Total Synthesis of Microtubule-Stabilizing Agent (−)-Laulimalide[1]

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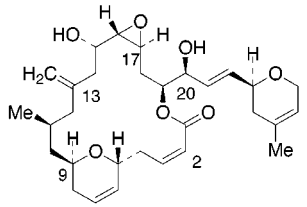
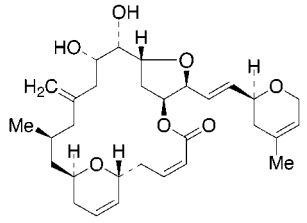
An enantioselective first total synthesis of laulimalide (**1**) is described. Laulimalide, a remarkably potent antitumor macrolide, has been isolated from the Indonesian sponge *Hyattella* sp. and the Okinawan sponge *Fasciospongia rimosa*. Laulimalide represents a new class of antitumor agents with significant clinical potential. The synthesis is convergent and involved the assembly of C_3-C_{16} segment **4** and $C_{17}-C_{28}$ segment **5** by Julia olefination. The sensitive C_2-C_3 *cis*-olefin functionality was installed by Yamaguchi macrolactonization of a hydroxy alkynic acid followed by hydrogenation of the resulting alkynoic lactone over Lindlar's catalyst. Initial attempts of intramolecular Still's variant of Horner−Emmons olefination between the C_{19}-phosphonocetate and C_3-aldehyde provided a 1:2 mixture of *cis*- and *trans*-macrolactones. The *trans*-isomer was photoisomerized to a mixture of *cis*- and *trans*-isomers. The other key steps involved ring-closing olefin metathesis to construct both dihydropyran units, stereoselective anomeric alkylation to functionalize the dihydropyran ring, stereoselective reduction of the resulting alkynyl ketone to set the C_{20}-hydroxyl stereochemistry, and a novel Julia olefination protocol for the installation of the C_{13}-*exo*-methylene unit. The sensitive epoxide at $C_{16}-C_{17}$ was introduced in a highly stereoselective manner by Sharpless epoxidation at the final stage of the synthesis.

Introduction

Macrocyclic marine natural products continue to provide a rich source of structurally diverse antitumor agents with significant therapeutic potential.[2] One such compound is laulimalide, a novel 18-membered macrolide which has exhibited remarkably potent antitumor properties. Laulimalide (**1**), also known as figianolide B, was isolated from the marine sponge *Cacospongia mycofijiensis* by Crews and co-workers in 1988.[3a] Moore et al. also isolated laulimalide from the Indonesian sponge *Hyattella* sp. in 1988.[3b] More recently, Higa and co-workers have isolated laulimalide (**1**, Figure 1) and isolaulimalide (**2**) from the Okinawan sponge *Fasciospongia rimosa*.[4] Upon treatment with 0.01 N HCl in acetone, laulimalide readily isomerizes to the tetrahydrofuran-containing metabolite isolaulimalide (**2**) via epoxide opening at C_{17} by the C_{20}-hydroxyl group. The gross structure of **1** was initially established by NMR studies.[3] Subsequently, its absolute configuration has been determined through X-ray analysis by Higa and co-workers.[4] Laulimalide exhibited very potent antitumor activity against numerous NCI cell lines. It displayed cytotoxicity against the KB cell line with an IC_{50} value of 15 ng/mL. Its cytotoxicity against P388, A549, HT29, and MEL28 cell lines ranged from 10 to 50 ng/mL (IC_{50} values).[3] Furthermore, laulimalide has maintained a high level of potency against the multidrug resistant cell line SKVLB-1 (IC_{50} = 1.2 μM). In contrast, isolaulimalide is significantly less potent against the KB cell line (IC_{50} > 200 nM) as well as the SKVLB-1 line (IC_{50} = 1.6 mM).[5] These results indicate that the epoxide moiety of laulimalide is critical for enhanced antitumor activities.



Laulimalide (1)



Isolaulimalide (2)

Figure 1.

Recently, Mooberry and co-workers have revealed that laulimalide shares the same mechanism of action as the anticancer drug Taxol (paclitaxel).[5] Thus far, only three other nontaxane natural products (epothilones,[6] disco-

(1) This work is dedicated to Professor A. I. Meyers with profound admiration and respect for his innumerable contributions to organic synthesis.

(2) Harris, C. R.; Danishefsky, S. J. *J. Org. Chem.* **1999**, *64*, 8434.

(3) (a) Quinoa, E.; Kakou, Y.; Crews, P. *J. Org. Chem.* **1988**, *53*, 3642. (b) Corley, D. G.; Herb, R.; Moore, R. E.; Scheuer, P. J.; Paul, V. J. *J. Org. Chem.* **1988**, *53*, 3644.

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dermolide,[7] and eleutherobin[8]) have shown similar microtubule stabilizing properties. One of the intriguing characteristics of laulimalide is that it not only exhibits potent microtubule-stabilizing properties but also inhibits the *P*-glycoprotein that is responsible for multiple-drug resistance in tumor cells. It has been shown that laulimalide is as much as 100-fold more potent than Taxol in multi-drug-resistant cell lines.[5] Thus, laulimalide represents a new class of microtubule-stabilizing agents with significant clinical potential.

The unique structural features, potent microtubule-stabilizing properties and low natural abundance of laulimalide, stimulated immense interest in its synthesis and structure−activity studies. Several synthetic approaches toward fragments of laulimalide have been reported by us[9] and others.[10] Paterson recently reported the synthesis of the laulimalide core in which the key step was an intramolecular Mitsunobu reaction to form the macrolactone ring.[10a] Mulzer also reported the synthesis of the C_1-C_{12} and $C_{15}-C_{28}$ fragments of laulimalide in which the key step was ring-closing olefin metathesis to form the dihydropyran ring.[10b] Nishiyama and Davidson also reported stereoselective syntheses of various fragments of laulimalide.[10d−f] Recently, we completed the first total synthesis of (−)-laulimalide (**1**).[11] An intramolecular Horner−Emmons reaction between the C_{19}-bis-(2,2,2-trifluroethyl)phophonoacetate and C_3-aldehyde was utilized in the key macrocyclization step. However, this macrocyclization reaction provided a mixture of C_2-C_3 *cis*- and *trans*-macrolactones. The isomers were separated, and the major *trans*-isomer was photoisomerized to the *cis*-isomer.[11] Subsequently, we have incorporated this sensitive C_2-C_3 *cis*-olefin functionality by macrolactonization of a hydroxy alkynoic acid followed by hydrogenation of the resulting alkyne derivative.[12] Herein, we report the full details of our synthetic studies.

Results and Discussion

Our synthetic strategy is outlined in Figure 2. Strategic disconnection of (−)-**1** at C_2-C_3 and removal of the epoxide functionality at $C_{16}-C_{17}$ provide the proper precursor (**3**) for the synthesis of (−)-**1**. An intramolecular Horner−Emmons reaction between the C_{19}-phosphonoacetate and the C_3-aldehyde, or Yamaguchi lactonization followed by Sharpless epoxidation would install the sensitive epoxide at $C_{16}-C_{17}$ at the final stage of the synthesis. In a retrosynthetic manner, the synthesis of **3** requires the assembly of C_3-C_{16} fragment **4** and $C_{17}-C_{28}$ fragment **5** by Julia olefination. Thus, this convergent approach involves the synthesis of key fragments **4** and **5** in enantiomerically pure form followed by coupling to form **3**. Aldehyde fragment **4** could be derived from alkylation of α-sulfonyl-γ-lactone (**6**) with iodide **8** followed by Julia olefination. Iodide **8** could be synthesized starting from known alcohol **10** using ring-closing olefin metathesis as the key step. Fragment **5** would be derived from a nucleophilic addition of **7**-derived alkynyl anion to aldehyde **9**. The corresponding stereogenic centers in **7** and **9** could be derived from glycidol THP ether **11**. Both dihydropyran rings of laulimalide would be constructed by ring-closing metathesis utilizing Grubbs' catalyst as the key step.[13]

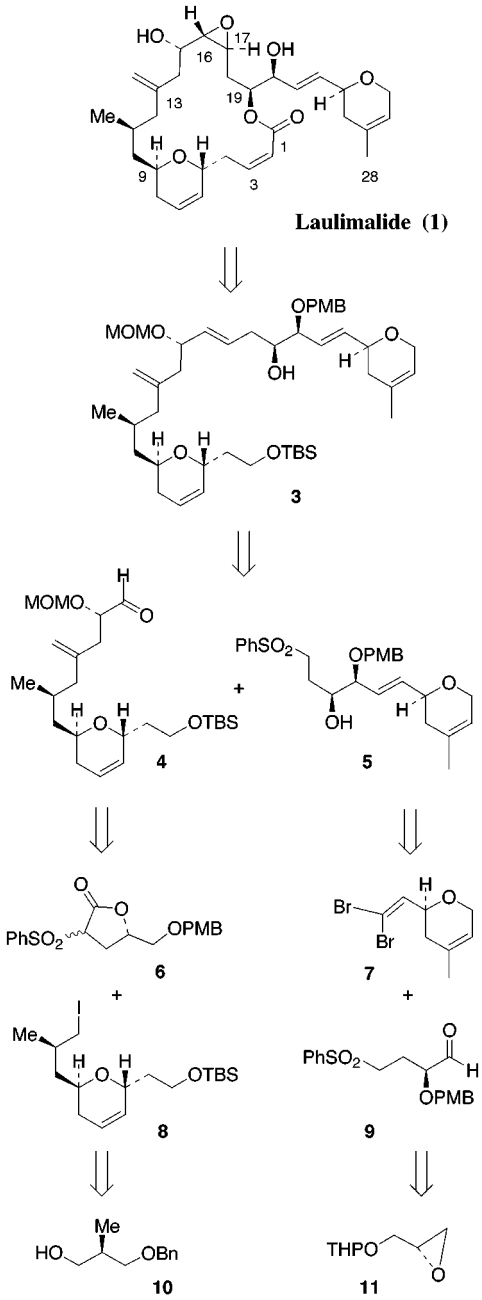

Figure 2. Retrosynthetic analysis.

