Total Synthesis of Sarcodictyins A and B

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Received March 30, 1998

Abstract: The total synthesis of cytotoxic marine natural products possessing tubulin polymerization and microtubule stabilization properties, sarcodictyins A (**7**) and B (**8**), is described. Two related approaches to these target molecules have been developed, both utilizing (+)-carvone (**9**) as starting material. The first approach involves a stereoselective construction of acetylenic aldehyde **27** (Scheme 2) while the second approach proceeds through a more direct but less selective sequence to the similar intermediate **36** (Scheme 3). Both strategies involve ring closures of the acetylenic aldehyde precursors to 10-membered rings under basic conditions followed by elaboration and selective reduction of the acetylenic linkage to a *cis* double bond. This promotes bridging to form the required tricyclic skeleton of the sarcodictyins (**27** → **37** → **38** → **39** → **4**, Scheme 4 and **37** → **44** → **45** → **46** → **47** → **42**, Scheme 5) and (**36** → **48** → **45**, Scheme 6). Installation of the (*E*)-*N*(6′)-methylurocanic acid residue was achieved by esterification with mixed anhydride **52**, while the C-3 ester moieties were installed by standard deprotection, oxidation, and esterification procedures.

1. Introduction

The success of Taxol (**1**, Figure 1) in the clinic as an anticancer agent[1] and the emergence of the epothilones (Figure 1) as potential new chemotherapeutic agents[2] has elevated tubulin-binding agents[3] to the forefront of chemical and biological research.[4] Among the most exciting new tubulin polymerization and microtubule stabilizing agents are eleutherobin (**4**, Figure 1),[5] eleuthosides A and B (**5** and **6**, Figure 1),[6] and sarcodictyins A and B (**7** and **8**, Figure 1). The latter compounds (**7** and **8**) are rare natural substances originally found by Pietra and his group in the Mediterranean stoloniferan coral *Sarcodictyon roseum*.[7] Their potent antitumor properties and Taxol-like mechanism of action[3] were reported in 1997 by an Upjohn-Pharmacia group.[8] As part of our program studying the chemistry and biology of tubulin-binding agents, we have pursued and accomplished the total synthesis of paclitaxel (tradename Taxol, **1**),[9] epothilones A (**2**)[10] and B (**3**),[10d,11] eleutherobin (**4**),[12] and sarcodictyins A (**7**)[13] and B (**8**).[14] In this paper, we describe the details of the total synthesis of sarcodictyins A (**7**) and B (**8**).

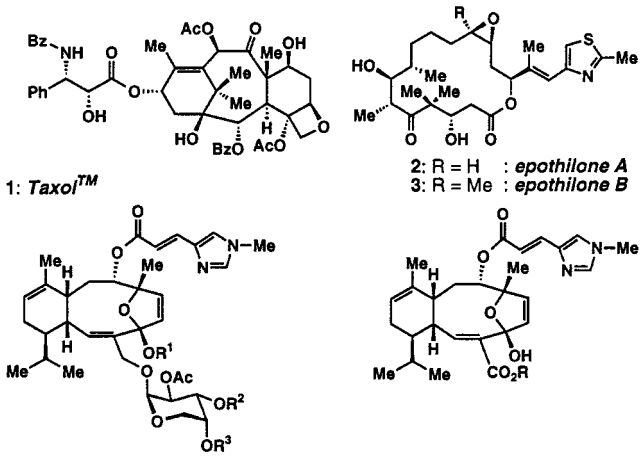

Figure 1. Molecular structures of paclitaxel (tradename Taxol, **1**), epothilones A (**2**) and B (**3**), eleutherobin (**4**), eleuthosides A (**5**) and B (**6**), and sarcodictyins A (**7**) and B (**8**) (Ac = acetyl, Bz benzoyl).

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S0002-7863(98)01062-2 CCC: $15.00
Published on Web 08/13/1998

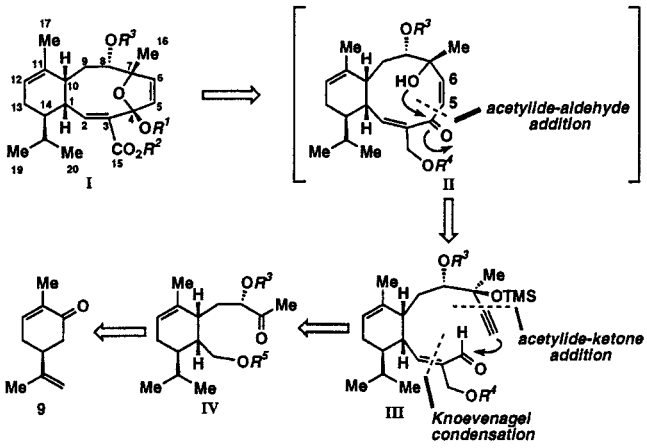


Figure 2. Retrosynthetic analysis of the core structure of sarcodictyins A (**7**) and B (**8**).

2. Retrosynthetic Analysis and Strategy

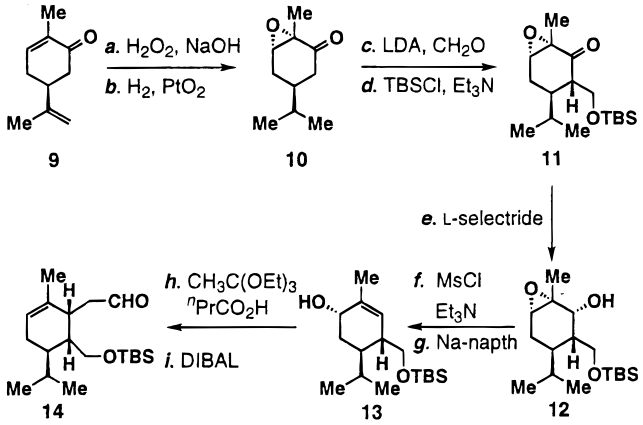
The general structures of sarcodictyins (**I**, Figure 2) are characterized by a rigid tricyclic framework from which a number of appendages branch out. Prominent among these appendages are the carboxylate group at C-3, the hydroxyl group at C-4, and the ester group at C-8 carrying the (*E*)-*N*(6′)-methylurocanic acid residue. The bridging oxygen involved in the lactol functionality at C-4 allows a strategic disconnection that unravels the [6.2.1]bicyclic structure of **I** into the 10-membered ring **II**. The latter structure is expected to spontaneously collapse back into **I** in the synthetic directions. The $\Delta^{5,6}$-*cis* double bond in **II** can be derived from the corresponding acetylene moiety whose disconnection at C4−C5 via a retro acetylide−aldehyde addition leads to open-chain acetylenic aldehyde **III**. Two further disconnections, indicated in structure **III** through retro acetylide−ketone addition and Knoevenagel condensation, furnish intermediate **IV** whose structure is highly suggestive of (+)-carvone (**9**).

