *J* = 17.9 Hz, 1H), 5.08 (d, *J* = 10.0 Hz, 1H), 4.25 (d, *J* = 10.8 Hz, 1H), 4.06 (ddd, *J* = 9.9, 8.0, 6.0 Hz, 1H), 3.99 (s, 2H), 3.97 (d, *J* = 9.8 Hz, 1H), 3.89 (d, *J* = 10.8 Hz, 1H), 2.37 (m, 1H), 2.34 (d, *J* = 9.8 Hz, 1H), 2.19 (m, 1H), 1.44 (s, 3H), 1.42 (s, 3H), 1.37 (s, 9H), 1.07 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.2, 135.6, 135.5, 134.1, 132.8, 132.7, 129.9, 129.8, 127.8, 127.7, 118.0, 99.5, 78.9, 70.9, 68.9, 63.9, 63.4, 57.1, 40.1, 28.4, 27.0, 26.9, 20.8, 19.2; HRMS (FAB) *m/z* calcd for $C_{32}H_{47}NO_6SSi$ $(M+H)^+$ 570.3251, found 570.3216. **23'**: $[\alpha]_D^{23}$ –2.50 (*c* 0.5, $CHCl_3$); IR (film, cm^{-1}) ν 3432, 3073, 1695, 1506; ^1H NMR (400 MHz, $CDCl_3$) δ 7.67–7.64 (m, 4H), 7.45–7.34 (m, 6H), 5.90 (m, 1H), 5.30 (s, 1H), 5.07 (d, *J* = 17.6 Hz, 1H), 5.06 (d, *J* = 10.0 Hz, 1H), 4.69 (br s, 1H), 4.53 (d, *J* = 10.6 Hz, 1H), 3.90 (s, 2H), 3.79 (d, *J* = 10.6 Hz, 1H), 3.65–3.57 (m, 2H), 2.48–2.44 (m, 2H), 2.15 (ddd, *J* = 13.6, 12.3, 10.2 Hz, 1H), 1.42 (s, 3H), 1.40 (s, 3H), 1.36 (s, 9H), 1.05 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.5, 135.6, 135.1, 132.9, 132.8, 129.8, 129.7, 127.7, 127.6, 117.0, 98.8, 79.9, 74.6, 70.0, 66.8, 63.0, 56.7, 37.7, 28.34, 28.29, 26.8, 19.3; HRMS (FAB) *m/z* calcd for $C_{32}H_{48}NO_6SSi$ $(M+H)^+$ 570.3251, found 570.3267.

4.4.2. [1R,1(4R,5R)]-1-[5-(tert-Butyldiphenylsilyloxy)methyl-2,2-dimethyl-5-(1,1-dimethylethoxycarbonyl)amino-1,3-dioxane-4-yl]-3-butenyl acetate ***(24)***. Ac_2O (4 mL) was added to a solution of **23** (408 mg, 0.71 mmol) in pyridine (4 mL) at room temperature. After stirring overnight, the solvent was removed in vacuo. The resulting residue was solved with EtOAc (20 mL), and washed water (10 mL) and brine (10 mL), and dried over anhydrous $MgSO_4$. Filtrate was concentrated in vacuo, and the residue was purified by column chromatography (silica gel, 10% EtOAc in hexane) to provide **24** (417 mg, 96%) as a colorless oil: $[\alpha]_D^{21}$ +50.0 (*c* 0.50, $CHCl_3$); IR (film, cm^{-1}) ν 3441, 3074, 3051, 1748, 1722, 1496; ^1H NMR (400 MHz, $CDCl_3$) δ 7.67–7.61 (m, 4H), 7,47–7.36 (m, 6H), 5.64 (br s, 1H), 5.48 (br s, 1H), 5.39 (br s, 1H), 5.11 (d, *J* = 17.6 Hz, 1H), 5.06 (d, *J* = 10.0 Hz, 1H), 4.41 (s, 1H), 4.30 (d, *J* = 10.8 Hz, 1H), 4.16 (m, 1H), 4.00 (d, *J* = 10.8 Hz, 1H), 3.84 (d, *J* = 10.8 Hz, 1H), 2.39 (t, *J* = 6.4 Hz, 2H), 2.08 (s, 3H), 1.50 (s, 3H), 1.46 (s, 3H), 1.34 (s, 9H), 1.08 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.0, 154.7, 135.6, 135.5, 133.2, 132.7, 129.9, 127.82, 127.81, 118.5, 99.4, 78.9, 70.2, 70.0, 63.5, 62.9, 55.6, 44.3, 36.1, 29.2, 28.3, 27.0, 21.0, 19.2, 18.8; HRMS (EI) *m/z* calcd for $C_{34}H_{49}NO_7SSi$ $(M)^+$ 611.3278, found 611.3238.