Synthesis of C_3-C_{16} Fragment 4. As depicted in Scheme 1, synthesis of the C_3-C_{16} fragment began with

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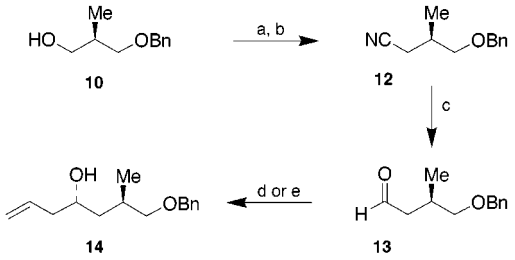
(12) Ghosh, A. K.; Wang, Y. *Tetrahedron Lett.* **2001**, *42*, 3399.

(13) For an excellent review, see: Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413.

Scheme 1[a]

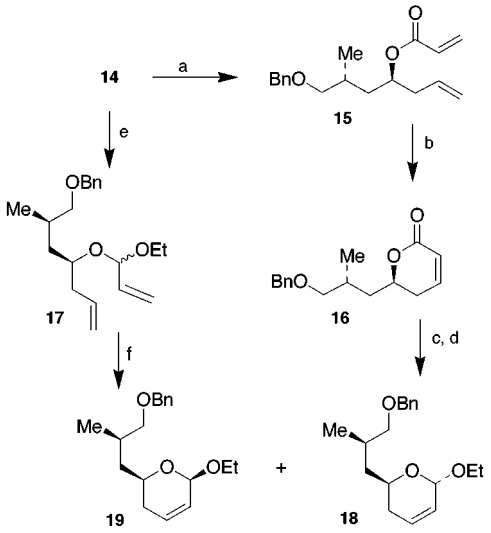


[a] Key: (a) MsCl, Et_3N, CH_2Cl_2, 0 °C; (b) NaCN, DMSO, 60 °C (95%); (c) DIBAL, CH_2Cl_2, 0 °C (93%); (d) $CH_2{=}CHCH_2B[(-)\text{-Ipc}]_2$, THF, −100 °C (75%); (e) (*S*)-BINOL, $Ti(OiPr)_4$, allyltributyltin, CH_2Cl_2, −20 °C (46%).

known optically active alcohol **10**,[14] which is readily prepared in two steps from commercially available methyl (*S*)-3-hydroxy-2-methylpropionate. Reaction of alcohol **10** with mesyl chloride and triethylamine in CH_2Cl_2 at 0 °C for 30 min followed by displacement of the resulting mesylate with sodium cyanide in dimethylsulfoxide (DMSO) at 60 °C for 2 h gave cyanide **12** in 95% yield for two steps. DIBAL reduction of cyanide **12** in CH_2Cl_2 at 0 °C for 30 min afforded aldehyde **13** in 93% yield. Subjection of aldehyde **13** to Brown's asymmetric allyboration protocol with allyldiisopinocampheylborane afforded homoallylic alcohol **14** diastereoselectively in 75% yield.[15] A diastereomeric ratio of 96:4 was determined by ^{1}H- and ^{13}C-NMR analysis. Alcohol **14** was also prepared diastereoselectively by an alternative procedure utilizing Keck's allylation protocol employing a catalytic amount of (*S*)-BINOL and titanium isopropoxide.[16] The observed diastereoselectivity was comparable (*de* 92% by ^{1}H- and ^{13}C-NMR analysis) to Brown's asymmetric allylation procedure; however, the reaction yield was poor (46% yield).

To construct the dihydropyran ring of fragment **4** with the appropriate stereochemistry, our plan was to form an α,β-unsaturated δ-lactone and then append the side chain at C_5 stereoselectively. For the synthesis of the corresponding α,β-unsaturated δ-lactone, we utilized the ring-closing olefin metathesis protocol described recently.[17] As shown in Scheme 2, alcohol **14** was reacted with acryloyl chloride and Et_3N in CH_2Cl_2 at 0 °C to afford acrylate ester **15** in 76% yield. Acrylate ester **15**, upon exposure to a catalytic amount of commercial Grubbs' catalyst (10 mol %) in CH_2Cl_2 in the presence of a catalytic amount (30%) of $Ti(O^iPr)_4$ at 40 °C for 5 h, provided α,β-unsaturated δ-lactone in 72% yield after silica gel chromatography. Reduction of δ-lactone **16** with DIBAL at −78 °C followed by reaction of the resulting lactol with EtOH in the presence of CSA furnished ethyl glycoside **18** in 82% yield. Glycoside **18** was formed as a single anomer due to the anomeric effect.[18,19] A mixture of anomeric ethyl glycosides **18** and **19** has also been

Scheme 2[a]



[a] Key: (a) $CH_2{=}CHCOCl$, Et_3N, CH_2Cl_2, 0 to 23 °C (76%); (b) $Cl_2(PCy_3)_2Ru{=}CHPh$ (10%), $Ti(OiPr)_4$ (30%), CH_2Cl_2, 40 °C (72%); (c) DIBAL, CH_2Cl_2, −78 °C; (d) CSA, EtOH (82%); (e) acrolein diethyl acetal, PPTS, benzene (83%); (f) $Cl_2(PCy_3)_2Ru{=}CHPh$ (10 mol %), CH_2Cl_2 (97%).

prepared by ring-closing metathesis of diene **17**.[20] Thus, transketalization of alcohol **14** with acrolein diethyl acetal in the presence of a catalytic amount of PPTS afforded diene **17** in 83% yield. Ring-closing olefin metathesis of **17** with Grubbs' catalyst[13] gave a mixture (1:1) of ethyl glycosides **18** and **19** in 97% yield.

The C_5 side chain was introduced by a highly stereoselective anomeric alkylation reaction. As illustrated in Scheme 3, ethyl acetals **18** and **19** were reacted with *tert*-butyldimethylsilyl vinyl ether in CH_2Cl_2 at 23 °C in the presence of Montmorillonite K-10 as the Lewis acid.[9c] The resulting aldehyde was reduced by $NaBH_4$ to furnish the corresponding dihydropyran derivative. The ^{1}H- and ^{13}C-NMR analysis revealed the presence of a single isomer, and the assigned stereochemistry was supported by NOESY experiments. The hydroxyl group was protected with TBSCl and imidazole to provide TBS ether **20**. Exposure of **20** to lithium in liquid ammonia removed the benzyl group, and the corresponding alcohol was obtained in 95% yield. Exposure of the resulting alcohol to iodine, triphenylphosphine, and imidazole in a mixture (2:1) of Et_2O and CH_3CN provided iodide **8**.[21]

The C_{13}-methylene unit and C_{15}-hydroxyl group were installed by a novel protocol utilizing alkylation of **6** followed by a Julia olefination reaction.[22] The requisite sulfonyl lactone **6** was prepared in multigram quantities by reaction of known[23] glycidol PMB ether **21** with the sodium enolate of methyl phenylsulfonyl acetate in EtOH at 23 °C for 12 h. Lactone **6** was isolated in 83% yield as a 2.4:1 mixture of diastereomers. Alkylation of **6** was

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(16) Keck, G. E.; Tarbet, K. H.; Geraci, L. S. *J. Am. Chem. Soc.* **1994**, *115*, 8467.

(17) (a) Ghosh, A. K.; Cappiello, J.; Shin, D. *Tetrahedron Lett.* **1998**, *39*, 4651. (b) Ghosh, A. K.; Liu, C. *Chem. Commun.* **1999**, 1743. (c) Nicolaou, K. C.; Rodriguez, R. M.; Mitchell, H. J.; van Delft, F. L. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 1874.

(18) Dahanukar, V. H.; Rynchnovsky, S. D. *J. Org. Chem.* **1994**, *61*, 8317.

(19) The stereochemistry of **18** was supported by NOESY ($CDCl_3$) experiment in which no NOE was observed between the C_5 proton and C_1 proton. However, a NOE was observed for the isomer **19**, which was prepared as a mixture in subsequent experiments.

(20) This approach was also utilized by Mulzer and Hanbauer during their synthesis of $C_1{-}C_{12}$ fragment of laulimalide; see: ref 10b.

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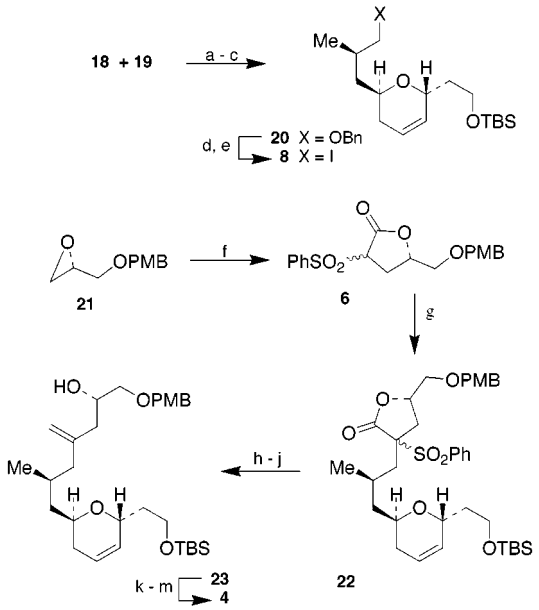
(22) Julia, M.; Paris, J. M. *Tetrahedron Lett.* **1973**, *14*, 4833.