This retrosynthetic analysis led to a strategy whose execution resulted in efficient total synthesis of both sarcodictyins A (**7**) and B (**8**). The sequence can be divided in three subsequences: the construction of the key cyclization precursors, the cyclization and formation of the tricyclic framework, and the construction of the remaining side chains.

3. Construction of Cyclization Precursors 27 and 36

The synthetic plan called for the initial construction of cyclization precursors of general formula (**III**, Figure 2). Consideration of protecting groups and possible routes defined structure **27** (Scheme 2) as a subtarget and compound **14**

Scheme 1. Synthesis of Key Intermediate **14**[a]



[a] Reagents and conditions: a. 1.2 equiv of H_2O_2, 0.3 equiv of NaOH, MeOH, 2 h, 0 °C; b. H_2, 0.005 equiv of PtO_2, EtOH, 12 h, 25 °C, 87% for two steps; c. 1.4 equiv of LDA, 5.0 equiv of CH_2O, THF, −78 → 0 °C, 2 h; d. 1.2 equiv of TBSCl, 4.0 equiv of Et_3N, CH_2Cl_2, 12 h, 53% for two steps; 3. 1.2 equiv of L-selectride, THF, −78 °C, 2 h, 93%; f. 1.2 equiv of MsCl, 2.5 equiv of Et_3N, CH_2Cl_2, 0 °C, 0.5 h; g. 5.0 equiv of sodium naphthalenide, THF, 0 °C, 0.5 h, 85% for two steps; h. 40 equiv of $CH_3C(OEt)_3$, 0.1 equiv of $^nPrCO_2H$, 170 °C, 72 h, 74%; i. 1.2 equiv of DIBAL, CH_2Cl_2, −78 °C, 0.5 h, 97%. LDA = lithium diisopropylamide. TBS = *t*-butyldimethylsilyl. MsCl = methanesulfonyl chloride. DIBAL = diisobutylaluminum hydride.

(Scheme 1) as a key intermediate required for its construction. The appeal of (+)-carvone (**9**) as a starting material for this synthesis was considerably enhanced by the work of Trost[15] who described its conversion to compound **13** (Scheme 1). Thus, following a modification of the communicated protocols **13** was prepared as shown in Scheme 1. Epoxidation of (+)-carvone under basic hydrogen peroxide conditions followed by hydrogenation of this exocyclic double bond gave **10** in 87% overall yield. Treatment of **10** with LDA (for abbreviations see legends in the schemes) followed by quenching with formaldehyde and silylation of the resulting alcohol furnished silyl ether **11** in 53% overall yield. Stereoselective L-Selectride reduction of the ketone functionality in **11** led to **12** (93%). Subsequent mesylation followed by reduction with sodium naphthalenide provided allylic alcohol **13** (85% overall). Finally, exposure of **13** to $CH_3C(OEt)_3$ and *n*-$PrCO_2H$ furnished, via Claisen rearrangement, the expected ethyl ester, which was cleanly reduced with DIBAL to produce aldehyde **14** (72% yield, two steps).

The stereoselective conversion of **14** to **27** is shown in Scheme 2. Thus, olefination of aldehyde **14** with triethylphosphonoacetate proceeded quantitatively in the presence of NaH to afford ethyl ester **15**. DIBAL reduction of **15** gave allylic alcohol **16** in 91% yield and subsequent Sharpless asymmetric epoxidation[16] (diethyl L-tartrate) furnished epoxide **17** (91% yield). The transformation of epoxide **17** to allylic alcohol **19** was accomplished via mesylate **18** in 90% overall yield. Protection of **19** as a PMB-ether [PMBOC(=NH)CCl_3, PPTS, 89% yield based on ca. 50% conversion][17] followed by sequential treatment with $Hg(OAc)_2$ and Li_2PdCl_4−$CuCl_2$[18] furnished methyl ketone **21** (65% yield). Chelation-controlled addition of HC≡CMgBr (excess)[19] to ketone **21**, followed by

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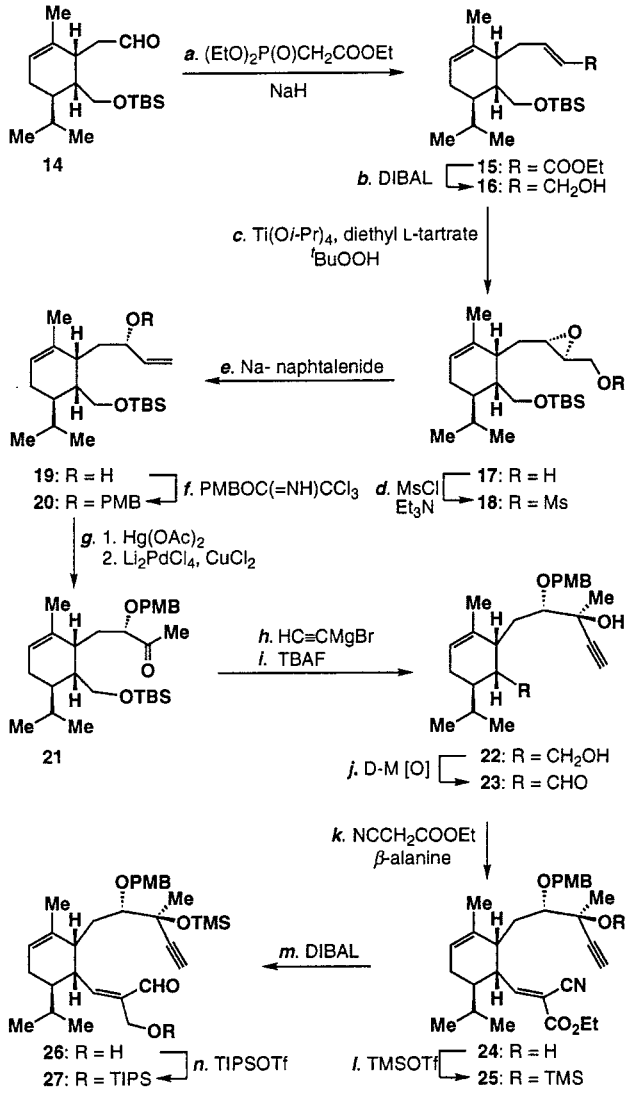
Scheme 2. First Generation Synthesis of Acetylene−Aldehyde Compound **27**[a]