4.4.3. [1R,1(4R,5R),3E]-1-Acetoxy-1-[5-(tert-butyldiphenylsilyloxy)methyl-2,2-dimethyl-5-(1,1-dimethylethoxycarbonyl)amino-1,3-dioxane-4-yl]heptadec-3-en-11-one ***(25)***. Pentadec-1-en-9-one (**5**,[11] 88 mg, 0.42 mmol) and second generation Grubbs catalyst (4.5 mg, 0.0053 mmol) were added to a solution of alkene **24** (64 mg, 0.11 mmol) in CH_2Cl_2 (3.3 mL). After stirring at reflux for 5.5 h, the solvent was removed in vacuo. The resulting residue was purified by column chromatography (silica gel, 5% EtOAc in hexane) to provide **25** (81 mg, 96%) as a colorless oil: $[\alpha]_D^{13}$ +33.5 (*c* 1.00, $CHCl_3$); IR (film, cm^{-1}) ν 3450, 3073, 1745, 1718, 1499; ^1H NMR (400 MHz, $CDCl_3$) δ 7.67–7.62 (m, 4H), 7.45–7.36 (m, 6H), 5.49 (br s, 2H), 5.37 (br s, 1H), 5.26 (br s, 1H), 4.40 (s, 1H), 4.28 (d, *J* = 10.0 Hz, 1H), 4.17 (m, 1H), 4.00 (d, *J* = 11.2 Hz, 1H), 3.83 (d, *J* = 10.0 Hz, 1H), 2.38 (t, *J* = 7.6 Hz, 4H), 2.33 (m, 1H), 2.07 (br s, 3H), 1.93 (d, *J* = 5.6 Hz, 2H), 1.55 (dd, *J* = 14.4, 7.2 Hz, 2H), 1.55 (m, 1H), 1.50 (s, 3H), 1.46 (s, 3H), 1.33 (s, 9H), 1.20 (br s, 11H), 1.08 (s, 9H), 0.88 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.5, 169.9, 154.6, 150.0, 135.5, 134.7, 132.7, 129.9, 127.8, 124.3, 124.2, 99.4, 78.8, 70.5, 70.1, 63.4, 62.9, 55.7, 49.3, 42.8, 34.9, 32.5, 31.6, 29.2, 29.1, 28.9, 26.9, 23.82, 23.76, 23.6, 22.5, 21.1, 19.2, 18.8, 14.0; HRMS (FAB) *m/z* calcd for $C_{47}H_{74}NO_7SSi$ $(M+H)^+$ 808.5184, found 808.5166.

4.4.4. [1R,1(4R,5S),3E]-1-Acetoxy-1-[2,2-dimethyl-5-(1,1-dimethylethoxycarbonyl)amino-5-hydroxymethyl-1,3-dioxane-4-yl]heptadec-3-en-11-one ***(33)***. Tetrabutylammonium fluoride (TBAF, 0.14 mL, 1 M in THF, 0.14 mmol) and a solution of acetic acid (8 mg, 0.14 mmol) in THF (0.2 mL) were added to a solution of **25** (37 mg, 0.046 mmol) in THF (0.24 mL) at 0 °C. After stirring at 50 °C for 24 h, the reaction was quenched with water and the whole mixture was extracted with EtOAc (3 x 5 mL). The combined organic layers were washed with water (5 mL) and brine (5 mL), and dried over anhydrous $MgSO_4$. Filtrate was concentrated in vacuo, and the residue was purified by column chromatography (silica gel, 10% EtOAc in hexane) to provide **33** (22 mg, 84%) as a colorless oil: $[\alpha]_D^{13}$ +56.6 (*c* 1.00, $CHCl_3$); IR (film, cm^{-1}) ν 3438, 1744, 1711, 1701; ^1H NMR (400 MHz, $CDCl_3$) δ 5.61 (s, 1H), 5.50 (dt, *J* = 15.2, 6.8 Hz, 1H), 5.26 (dt, *J* = 15.2, 6.8 Hz, 1H), 5.02 (t, *J* = 6.8 Hz, 1H), 4.75 (d, *J* = 9.6 Hz, 1H), 4.08 (d, *J* = 12.4 Hz, 1H), 4.00 (d, *J* = 12.0 Hz, 1H), 3.75 (d, *J* =12.4 Hz, 1H), 3.75 (d, *J* =12.0 Hz, 1H), 3.45 (t, *J* = 10.8 Hz, 1H), 2.39 (t, *J* = 7.2 Hz, 4H), 2.30–2.26 (m, 2H), 2.10 (s, 3H), 2.01–1.95 (m, 2H), 1.57–1.54 (m, 3H), 1.52 (s, 3H), 1.43 (s, 12H), 1.27 (br s, 12H), 0.88 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.5, 169.9, 156.4, 135.2, 123.9, 99.6,