(23) Smith, A. B.; Zhuang, L.; Brook, C. S.; Boldi, A. M.; MaBriar, M. D.; Moser, W. H.; Murase, N.; Nakayama, K.; Verhoest, P. R.; Lin, Q. *Tetrahedron Lett.* **1997**, *38*, 8667.

Scheme 3[a]

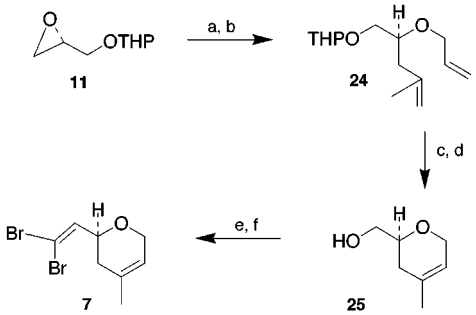


[a] Key: (a) K-10, CH_2=CHOTBS, CH_2Cl_2, 23 °C; (b) $NaBH_4$, MeOH, 0 °C (54%); (c) TBSCl, imidazole, DMF, 23 °C (75%); (d) Li, NH_3 (95%); (e) I_2, PPh_3, imidazole, Et_2O/CH_3CN (96%); (f) NaH, $PhSO_2CH_2CO_2Me$, EtOH, 23 °C (83%); (g) NaH, DMF, 0 °C then iodide **8**, 60 °C (89%); (h) Red-Al, THF, 0 °C; (i) PhCOCl, Et_3N, DMAP (cat.), CH_2Cl_2; (j) Na(Hg), Na_2HPO_4, MeOH, −20 to +23 °C (72%); (k) MOMCl, $^iPr_2NEt$, CH_2Cl_2; (l) DDQ, pH 7 buffer (81%); (m) DMSO, $(COCl)_2$, $^iPr_2NEt$, CH_2Cl_2, −78 °C (85%).

effectively carried out by treatment of **6** with NaH and iodide **8** in DMF initially at 0 °C for 15 min and then at 60 °C for 12 h. Alkylated lactone **22** was obtained in 89% yield as a mixture of isomers (4.2:1) by ^{1}H-NMR analysis. No attempts were made to determine the stereochemistry of the alkylated products, and the mixture was utilized in the next reaction. Red-Al reduction of lactone mixture **22** afforded the corresponding diols. Benzoylation of the resulting diols furnished the dibenzoate derivatives. Exposure of these dibenzoates to Na(Hg) in MeOH at −20° to +23 °C afforded **23** in 72% yield over the three step sequence.[24] Thus, the above methodology efficiently introduced the C_{13}-methylene unit and C_{15}-hydroxyl group in **23**, and this protocol may find further use in synthesis. Our subsequent synthetic plan was to convert **23** to aldehyde fragment **4**. This was accomplished in a three step sequence involving: (1) protection of the C_{15} -hydroxyl group as a MOM ether, (2) removal of the PMB group by exposure to DDQ, and (3) Swern oxidation of the resulting alcohol to furnish C_3−C_{16} segment **4** in 69% yield (from **23**).

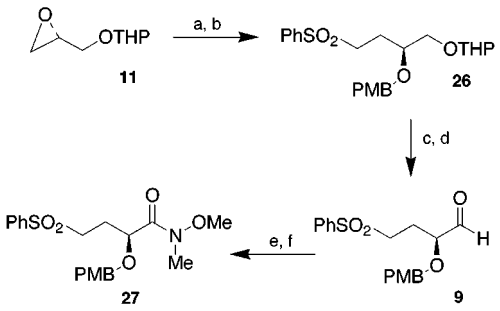
Synthesis of C_{17}−C_{28} Fragment 5. The synthesis of fragment **5** began with tetrahydropyranyl glycidol **11**[25] and utilized ring-closing olefin metathesis as the key step. Epoxide opening by isopropenylmagnesium bromide in the presence of a catalytic amount of CuCN at −78 to +23 °C for 2 h afforded the homoallylic alcohol in 94% yield. Treatment of the homoallylic alcohol with potassium hydride and allyl bromide in the presence of a catalytic amount of 18-crown-6 in THF furnished allyl ether **24** in quantitative yield. Exposure of **24** to Grubbs' catalyst (10 mol %) in CH_2Cl_2 at 23 °C for 2 h afforded the dihydropyran derivative which, upon exposure to CSA in methanol, provided alcohol **25** in 81% yield over two steps. Our next synthetic plan requires the conversion of dihydropyran **25** to dibromo olefin **7**, an alkynyl anion precursor. Thus, Swern oxidation of **25** followed by exposure of the resulting aldehyde to Corey−Fuchs' homologation conditions[26] with carbon tetrabromide and triphenylphosphine in CH_2Cl_2 at 0−23 °C for 30 min afforded dibromo olefin **7** in 67% yield over two steps (Scheme 4).

Scheme 4[a]



[a] Key: (a) Isopropenylmagnesium bromide, CuCN (10%), THF, −78 to +23 °C (94%); (b) KH, 18-crown-6 (cat.), allyl bromide, THF, 0 to 23 °C (quantitative); (c) $Cl_2(PCy_3)_2Ru$=CHPh (10%), CH_2Cl_2; (d) CSA, MeOH (81%); (e) DMSO, $(COCl)_2$, $^iPr_2NEt$, CH_2Cl_2, −78 °C; (f) CBr_4, PPh_3, CH_2Cl_2, 0−23 °C (67%).

Scheme 5[a]



[a] Key: (a) $PhSO_2CH_3$, ^{n}BuLi, THF, 0 °C, 1 h then HMPA, **11**, −78 to +23 °C (94%); (b) NaH, PMBCl, DMF, 0−23 °C (85%); (c) CSA, MeOH (91%); (d) DMSO, $(COCl)_2$, $^iPr_2NEt$, CH_2Cl_2, −78 °C (90%); (e) $NaClO_2$, 2-methyl-2-butene, NaH_2PO_4, ^{t}BuOH; (f) MeONHMe·HCl, *N*-methylpiperidine, isobutyl chloroformate, CH_2Cl_2, 0−23 °C (83%).

Optically active glycidol derivative **11** was also utilized in the preparation of aldehyde **9** and Weinreb amide **27.** As shown in Scheme 5, opening of epoxide **11** with lithiated methyl phenylsulfone in the presence of HMPA at −78 to +23 °C for 2 h provided the corresponding alcohol in 94% yield. Protection of the resulting alcohol with NaH and PMBCl in DMF at 0−23 °C furnished PMB ether **26**. Removal of the THP group by treatment with CSA in methanol followed by Swern oxidation of the resulting alcohol afforded aldehyde **9** in 82% for the two step sequence. Oxidation of aldehyde **9** by $NaClO_2$ gave the corresponding acid which was exposed to isobutyl chloroformate, *N*-methylpiperidine and *N*,*O*-dimethylhydroxyamine in CH_2Cl_2 at 0 °C to give Weinreb amide **27** in 83% yield for two steps.[27] Thus, with the preparation

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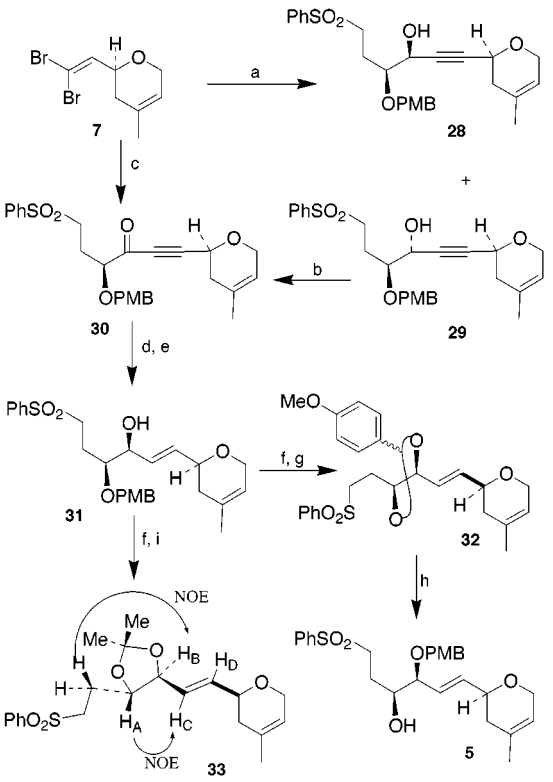
Scheme 6[a]