[a] Reagents and conditions: a. 1.5 equiv of $(EtO)_2P(O)CH_2CO_2Et$, 2.0 equiv of NaH, THF, 0 °C for 1 h, then 25 °C for 4 h, 100%; b. 4.0 equiv of DIBAL, CH_2Cl_2, −78 °C, 2 h, 91%; c. 0.2 equiv of $Ti(O^iPr)_4$, 0.24 equiv of diethyl L-tartrate, 2.0 equiv of ^{t}BuOOH, 4 Å MS, CH_2Cl_2, −20 °C, 8 h, 91%; d. 5.0 equiv of MsCl, 6.0 equiv of Et_3N, CH_2Cl_2, −20 °C, 1 h; e. 5.0 equiv of sodium naphthalenide, THF, 0 °C, 10 min, 90% for two steps; f. 5.0 equiv of $PMBOC(=NH)CCl_3$, 1.0 equiv of PPTS, CH_2Cl_2, 25 °C, 48 h, 89% based on ca. 50% conversion; g. 1.1 equiv of $Hg(OAc)_2$, MeOH, 25 °C, 12 h; then 1.0 equiv of Li_2PdCl_4, 3.0 equiv of $CuCl_2$, MeOH, 55 °C, 3 h, 65%; h. 15 equiv of HC≡CMgBr (0.5 M in THF), CH_2Cl_2−THF−(3:1), −78 → 25 °C, 12 h; i. 4.0 equiv of TBAF, THF, 25 °C, 1 h, 72% for two steps, ds ratio ca. 7:1; j. 1.5 equiv of Dess−Martin periodinane, 20 equiv of pyridine, 20 equiv of $NaHCO_3$, CH_2Cl_2, 0 → 25 °C, 4 h; k. 30 equiv of $NCCH_2COOEt$, 4.0 equiv of β-alanine, 95% EtOH, 25 °C, 72 h; l. 5.0 equiv of TMSOTf, 10 equiv of ^{i}Pr$_2$NEt, CH_2Cl_2, −78 °C, 10 min, 71% for three steps; m. 10 equiv of DIBAL, CH_2Cl_2, −78 °C for 7 h then -40 °C for 1 h, 80%; n. 10 equiv of TIPSOTf, 20 equiv of ^{i}Pr$_2$NEt, CH_2Cl_2, −78°C, 1 h, 91%. TBS = ^{t}butyldimethylsilyl. DIBAL = diisobutylaluminum hydride. PMB = *p*-methoxybenzyl. PPTS = pyridinium *p*-toluenesulfonate. TMS = trimethylsilyl. TIPS = triisopropylsilyl. Ms = methanosulfonyl. TBAF = tetra-*n*-butylammonium fluoride. D-M [O] = Dess−Martin oxidation. Tf = trifluoromethanesulfonate. MS = molecular sieves. THF = tetrahydrofuran.

desilylation with TBAF gave acetylenic diol **22** as the major diastereoisomer (72% yield, ca. 7:1 de). Attempted oxidation of alcohol **22** to aldehyde **23** with excess Dess−Martin reagent[20] resulted in the formation of lactone A [(Figure 3), mp 120−121 °C (ether−hexanes)] in 60% yield. The serendipitous preparation of this crystalline compound allowed the assignment of relative stereochemistry within **22** and subsequent intermediates (by X-ray crystallographic analysis) (see ORTEP drawing, Figure 3).

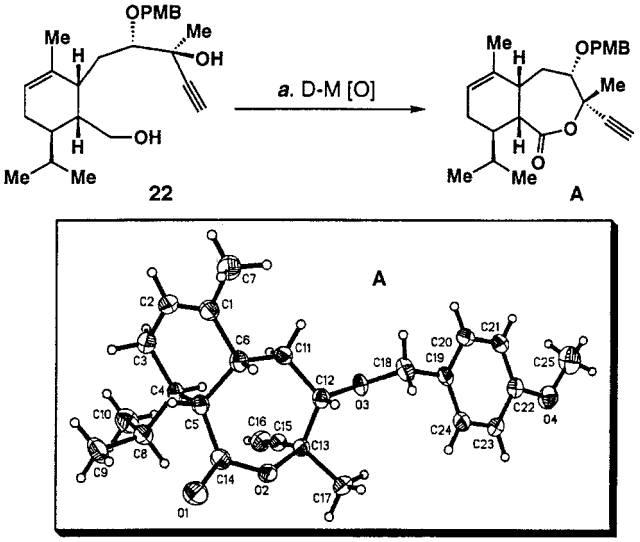


Figure 3. Synthesis and crystal structure of **A** providing evidence of the absolute stereochemistry of advanced intermediate **22**. a. 3.0 equiv of Dess−Martin periodinane, 20 equiv of $NaHCO_3$, CH_2Cl_2, 0 → 25 °C, 12 h, 70%. D-M [O] = Dess−Martin oxidation.

Controlled oxidation of **22** with 1.5 equiv of Dess−Martin reagent[20] in the presence of pyridine and $NaHCO_3$ led to the desired aldehyde **23** in good yield. Aldehyde **23** was subjected to Knoevenagel condensation conditions with ethyl cyanoacetate[21] in the presence of β-alanine leading, after silylation with TMSOTf and *i*-Pr_2NEt, to the (*E*)-α,β-unsaturated cyano ester **25** via **24** (in 71% overall yield). The geometry of the cyano ester bearing double bond was later confirmed by successful ring closure to intermediate **37** (vide infra, Scheme 4). A highly regioselective reduction of the cyano ester moiety of **25** was effected with DIBAL to afford hydroxy aldehyde **26** in 80% yield. Finally, protection of the primary alcohol in **26** with TIPSOTf and *i*-Pr_2NEt gave the targeted protected acetylenic aldehyde precursor **27** in 91% yield.

A second, less stereoselective but more direct, route to a cyclization precursor acetylenic aldehyde **36** was also undertaken,[12] as shown in Scheme 3. Thus, aldehyde **14**[13]was reacted with 1-ethoxyvinyllithium followed by exposure to acid to afford a 1.25:1 mixture of C-8 epimeric hydroxy ketones **28** in 82% overall yield. This mixture was then reacted with excess HC≡CMgBr in a stereoselective manner,[22] affording a chromatographically separable mixture of the two epimeric acetylenic diols, **29** (43% yield) along with its C-7,C-8 diastereoisomer (33% yield). Removal of the silyl protecting group from **29** was accomplished by exposure to TBAF furnishing, after flash column chromatography, the pure triol **30** (92%). The identity of **30** was proven by comparison to an authentic sample obtained from **22** (whose structure was unambiguously proven by X-ray analysis as discussed above).[13] The conversion of **30** to aldehyde **33** required a sequence defined by intermediates

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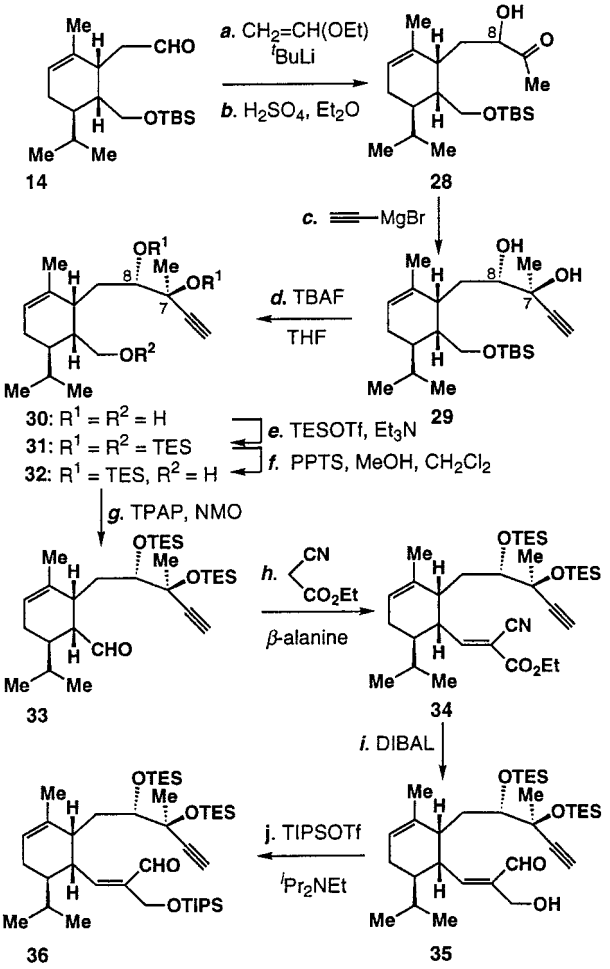
Scheme 3. Second Generation Synthesis of Acetylene−Aldehyde Compound **36**[a]