80.0, 72.6, 69.9, 64.7, 64.6, 55.7, 42.8, 42.6, 34.5, 32.4, 31.5, 29.1, 28.95, 28.95, 28.7, 28.3, 23.8, 23.5, 22.4, 21.0, 18.3, 14.0; HRMS (EI) *m/z* calcd for $C_{31}H_{55}NO_8$ $(M)^+$ 569.3928, found 569.3979.

*4.4.5. [1R,1(4R,5S),3E]-1-Acetoxy-1-[2,2-dimethyl-5-(1,1-dimethylethoxycarbonyl)amino-5-formyl-1,3-dioxane-4-yl]heptadec-3-en-11-one (**26**).* TEMPO (3.8 mg, 0.024 mmol), $PhI(OAc)_2$ (51 mg, 0.16 mmol) and MgO (13 mg, 0.32 mmol) were added to a solution of alcohol **33** (45 mg, 0.079 mmol) in CH_2Cl_2 (1.8 mL). After stirring at room temperature overnight, the reaction mixture was filtered through a pad of Celite. The filter cake was rinsed with EtOAc and the combined filtrate was concentrated in vacuo. The resulting residue was purified by column chromatography (silica gel, 10% EtOAc in hexane) to provide **26** (36 mg, 81%) as a colorless oil: $[\alpha]_D^{25}$ +46.7 (*c* 1.00, $CHCl_3$); IR (film, cm^{-1}) ν 3456, 1746, 1723, 1717; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.67 (s, 1H), 5.65 (s, 1H), 5.47 (dt, *J* = 15.2, 6.8 Hz, 1H), 5.20 (dt, *J* = 15.2, 6.8 Hz, 1H), 5.02 (td, *J* = 7.2, 2.0 Hz, 1H), 4.15 (d, *J* = 12.4 Hz, 1H), 4.01 (d, *J* = 12.4 Hz, 1H), 3.95 (d, *J* = 2.0 Hz, 1H), 2.39 (t, *J* = 7.2 Hz, 4H), 2.34–2.26 (m, 2H), 2.13 (s, 3H), 2.00–1.93 (m, 2H), 1.57–1.52 (m, 3H), 1.50 (s, 3H), 1.46 (s, 12 H), 1.32–1.26 (m, 12 H), 0.88 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.5, 200.8, 170.0, 155.3, 135.2, 123.5, 99.9, 80.7, 72.1, 71.0, 63.4, 63.0, 42.7, 42.6, 34.2, 32.2, 31.5, 29.02, 28.98, 28.8, 28.6, 28.2, 23.8, 23.5, 22.4, 20.1, 18.2, 14.0; HRMS (FAB) *m/z* calcd for $C_{31}H_{54}NO_8$ $(M+H)^+$ 568.3849, found 568.3842.

*4.4.6. (2S,3R,4R)-2-Acetamido-3-acetoxy-2-acetoxymethyl-4-[(E)-10-oxohexadec-2-en-1-yl]-4-butanolide (**27**).*[6i,k,l,o] A solution of $NaClO_2$ (29 mg, 0.32 mmol) and $NaH_2PO_4{\cdot}H_2O$ (22 mg, 0.16 mmol) in water (0.45 mL) was added to a solution of **26** (45 mg, 0.0793 mmol) and 2-methyl-2-butene (0.21 ml) in *t*-BuOH (1.4 mL). After stirring at room temperature for 3 h, the reaction was quenched with H_2O and the whole mixture was extracted with EtOAc (3 x 5 mL). The combined organic layers were washed with brine (10 mL), and dried over anhydrous $MgSO_4$. Filtrate was concentrated in vacuo to provide the crude carboxylic acid (45 mg), which was used in the next step without further purification.