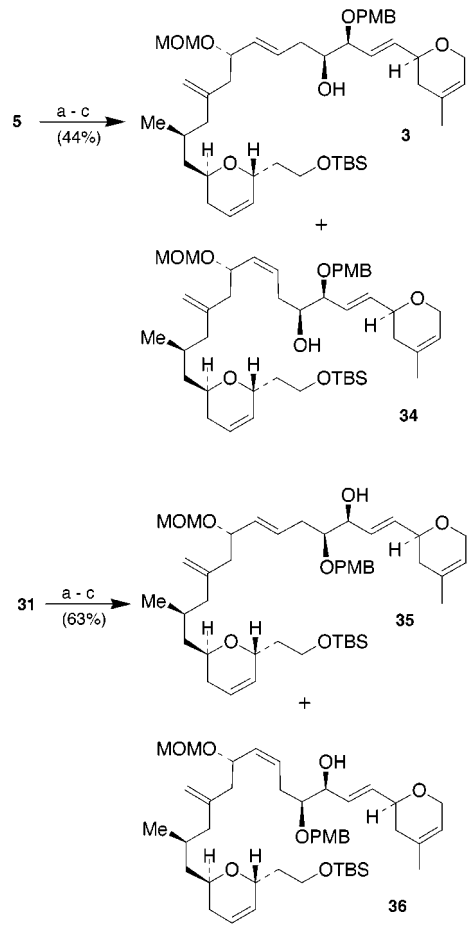
[a] Key: (a) *n*BuLi, −78 °C, THF, 1 h and 23 °C, 1 h then **9**, −78 °C (64%); (b) Dess−Martin, CH_2Cl_2, 23 °C (81%); (c) *n*BuLi, −78 °C, THF, 1 h and 23 °C, 1 h then **27**, −78 °C (59%); (d) L-Selectride, THF, −78 °C (87%); (e) Red-Al, THF, −20 °C (81%); (f) CF_3CO_2H, CH_2Cl_2, 23 °C; (g) *p*-MeO−Ph-$CH(OMe)_2$, CSA, CH_2Cl_2, 23 °C (71%); (h) DIBAL, CH_2Cl_2, −78 °C (74%); (i) $Me_2C(OMe)_2$, CSA, CH_2Cl_2, 23 °C (70%).

of aldehyde **9**, the stage was set for coupling with dibromo olefin **7**-derived alkynyl anion.

As illustrated in Scheme 6, coupling of the anion of **7** and aldehyde **9** was carried out by treatment of **7** with *n*BuLi followed by reaction of the resulting alkynyl anion with aldehyde **9** to provide an inseparable mixture of syn-alcohol **28** and *anti*-alcohol **29** (*syn:anti* = 1.8:1) in 64% yield. The selectivity for the desired *syn* isomer was improved by an oxidation/reduction sequence. Thus, the mixture of alcohols **28** and **29** were oxidized by Dess−Martin periodinane[28] to give alkynyl ketone **30**. Reduction of ketone **30** by L-selectride at −78 °C provided desired *syn*-alkynyl alcohol **28** as a single diasteromer by ^{1}H- and ^{13}C-NMR analysis. The reaction presumably proceeded via a Felkin−Anh model as described previously.[29] Attempts to obtain **28** by nucleophilic addition of the **7**-derived alkynyl anion to aldehyde **9** under chelation control were unsuccessful. Treatment of the dibromo olefin **7**-derived alkynyl anion with Weinreb amide **27** at −78 °C also provided an alternative access to alkynyl ketone **30** in 59% yield.

Reduction of alkynyl alcohol **28** with Red-Al in THF at −20 °C for 1 h set the C_{21}−C_{22} *trans*-olefin geometry. *Trans*-allylic alcohol **31** was obtained exclusively in 81% isolated yield. As outlined in our retrosynthetic analysis, fragment **5** requires the protection of the allylic alcohol

Scheme 7[a]



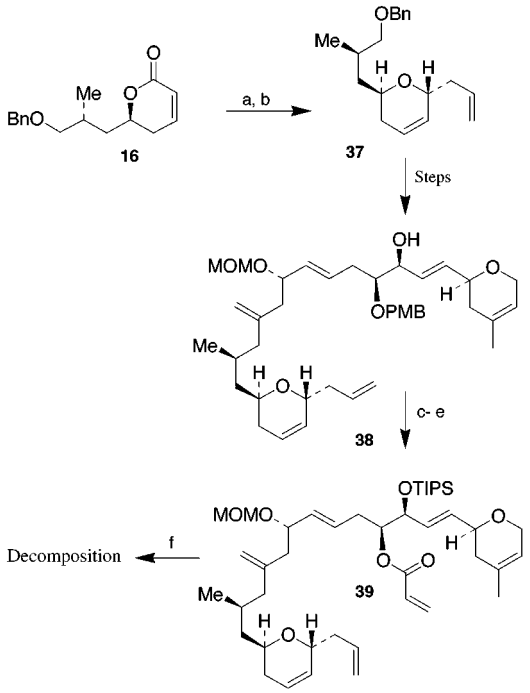
[a] Key: (a) ^{n}BuLi, −78 °C, THF, 15 min, and then **4**, −78 to −40 °C; (b) Ac_2O, Et_3N, DMAP (cat.); CH_2Cl_2; (c) Na(Hg), Na_2HPO_4, MeOH, −20 to +23 °C.

as a PMB ether. Thus, the C_{19}-PMB group was removed by exposure to TFA[30] and the resulting diol was treated with *p*-methoxybenzylidene acetal and CSA in CH_2Cl_2 to provide acetal **32** as a mixture of isomers in 71% combined yield (isomer ratio 4.3:1 by ^{13}C-NMR). DIBAL reduction of acetal **32** at −78 °C afforded C_{17}−C_{28} sulfone segment **5** as a single regioisomer by ^{1}H- and ^{13}C-NMR analysis. The observed regioselectivity of Dibal reduction is presumably due to stabilization of Al chelation by the sulfone oxygens.[31] To ascertain the C_{20}-hydroxyl stereochemistry and the C_{21}−C_{22} *trans*-olefin geometry, the PMB group of **31** was removed with trifluoroacetic acid in CH_2Cl_2 and the resulting diol was converted to isopropylidene derivative **33**. In compound **33**, NOEs were observed between H_A and H_C as well as between the β-sulfonyl hydrogens and H_B. The coupling constant (J_{CD}) of 15.5 Hz provided evidence of *trans*-olefin geometry.

Coupling of Fragments 4 and 5. With the efficient preparation of C_3−C_{16} aldehyde fragment **4** and C_{16}−C_{28} sulfone fragment **5**, our synthetic efforts were then focused on the assembly of these fragments by Julia olefination.[22] As shown in Scheme 7, sulfone **5** was first lithiated with 2.1 equiv of *n*BuLi in THF at −78 °C for 15 min. The resulting dianion was reacted with aldehyde **4** at −78 to −40 °C for 2 h to provide the corresponding

(27) Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, *22*, 3815.
(28) Merger, S. D.; Schreiber, S. L. *J. Org. Chem.* **1994**, *59*, 7549.
(29) Larcheveque, M.; Lalanov, J. *Chem. Commun.* **1985**, 83.
(30) Yan, L.; Kahne, D. *Synlett* **1995**, 523.
(31) We are currently investigating similar chelation controlled reduction in our laboratory.

Scheme 8[a]

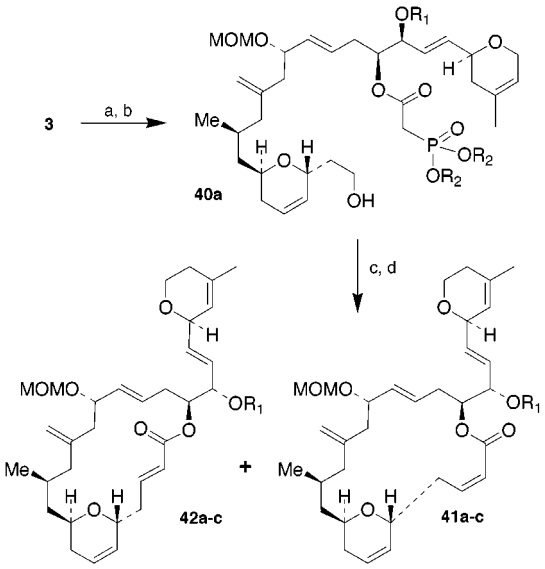


[a] Key: (a) DIBAL, CH_2Cl_2, −78 °C, and then Ac_2O, pyridine, DMAP, −78 to +23 °C; (b) $BF_3{\cdot}OEt_2$, CH_2Cl_2, $CH_2{=}CHCH_2SiMe_3$, −78 °C (82%); (c) TIPSOTf, 2,6-lutidine, CH_2Cl_2, 0−23 °C (80%); (d) DDQ, pH 7 buffer, CH_2Cl_2 (43%); (e) acryloyl chloride, Et_3N, CH_2Cl_2, 0 °C (49%); (f) $Cl_2(PCy_3)_2Ru{=}CHPh$ (10%), CH_2Cl_2.

mixture of α-hydroxy sulfone derivatives. Acylation of the resulting mixture with Ac_2O, Et_3N, and a catalytic amount of DMAP followed by exposure of the resulting diacetate to Na(Hg) in methanol at −20 to +23 °C furnished a mixture (3.4:1) of C_{16}−C_{17} *trans*-olefin **3** and *cis*-olefin **34** in 44% combined yield. Both isomers were separated by silica gel chromatography. Similarly, Julia reaction of isomeric sulfone **31** with aldehyde **4** as described above provided a mixture (2.7:1) of *trans*-olefin **35** and *cis*-olefin **36** in 63% combined yields. The isomers were again readily separated by silica gel chromatography.