[a] Reagents and conditions: a. 2.0 equiv of CH_2=CH(OEt), 1.8 equiv of ^{t}BuLi (1.7 M in THF), THF, −78 → 0 °C, 1 h; then cool to −78 °C and add **14** in THF; then slowly warm to −40 °C; b. conc. H_2SO_4, Et_2O, 25 °C, 2 min, 82% for two steps as a ca. 1.25:1 mixture of diastereoisomers; c. 5.0 equiv of ethynylmagnesium bromide (0.5 M in THF), THF, −78 → 20 °C, 14 h, 76%, **29** (43%) plus 7,8-diastereoisomer (33%); d. **29**, 2.0 equiv of TBAF (1.0 M in THF), THF, 0 → 25 °C, 1 h, 92%; e. 5.0 equiv of TESOTf, 10 equiv of Et_3N, CH_2Cl_2, 25 °C, 2 h, 100%; f. 0.1 equiv of PPTS, MeOH−CH_2Cl_2, (3:1), 25 °C, 45 min, 98%; g. 0.05 equiv of TPAP, 1.5 equiv of NMO, CH_2Cl_2, 4 Å MS, 1.5 h, 98%; h. 30 equiv of ethyl cyanoacetate, 4.0 equiv of β-alanine, 95% EtOH, 72 h, 50 °C, 95%; i. 10 equiv of DIBAL, hexanes −78 °C for 6 h, then −40 °C for 1 h, then −10 °C for 1 h, 90%; j. 5.0 equiv of TIPSOTf, 10 equiv of ^{i}Pr$_2$NEt, CH_2Cl_2, −78 °C, 1 h, 93%. THF = tetrahydrofuran. TBAF = tetra-*n*-butylammonium fluoride. TESOTf = triethylsilyl trifluoromethanesulfonate. PPTS = pyridinium *p*-toluenesulfonate. TPAP = tetra-*n*-propylammonium perruthenate. NMO = 4-methylmorpholine *N*-oxide. MS = molecular sieves. DIBAL = diisobutylaluminium hydride. TIPSOTf = triisopropylsilyl trifluoromethanesulfonate.

31 (persilylation with TESOTf−Et_3N, 100% yield) and **32** (selective desilylation with PPTS in MeOH, 98% yield), and oxidation of the latter compound with TPAP−NMO in CH_2Cl_2 (98% yield).[23] The Knoevenagel condensation of **33** with ethyl cyanoacetate[21] proceeded smoothly as described above for **33** furnishing (*E*)-α,β-unsaturated cyano ester **34** (95% yield) whose DIBAL reduction gave, regioselectively, hydroxy aldehyde **35** (90% yield). Silylation of **35** with TIPSOTf and *i*-Pr_2NEt finally led to the desired acetylenic aldehyde precursor **36** in 93% yield.

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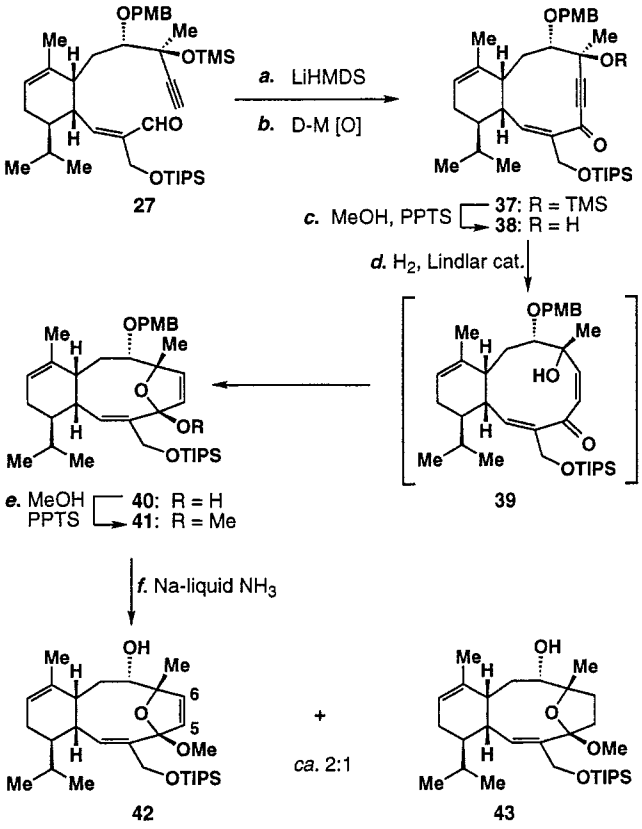
Scheme 4. First Generation Synthesis of the Sarcodictyin Tricyclic Core Structure **42**

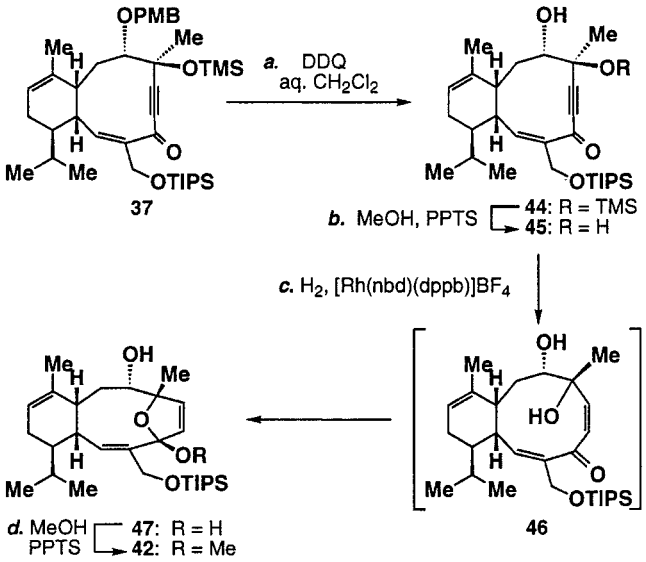


[a] Reagents and conditions: a. 1.5 equiv of LiHMDS, THF, 25 °C, 10 min; b. 2.5 equiv of Dess−Martin periodinane, 20 equiv of $NaHCO_3$, CH_2Cl_2, o → 25 °C, 4.5 h, 85% for two steps; c. 1.0 equiv of PPTS, MeOH, 25 °C, 30 min, 94%; d. 0.3 equiv of Lindlar's cat., H_2, toluene, 25 °C, 20 min, 75% for **40**, plus 15% for 5,6-dihydro analog; e. 1.0 equiv of PPTS, MeOH, 25 °C, 10 min, 100%; f. 10 equiv of Na−liq NH_3, −78 °C; then add **41** in THF−EtOH, 5 min, 95% yield, ca. 2:1 mixture of **42** and 5,6-dihydro analogue **43**. THF = tetrahydrofuran. LiHMDS = lithium bis(trimethylsilyl)amide. PPTS = pyridinium *p*-toluenesulfonate. Lindlar's cat. = Pd/$CaCO_3$/Pb. D-M [O] = Dess−Martin oxidation.