10% NaOH (0.63 mL) was added to a solution of the crude carboxylic acid in MeOH (0.63 mL). After stirring at 70 °C overnight, the reaction mixture was acidified to pH 3 with 10 % HCl, and extracted with EtOAc (3 x 5 mL). The combined organic layers were washed with brine (5 mL), and dried over anhydrous $MgSO_4$. Filtrate was concentrated in vacuo to provide the crude alcohol (50 mg), which was used in the next step without further purification.

10% HCl (0.63 mL) was added to a solution of the crude alcohol in MeOH (0.63 mL). After stirring at 80°C overnight, the reaction mixture was alkalified with K_2CO_3. Insoluble materials were filtered off, and the filtrate was concentrated in vacuo to provide the crude product (90 mg), which was used in the next step without further purification.

Ac_2O (0.63 mL, 6.7 mmol) was added to a solution of the crude product in pyridine (0.63 mL). After stirring at room temperature overnight, the solvent was removed in vacuo. The resulting residue was solved with EtOAc (10 mL), and washed with water (5 mL) and brine (5 mL), and dried over anhydrous $MgSO_4$. Filtrate was concentrated in vacuo, and the residue was purified by column chromatography (silica gel, 40% EtOAc in hexane) to provide **27** (20 mg, 51% for 4 steps) as a colorless oil: $[\alpha]_D^{18}$ +55.6 (*c* 1.00, $CHCl_3$) {lit.[6h] $[\alpha]_D^{23}$ +52.5 (*c* 0.85, $CHCl_3$)}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.30 (s, 1H), 5.79 (d, *J* = 4.0 Hz, 1H), 5.56 (dt, *J* = 15.2, 6.8 Hz, 1H), 5.39 (dt , *J* = 15.2, 6.4 Hz, 1H), 4.72 (dt, *J* = 8.4, 4.8 Hz, 1H), 4.52 (s 2H), 2.38 (t, *J* = 7.2 Hz, 4H), 2.46–2.36 (m, 2H), 2.10 (s, 3H), 2.05 (s, 3H), 2.03 (s, 3H), 2.07–1.98 (m, 2H), 1.59–1.52 (m, 4H), 1.37–1.27 (m, 12H), 0.88 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.7, 172.4, 170.2, 169.4, 168.9, 135.0, 123.1, 81.6, 71.9, 62.62, 62.57, 42.8, 42.7, 32.4, 32.1, 31.6, 29.0, 28.93, 28.90, 28.86, 23.80, 23.76, 22.7, 22.5, 20.6, 20.3, 14.0.

*4.4.7. Myriocin (**1**).* 10% NaOH (1.3 mL) was added to **27** (20 mg, 0.039 mmol) in MeOH (1.3 mL) and stirring at 80 °C for 2 h. The reaction mixture was cooled to 0 °C, and then neutralized with Amberlite® IRC-86 (H^+ type). The insoluble material was removed by filtration and the filtrate was concentrated in vacuo. The resulting residue was purified by column chromatography (1:1:10 to 1:3:10 (gradient) H_2O/MeOH/$CHCl_3$ (lower phase)) to afford myriocin (**1**, 14 mg, 88%) as white crystals: mp 165–168 °C (lit.[3] mp 164–168 °C); $[\alpha]_D^{23}$ +5.6 (*c* 0.30, DMSO) {lit.[6h] $[\alpha]_D^{20}$ +6.1 (*c* 0.26, DMSO)}; IR (KBr, cm^{-1}) ν 3278, 3203, 1714, 1635, 1465, 1387, 1104, 970; ^{1}H NMR (400 MHz, CD_3OD) δ 5.54 (dt, *J* = 16.4, 6.4 Hz, 1H), 5.40 (dt, *J* = 14.8, 7.2 Hz, 1H), 4.00 (d, *J* = 11.2 Hz, 1H), 3.87 (d, *J* = 11.6 Hz, 1H), 3.83 (t, *J* = 5.6 Hz, 1H), 3.81 (s, 1H), 2.43 (t, *J* = 7.2 Hz, 4H), 2.27 (t, *J* = 6.8 Hz, 2 H), 2.00 (dd, *J* = 14.0, 7.2 Hz, 2H), 1.55 (t, *J* = 6.8 Hz, 4H), 1.29 (br s, 12H), 0.90 (t, *J* = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ 214.4, 173.5, 134.7, 126.9, 73.7, 71.3, 70.4, 65.1, 43.54, 43.53, 38.7, 33.8, 32.9, 30.5, 30.23, 30.16, 30.1, 30.0, 24.9, 23.6, 14.4.

