The First Total Synthesis of Concanamycin F (Concanolide A)

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A highly stereoselective total synthesis of the macrolide antibiotic concanamycin F (**1**), a specific and potent inhibitor of vacuolar H^+-ATPase, has been achieved by a convergent route involving the synthesis and coupling of its 18-membered tetraenic lactone and β-hydroxyl hemiacetal side chain subunits. The C1−C19 18-membered lactone aldehyde **4** was synthesized through the intermolecular Stille coupling of the C5−C13 vinyl iodide **24** and the C14−C19 vinyl stannane **25**, followed by construction of the C1−C4 diene and macrolactonization. Synthesis of **4** via a second convergent route including the esterification of the C1−C13 vinyl iodide **45** and the C14−C19 vinyl stannane **47** followed by the intramolecular Stille coupling was also realized. The highly stereoselective aldol coupling of **4** and the C20−C28 ethyl ketone **5** followed by desilylation provided **1** which was identical with natural concanamycin F.

Introduction

The concanamycins A−F,[2] a new class of 18-membered macrolide antibiotics, are potent and specific inhibitors of vacuolar H^+-ATPase attracting particular interest.[3] The ability of the concanamycins to disrupt cellular acidification leads to a wide range of diverse biological activity such as antiviral[4a] and immunosuppressant[4b] activity and the attenuation of resistance in MDR tumor cell lines.[4c] Furthermore, concanamycins as well as bafilomycins have attracted attention as candidates of novel therapeutic agents for osteoporosis.[4d,e] Concanamycin A (**2**), first isolated in 1981 by Kinashi et al.,[2a,c] is a major component of concanamycins; the structure and absolute configuration have been established by chemical degradation,[2a] NMR analysis,[2a] and X-ray crystallographic analysis[2d] of its diacetate derivative. On the other hand, concanolide A (**1**) is the common aglycon of both concanamycins A (**2**) and C (**3**); it also identical with natural concanamycin F.[2e,5] The most striking and unique structural feature of this class of macrolides is an unusual 18-membered tetraenic lactone ring with a methyl enol ether and a β-hydroxy hemiacetal side chain with/without the 2-deoxy-β-D-rhamnose moiety. Although the other polyketide macrolides such as the bafilomycins,[6,7] the hygrolidins,[8,9] and the recently discovered formamicin[10] are closely related to the concanamycins, the concanamycins possess one of the most complex architectures among them. Because of the unique structural and impressive biological features of concanamycins, great effort has been devoted to the chemical synthesis of **1** and **2**. Previously, we reported the synthesis of the C20−C28 fragment of **1** and **2** starting from carbohydrate building blocks[11] and the first total synthesis of **1** as communications.[12] Elegant synthetic studies of the C19−C28 and C1−C13 segments of **1** and **2** have

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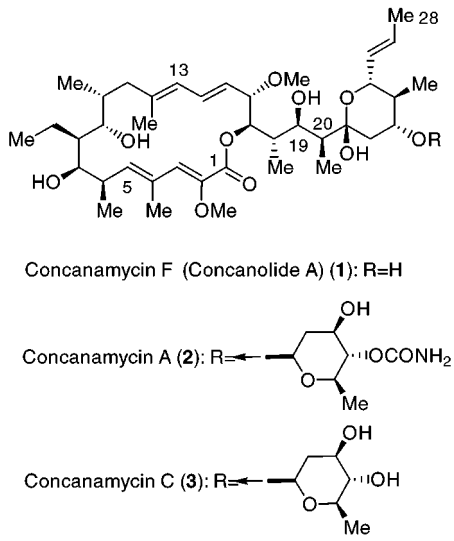

Figure 1. Molecular structures of concanamycin F (concanolide A), concanamycin A, and concanamycin C.

been announced by Paterson's group, and the total synthesis of concanamycin F (**1**) has also been described recently by his group.[13] In this paper, we describe the full account of our first total synthesis of the architecturally and biologically attractive natural product, concanamycin F (concanolide A) (**1**) (Figure 1).

Synthetic Plan. The retrosynthetic analysis of concanamycin F (concanolide A) (**1**) is shown in Figure 2. Central to our synthetic strategy for **1** was the stereoselective aldol reaction[14] of macrocyclic lactone aldehyde **B** and ethyl ketone **C**, followed by deprotection of aldol **A**. The synthetic plan for the 18-membered lactone **B** was based on the effective three-component assembly of the suitably protected C1−C4 **D**, C5−C13 **E**, and C14−C19 **F**. In the synthetic direction, each of these analogues' bond constructions is based on powerful synthetic reactions. For example, the synthesis of dienes through the Pd(0)-catalyzed coupling of vinyl halides and vinyl stannanes (Stille coupling)[15,16] is reported to work well with highly functionalized coupling partners. The synthesis of dienes by the Wittig reaction also has a high potential. Furthermore, the highly evolved methods for esterification or macrolactonization are currently available.[17] The highly stereoselective synthesis of an appropriately protected 18-membered lactone aldehyde **4**, which makes use of the fragments **6**, **7**, and **D**, and a suitably protected ethyl ketone **5** and aldol coupling of **4** and **5** leading to the total synthesis of **1**, are described in the following discussion.