4. Cyclization and Formation of Tricyclic Framework

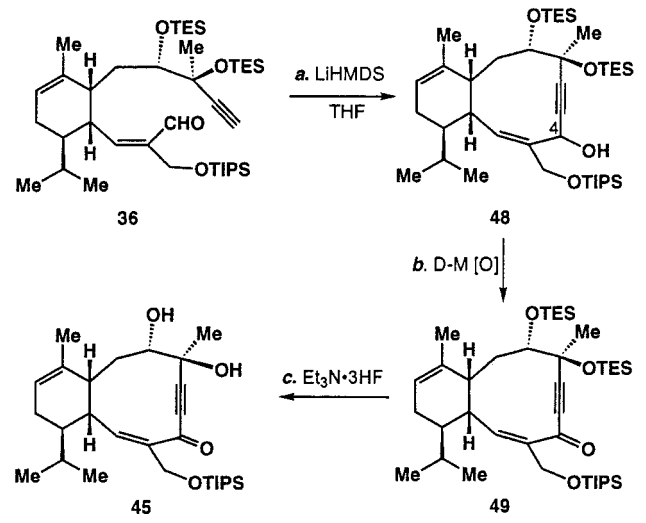
The first approach to sarcodictyins involved key intermediate **27** and had as its initial subtarget tricyclic compound **42** (Scheme 4). The ring closure of **27** was effected by the action of LiHMDS in THF at 25 °C yielding the expected 10-membered ring alcohol (mixture of two isomers) whose oxidation with Dess−Martin reagent[20] led to eneynone **37** in 85% overall yield. The TMS group was then removed from **37** by exposure to PPTS in MeOH furnishing alcohol **38** in 94% yield. Hydrogenation of eneynone **38** in the presence of Lindlar's catalyst resulted in the formation of tricyclic system **40** (75% yield), presumably via spontaneous collapse of the initially formed dienone **39**. Quantitative conversion of hemiketal **40** to its methoxy derivative **41** was effected by exposure to PPTS in MeOH. Removal of the PMB group from **41** for the purposes of side-chain attachment was carried out by Na in liquid NH_3 (THF−EtOH) and furnished the targeted tricyclic system **42** along with its C-5,C-6 saturated counterpart, compound **43** (95% combined yield, ca. 2:1 ratio.). A slightly modified sequence is presented in Scheme 5. Specifically, removal of the PMP-ether from **37** was accomplished after its treatment with DDQ in aqueous CH_2Cl_2 resulting in the formation of ynone hydroxy **44** in 80% yield. Liberation of the propargylic hydroxy moiety

Scheme 5. Alternative Route to Tricyclic Core **42**[a]



[a] Reagents and conditions: a. 2.0 equiv of DDQ, $CH_2Cl_2-H_2O$ (18:1), 25 °C, 0.5 h, 80%; b. 1.0 equiv of PPTS, MeOH, 25 °C, 1 h, 80%; c. 0.05 equiv of $[Rh(nbd)(dppb)]BF_4$, H_2, acetone, 25 °C, 10 min; d. 0.5 equiv of PPTS, MeOH, 25 °C, 10 min, 80% for two steps. DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone. PPTS = pyridinium *p*-toluenesulfonate. nbd = 2,5-norbornadiene. dppb = 1,4-bis(diphenylphosphino)butane.

Scheme 6. Second Generation Synthesis of Alkynone **45**[a]



[a] Reagents and conditions: a. 2.0 equiv of LiHMDS, THF, −20 °C, 20 min; b. 2.0 equiv of Dess−Martin periodinane, 6.0 equiv of $NaHCO_3$, 6.0 equiv of pyridine, CH_2Cl_2, 0 °C, 1 h, 89% for two steps; c. 5.0 equiv of $Et_3N{\cdot}3HF$, THF (1:5), 25 °C, 1.5 h, 78%. LiHMDS = lithium bis(trimethylsilyl)amide. THF = tetrahydrofuran. D-M [O] = Dess−Martin oxidation.

was performed by the action of PPTS in MeOH furnishing diol **45** in 80% yield. The employment of $[Rh(nbd)(dppb)]BF_4$ as the hydrogenation catalyst[24] proved to be beneficial since tricyclic alcohol **42** was isolated in 80% yield after the formation of the methyl ketal functionality (PPTS, MeOH).

The significant extent of reduction of the C-5,C-6 double bond in our first approach, which was observed in the hydrogenation of **38** to **40**, prompted the second general approach to the sarcodictyins which involved intermediate **36** (Scheme 6) carrying different protecting groups for easier removal. Its conversion to the key dihydroxy ynone **45** is detailed in Scheme 6. Thus, treatment of **36** with LiHMDS in THF at −20 °C resulted, as before, in the formation of the 10-membered ring alcohol **48** (mixture of diastereoisomers) which was immediately oxidized with Dess−Martin reagent to eneynone **49** (89% yield for two steps). Selective removal of both TES groups was achieved by exposure to $Et_3N{\cdot}3HF$ (78% yield) furnishing diol **45** and setting the stage for selective hydrogenation and internal cyclization. To this end, the experiments summarized in Table 1 were carried out using acetylenic substrates **37** (Scheme 4), **38** (Scheme 4), and **45** (Scheme 6) and a variety of hydrogenation conditions. The exploration led quickly to the adoption of the rhodium complex $[Rh(nbd)(dppb)]BF_4$ in acetone solution as the catalyst of choice (ca. >10:1 ratio in favor of the desired product **42** which was obtained in 80% yield). With the solution of the reduction problem at hand, the only remaining task was the construction of the side chains before the final targets were reached.