4.5. Total synthesis of mycestericin D (2)

*4.5.1. Methyl [1(4R,5R),2E]-3-[5-(tert-butyldiphenylsilyloxy)methyl-2,2-dimethyl-5-(1,1-dimethylethoxycarbonyl)amino-1,3-dioxane-4-yl]-2-butenoate (**34**).* $Ph_3PCH{=}CO_2Me$ (257 mg, 0.77 mmol) was added to a solution of aldehyde **22** (369 mg, 0.70 mmol) in benzene (6.7 mL) at room temperature. After stirring 1 h, the solvent was removed in vacuo. The resulting residue was purified by column chromatography (silica gel, 10% EtOAc in hexane) to provide **34** (392 mg, 96%) as a colorless oil: $[\alpha]_D^{22}$ +17.8 (*c* 1.00, $CHCl_3$); IR (film, cm^{-1}) ν 3431, 3073, 1723, 1716, 1495; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66–7.63 (m, 4H), 7.47–7.38 (m, 6H), 6.93 (dd, *J* = 15.8, 2.5 Hz, 1H), 6.17 (dd, *J* = 15.8, 2.5 Hz, 1H), 5.00 (s, 1H), 4.73 (s, 1H), 4.16–4.09 (m, 3H), 3.88 (d, *J* = 11.0 Hz, 1H), 3.74 (s, 3H), 1.48 (s, 3H), 1.45 (s, 3H), 1.34 (s, 9H), 1.10 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.3, 154.9, 142.4, 135.6, 135.5, 132.5, 129.97, 129.93, 127.9, 122.7, 99.1, 79.5, 77.2, 70.7, 63.5, 62.9, 55.8, 51.5, 28.6, 28.2, 26.9, 19.23, 19.21; HRMS (FAB) *m/z* calcd for $C_{32}H_{46}NO_7Si$ $(M+H)^+$ 584.3044, found 584.3066.

*4.5.2. Methyl [1(4R,5R)]-3-[5-(tert-butyldiphenylsilyloxy)methyl-2,2-dimethyl-5-(1,1-dimethylethoxycarbonyl)amino-1,3-dioxane-4-yl]butanoate (**29**).* Pd/C (13 mg) was added to a solution of alkene **34** (130 mg, 0.223 mmol) in MeOH (3.9 mL). After stirring at room temperature for 4.5 h under hydrogen, the reaction mixture was filtered through a pad of Celite. The filter cake was rinsed with EtOAc and the combined filtrate was concentrated in vacuo. The resulting residue was purified by column chromatography (silica gel, 10% EtOAc in hexane) to provide **29** (125 mg, 96%) as a colorless oil: $[\alpha]_D^{25}$ +17.6 (*c* 0.5, $CHCl_3$); IR (film, cm^{-1}) ν 3427, 1739, 1715, 1495; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65–7.61 (m, 4H), 7.45–7.36 (m, 6H), 4.97 (s, 1H), 4.21 (br s, 1H), 4.20 (d, *J* = 10.0 Hz, 1H), 4.06 (d, *J* = 11.2 Hz, 1H), 4.01 (br s, 1H), 3.81 (d, *J* = 11.2 Hz, 1H), 3.65 (s, 1H), 2.43 (ddd, *J* = 15.0, 8.4, 7.1 Hz, 1H), 2.23 (td, *J* = 15.0, 7.1 Hz, 1H), 1.82 (td, *J* = 15.0, 7.1 Hz, 1H), 1.74-1.64 (m, 1H), 1.43 (s, 3H), 1.39 (s, 3H), 1.37 (s, 9H), 1.08 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.6, 155.3, 135.60, 135.58, 132.81, 132.76,

129.9, 129.83, 127.78, 99.0, 79.1, 77.2, 71.5, 63.9, 63.2, 55.4, 51.4, 30.6, 28.9, 28.3, 26.9, 24.1, 19.2, 19.0; HRMS (FAB) *m/z* calcd for $C_{32}H_{48}NO_7SSi$ $(M+H)^+$ 585.3200, found 585.3206.