Results and Discussion

Synthesis of the C5−C13 Segment 24. The synthesis of the suitably protected vinyl iodide **24** corresponding to the C5−C13 segment of **1** is summarized in Scheme 1. The 1,3-diol of the starting material **8** (erythro/threo = 85:15), which was readily obtained from D-malic acid by Seebach's alkylation method,[18] was first regioselectively protected by formation of the *p*-methoxybenzylidene to give the pure primary alcohol **9** in 64% yield. Swern oxidation of **9** followed by Grignard reaction using EtMgBr in Et_2O at 25 °C for 3 h afforded the secondary alcohol **11** in 87% overall yield. The secondary alcohol **11** was subjected to Swern oxidation and then Wittig reaction employing $Ph_3P{=}CH_2$ in benzene to furnish **13** in 88% overall yield. As expected from our bafilomycin A_1 synthesis,[7a,c] substrate-controlled hydroboration of **13** utilizing dicyclohexylborane in THF at room temperature for 3 h proceeded with complete stereoselectivity to give only the desired alcohol **14** in 89% yield after the subsequent oxidative workup. Swern oxidation of the resultant alcohol **14** yielded the aldehyde **15** which was subjected to Evans' aldol reaction[19] using *N*-propionyl-(4*S*)-benzyl-2-oxazolidinone, *n*-Bu_2BOTf, and Et_3N in CH_2Cl_2 at −78−0 °C for 2 h to give the desired aldol **16** as the sole isomer in 81% overall yield from **14**. Removal of the chiral auxiliary in **16** using $LiBH_4$ and EtOH in Et_2O at −10 °C for 1 h gave the diol **17** in quantitative yield. Regioselective tosylation of the primary alcohol in **17** (TsCl, Py, 97%) and the silylation with *tert*-butyldimethylsilyl (TBS) group (TBSOTf, 2,6-lutidine, CH_2Cl_2, 99%) of the resultant alcohol **18** yielded the tosylate **19** which was subjected to the reaction with 5 equiv of lithium acetylide in dimethyl sulfoxide (DMSO) to give the acetylene **20** in 69% yield. Unfortunately, introduction of acetylene into the tosylate **18** under similar conditions was unsuccessful. After concurrent deprotection of the *p*-methoxybenzylidene and silyl groups in **20** under acidic conditions (HF (aq), THF−MeCN, 70%), the resultant triol **21** was selectively pivaloylated (PvCl, Py, 4-(dimethylamino)pyridine (4-DMAP), CH_2Cl_2) at the primary alcohol and then silylated with diethylisopropylsilyl (DEIPS) group[20] using DEIPSOTf and 2,6-lutidine in CH_2Cl_2 to furnish the acetylene **23** in 82% overall yield. Finally, treatment of **23** with Cp_2ZrCl_2,

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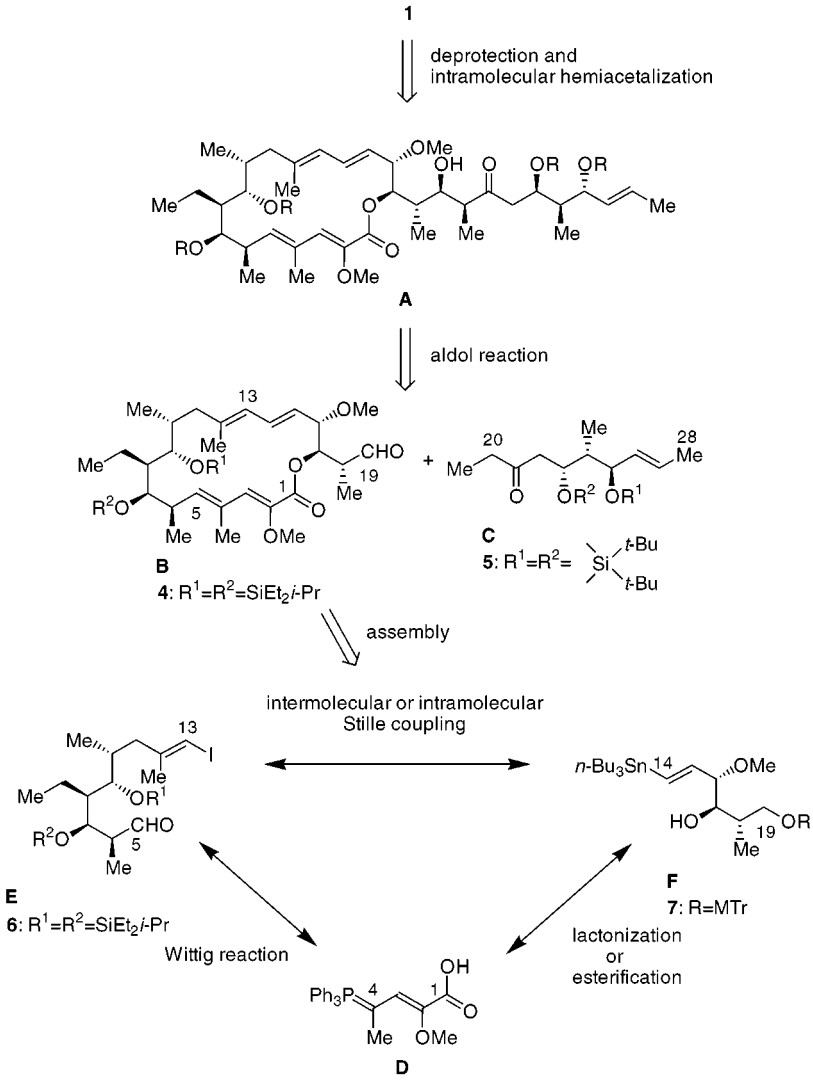

Figure 2. Retrosynthetic analysis of concanamycin F (**1**).

Me_3Al, and I_2 in 1,2-dichloroethane[21] afforded the trisubstituted *trans* vinyl iodide **24** in 88% yield. The *trans* configuration of the trisubstituted olefin of **24** was clearly confirmed by NOE experiments. Thus, NOE between the vinyl hydrogen and the methylene hydrogens was observed while no NOE between the vinyl hydrogen and the methyl group at the vinyl position was detected. Furthermore, the DEIPS groups in **24** were key protecting groups for the total synthesis of **1** because it was found that, in contrast to the corresponding triethylsilyl, *tert*-butyldimethylsilyl, and *p*-methoxybenzyl ethers, this silyl ether had sufficient stability in subsequent reactions, while still offering reasonable lability in the final deprotection step using tetrabutylammonium fluoride (TBAF) in THF.

Synthesis of the C1−C19 Macrocyclic Lactone via Macrolactonization. With the suitably protected vinyl iodide **24** corresponding to the C5−C13 fragment of **1** in hand, the synthesis of the C1−C19 macrocyclic lactone via macrolactonization was first addressed (Scheme 2). We examined the cross coupling reaction between the vinyl iodide **24** and the vinyl stannane **25**, which was recently synthesized in our laboratory,[7a,c] by Stille method[15,16] under several conditions. From the results shown in Table 1, the use of $Pd_2(dba)_3$ in the presence of Ph_3As and LiCl in *N*-methylpyrrolidinone (NMP) was found to be superior in this coupling reaction. Thus, the reaction of 1 equiv of **24** and 1 equiv of **25** using a catalytic amount of $Pd_2(dba)_3$ in the presence of Ph_3As and LiCl in *N*-methylpyrrolidinone (NMP)[22] at 40 °C for 16 h proceeded effectively to afford the desired *E*,*E*-diene **26** in 72% yield as the only isolated product. The ^1H NMR spectrum of **26**, interestingly, showed that it consisted of a ca. 3:1 inseparable mixture. The ^1H NMR spectra of **29**, **30**, and **33** also showed similar phenomenon. On the other hand, it was found that the ^1H NMR spectra of the desilylation product of **26** and the conformationally rigid lactone **37** indicated that they are single compounds. Therefore, it is reasonable to assume that this inseparable mixture should be due to the conformational isomers.[7c] Deprotection of the pivaloyl group in **26** using methyllithium in Et_2O, followed by Swern oxidation of the resultant alcohol **27**, gave the aldehyde **28**. At this stage, we first tried the Horner−Wadsworth−Emmons