Attempted Macrocyclization by Ring-Closing Olefin Metathesis. With successful Julia coupling of the key fragments, we now approached the crucial macrocyclization step which required the formation of an 18-membered α,β-unsaturated macrolactone with C_2−C_3 *cis*-olefin geometry. Initially, we relied upon a ring-closing olefin metathesis approach to construct the macrolactone.[13] To incorporate the corresponding allyl side chain at C_5, δ-lactone **16** was utilized. As depicted in Scheme 8, reduction of **16** with DIBAL at −78 °C followed by reaction of the resulting lactol with acetic anhydride, pyridine, and DMAP, as described by Dahanukar and Rychnovsky provided the corresponding glycosyl acetate.[18] Exposure of the acetate to allyltrimethylsilane in the presence of $BF_3{\cdot}Et_2O$ in CH_2Cl_2 at −78 °C afforded anomeric allyation product **37** as a single isomer (82% from **16**). Allyl derivative **37** was transformed into the key macrolactonization precursor **38** as described above. Protection of **38** as a TIPS ether followed by removal of the PMB group by DDQ and acylation with acryloyl chloride and Et_3N afforded acrylate ester **39**. Unfortunately, attempted ring-closing olefin metathesis of **39** under a variety of reaction conditions resulted in decomposition of the starting material. We then focused our attention on the following intramolecular Horner−Emmons olefination-based approach.

Scheme 9[a]



Compd.	R_1	R_2	*cis/trans* (**41:42**)	Yield
40a	PMB	CH_2CF_3	1 : 2	84%
40b	TIPS	CH_2CF_3	1 : 10	64%
40c	MOM	CH_2CF_3	1 : 1.5	88%
40d	PMB	Ph	1 : 1.7	69%

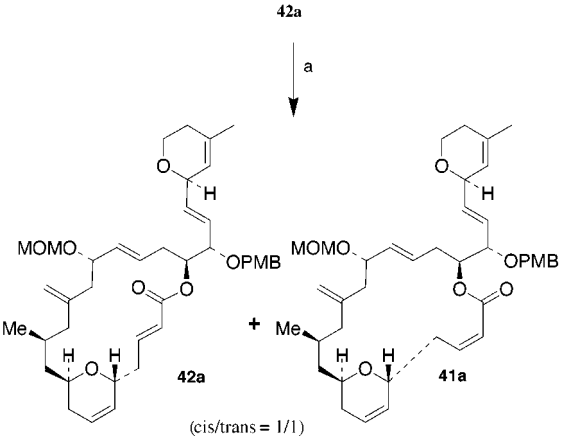
[a] Key: (a) $(CF_3CH_2O)_2P(O)CH_2CO_2H$, $Cl_3C_6H_2COCl$, $^iPr_2NEt$, DMAP, benzene; (b) AcOH−THF−H_2O (3:1:1), 23 °C (99%); (c) Dess−Martin, CH_2Cl_2, 23 °C (79%); (d) K_2CO_3, 18-crown-6, toluene, −20 to 0 °C (84%).

Macrocyclization by Intramolecular Horner−Emmons Reaction. Intramolecular Horner−Emmons reactions have been utilized in the syntheses of many functionalized macrolactones.[32] Recently, Forsyth[33] employed this reaction to install the key *cis*-macrolactone moiety of phorboxazole. Encouraged by this precedence, we planned to carry out the intramolecular Horner−Emmons reaction between the C_{19}-phosphonoacetate and C_3-aldehyde using Still's protocol.[34] As outlined in Scheme 9, acylation of the C_{19}-hydroxy group with bis(2,2,2-trifluoroethyl)phosphonoacetic acid under Yamaguchi conditions afforded the corresponding ester.[35] Removal of the TBS group by exposure to aqueous acetic acid in THF at 23 °C furnished alcohol **40a** in near quantitative yield. Oxidation of alcohol **40a** with Dess−Martin periodinane[28] followed by treatment of the resulting aldehyde with K_2CO_3 in the presence of 18-crown-6 in toluene at −20 to 0 °C afforded a mixture (1:2) of *cis*- and *trans*-macrolactones **41a** and **42b** in 84% isolated yield. Both isomers were separated by silica gel chromatography.

Many attempts to improve the ratio of the desired cis-isomer by changing the protecting group at C_{20} were

(32) Maryanoff, B. E.; Reitz, A. B. *Chem. Rev.* **1989**, *89*, 863.
(33) Forsyth, C. J.; Ajmed, F.; Cink, R. D.; Lee, C. S. *J. Am. Chem. Soc.* **1998**, *120*, 5597.
(34) Still, W. C.; Gennari, C. *Tetrahedron Lett.* **1983**, *24*, 4405.
(35) Inanaga, J.; Hirata, K.; Saeki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *53*, 1989.

Scheme 10[a]



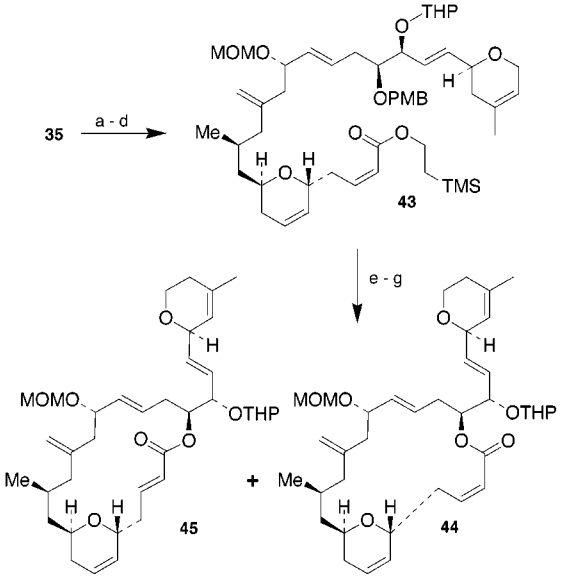
[a] Key: (a) *hν*, Et_2O (66%).

unsuccessful. Horner−Emmons reaction of **40b** with the C_{20} alcohol protected as a TIPS ether under the above reaction conditions provided a mixture of macrolactones **41b** and **42b** (*cis:trans* = 1:10) in 64% yield. Small protecting groups such as MOM and MEM (**40c** for MOM) resulted in a slight improvement in the *cis*-isomer ratio. Formation of (diphenylphosphono)acetate derivative **40d** and subsequent Horner−Emmons reaction resulted in only slight improvement of *cis*-selectivity (*cis*:*trans* = 1:1.7) at the expense of yield.[36] Attempts to improve the ratio by forming the C_{16}−C_{17} epoxide or changing reaction conditions were also unsuccessful.

To improve the overall yield of *cis*-macrolactone **41**, we attempted photoisomerization of *trans*-macrolactone **42a**. As depicted in Scheme 10, irradiation of **41a** was performed in ether under UV in a Rayonet photochemical reactor for 50 min to furnish a 1:1 mixture of *trans*-macrolactone **42a** and *cis*-macrolactone **41a** in 66% yield.[37] Reaction time is critical as prolonged time of irradiation did not increase the yield of the *cis*-isomer, but resulted in decomposition of both isomers. Since both isomers were separated, the overall yield of desired *cis*-macrolactone **41a** was improved to 47% after photoisomerization. The identity of the olefin geometry of the *cis*- and *trans*-isomers were established by their observed coupling constants (J = 11.6 Hz for **41a** and 17 Hz for **42b**).

Yamaguchi Macrocyclization. To set the *cis*-olefin geometry, we investigated the Yamaguchi macrolactonization of the appropriate *cis*-α,*β*-unsaturated acid. Preparation of such a sensitive *cis*-α,*β*-unsaturated acid was previously reported by Roush during the synthesis of verrucarin B.[38] We therefore examined the macrolactonization between the C_{19}-hydroxyl group and the C_1-alkenyl acid utilizing Yamaguchi protocol. As illustrated in Scheme 11, we chose to use a 2-(trimethylsilyl)ethyl ester as the precursor for the C_1-alkenyl acid. It has been shown by Roush and Blizzard that such an ester blocking group can be removed under mild conditions.[38b] It should be noted that attempts to obtain the *Z*-acid by hydrolyzing the corresponding methyl ester resulted in deconjugation and isomerization, which was also observed by

Scheme 11[a]



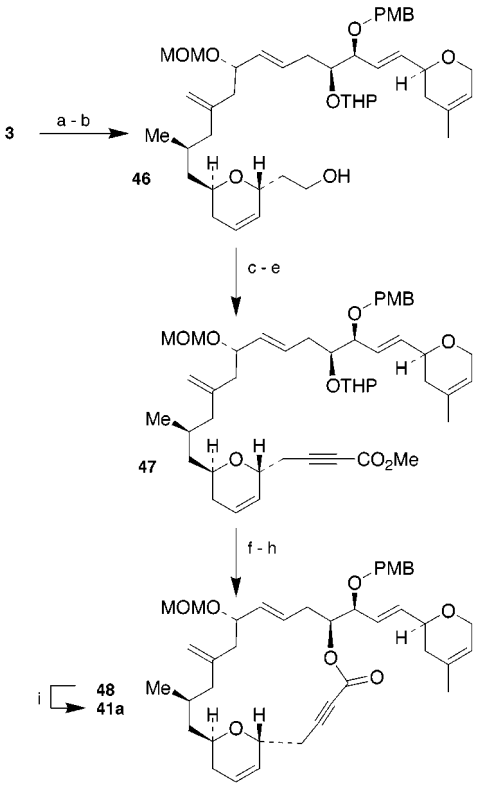
[a] Key: (a) Dihydropyran, PPTS, CH_2Cl_2; (b) TBAF, THF (76%); (c) Dess−Martin, CH_2Cl_2; (d) KN(TMS)$_2$, 18-crown-6, $(PhO)_2P(O)CH_2CO_2CH_2CH_2SiMe_3$, THF, −78 °C (64%); (e) DDQ, pH 7 buffer; (f) TBAF, THF (60%); (g) $Cl_3PhCOCl$, $^iPr_2NEt$, THF and then DMAP, benzene (65%).