5. Construction of the Side Chain and Completion of the Synthesis

For the attachment of the C-8 ester functionality, a mixed anhydride protocol was adopted.[12] To this end, ethyl (*E*)-*N*(6′)-methylurocanate (**50**, Scheme 7)[25] was sequentially converted to its sodium salt **51** by the action of NaOH ($THF-H_2O$, 100%) and then to *tert*-butyl mixed anhydride **52** by treatment with *t*-BuCOCl in THF (75% yield). Reaction of **42** with **52** in the presence of Et_3N and DMAP resulted in the formation of ester **53** in 83% yield. For the purposes of completing the side chain at C-3, a carboxylic acid group was formed at this position as follows: (i) desilylation with TBAF to afford alcohol **54** in 100% yield; (ii) Dess−Martin oxidation to aldehyde **55**; and (iii) further oxidation of **55** with $NaClO_2$ to furnish **56**. Exposure of carboxylic acid to CH_2N_2 or CH_3CHN_2 furnished methoxysarcodictyin A (**57**, 88% overall yield from **54**) or methoxysarcodictyin B (**58**, 86% overall yield from **54**). Finally, sarcodictyins A (**7**) and B (**8**) were generated from their respective methoxy derivatives by treatment with CSA in $CH_2Cl_2-H_2O$ (80% yield for **7** and 86% for **8**).

To evaluate the importance of the C-5,C-6 double bond of sarcodictyins for biological activity, C-5,C-6 dihydrosarcodictyin A (**61**) was targeted for chemical synthesis. Scheme 8 summarizes an efficient route to **61** from intermediate **45**. Thus, hydrogenation of **45** in the presence of 5% $Pd/BaSO_4$ in EtOAc, followed by exposure to PPTS in MeOH resulted in the formation of tricyclic compound **43** (64% overall yield) in which the C-5,C-6 bond was completely reduced. The construction of the two side chains proceeded smoothly as described already for compound **42** (Scheme 5) and via compounds **59** and **60** furnishing the desired dihydrosarcodictyin A (**61**) in excellent overall yield (see Scheme 8).

6. Conclusion

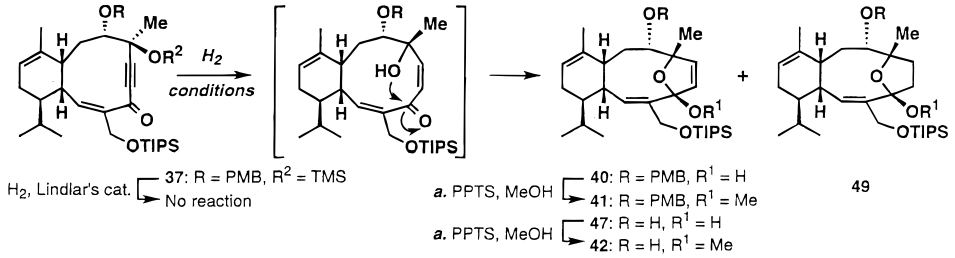
In this paper, we detailed two slightly different approaches to sarcodictyins A (**7**) and B (**8**) and C-5,C-6 dihydrosarcodictyin A (**61**). Both approaches utilize an intramolecular acetylide−aldehyde addition to construct a 10-membered ring, whose elaboration and selective hydrogenation results in the formation of a transient hydroxy dienone which spontaneously collapses to the tricyclic ring system of sarcodictyins A and B. Appropriate appendage attachments at C-8 and C-15 then lead to

(24) Schrock, R. R.; Osborn, J. A. *J. Am. Chem. Soc.* **1976**, *98*, 2143−2147.

(25) Viguerie, N. L.; Sergueeva, N.; Damiot, M.; Mawlawi, H.; Riviere, M.; Lattes, A. *Heterocycles* **1994**, *37*, 1561−1576.

(26) Numbering is depicted in Figure 2.

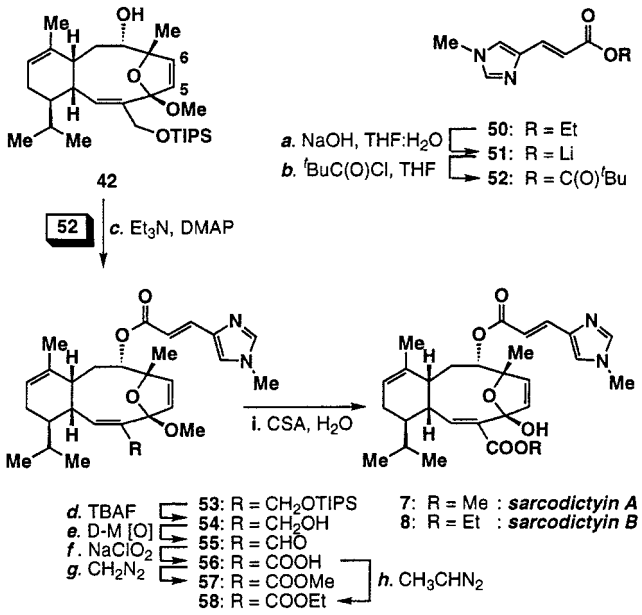
Table 1. Selective Hydrogenation Studies for the Construction of the Sarcodictyin Tricyclic Core[a]



substrate	conditions	products (ratio)	yield (%)
38: R = PMB, R^2 = H	Lindlar's cat., MeOH	**40:49** (ca. 2:1)	50 (of **40**)
38: R = PMB, R^2 = H	Lindlar's cat., CH_2Cl_2	**40:49** (ca. 3:1)	60 (of **40**)
38: R = PMB, R^2 = H	Lindlar's cat., EtOAc	**40:49** (ca. 3:1)	60 (of **40**)
38: R = PMB, R^2 = H	Lindlar's cat., toluene; then PPTS, MeOH	**41:49** (ca. 5:1)	75 (of **41**, two steps)
38: R = PMB, R^2 = H	Pd/$BaSO_4$, pyridine	**40:49** (ca. 3−5:1)	74 (of **40**)
45: R = H, R^2 = H	Lindlar's cat., toluene; then PPTS, MeOH	**42:49** (ca. 2−3:1)	52 (of **42**, two steps)
45: R = H, R^2 = H	[Rh(nbd)(dppb)]BF_4, acetone; then PPTS, MeOH	**42:49** (ca. >10:1)	80 (of **42**, two steps)

[a] Reagents and conditions. a. 1.0 equiv of PPTS, MeOH, 25 °C, 30 min 94%. Lindlar's cat. = Pd/$CaCO_3$/Pb. PPTS = pyridinium *p*-toluenesulfonate. nbd = 2,5-norbornadiene. dppb = 1,4-bis(diphenylphosphino)butane.