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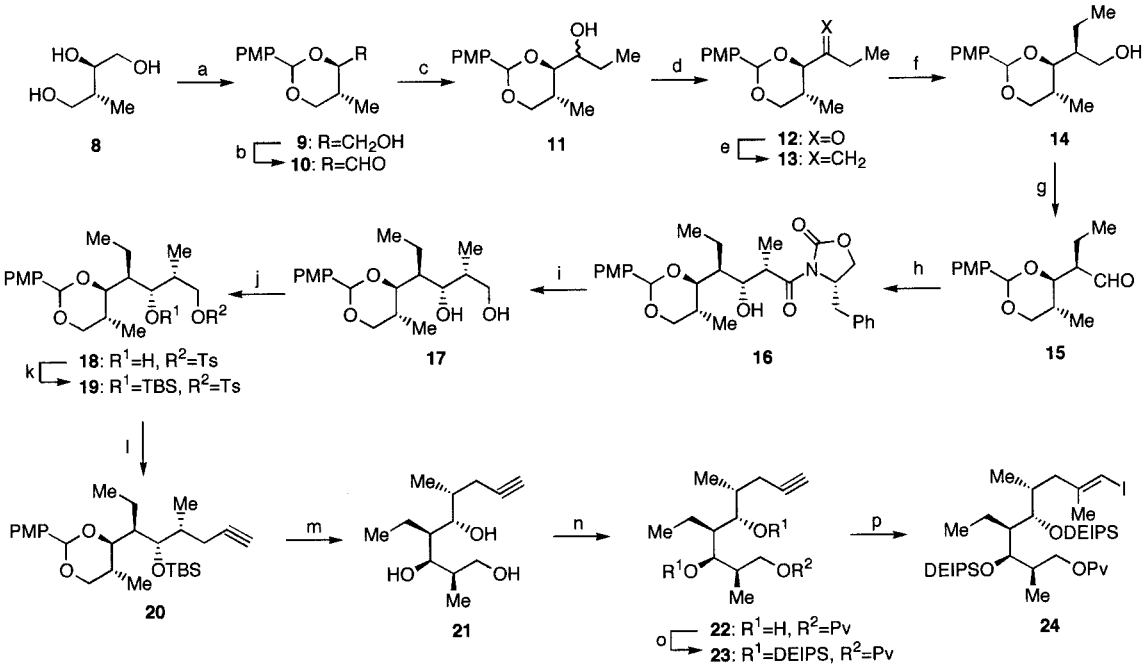
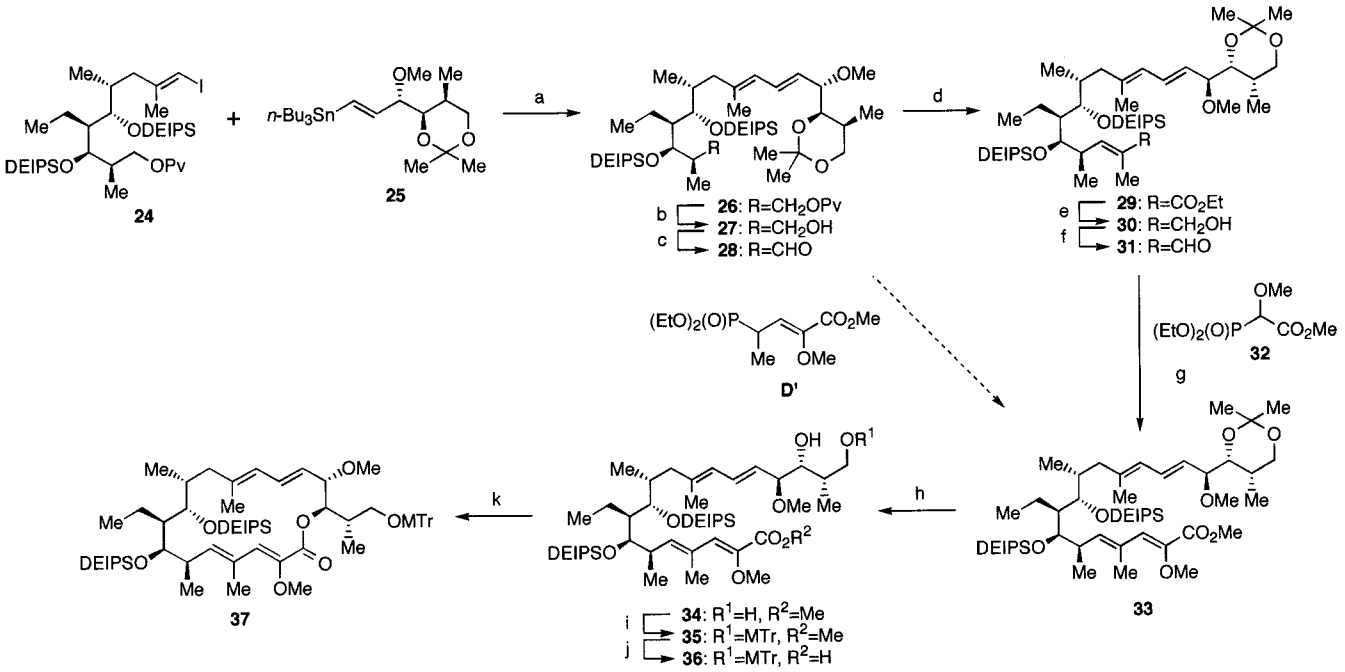
Scheme 1[a]