Paterson.[10a] Thus, alcohol **35** was reacted with dihydropyran and a catalytic amount of PPTS in CH_2Cl_2 and the resulting THP ether was treated with TBAF in THF to provide the corresponding primary alcohol in 76% yield for two steps. Oxidation of the primary alcohol with Dess−Martin periodinane[28] and subsequent Horner−Emmons reaction of the resulting aldehyde with $(PhO)_2P(O)CH_2CO_2CH_2CH_2SiMe_3$, KN(TMS)$_2$, and 18-crown-6 furnished *cis*-α,*β*-unsaturated ester **43** in 64% yield as a single isomer by ^{1}H-NMR (400 MHz) analysis. Successive treatment of **43** with DDQ and TBAF in THF resulted in the removal of the PMB ether and silyl ester, respectively. The corresponding *cis*-hydroxy acid was obtained in 60% yield. Exposure of the resulting acid to Yamaguchi lactonization conditions[35] at 23 °C, however, provided a mixture of *cis*- and *trans*-macrolactones **44** and **45** (*cis*:*trans* = 1:2) in 65% isolated yield. Roush had previously observed such an isomerization of a *cis*-olefin during the macrolactonization step of the verrucarin B synthesis. He proposed that the reason for this olefin isomerization was probably due to the reversible Michael addition of the acylating catalyst (DMAP) to the active acylating agent.[38] Numerous attempts to effect this cyclization under a variety of reaction conditions (base, acylating agent, etc.) did not increase the ratio of desired *cis*-isomer **44**. The inability of the Horner−Emmons reaction or the Yamaguchi macrolactonization of the *cis*-α,*β*-unsaturated acid to set the *Z*-olefin geometry efficiently prompted us to investigate the Yamaguchi macrolactonization of a hydroxy alkynoic acid. Once this alkynyl macrolactone is formed, one can easily set the *cis*-olefin geometry by selective hydrogenation of the alkyne functionality.

As shown in Scheme 12, the C_{19}-alcohol of **3** was first protected as a THP ether by treatment with dihydropyran in the presence of PPTS in CH_2Cl_2. Subsequent removal of the TBS ether by reaction with nBu$_4$N$^+$F$^-$ in THF furnished primary alcohol **46** in 87% yield for the two step sequence. Oxidation of alcohol **46** with Dess−

(36) Ando, K. *J. Org. Chem.* **1999**, *64*, 8409, and references therein.
(37) Smith, A. B.; Lupo, A. T.; Ohba, M.; Chen, K. *J. Am. Chem. Soc.* **1989**, *111*, 6648.
(38) (a) Roush, W. R.; Spada, A. P. *Tetrahedron Lett.* **1983**, *24*, 3693. (b) Roush, W. R.; Blizzard, T. A. *J. Org. Chem.* **1994**, *59*, 7549.

Scheme 12[a]



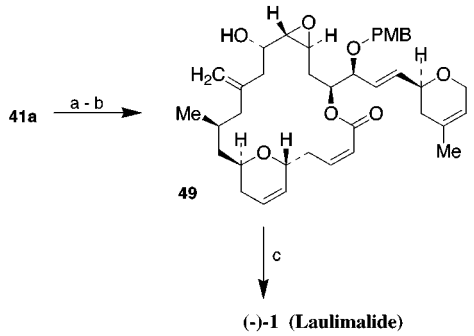
[a] Key: (a) Dihydropyran, PPTS, CH_2Cl_2; (b) TBAF, THF (87%); (c) Dess−Martin, CH_2Cl_2; (d) CBr_4, PPh_3, CH_2Cl_2, 0 °C; (e) ^{n}BuLi, THF, −78 °C, and then $ClCO_2Me$, −78 °C (59%); (f) CSA, MeOH; (g) LiOH, THF, H_2O (74%); (h) $Cl_3PhCOCl$, $^i Pr_2NEt$, THF and then DMAP, benzene (68%); (i) H_2, Lindlar's catalyst, 1-hexene, EtOAc (94%).

Martin periodinane provided the aldehyde which was subjected to Corey−Fuchs' homologation conditions[26] using CBr_4 and PPh_3 in CH_2Cl_2 at 0 °C to afford the corresponding dibromo olefin. This olefin was then converted to alkynyl ester **47** in a one-pot procedure. Thus, reaction of the dibromo olefin with *n*BuLi at −78 °C afforded the alkynyl anion, which, upon treatment with methyl chloroformate at −78 °C, furnished **47** in 59% yield for the three-step sequence. Removal of the THP ether by exposure to CSA in methanol followed by saponification of the methyl ester by treatment with aqueous lithium hydroxide afforded the precursor hydroxy acid in 74% yield. We now arrived at the critical macrolactonization step. Thus, subjection of the hydroxy acid to Yamaguchi conditions[35] with 2,4,6-trichlorobenzoyl chloride, *N*,*N*-diisopropylethylamine and DMAP furnished macrolactone **48** in 68% yield. Hydrogenation of lactone **48** over Lindlar's catalyst in a mixture (1:1) of 1-hexene and EtOAc provided *cis*-macrolactone **41a** as a single isomer in 94% yield.[39]

Synthesis of Laulimalide. The completion of the synthesis of (−)-laulimalide is outlined in Scheme 13. At this point, our synthetic plan required selective removal of the C_{15}-MOM protecting group to effect selective epoxidation of the resulting allylic alcohol utilizing Sharpless epoxidation. Thus, the C_{15}-MOM group of **41a** was selectively removed by treatment with excess PPTS in *t*BuOH followed by heating the resulting mixture at

(39) Ho, T.-L.; Liu, S. H. *Synth. Commun.* **1987**, *17*, 969.

Scheme 13[a]



[a] Key: (a) PPTS, *tert*-butyl alcohol, 84 °C (45%); (b) TBHP, (+)-DET, $Ti(O^iPr)_4$, CH_2Cl_2, −20 °C; (c) DDQ, pH 7 buffer, CH_2Cl_2 (48%).

reflux for 8 h.[40] The desired allylic alcohol was obtained in 45% isolated yield. Attempts to improve this selective deprotection with other acid-catalyzed reaction conditions were less effective because of substantial decomposition of the molecule. Sharpless epoxidation[41] of the resulting alcohol with (+)-DET proceeded uneventfully to afford epoxide **49** as a single isomer by ^{1}H-NMR and ^{13}C-NMR analysis. Removal of the C_{20}−PMB ether by exposure to DDQ furnished synthetic (−)-laulimalide (**1**) in 48% yield for the two step sequence. Spectral data (^{1}H- and ^{13}C-NMR) and TLC characteristics of synthetic laulimalide ($[\alpha]^{23}_D = -196$ *c* 0.23, $CHCl_3$) are in full agreement with a sample of natural laulimalide (lit.[4] $[\alpha]^{29}_D = -200$ *c* 1.03, $CHCl_3$) kindly provided by Professor Higa.

Conclusion

A stereocontrolled and convergent synthesis of (−)-laulimalide has been achieved in 30 steps (the longest linear sequence). A number of key features of this synthesis are noteworthy. The synthesis features a Julia reaction for coupling of the C_3−C_{16} and C_{17}−C_{28} fragments and development of both intramolecular Horner−Emmons reaction and Yamaguchi lactonization protocols for the construction of the macrolactone with *cis*-olefin geometry. The *trans*-macrolactone could be photoisomerized to a 1:1 mixture of *cis*- and *trans*-isomers. Other key steps included the ring-closing olefin metathesis to construct both dihydropyran rings, a highly diastereoselective anomeric alkylation to append the side chain of one of the dihydropyrans, and a novel Julia reaction protocol for installation of the C_{13}-*exo*-methlene and C_{15}-hydroxy group. The present synthesis will provide convenient access to a variety of structural analogues of laulimalide for biological studies.

Experimental Section

Melting points were recorded and are uncorrected.Anhydrous solvents and reagents were obtained as follows: tetrahydrofuran and diethyl ether, distillation from sodium and benzophenone; methylene chloride, distillation from CaH_2; triethylamine, distillation from CaH_2. All other solvents were HPLC grade. Column chromatography was performed with Whatman 240−400 mesh silica gel under low pressure of 5−10

(40) Monti, H.; Leandri, G.; Klos-Ringquet, M.; Corriol, C. *Synth. Commun.* **1983**, *37*, 1013.

(41) Johnson, R. A.; Sharpless, K. B. In *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; VCH Publishers: New York, 1993; pp 103−158.

psi. Thin-layer chromatography (TLC) was carried out with E. Merck silica gel 60 F-254 plates.