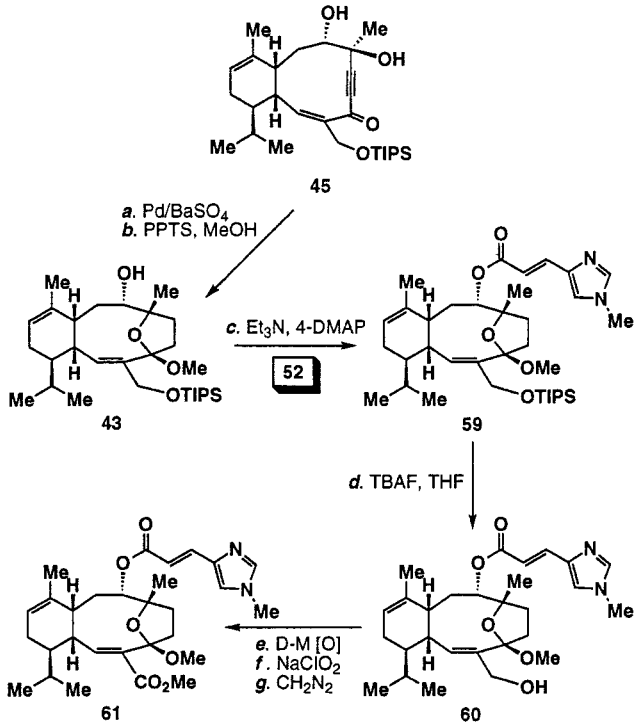
Scheme 7. Total Synthesis of the Sarcodictyins A (**7**) and B (**8**)[a]



[a] Reagents and conditions: a. 1.05 equiv of LiOH·H_2O, THF−H_2O, 1:1, 25 °C, 12 h, 100%; b. 1.1 equiv ^{t}BuC(O)Cl, THF, 25 °C, 12 h, 75%; c. 2.0 equiv of **52**, 20 equiv of Et_3N, 1.0 equiv of DMAP, CH_2Cl_2, 25 °C, 48 h, 83%; d. 2.0 equiv of TBAF, THF, 25 °C, 2 h, 100%; e. 2.0 equiv of Dess−Martin periodinane, 10 equiv of $NaHCO_3$, CH_2Cl_2, 25 °C, 0.5 h, 100%; f. 6.0 equiv of $NaClO_2$, 3.0 equiv of NaH_2PO_4, 50 equiv of 2-methyl-2-butene, THF, ^{t}BuOH, H_2O, 2 h; g. excess CH_2N_2, Et_2O, 10 min, 88% for two steps; h. excess $CH_3CH_2N_2$, Et_2O, 0.5 h, 89% for two steps; i. 2.0 equiv of CSA, CH_2Cl_2−H_2O (10:1), 25 °C, 48 h, 80% for **7**, 86% for **8**. THF = tetrahydrofuran. DMAP = 4-(*N*,*N*′-dimethylamino)pyridine. TBAF = tetra-*n*-butylammonium fluoride. D-M [O] = Dess−Martin oxidation. CSA = 10-camphorsulfonic acid.

completion of the syntheses. The designed strategy allows for a solid-phase synthesis, specific analogue construction, and combinatorial library generation. The solid-phase synthesis of sarcodictyins A and B and analogues thereof has already been accomplished and will be reported elsewhere in due course. These studies should facilitate further investigations of the chemical biology of sarcodictyins and related compounds. In the following paper. we describe details of our total syntheses of eluetherobin and eleuthosides A and B.

Scheme 8. Synthesis of C5,C6-Dihydrosarcodictyin A (**61**)[a]



[a] Reagents and conditions: a. 1.0 equiv of 5% Pd/$BaSO_4$, EtOAc, 25 °C, 1 h; b. 2.0 equiv of PPTS, MeOH, 25 °C, 6 h, 64% for two steps; c. 5.0 equiv of **52**, 20 equiv of Et_3N, 2.0 equiv of DMAP, CH_2Cl_2, 25 °C, 48 h, 83%; d. 2.0 equiv of TBAF, THF, 25 °C, 2 h, 100%; e. 2.5 equiv of Dess−Martin periodinane, 10 equiv of $NaHCO_3$, CH_2Cl_2, 25 °C, 0.5 h; f. 6.0 equiv of $NaClO_2$, 3.0 equiv of NaH_2PO_4, 50 equiv of 2-methyl-2-butene, THF, ^{t}BuOH, H_2O; g. excess of CH_2N_2, Et_2O, 88% for three steps. PPTS = pyridinium *p*-toluenesulfonate. DMAP = 4-(*N*,*N*′-dimethylamino)pyridine. TBAF = tetra-*n*-butylammonium fluoride. D-M [O] = Dess−Martin oxidation.

7. Experimental Section

General Techniques. All reactions were carried out under an argon atmosphere with dry, freshly distilled solvents under anhydrous conditions, unless otherwise noted. Tetrahydrofuran (THF), toluene, and ethyl ether (ether) were distilled from sodium benzophenone, and methylene chloride (CH_2Cl_2) was from calcium hydride. Anhydrous solvents were also obtained by passing them through commercially available alumina column. Yields refer to chromatographically and

spectroscopically (^{1}H NMR) homogeneous materials, unless otherwise stated. Reagents were purchased at highest commercial quality and used without further purification, unless otherwise stated. Reactions were monitored by thin-layer chromatography carried out on 0.25 mm E. Merck silica gel plates (60F-254) using UV light as visualizing agent and 7% ethanolic phosphomolybdic acid or *p*-anisaldehyde solution and heat as developing agents. E. Merck silica gel (60, particle size 0.040−0.063 mm) was used for flash column chromatography. Preparative thin-layer chromatography (PTLC) separations were carried out on 0.25, 0.50, or 1 mm E. Merck silica gel plates (60F-254). NMR spectra were recorded on Brucker DRX-600, AMX-500 or AMX-400 instruments and calibrated using residual undeuterated solvent as an internal reference. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, sept = septet, m = multiplet, br = broad. IR spectra were recorded on a Perkin-Elmer 1600 series FT-IR spectrometer. Optical rotations were recorded on a Perkin-Elmer 241 polarimeter. High-resolution mass spectra (HRMS) were recorded on a VG ZAB-ZSE mass spectrometer under fast atom bombardment (FAB) conditions with NBA as the matrix. Melting points (mp) are uncorrected and were recorded on a Thomas-Hoover Unimelt capillary melting point apparatus. Full procedures and data for compounds **10**−**13** can be found in the Supporting Information accompanying this paper.