[a] Reagents and conditions: (a) $(MeO)_2CHC_6H_4OMe$, CSA, CH_2Cl_2, r.t., 16 h, 64%; (b) $(COCl)_2$, DMSO, TEA, CH_2Cl_2, −78 °C, 20 min; (c) EtMgBr, Et_2O, r.t., 3 h, 87% from **9**; (d) $(COCl)_2$, DMSO, TEA, CH_2Cl_2, −78 °C, 20 min; (e) $Ph_3P{=}CH_2$, PhH, r.t., 0.5 h, 88% from **11**; (f) $BH_3{\cdot}Me_2S$, C_6H_{10}, THF, r.t., 3 h then NaOH−H_2O, H_2O_2, 50 °C, 1 h, 89%; (g) $(COCl)_2$, DMSO, TEA, CH_2Cl_2, −78 °C, 20 min; (h) *N*-propionyl-(4*S*)-benzyl-2-oxazolidinone, *n*-Bu_2BOTf, Et_3N, CH_2Cl_2, −78−0 °C, 2 h, 81% from **14**; (i) $LiBH_4$, EtOH, Et_2O, −10 °C, 1 h, 100%; (j) TsCl, Py, r.t., 2 h, 97%; (k) TBSOTf, 2,6-lutidine, CH_2Cl_2, r.t., 2 h, 99%; (l) HC≡CLi, DMSO, r.t., 3 h, 69%; (m) HF (aq), THF, MeCN, 40 °C, 48 h, 70%; (n) PvCl, 4-DMAP, Py, CH_2Cl_2, r.t., 16 h, 83%; (o) DEIPSOTf, 2,6-lutidine, CH_2Cl_2, r.t., 4 h, 99%; (p) Cp_2ZrCl_2, Me_3Al, I_2, $(ClCH_2)_2$, r.t., 16 h, 88%.

Scheme 2[a]



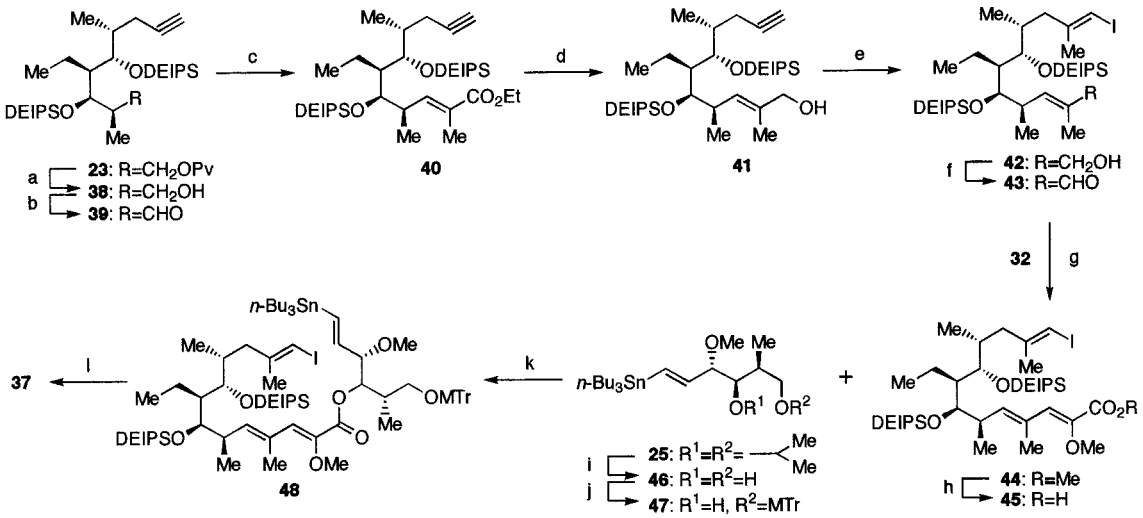
[a] Reagents and conditions: (a) $Pd_2(dba)_3$, Ph_3As, LiCl, NMP, 40 °C, 16 h, 72%; (b) MeLi, Et_2O, r.t., 0.5 h, 96%; (c) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C, 20 min; (d) $Ph_3P{=}C(Me)CO_2Et$, PhMe, 100 °C, 16 h, 89% from **27**; (e) DIBAL, PhMe, −78 °C, 0.5 h, 90%; (f) MnO_2, CH_2Cl_2, r.t., 1.5 h, 100%; (g) KHMDS, 18-crown-6, THF, −20 °C, 16 h, 99%; (h) PPTS, MeOH, r.t., 1 h, 96%; (i) MTrCl, Et_3N, 4-DMAP, CH_2Cl_2, r.t., 3 h, 100%; (j) 1 N KOH, 1,4-dioxane, 80 °C, 3 h, 82%; (k) 2,4,6-trichlorobenzoyl chloride, Et_3N, THF (0.01 M for **36**), 4-DMAP, PhMe (0.002 M for **36**), 110 °C, 14 h, 82%.

reaction of **28** and **D**′[7c] to construct the C1−C4 diene in one step. However, this reaction in the presence of several bases such as lithium bis(trimethylsilyl)amide (LiHMDS), sodium bis(trimethylsilyl)amide (NaHMDS), potassium bis(trimethylsilyl)amide (KHMDS), and NaH caused only β-elimination of **28** even at low temperature, and the desired tetraene **33** was not obtained at all. Therefore, stepwise construction of the diene, which

Table 1. The Cross Couplings of 24 and 25 by Pd Catalyts

24 (1 equiv) + **25** (1 equiv) → **26**						
entry	Pd catalyst (equiv)	additive(s) (equiv)	solvent	*T* (°C)	time (h)	yield (%)
1	$PdCl_2$(dppf) (0.25)	none	DMF	40	15	43
2	$PdCl_2$(dppf) (0.2)	LiCl (3.0)	NMP	40	16	49
3	$Pd_2(dba)_3$ (0.2)	CuI (0.4), Ph_3As (0.8)	NMP	40	16	68
4	$Pd_2(dba)_3$ (0.25)	LiCl (3.0), Ph_3As (2.0)	NMP	40	16	72

Scheme 3[a]



[a] Reagents and conditions: (a) DIBAL, PhMe, −78 °C, 15 min, 90%; (b) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C, 20 min; (c) $Ph_3P{=}C(Me)CO_2Et$, PhMe, 100 °C, 16 h, 92% from **38**; (d) DIBAL, PhMe, −78 °C, 15 min, 92%; (e) Cp_2ZrCl_2, $AlMe_3$, I_2, $(CH_2Cl)_2$, r.t., 16h, 84%; (f) MnO_2, CH_2Cl_2, r.t., 1.5 h, 96%; (g) KHMDS, 18-crown-6, THF, −20 °C, 16 h, 96%; (h) 1 N KOH, 1,4-dioxane, 80 °C, 3 h, 95%; (i) PPTS, MeOH, r.t., 2 h, 81%; (j) MTrCl, Et_3N, 4-DMAP, CH_2Cl_2, r.t., 1 h, 96%; (k) 2,4,6-trichlorobenzoyl chloride, Et_3N, THF, 4-DMAP, PhMe, r.t., 16 h, 79%; (l) $Pd_2(dba)_3$, Ph_3As, *i*-$PrNEt_2$, DMF−THF, 60 °C, 18 h, 72%.