*4.5.3. [1(4R,5R)]-1-[5-(tert-Butyldiphenylsilyloxy)methyl-2,2-dimethyl-5-(1,1-dimethylethoxycarbonyl)amino-1,3-dioxane-4-yl]-3-butene (**30**).* DIBAL-H (0.28 ml, 0.28 mmol) was added dropwise to a solution of ester **29** (83 mg, 0.14 mmol) in CH_2Cl_2 (4.0 mL) at –78 °C under nitrogen. After stirring for 1 h, the reaction was quenched with saturated potassium sodium tartrate and the whole mixture was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with water (10 mL) and brine (10 mL), and dried over anhydrous $MgSO_4$. Filtrate was concentrated in vacuo, and the residue was filtered through a pad of Celite to provide crude aldehyde (81 mg), which was used in the next step without further purification.

Ph_3PCH_3Br (550 mg, 1.54 mmol) was added slowly to a suspension of NaH (60% in mineral oil, 56 mg, 1.4 mmol) in THF (2 mL) at 0 °C. After stirring for 3 h under nitrogen at room temperature, crude aldehyde (81 mg) in THF (3.3 mL) was added dropwise to the reaction mixture at 0 °C, and the resulting mixture was warmed to room temperature and stirred for 2 h. The reaction mixture was quenched with saturated NH_4Cl and the whole mixture was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with water (10 mL) and brine (10 mL), and dried over anhydrous $MgSO_4$. Filtrate was concentrated in vacuo, and the residue was purified by column chromatography (silica gel, 10% EtOAc in hexane) to provide **30** (53 mg, 70% for 2 steps) as a colorless oil: $[\alpha]_D^{15}$ +22.9 (*c* 0.5, $CHCl_3$); IR (film, cm^{-1}) ν 3427, 3073, 1722, 1495, 998, 913; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64–7.62 (m, 4H), 7.45–7.36 (m, 6H), 5.76 (m, 1H), 5.01 (d, *J* = 18.8 Hz, 1H), 4.96 (d, *J* = 10.0 Hz, 1H), 4.24 (d, *J* = 10.0 Hz, 1H), 4.08 (d, *J* = 11.4 Hz, 1H), 4.00 (d, *J* = 11.4 Hz, 1H), 4.00 (d, *J* = 10.0 Hz, 1H), 3.81 (d, *J* = 10.0 Hz, 1H), 2.24 (m, 1H), 2.02 (m, 1H), 1.66–1.59 (m, 2H), 1.45 (s, 3H), 1.42 (s, 3H), 1.36 (s, 9H), 1.07 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.3, 138.1, 135.62, 135.60, 132.9, 132.8, 129.9, 129.8, 127.8, 115.1, 99.0, 79.0, 71.5, 64.0, 63.4, 55.5, 29.9, 29.0, 28.3, 27.7, 26.9, 19.28, 19.24; HRMS (FAB) *m/z* calcd for $C_{32}H_{48}NO_5SSi$ $(M+H)^+$ 554.3302, found 554.3307.