Alcohol 46. To a stirred solution of alcohol **3** (125 mg, 0.17 mmol) in CH_2Cl_2 (3 mL) was added dihydropyran (0.3 mL) followed by PPTS (10 mg). The resulting mixture was stirred at 23 °C for 5 h. After this period, the mixture was washed with saturated aqueous $NaHCO_3$ and brine. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. After azeotropic removal of water with benzen, the residue was dissolved in THF. TBAF (0.5 mL, 1.0 M in THF; 0.5 mmol) was added dropwise. The resulting mixture was stirred at 23 °C for 3 h. The mixture was quenched with saturated aqueous NH_4Cl and extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (40% EtOAc/hexane) to afford alcohol **46** as a colorless oil (102 mg, 87%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.22 (d, J = 8.4 Hz, 2H), 6.86 (d, J = 8.4 Hz, 2H), 5.87−5.75 (m, 2H), 5.72−5.63 (m, 2H), 5.57 (m, 1H), 5.43 (s, 1H), 5.29 (m, 1H), 4.84 (s, 1H), 4.78 (s, 1H), 4.68 (d, J = 6.8 Hz, 1H), 4.57 (d, J = 11.6 Hz, 1H), 4.46 (d, J = 6.8 Hz, 1H), 4.36 (m, 1H), 4.35 (d, J = 11.6 Hz, 2H), 4.19 (s, 2H), 4.15−4.05 (m, 2H), 3.88 (m, 1H), 3.83−3.70 (m, 5H), 3.80 (s, 3H), 3.42 (m, 1H), 3.31 (s, 3H), 2.38−1.78 (m, 20H), 1.72 (s, 3H), 1.69−1.63 (m, 2H), 1.10 (m, 1H), 0.87 (d, J = 6.7 Hz, 3H). HRMS (FAB). Calcd for $C_{43}H_{64}O_9Na$ [$(M + Na)^+$]: 747.4448. Found: 747.4479.

Alkynyl Ester 47. To a stirred solution of alcohol **46** (100 mg, 0.138 mmol) in wet CH_2Cl_2 (3 mL) was added Dess−Martin periodinane (114 mg, 0.263 mmol). The resulting white suspension was stirred for 30 min. After this period, the mixture was subjected to direct silica gel chromatography eluting with 20−25% EtOAc/hexane to afford the aldehyde (87.5 mg, 88%) as a colorless oil which was used for next reaction immediately. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.80 (t, J = 1.4 Hz, 1H), 7.22 (d, J = 8.4 Hz, 2H), 6.86 (d, J = 8.4 Hz, 2H), 5.87−5.75 (m, 2H), 5.72−5.63 (m, 2H), 5.57 (m, 1H), 5.43 (s, 1H), 5.29 (m, 1H), 4.84 (s, 1H), 4.78 (s, 1H), 4.68 (d, J = 6.8 Hz, 1H), 4.57 (d, J = 11.6 Hz, 1H), 4.46 (d, J = 6.8 Hz, 1H), 4.35 (d, J = 11.6 Hz, 2H), 4.19 (s, 2H), 4.15−4.05 (m, 2H), 3.89−3.70 (m, 4H), 3.80 (s, 3H), 3.42 (m, 1H), 3.31 (s, 3H), 2.73 (m, 1H), 2.52 (dd, J = 15.9, 4.5 Hz, 1H), 2.38−1.78 (m, 16H), 1.72 (s, 3H), 1.69−1.63 (m, 2H), 1.10 (m, 1H), 0.86 (d, J = 6.7 Hz, 3H).

To a stirred solution of CBr_4 (102 mg, 0.31 mmol) in CH_2Cl_2 (3 mL) at 0 °C was sequentially added triphenylphosphine (161 mg, 0.61 mmol) and triethylamine (0.1 mL, 0.7 mmol). The resulting yellow solution was stirred for 10 min. A solution of the above aldehyde in CH_2Cl_2 (3 mL) was added dropwise. The mixture was stirred at 0 °C for 30 min. After this period, the mixture was washed with saturated aqueous $NaHCO_3$, 1 M $NaHSO_4$, and brine. The organic layer was dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by silica gel chromatography (15% EtOAc/hexane) to provide the dibromide (94.3 mg, 89%) which was used for next reaction immediately. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.22 (d, J = 8.4 Hz, 2H), 6.86 (d, J = 8.4 Hz, 2H), 6.50 (t, J = 6.7 Hz, 1H), 5.87−5.75 (m, 2H), 5.72−5.63 (m, 2H), 5.57 (m, 1H), 5.43 (s, 1H), 5.29 (m, 1H), 4.84 (s, 1H), 4.78 (s, 1H), 4.68 (d, J = 6.8 Hz, 1H), 4.57 (d, J = 11.6 Hz, 1H), 4.46 (d, J = 6.8 Hz, 1H), 4.35 (d, J = 11.6 Hz, 2H), 4.19 (s, 2H), 4.15−4.05 (m, 2H), 3.89−3.70 (m, 4H), 3.80 (s, 3H), 3.42(m, 1H), 3.31 (s, 3H), 2.43−1.49 (m, 17H), 1.72 (s, 3H), 1.10 (m, 1H), 0.87 (d, J = 6.7 Hz, 3H).

To a stirred solution of the above dibromide (94.3 mg, 0.108 mmol) in THF (3 mL) at −78 °C was added ^{n}BuLi (0.15 mL, 1.6 M in hexane; 0.24 mmol) dropwise. The resulting red mixture was stirred for 10 min. $ClCO_2Me$ (20 μL, 0.258 mmol) was added dropwise. The mixture was stirred at −78 °C for 30 min before being quenched by saturated aqueous NH_4Cl. The mixture was extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by silica gel chromatography (20% EtOAc/hexane) to afford alkynyl ester **47** (63 mg, 75% yield, 59% for three steps). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.20 (d, J = 8.6 Hz, 2H), 6.85 (d, J = 8.6 Hz, 2H), 5.91 (m, 1H), 5.86−5.50 (m, 4H), 5.42 (s, 1H), 5.28 (m, 1H), 4.83 (s, 1H), 4.78 (s, 1H), 4.67 (d, J = 6.8 Hz, 1H), 4.57 (d, J = 11.6 Hz, 1H), 4.44 (d, J = 6.8 Hz, 1H), 4.31 (d, J = 11.6 Hz, 2H), 4.18 (s, 2H), 4.10−3.99 (m, 3H), 3.88 (m, 1H), 3.83−3.69 (m, 4H), 3.79 (s, 3H), 3.73 (s, 3H), 3.41 (m, 1H), 3.31 (s, 3H), 2.61 (dd, J = 16.8, 6.7 Hz, 2H), 2.41−1.79 (m, 11H), 1.71 (s, 3H), 1.68−1.41 (m, 6H), 1.11 (m, 1H), 0.88 (d, J = 6.1 Hz, 3H). HRMS (FAB). Calcd for $C_{46}H_{64}O_{10}Na$ [$(M + Na)^+$]: 799.4397. Found: 799.4395.

Macrolactone 48. To a stirred solution of ester **47** (34 mg, 0.044 mmol) in MeOH (2 mL) was added CSA (4 mg). The resulting mixture was stirred for 1 h. After this period, Et_3N (1 drop) was added. The mixture was concentrated under reduced pressure. The residue was dissolved in THF (2.5 mL). A solution of LiOH (10 mg, 0.24 mmol) in H_2O (0.5 mL) was added. The resulting mixture was stirred for 2 h. After this period, saturated aqueous NH_4Cl was added. The mixture was extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by silica gel chromatography (20% MeOH/EtOAc) to afford the hydroxy acid (22 mg, 74%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.23 (d, J = 8.6 Hz, 2H), 6.86 (d, J = 8.6 Hz, 2H), 5.85−5.60 (m, 5H), 5.43 (s, 1H), 5.37 (dd, J = 15.6, 7.5 Hz 1H), 4.85 (s, 1H), 4.78 (s, 1H), 4.63 (d, J = 6.9 Hz, 1H), 4.59 (d, J = 11.8 Hz, 1H), 4.47 (d, J = 6.8 Hz, 1H), 4.32 (m, 1H), 4.28 (d, J = 11.8 Hz, 1H), 4.20 (brs, 2H), 4.14−4.08 (m, 2H), 3.80 (s, 3H), 3.74−3.63 (m, 3H), 3.30 (s, 3H), 2.71 (dd, J = 17.4, 11.1 Hz, 1H), 2.37 (dd, J = 17.4, 2.7 Hz, 1H), 2.34−1.79 (m, 12H), 1.71 (s, 3H), 1.68−1.63 (m, 2H), 1.08 (m, 1H), 0.82 (d, J = 6.4 Hz, 3H). HRMS (FAB). Calcd for $C_{40}H_{54}O_9Na$ [$(M + Na)^+$]: 701.3666. Found: 701.3677.