included the use of the base free Wittig reagent in the first step, was next carried out. The Wittig reaction of **28** with ethyl 2-(triphenylphosphoranylidene)propionate in toluene at 100 °C for 16 h proceeded smoothly to yield only the trans isomer **29** in 89% overall yield from **27**. Reduction of the ethyl ester in **29** using diisobutylaluminum hydride (DIBAL) in toluene at −78 °C afforded the allyl alcohol **30** in 90% yield. Oxidation of **30** employing MnO_2 provided the α,β-unsaturated aldehyde **31** which was subjected to Horner−Wadsworth−Emmons reaction with phosphonic ester **32**[23] using potassium bis(trimethylsilyl)amide (KHMDS) in the presence of 18-crown-6[12b,24] in THF at −20 °C to give the desired *cis*-isomer **33** (*E*/*Z* = 1:>99) in 99% overall yield. The isopropylidene group in **33** was removed under mild acidic conditions using pyridinium *p*-toluenesulfonate (PPTS) in MeOH, and then the resultant diol **34** was selectively protected with a monomethoxytrityl (MTr) group (MTrCl, Et_3N, 4-DMAP, CH_2Cl_2) to afford the secondary alcohol **35** in 96% overall yield. Hydrolysis of the methyl ester of **35** under basic conditions (1 N KOH, 1,4-dioxane) yielded the carboxylic acid **36** in 82% yield. The macrolactonization of the seco-acid **36** to construct the 18-membered lactone ring was best effected by the Yamaguchi method[25] under high dilution conditions to give the macrocyclic lactone **37** in 82% yield. We found that the low concentration of **36** in THF (0.01 M) in the formation of the mixed anhydride of **36** and 2,4,6-trichlorobenzoyl chloride was very important to get a high yield of **37**. When the mixed anhydride formation was performed at normal concentration (0.1 M), significant amounts of a byproduct from the isomerization of the C1−C4 diene in **36** was produced.

Synthesis of the C1−C19 Macrocyclic Lactone via Intramolecular Stille Coupling. The effective synthesis of the macrocyclic lactone **37** was also achieved by another route involving intramolecular Stille coupling[16b] (Scheme 3). The fully protected acetylene **23** was first converted into the allyl alcohol **41** in high overall yield (4 steps, 76% overall yield) by a series of reactions presented in the synthesis of **30** from **26**. At this stage, the acetylene **41** was effectively transformed to the vinyl iodide **42** in 84% yield via zirconium-catalyzed carboalumination.[21] Oxidation of **42** using MnO_2 provided the α,β-unsaturated aldehyde **43** which was subjected to the previously mentioned Horner−Wadsworth−Emmons reaction with **32**[23] to give the desired *cis* isomer **44** (*E*/*Z* = 1:>99) in 92% overall yield. Hydrolysis of **44** under basic conditions using 1 N KOH in 1,4-dioxane yielded the carboxylic acid **45** in 95% yield. The esterification of the carboxylic acid **45** and the secondary alcohol **47** were examined at this stage. The secondary alcohol **47** was derived from **25** in two steps involving deisopropylidenation and regioselective protection with MTr group. From the results shown in Table 2, the esterification of the carboxylic acid **45** and the secondary alcohol **47** proceeded smoothly by the modified Yamaguchi method[25] at 25 °C to give the ester **48** in 79% yield. It was found that when 1,3-dicyclohexylcarbodiimide (DCC) was used as an esterification reagent, only dimeric anhydride **45′** was produced. The cyclization of **48** by intramolecular Stille coupling[16b] was next examined under several

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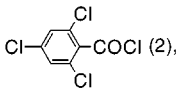
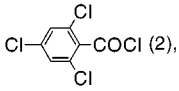
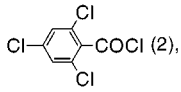
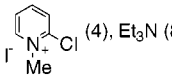
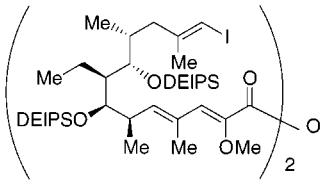
Table 2. Esterification of 45 with 47

45 (1 equiv) + **47** (1.5 equiv) ⟶ **48**

entry	reagents (equiv)	solvent	*T* (°C)	time (h)	yield (%)
1	DCC (2), 4-DMAP (3)	$CHCl_3$	23	16	0
2	DCC (2), 4-DMAP (3), 4-DMAP•HCl (2)	$CHCl_3$	25	16	0
3	 COCl (2), Et_3N (2.4), 4-DMAP (4)	PhMe	25	16	79
4	 COCl (2), Et_3N (2.4), 4-DMAP (4)	PhMe	110	16	10
5	 COCl (2), Et_3N (2.4), 4-DMAP (4)	THF	25	16	49
6	 (4), Et_3N (8)	MeCN	25	16	0



45'

Table 3. Intramolecular Stille Coupling Reaction of 48

48 → **37**

entry	Pd catalyst (equiv)	additive(s) (equiv)	solvent	*T* (°C)	time (h)	yield (%)
1	$Pd(Ph_3)_4$ (0.2)	*i*-Pr_2NEt (3.0)	DMF-THF	60	18	67
2	$PdCl_2$(dppf) (0.2)	*i*-Pr_2NEt (3.0)	DMF-THF	60	16	57
3	$Pd_2(dba)_3$ (0.2)	Ph_3As (2.0)	NMP	25	15	61
4	$Pd_2(dba)_3$ (0.2)	LiCl (3.0), Ph_3As (2.0)	NMP	25	18	66
5	$Pd_2(dba)_3$ (0.2)	CuI (3.0), Ph_3As (2.0)	NMP	25	18	35
6	$Pd_2(dba)_3$ (0.2)	*i*-Pr_2NEt (3.0), Ph_3As (2.0)	DMF−THF	60	18	72
7	$Pd_2(dba)_3$ (0.2)	*i*-Pr_2NEt (3.0), Ph_3As (2.0)	DMF−THF	25	18	55

conditions. From the results shown in Table 3, **48** was effectively cyclized using a catalytic amount of $Pd_2(dba)_3$ in the presence of Ph_3As and *i*-$PrNEt_2$ in DMF-THF(1:1)[22] at 60 °C for 18 h to furnish the 18-membered lactone **37** in 72% yield as the only isolated product. Furthermore, it was found that high dilution conditions were not necessary for getting a high yield of **37**.