*4.5.4. [1(4R,5R),3E]-1-[5-(tert-Butyldiphenylsilyloxy)methyl-2,2-dimethyl-5-(1,1-dimethylethoxycarbonyl)amino-1,3-dioxane-4-yl]heptadec-3-en-11-one (**31**).* Pentadec-1-en-9-one (**5**,[11] 61 mg, 0.29 mmol) and second generation Grubbs catalyst (3 mg, 0.0036 mmol) were added to a solution of alkene **30** (40 mg, 0.072 mmol) in CH_2Cl_2 (2.3 mL). After stirring at reflux for 1 h, the solvent was removed in vacuo. The resulting residue was purified by column chromatography (silica gel, 5% EtOAc in hexane) to provide **31** (52 mg, 96%) as a colorless oil: $[\alpha]_D^{22}$ +22.6 (*c* 0.5, $CHCl_3$); IR (film, cm^{-1}) ν 3425, 3072, 1721, 1717, 1495; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64–7.62 (m, 4H), 7.45–7.36 (m, 6H), 5.44-5.31 (m, 2H), 4.98 (s, 1H), 4.23 (d, *J* = 9.0 Hz, 1H), 4.17 (br s, 1H), 4.08 (dd, *J* = 11.6, 4.8 Hz, 1H), 4.01 (br s, 1H), 3.80 (d, *J* = 9.0 Hz, 1H), 2.38 (t, *J* = 7.2 Hz, 4H), 2.16 (m, 1H), 2.08-1.94 (m, 3H), 1.62-1.54 (m, 6H), 1.44 (s, 3H), 1.41 (s, 3H), 1.36 (s, 9H), 1.27 (br s, 12H), 1.07 (s, 9H), 0.88 (t, *J* = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.6, 181.3, 155.3, 135.62, 135.59, 132.9, 131.2, 130.4, 129.4, 127.8, 98.9, 78.9, 71.5, 64.0, 63.4, 55.6, 42.80, 42.77, 32.6, 31.6, 29.5, 29.3, 29.1, 29.01, 28.96, 28.9, 28.7, 28.3, 28.2, 26.9, 23.8, 23.7, 23.2, 22.5, 19.3, 19.2, 14.0; HRMS (FAB) *m/z* calcd for $C_{45}H_{72}NO_6SSi$ $(M+H)^+$ 750.5129, found 750.5103.

*4.5.5. [1(4R,5S),3E]-1-[2,2-Dimethyl-5-(1,1-dimethylethoxycarbonyl)amino-5-hydroxymethyl-1,3-dioxane-4-yl]heptadec-3-en-11-one (**35**).* TBAF (0.13 mL, 1 M in THF, 0.13 mmol) were added to a solution of **31** (47 mg, 0.063 mmol) in THF (0.58 mL) at 0 °C. After stirring at room temperature for 3 h, the reaction was quenched with water and the whole mixture was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with water (10 mL) and brine (10 mL), and dried over anhydrous $MgSO_4$. Filtrate was concentrated in vacuo, and the residue was purified by column chromatography (silica gel, 20% EtOAc in hexane) to provide **35** (28 mg, 88%) as a colorless oil: $[\alpha]_D^{20}$ +25.9 (*c* 0.5, $CHCl_3$); IR (film, cm^{-1}) ν 3424, 1712, 1697; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.50–5.25 (m, 2H), 4.78 (d, *J* = 12 Hz, 1H), 3.99 (d, *J* = 12.4 Hz, 1H), 3.93 (dd, *J* = 12.2, 2.4 Hz, 1H), 3.76 (d, *J* = 12.4 Hz, 1H), 3.68 (dd, *J* = 12.2, 2.4 Hz, 1H), 3.42 (t, *J* = 12.2 Hz, 1H), 2.38 (t, *J* = 7.2 Hz, 4H), 2.17–1.89 (m, 5H), 1.61–1.52 (m, 5H), 1.45 (s, 9H), 1.43 (s, 3H), 1.41 (s, 3H), 1.34–1.27 (m, 12H), 0.88 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.6, 157.2, 131.6, 128.9, 98.9, 80.3, 73.6, 65.0, 64.8, 55.6, 42.8, 42.7, 32.5, 31.6, 29.4, 29.1, 28.94, 28.91, 28.4, 28.3, 28.0, 23.82, 23.79, 22.5, 18.6, 14.0; HRMS (FAB) *m/z* calcd for $C_{29}H_{54}NO_6$ $(M+H)^+$ 512.3951, found 512.3946.