To a stirred solution of the above hydroxy acid (14 mg, 0.02 mmol) in THF (1.5 mL) was added ^{i}Pr$_2$NEt (0.17 mL, 0.4 M in benzene; 0.07 mmol) and trichlorobenzoyl chloride (0.11 mL, 0.4 M in benzene; 0.044 mmol). The resulting mixture was stirred for 30 min. The mixture was concentrated under reduced pressure. The residue was dissolved in benzene (21 mL). DMAP (10 mg, 0.082 mmol) in benzene (3 mL) was added dropwise over a period of 30 min. The resulting suspension was stirred for 12 h. The mixture was diluted with EtOAc and washed with saturated aqueous $NaHCO_3$ and aqueous 1 M $NaHSO_4$. The aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by silica gel chromatography (20% EtOAc/hexane) to afford lactone **48** as a colorless oil (9.2 mg, 68%). $[\alpha]_D^{23}$ −46 (*c* 0.92, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.23 (d, J = 8.6 Hz, 2H), 6.86 (d, J = 8.6 Hz, 2H), 5.89 (m, 1H), 5.86 (dd, J = 15.6, 5.6 Hz, 1H), 5.63−5.57 (m, 3H), 5.51 (dd, J = 15.6, 6.8 Hz, 1H), 5.43 (s, 1H), 5.10 (m, 1H), 4.85 (s, 1H), 4.78 (s, 1H), 4.63 (d, J = 6.9 Hz, 1H), 4.59 (d, J = 11.8 Hz, 1H), 4.47 (d, J = 6.8 Hz, 1H), 4.43 (brd, 11.0 Hz, 1H), 4.32 (d, J = 11.8 Hz, 1H), 4.20 (brs, 2H), 4.08 (m, 1H), 3.85 (t, J = 6.4 Hz, 1H), 3.80 (s, 3H), 3.69 (m, 1H), 3.30 (s, 3H), 2.71 (dd, J = 17.4, 11.1 Hz, 1H), 2.37 (dd, J = 17.4, 2.7 Hz, 1H), 2.34−1.79 (m, 12H), 1.71 (s, 3H), 1.58 (m, 1H), 1.08 (m, 1H), 0.82 (d, J = 6.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.2, 159.1, 153.1, 144.7, 135.8, 134.9, 131.3, 130.1, 129.3, 127.6, 126.9, 126.7, 126.2, 119.7, 113.7, 113.5, 94.0, 86.8, 79.2, 76.2, 73.9, 73.2, 71.1, 70.1, 65.6, 65.1, 55.4, 55.2, 45.0, 43.2, 41.1, 35.7, 32.2, 31.3, 26.0, 24.0, 23.0, 18.5. HRMS (FAB). Calcd for $C_{40}H_{52}O_8Na$ [$(M + Na)^+$]: 683.3560. Found: 683.3593.

Macrolactone 41a (from 48). To a solution of lactone **48** (8.5 mg, 0.013 mmol) in 1-hexene (1 mL) and EtOAc (1 mL) was added Lindlar catalyst (2 mg). The resulting suspension was vigorously stirred under a hydrogen balloon for 1.5 h. The mixture was filtered through a pad of Celite and washed with EtOAc. Concentration of the filtrate gave a residue, which was purified by silica gel chromatography (20% EtOAc/hexane) to afford *cis*-macrolactone **41a** (8.0 mg, 94%).

Epoxide 49. A mixture of macrolactone **41a** (15.6 mg, 0.024 mmol) and PPTS (81 mg, 0.32 mmol) in *tert*-butyl alcohol (1 mL) was heated at 83 °C for 8 h. The mixture was cooled to 23 °C and poured into water. The resulting mixture was extracted with 25% EtOAc/hexane. The combined organic

layers were washed with brine, dried over anhydrous Na_2SO_4, and evaporated. The residue was chromatographed over silica gel eluting with 20% EtOAc/hexane to furnish the allylic alcohol as a colorless oil (6.5 mg, 45%). $[\alpha]_d^{23} = -125$ (*c* 0.14, $CHCl_3$). IR (thin film): 3500, 1718 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.22 (d, $J = 8.6$ Hz, 2H), 6.86 (d, $J = 8.6$ Hz, 2H), 6.31 (m, 1H), 5.91(d, $J = 11.6$ Hz, 1H), 5.84 (dd, $J = 15.6$, 6.2 Hz, 1H), 5.83 (m, 1H), 5.70 (d, $J = 10.6$ Hz, 1H), 5.63−5.58 (m, 3H), 5.43 (s, 1H), 5.06 (m, 1H), 4.84 (s, 2H), 4.59 (d, $J =$ 11.8 Hz, 1H), 4.31 (d, $J = 11.8$ Hz, 1H), 4.19 (s, 2H), 4.15−4.06 (m, 3H), 3.85 (m, 1H), 3.80 (s, 3H), 3.55 (m, 1H), 2.33−1.76 (m, 12H), 1.71 (s, 3H), 1.65 (m, 1H), 1.37−1.12 (m, 3H), 0.79 (d, $J = 6.8$ Hz, 3H). MS (ESI): 641 ($M^+ + Na$).

To a suspension of powdered 4 Å molecular sieves (50 mg) in CH_2Cl_2 (1 mL) at −20 °C were sequentially added diethyl-D-tartrate (16.4 mg, 0.08 mmol) and $Ti(OiPr)_4$ (20 μL, 0.067 mmol). The resulting mixture was stirred for 15 min at −20 °C, and then *tert*-butyl hydroperoxide (20 μL, 0.13 mmol; 6.7 M in *n*-decane) was added dropwise. The mixture was stirred for 15 min, and then a solution of the above alcohol (6.5 mg, 0.011 mmol) in CH_2Cl_2 (2 mL) was added dropwise. The resulting mixture was stirred for 1 h at −20 °C. After this period, a mixture of 4 N NaOH (1 mL) and brine (1 mL) was added and the resulting mixture was stirred at 0 °C for 1 h. The layers were separated. The aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated to give a residue which was used for next reaction immediately. An analytical sample of **49** was isolated by silica gel chromatography (20% EtOAc/hexanes). ^1H NMR (400 MHz, $CDCl_3$): δ 7.21 (d, $J = 8.6$ Hz, 2H), 6.86 (dd, $J = 6.8$, 2.0 Hz, 2H), 6.42 (dt, $J = 11.3$, 3.6 Hz, 1H), 5.91−5.81 (m, 3H), 5.68 (d, $J =$ 10.2 Hz, 1H), 5.59 (ddd, $J = 15.8$, 6.9, 1.1 Hz, 1H), 5.43 (s, 1H), 5.21 (dd, $J = 10.4$, 5.1 Hz, 1H), 4.84 (s, 1H), 4.83 (s, 1H), 4.59 (d, $J = 11.7$ Hz, 1H), 4.32 (d, $J = 11.7$ Hz, 1H), 4.30 (m, 1H), 4.19 (s, 2H), 4.09−4.03 (m, 3H), 3.87 (t, $J = 6.0$ Hz, 1H), 3.80 (s, 3H), 3.75 (m, 1H), 3.04 (m, 1H), 2.87 (t, $J = 2.5$ Hz, 1H), 2.40−1.74 (m, 12H), 1.59 (s, 3H), 1.45−1.30 (m, 3H), 0.82 (d, $J = 6.3$ Hz, 3H).

Laulimalide 1. To a suspension of epoxide **49** in CH_2Cl_2 (1 mL) and pH 7 buffer (50 μL) was added DDQ (8 mg, 0.0352 mmol). The green mixture was stirred at 23 °C for 2 h. The resulting orange suspension was then washed with saturated aqueous $NaHCO_3$. The aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried over anhydrous Na_2SO_4 and evaporated. The residue was chromatographed over silica gel eluting with 25% EtOAc/hexane to give synthetic laulimalide **1** as a colorless oil (2.6 mg, 48%). $[\alpha]_D^{23} = -196$ (*c* 0.23, $CHCl_3$); lit.[5c] $[\alpha]_D^{29} = -200$ (*c* 0.23, $CHCl_3$). IR (thin film): 3427, 1716 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 6.45 (m, 1H), 5.91 (d, $J = 10.3$ Hz, 1H), 5.84 (ddd, $J = 16.2$, 5.3, 0.9 Hz, 1H), 5.83 (m, 1H), 5.74 (ddd, $J = 16.2$, 6.2, 0.9 Hz, 1H), 5.69 (brd, $J = 10.1$ Hz, 1H), 5.42 (s, 1H), 5.16 (ddd, $J =$ 11.2, 5.2, 1.6 Hz, 1H), 4.86 (s, 1H), 4.85 (s, 1H), 4.31 (brd, $J =$ 9.1 Hz, 1H), 4.22 (m, 1H), 4.17 (brs, 2H), 4.07 (m, 1H), 4.03 (m, 1H), 3.76 (m, 1H), 3.72 (m, 1H), 3.08 (m, 1H), 2.90 (t, $J =$ 2.6 Hz, 1H), 2.38 (m, 1H), 2.36 (m, 1H), 2.22 (m, 1H), 2.12 (brd, $J = 15.7$ Hz, 1H), 2.02−1.72 (m, 7H), 1.69 (s, 3H), 1.49 (m, 1H), 1.45 (m,1H), 1.33 (m, 1H), 0.82 (d, $J = 6.3$ Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 166.5, 150.7, 145.3, 134.3, 131.6, 129.1, 128.9, 125.6, 120.9, 120.1, 113.0, 73.9, 73.5, 73.4, 72.7, 68.3, 67.0, 66.1, 61.1, 52.5, 46.0, 43.8, 37.5, 36.0, 34.2, 33.8, 32.1, 29.9, 23.3, 21.2. MS (ESI): 515 ($M^+ + H$). HRMS (FAB). Calcd for $C_{30}H_{42}O_7Na$ [$(M + Na)^+$]: 537.2828. Found: 537.2851.

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Supporting Information Available: Text describing experimental details for synthesis of **3**−**9**, **12**, **13**, **16**, **18**−**37**, and **39**−**45** and figures showing ^1H and ^{13}C NMR spectra for compounds **1**, **3**−**9**, **15**, **16**, **20**, **22**−**23**, **27**, **30**−**33**, **40a**, **42a** and ^1H NMR for **37**−**39**, **41a**, **43**−**45,** and **48, 49**. This material is available free of charge via the Internet at http://pubs.acs.org.

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