Synthesis of the C20−C28 Segment 5. The improved[11] asymmetric synthesis of the ethyl ketone **5** corresponding to the C20−C28 segment of concanamycin F (**1**) from *trans*-crotonaldehyde (**49**) is depicted in Scheme 4. The reaction of *trans*-crotonaldehyde and Brown's chiral (*E*)-crotyldiisopinocamphenylborane **50**,[26] which was prepared from *trans*-2-butene, *n*-BuLi, and (−)-Ipc_2BOMe, in the presence of BF_3•Et_2O in THF-Et_2O at −78 °C for 2 h, gave the allyl alcohol **51** (>99% ee)[27] in 58% yield with 1:14 *syn*/*anti* selectivity. *p*-Methoxybenzylation of the resultant alcohol **51** with *p*-methoxylbenzyl trichloroacetimidate[28] gave **52** in 75% yield. Regioselective dihydroxylation of the terminal olefin in **52** was best effected by Sharpless method[29,30] using the bulky reagent, AD-mix-α, in *t*-BuOH−H_2O to give the diol **53** in 50% yield. Oxidative cleavage of the diol in **53** using $NaIO_4$ gave the aldehyde **54** in 95% yield. Mukaiyama aldol reaction[31] of **54** and the silyl enol ether **55** using BF_3•Et_2O in CH_2Cl_2 at −78 °C for 1 h proceeded smoothly to furnish the Cram product, ethyl ketone **56**, in 60% yield as a sole aldol product. Treatment of **56** with DDQ in CH_2Cl_2 gave the fully protected ethyl ketone **57** in 69% yield.[32] However, the ethyl ketone **57** was unfortunately found to be not suitable for aldol reactions using several boron reagents due to the removal of the *p*-methoxybenzylidene group. Therefore, **57** was converted into the

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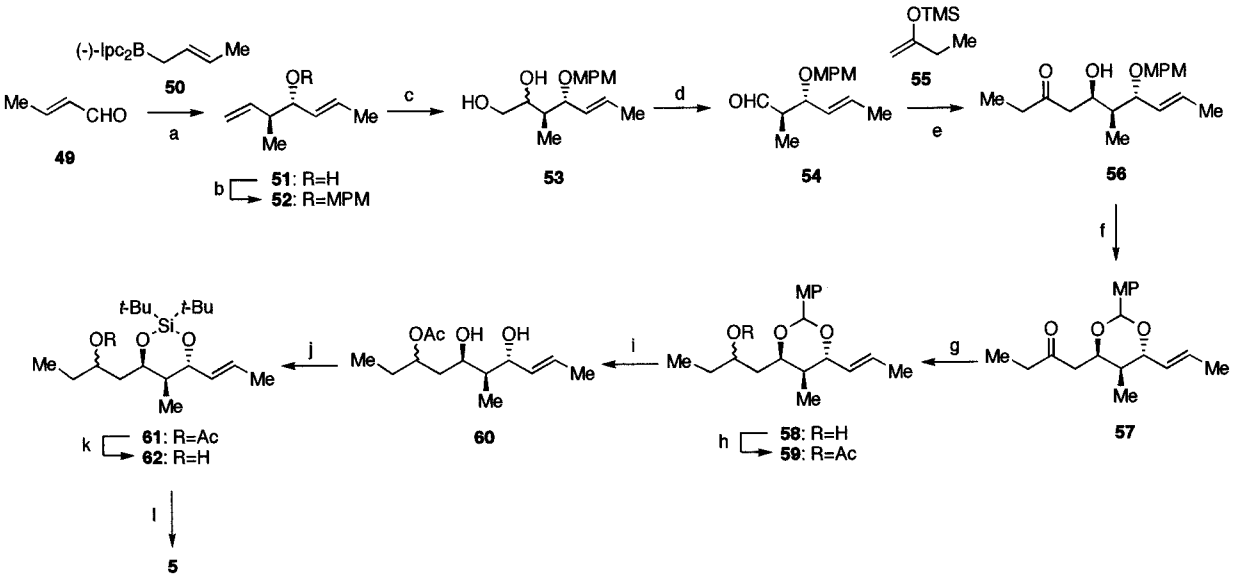
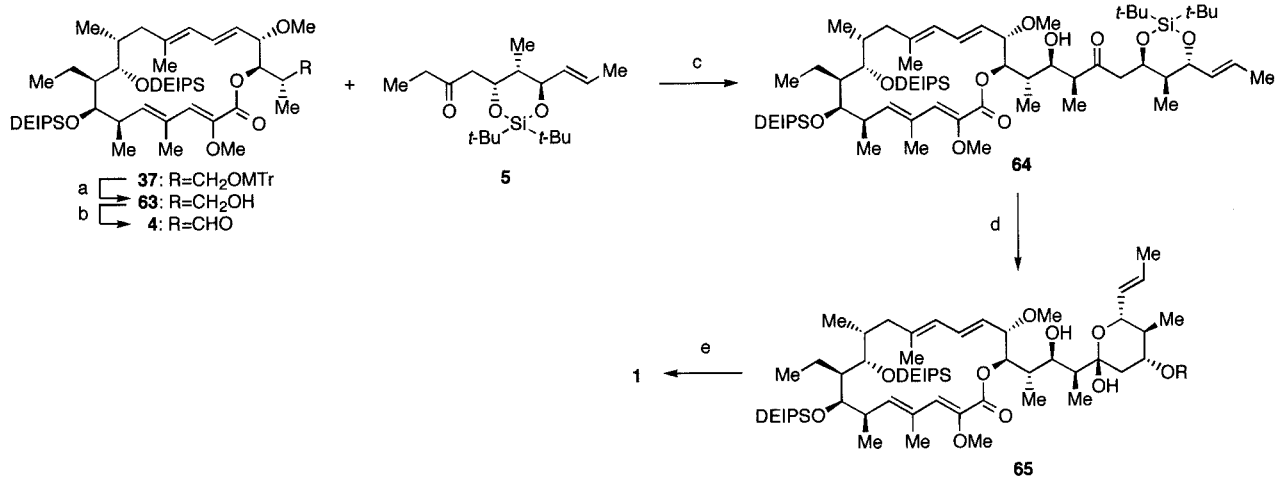
Scheme 4[a]



[a] Reagents and conditions: (a) $BF_3{\cdot}Et_2O$, THF/Et_2O, −78 °C, 2h, 58%; (b) $MeOC_6H_4CH_2OC(=NH)CCl_3$, CSA, CH_2Cl_2, r.t., 14 h, 75%; (c) AD-mix-α, t-BuOH/H_2O, r.t., 19 h, 50%; (d) $NaIO_4$, MeOH/H_2O, r.t., 0.5 h, 95%; (e) $BF_3{\cdot}Et_2O$, CH_2Cl_2, −78 °C, 1 h, 60%; (f) DDQ, CH_2Cl_2, 0 °C, 1.5 h, 69%; (g) $NaBH_4$, MeOH/CH_2Cl_2, 0 °C, 2 h, 67%; (h) Ac_2O, 4-DMAP, Py, r.t., 17 h, 95%; (i) AcOH/THF/H_2O = 1:1:1, 40 °C, 0.5 h, 90%; (j) *t*-$Bu_2Si(OTf)_2$, 2,6-lutidine, DMF, 0 °C, 2 h, 84%; (k) NaOMe, MeOH, r.t., 4 h, 91%; (l) Dess−Martin periodinane, Py, CH_2Cl_2, r.t., 2.5 h, 93%.