*4.5.6. [1(4R,5S),3E]-1-[2,2-Dimethyl-5-(1,1-dimethylethoxycarbonyl)amino-5-formyl-1,3-dioxane-4-yl]heptadec-3-en-11-one (**36**).* A solution of DMSO (26 mg, 0.328 mmol) in CH_2Cl_2 (0.3 mL) was added dropwise to a solution of oxalyl chloride (28 mg, 0.219 mmol) in CH_2Cl_2 (0.4 mL) at –78 °C under nitrogen and stirred for 5 min. A solution of alcohol **35** (28 mg, 0.0547 mmol) in CH_2Cl_2 (0.5 mL) was added dropwise to the reaction mixture and stirred for 20 min. A solution of Et_3N (56 mg, 0.547 mmol) in CH_2Cl_2 (0.3 mL) was added dropwise to the reaction mixture at –78 °C. The reaction mixture was warmed to –40 °C and stirred for 1 h. The reaction was quenched with saturated NH_4Cl and the whole mixture was extracted with EtOAc (3 x 5 mL). The combined organic layers were washed with water (5 mL) and brine (5 mL), and dried over anhydrous $MgSO_4$. Filtrate was concentrated in vacuo, and the residue was purified by column chromatography (silica gel, 10% EtOAc in hexane) to provide **36** (26 mg, 93%) as a colorless oil: $[\alpha]_D^{21}$ +20.4 (*c* 0.5, $CHCl_3$); IR (film, cm^{-1}) ν 3437, 3362, 1727, 1713, 1700; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.65 (s, 1H), 5.41 (s, 1H), 5.38 (m, 1H), 5.28 (m, 1H), 4.15 (d, *J* = 11.6 Hz, 1H), 3.97 (dd, *J* = 10.4, 2.0 Hz, 1H), 3.95 (d, *J* = 11.6 Hz, 1H), 2.38 (t, *J* = 8.0 Hz, 4H), 2.25–2.05 (m, 2H), 2.00–1.89 (m, 2H), 1.65 (m, 1H), 1.61–1.52 (m, 5H), 1.44 (s, 3H), 1.43 (s, 3H), 1.47 (s, 9H), 1.31–1.27 (m, 12H), 0.88 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.6, 200.3, 156.1, 131.8, 128.5, 99.3, 80.8, 72.8, 72.6, 63.3, 63.0, 42.79, 42.75, 32.4, 32.3, 31.6, 29.7, 29.3, 29.2, 29.1, 28.9, 28.2, 28.0, 23.8, 22.5, 18.5, 14.0; HRMS (FAB) *m/z* calcd for $C_{29}H_{52}NO_6$ $(M+H)^+$ 510.3795, found 510.3799.

*4.5.7. Mycestericin D (**2**).* A solution of $NaClO_2$ (18 mg, 0.204 mmol) and $NaH_2PO_4{\cdot}H_2O$ (14 mg, 0.102 mmol) in water (0.28 mL) was added to a solution of **36** (26 mg, 0.051 mmol) and 2-methyl-2-butene (0.14 ml) in *t*-BuOH (0.9 mL). After stirring at room temperature for 3 h, the reaction was quenched with H_2O and the whole mixture was extracted with EtOAc (3 x 5 mL). The combined organic layers were washed with brine (10 mL), and dried over anhydrous $MgSO_4$. Filtrate was concentrated in vacuo to provide the crude carboxylic acid (45 mg), which was used in the next step without further purification.

10% HCl (1 mL) was added to a solution of the crude carboxylic acid in MeOH (1 mL). After stirring at 80 °C overnight, the reaction mixture was alkalified to pH 7 with K_2CO_3. Insoluble materials were filtered off, and the filtrate was concentrated in vacuo. The resulting residue was purified by column chromatography (1:1:10 to 1:3:10 (gradient) H_2O/MeOH/$CHCl_3$

(lower phase)) to afford mycestericin D (**2**, 18 mg, 90% for 2 steps) as a white solid: mp 164–166 °C (lit.[5a] mp 162–167 °C); $[\alpha]_D^{25}$ –7.48 (*c* 0.30, MeOH) {lit.[5a] $[\alpha]_D$ –7.5 (*c* 0.16, MeOH)}; IR (KBr, cm^{-1}) ν 3348, 3087, 1711, 1618, 1466, 968; ^{1}H NMR (400 MHz, CD_3OD) δ 5.52–5.34 (m, 2H), 3.99 (d, *J* = 11.0 Hz, 1H), 3.84–3.80 (m, 1H), 3.81 (d, *J* = 11.0 Hz, 1H), 2.43 (t, *J* = 7.2 Hz, 4H), 2.24 (m, 1H), 2.07–1.94 (m, 2H), 1.56–1.49 (m, 6H), 1.34–1.26 (m, 12H), 0.89 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ 214.4, 132.0, 130.6, 70.9, 64.70, 64.69, 43.49, 43.48, 33.6, 32.8, 32.6, 30.6, 30.3, 30.2, 30.1, 30.0, 24.9, 23.6, 14.4.

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Supplementary Material

Supplementary data associated with this article can be found, in the online version, at http://….

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