Scheme 5[a]



[a] Reagents and conditions: (a) PPTS, MeOH, r.t., 5 h, 94%; (b) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C, 20 min, 94%; (c) $PhBCl_2$, *i*-Pr_2NEt, CH_2Cl_2, −78 °C, 1.5 h, 84%; (d) HF−Py, THF, 0 °C, 15 min, 94%; (e) TBAF, THF, r.t., 2.5 h, 59%.

suitably protected ethyl ketone **5** by standard procedures. Reduction of **57** using $NaBH_4$, followed by acetylation, gave the acetate **59** in 64% overall yield. Deprotection of *p*-methoxybenzylidene group under acidic conditions gave the diol **60**, which was silylated with a di-*tert*-butylsilyl group to give **61** in 76% overall yield. Finally, deacetylation of **61** followed by Dess−Martin oxidation[33] gave the suitably protected ethyl ketone **5** in 85% overall yield. The cyclic protection at the C5 and C7 positions in **5** was required for a high level of aldol stereoselectivity as suggested by bafilomycin A_1 syntheses.[7b−d]

Total Synthesis of 1. With the effective synthesis of the 18-membered lactone **37** and the ethyl ketone **5**, total synthesis of **1** was addressed (Scheme 5). Treatment of **37** with PPTS in MeOH gave the alcohol **63** which was subjected to Swern oxidation to furnish the 18-membered macrolactonic aldehyde **4** in 89% overall yield. We next attempted the stereoselective connection of **4** and **5** by an aldol reaction. The aldol condensation between 1 equiv of **4** and 2 equiv of **5** was best achieved using $PhBCl_2$[5b−d,9b,34,35] and *i*-Pr_2NEt in CH_2Cl_2 at −78 °C for 1.5 h to produce the desired aldol **64** as the sole isomer in 84% yield. Finally, successful removal of the silyl protecting groups of **64** necessitated stepwise treatment with HF−Py to give the hemiacetal **65** (94%), followed by tetrabutylammonium fluoride (TBAF) treatment to remove the DEIPS ethers (59%). Thus, the obtained **1** was identical to an authentic sample of natural concanamycin F (concanolide A) based on ^1H

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NMR, $[\alpha]_D$ (synthetic, $[\alpha]^{25}_D$ +10.3° (*c* 0.17, $CHCl_3$); natural, $[\alpha]^{20}_D$ +11.0° (*c* 0.30, $CHCl_3$)), and TLC behaviors in several solvent systems.[2e,5]

Conclusions

The first total synthesis of concanamycin F, a specific inhibitor of vacuolar H^+-ATPase, has been completed using three principle subunits. Our total synthesis is characterized by high convergency and stereocontrol at several stages. This synthetic strategy should find wide application in the synthesis of other structurally related and biologically important macrolide antibiotics and for the synthesis of designed concanamycin analogues with potential applications in biology and medicine.

Experimental Section

Ethyl Ketone 5. R_f 0.40 (5/1 *n*-hexane/EtOAc); $[\alpha]^{23}_D$ +101.6° (*c* 0.50, $CHCl_3$); ^{1}H NMR δ 5.61 (1H, dq, *J* = 6.4 and 15.2 Hz), 5.41 (1H, ddq, *J* = 1.7, 7.3 and 15.2 Hz), 4.65 (1H, ddd, *J* = 2.0, 3.3 and 10.8 Hz), 4.16 (1H, dd, *J* = 7.3 and 9.9 Hz), 2.72 (1H, dd, *J* = 10.8 and 15.0 Hz), 2.55 (2H, q, *J* = 7.6 Hz), 2.43 (1H, dd, *J* = 3.3 and 15.0 Hz), 2.17 (1H, ddq, *J* = 2.0, 9.9 and 7.2 Hz), 1.72 (3H, dd, *J* = 1.7 and 6.4 Hz), 1.08 (3H, t, *J* = 7.6 Hz), 1.00 and 0.99 (each 9H, each s), 0.69 (3H, d, *J* = 7.2 Hz). Anal. Calcd for $C_{19}H_{36}O_3Si$: C, 67.01; H, 10.65. Found: C, 66.91; H, 10.84.

Macrolactonic Aldehyde 4. R_f 0.55 (4/1 *n*-hexane/EtOAc); $[\alpha]^{26}_D$ −0.8° (*c* 0.25, $CHCl_3$), $[\alpha]^{26}_{435}$ −14.4° (*c* 0.25, $CHCl_3$); ^{1}H NMR δ 9.72 (1H, d, *J* = 2.0 Hz), 6.62 (1H, dd, *J* = 11.5 and 16.5 Hz), 6.12 (1H, s), 5.87 (1H, d, *J* = 11.5 Hz), 5.71 (1H, d, *J* = 9.5 Hz), 5.27 (1H, dd, *J* = 9.0 and 16.5 Hz), 5.18 (1H, dd, *J* = 4.0 and 9.5 Hz), 3.98 (1H, br d, *J* = 2.0 Hz), 3.85 (1H, m), 3.78 (1H, dd, *J* = 9.5 and 9.0 Hz), 3.54 (3H, s), 3.27 (3H, s), 2.90 (1H, m), 2.62−2.42 (2H, m), 2.20 (1H, dd, *J* = 7.2 and 7.2 Hz), 1.96 (3H, s), 1.98−1.94 (4H, m), 1.86−1.74 (1H, m), 1.25 (2H, m), 1.15−0.85 (38H, m), 0.83−0.68 (4H, m), 0.48 (4H, q, *J* = 7.1 Hz). Anal. Calcd for $C_{42}H_{76}O_7Si_2$: C, 67.33; H, 10.22. Found: C, 67.61; H, 10.58.

Aldol 64. R_f 0.43 (5/1 *n*-hexane/EtOAc); $[\alpha]^{25}_D$ +62.5° (*c* 0.24, $CHCl_3$); mp 69.0−69.5 °C (*n*-hexane, thin plate); ^{1}H NMR δ 6.60 (1H, dd, *J* = 11.2 and 15.0 Hz), 6.16 (1H, s), 5.86 (1H, d, *J* = 11.2 Hz), 5.74 (1H, d, *J* = 9.8 Hz), 5.63 (1H, dq, *J* = 7.0 and 15.2 Hz), 5.41 (1H, ddd, *J* = 1.8, 7.0 and 15.2 Hz), 5.27 (1H, dd, *J* = 9.2 and 15.0 Hz), 5.12 (1H, dd, *J* = 1.2 and 10.0 Hz), 4.69 (1H, ddd, *J* = 3.4, 5.2 and 9.8 Hz), 4.07 (1H, dd, *J* = 7.0 and 10.2 Hz), 3.99 (1H, br d, *J* = 1.4 Hz), 3.88−3.72 (4H, m), 3.58 (3H, s), 3.27 (3H, s), 2.83 (1H, dd, *J* = 9.8 and 16.0 Hz), 2.76 (1H, m), 2.60−2.42 (2H, m), 2.48 (1H, dd, *J* = 5.4 and 16.0 Hz), 2.26−2.07 (3H, m), 1.98 (3H, s), 1.96−1.92 (4H, m), 1.77 (1H, dd, *J* = 14.0 and 14.0 Hz), 1.72 (3H, dd, *J* = 1.8 and 7.0 Hz), 1.35−1.15 (2H, m), 1.16 (3H, d, *J* = 7.2 Hz), 1.10−0.85 (59H, m), 0.76−0.69 and 0.55−0.40 (each 4H, m). Anal. Calcd for $C_{61}H_{112}O_{10}Si_3$: C, 67.23; H, 10.36. Found: C, 67.42; H, 10.29.

Di-DEIPS−Concanamycin F 65. R_f 0.38 (3/2 *n*-hexane/EtOAc); $[\alpha]^{25}_D$ +62.49° (*c* 0.24, $CHCl_3$); mp 96.9−97.5 °C (*n*-hexane, thin plate); ^{1}H NMR δ 6.60 (1H, dd, *J* = 11.2 and 15.2 Hz), 6.07 (1H, s), 5.85 (1H, d, *J* = 11.2 Hz), 5.76 (1H, s), 5.70 (1H, d, *J* = 9.6 Hz), 5.52 (1H, dq, *J* = 6.8 and 15.2 Hz), 5.27 (1H, d, *J* = 15.2 Hz), 5.23 (1H, d, *J* = 15.2 Hz), 5.01 (1H, d, *J* = 9.8 Hz), 4.56 (1H, br d, *J* = 3.0 Hz), 4.01−3.80 (5H, m), 3.71 (1H, m), 3.49 (3H, s), 3.28 (3H, s), 2.58−2.42 (2H, m), 2.30 (1H, dd, *J* = 4.8 and 11.6 Hz), 2.25 (1H, m), 2.17 (1H, dd, *J* = 13.2 and 6.8 Hz), 1.98 (3H, s), 1.98−1.84 (4H, br s), 1.84−1.72 (2H, m), 1.70−1.58 (4H, m), 1.35−0.80 (48H, m), 0.54−0.35 (8H, m). Anal. Calcd for $C_{53}H_{96}O_{10}Si_2$: C, 67.04; H, 10.19. Found: C, 66.90; H, 10.22.

Concanamycin F (1). R_f 0.28 (1/1 *n*-hexane/EtOAc); $[\alpha]^{25}_D$ +10.3° (*c* 0.17, $CHCl_3$) [$[\alpha]^{20}_D$ of natural concanamycin F: +11.0° (*c* 0.30, $CHCl_3$); mp 96.6−97.2 °C (*n*-hexane, thin plate); ^{1}H NMR δ 6.54 (1H, dd, *J* = 15.0 and 10.5 Hz), 6.38 (1H, s), 5.79 (1H, d, *J* = 10.5 Hz), 5.73 (1H, br s), 5.68 (1H, br d, *J* = 10.0 Hz), 5.55 (1H, dq, *J* = 15.0 and 6.0 Hz), 5.29 (1H, ddd, *J* = 15.0, 7.8 and 1.8 Hz), 5.23 (1H, dd, *J* = 15.0 and 9.0 Hz), 5.02 (1H, br d, *J* = 9.0 Hz), 4.60 (1H, br s), 4.02 (1H, ddd, *J* = 2.8, 4.1 and 10.0 Hz), 3.96 (1H, dd, *J* = 10.0 and 7.8 Hz), 3.85 (1H, dd, *J* = 9.0 and 9.0 Hz), 3.90−3.78 (1H, m), 3.73 (1H, ddd, *J* = 4.2, 10.1 and 11.1 Hz), 3.63 (3H, s), 3.26 (3H, s), 3.27−3.23 (1H, m), 2.74 (1H, m), 2.31 (1H, dd, *J* = 4.2 and 12.1 Hz), 2.37−2.25 (1H, m), 2.17 (1H, m), 2.07−1.92 (3H, m), 1.96 (3H, br s), 1.94 (3H, br s), 1.92−1.79 (2H, m), 1.77−1.12 (3H, m), 1.57 (3H, dd, *J* = 6.0 and 1.8 Hz), 1.12−1.02 (3H, m), 1.06 (3H, d, *J* = 6.2 Hz), 1.06 (3H, d, *J* = 6.8 Hz), 1.00 (3H, d, *J* = 6.5 Hz), 0.92 (3H, d, *J* = 6.4 Hz), 0.82 (3H, d, *J* = 7.0 Hz), 0.82 (3H, br d, *J* = 7.0 Hz). Anal. Calcd for $C_{39}H_{64}O_{10}$: C, 67.60; H, 9.31. Found: C, 67.60; H, 9.70; HRMS (FAB, matrix, *m*-nitrobenzyl alcohol) *m*/*z* 715.4397 $(M+Na)^+$, calcd for $C_{39}H_{64}O_{10}Na$ 715.4440.

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Supporting Information Available: Spectroscopic and analytical data and experimental procedures for all synthetic intermediates. This material is available free of charge via the Internet at http://pubs.acs.org.

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