Synthesis of Key Intermediate Aldehyde 14. A mixture of alcohol **13** (1.61 g, 5.42 mmol, 1.0 equiv), triethyl orthoacetate (39.6 mL, 216.8 mmol, 40.0 equiv), and propionic acid (0.04 mL, 0.542 mmol, 0.1 equiv) was heated at 170 °C for 72 h. The excess triethyl orthoacetate was removed by vacuum distillation (25 mmHg), and the remaining residue was purified by flash chromatography (silica gel, 3% EtOAc in hexane) to produce the expected ethyl ester (1.50 g, 74%) which was used for the next step without further purification. A 1.0 M CH_2Cl_2 solution of DIBAL (4.6 mL, 4.60 mmol, 1.2 equiv) was gradually added to a solution of the ethyl ester (1.41 g, 3.83 mmol, 1.0 equiv) in CH_2Cl_2 (19 mL) at −78 °C, and the reaction mixture was stirred for 30 min at that temperature. Quenching was performed by addition of saturated NH_4Cl solution (20 mL) and stirring for 2 h at ambient temperature. The organic layer was separated, dried over Na_2SO_4, and concentrated. The residue was purified by flash chromatography (silica gel, 5% EtOAc in hexane) to provide aldehyde **14** (1.20 g, 97%) as a colorless oil. Data for ethyl ester: R_f = 0.34 (silica gel, EtOAc−hexane, 1:30); FT-IR (neat) ν_{max} 2929, 2857, 1738, 1470, 1369, 1255, 1156, 1100, 837, 775 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.38−5.30 (br s, 1 H, C-12), 4.09 (dq, J = 7.2, 1.6 Hz, 2 H, OCH_2CH$_3$), 3.65 (dd, J = 10.4, 5.7 Hz, 1 H, C-2), 3.55 (dd, J = 10.4, 5.7 Hz, 1 H, C-2), 2.80−2.70 (m, 1 H, C-10), 2.55 (dd, J = 15.2, 6.2 Hz, 1 H, C-9), 2.22 (dd, J = 15.2, 7.0 Hz, 1 H, C-9), 1.97−1.65 (m, 4 H), 1.62 (d, J = 1.3 Hz, 3 H, C-17), 1.52−1.37 (m, 1 H), 1.22 (t, J = 7.2 Hz, 3 H, OCH$_2$CH_3), 0.88 (d, J = 6.7 Hz, 3 H, C-19 or C-20), 0.87 (s, 9 H, Si-^{t}Bu), 0.79 (d, J = 6.7 Hz, 3 H, C-19 or C-20), 0.06 (s, 6 H, SiCH$_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$) d 173.9, 135.7, 121.9, 62.6, 60.1, 40.6, 36.8, 36.4, 35.0, 26.9, 25.9, 24.2, 22.3, 20.9, 18.2, 16.9, 14.1, −5.5, −5.6; HRMS (FAB) calcd for $C_{21}H_{41}SiO_3$ (M + H$^+$) 369.2825, found 369.2834(M + H$^+$). For **14**: R_f = 0.32 (silica gel, EtOAc−hexane, 1:30); FT-IR (neat) ν_{max} 2956, 2856, 1726, 1467, 1254, 1103, 1079, 838 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.74 (t, J = 2.3 Hz, 1 H, C-8), 5.38 (br s, 1 H, C-12), 3.71 (dd, J = 10.6, 4.6 Hz, 1 H, C-2), 3.45 (t, J = 10.6 Hz, 1 H, C-2), 2.85−2.78 (m, 1 H), 2.59 (ddd, J = 16.5, 7.3, 2.9 Hz, 1 H), 2.24 (ddd, J = 16.5, 4.3, 2.0 Hz, 1 H), 1.93−1.70 (m, 4 H), 1.66 (s, 3 H, C-17), 1.48−1.40 (m, 1 H, C-14), 0.87 (d, J = 6.5 Hz, 3 H, C-19 or C-20), 0.86 (s, 9 H), 0.77 (d, J = 6.8 Hz, 3 H, C-19 or C-20), 0.01 (s, 6 H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 203.6, 136.3, 122.3, 62.1, 44.3, 41.0, 35.8, 34.9, 26.5, 25.8, 24.1, 22.2, 21.1, 18.2, 15.5, −5.5, −5.6; HRMS (FAB) calcd for $C_{19}H_{36}$ NaO_2Si (M + Na$^+$) 347.2382, found 347.2372.

Synthesis of α,β-Unsaturated Ester 15. To a THF (30 mL) suspension of sodium hydride (60% w/w in mineral oil, 542 mg, 13.55 mmol, 2.0 equiv) was gradually added a solution of triethyl phosphonoacetate (2.7 mL, 13.55 mmol, 2.0 equiv) in THF (10 mL) via cannula at 0 °C. After the addition was complete, the reaction mixture was stirred at 25 °C for 30 min before being cooled back down to 0 °C. A solution of aldehyde **14** (2.20 g, 6.78 mmol, 1.0 equiv) in THF (15 mL) was slowly added to the reaction mixture via cannula at 0 °C, and the reaction mixture was stirred at the same temperature for 1 h and at 25 °C for 4 h. After the end of the reaction was established by TLC, the reaction was quenched by the addition of saturated NH_4Cl solution (50 mL), extracted with ether (2 × 100 mL), dried over Na_2SO_4, and concentrated. The residue was purified by flash chromatography (silica gel, 2% EtOAc in hexane) to furnish the α,β-unsaturated ester **15** (2.67 g, 100%) as a colorless oil: R_f = 0.53 (silica gel, EtOAc−hexane, 1:10); FT-IR (neat) ν_{max} 2956, 1722, 1651, 1465, 1367, 1258, 1159, 1078, 841 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.11−6.97 (m, 1 H, C-8), 5.78 (dd, J = 15.2, 6.2 Hz, 1 H, C-7), 5.38−5.30 (br s, 1 H, C-12), 4.09 (qd, J = 7.2, 1.6 Hz, 2 H, OCH_2CH$_3$), 3.65 (dd, J = 10.4, 5.7 Hz, 1 H, SiOC*H*H), 3.55 (dd, J = 10.4, 5.7 Hz, 1 H, C-2) 2.41−2.38 (m, 2H), 2.26−2.23 (m, 1 H), 1.87−1.65 (m, 4 H), 1.64 (d, J = 1.4 Hz, 3 H, C-17), 1.51−1.47 (m, 1 H), 1.25 (t, J = 7.2 Hz, 3 H, OCH$_2$CH_3), 0.84 (d, J = 6.7 Hz, 3 H, C-19 or C-20), 0.87 (s, 9 H, Si-^{t}Bu), 0.76 (d, J = 6.7 Hz, 3 H, C-19 or C-20), 0.09 (s, 6 H, SiCH_3); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 166.8, 150.4, 136.0, 122.1, 121.1, 62.2, 60.0, 41.3, 39.3, 36.0, 32.6, 26.7, 25.9, 24.2, 23.0, 21.1, 18.2, 15.7, 14.3, −5.4, −5.5; HRMS (FAB) calcd for $C_{23}H_{42}NaO_3Si$ (M + Na$^+$) 417.2801, found 417.2814.

Synthesis of Allylic Alcohol 16 from Ester 15. A 1.0 M CH_2Cl_2 solution of DIBAL (12.2 mL, 12.20 mmol, 4.0 equiv) was gradually added to a solution of α,β-unsaturated ethyl ester **15** (1.20 g, 3.05 mmol, 1.0 equiv) in CH_2Cl_2 (15 mL) at −78 °C, and the reaction was stirred for 2 h at the same temperature. The reaction mixture was quenched by addition of saturated NH_4Cl solution (30 mL), stirred vigorously at ambient temperature for 2 h, extracted with CH_2Cl_2 (3 × 50 mL), dried over Na_2SO_4, and concentrated. The residue was purified by flash chromatography (silica gel, 10% EtOAc in hexane) to provide allylic alcohol **16** (980 mg, 91%) as a light-yellow oil: R_f = 0.21 (silica gel, EtOAc−hexane, 1:10); FT-IR (neat) ν_{max} 3326, 2925, 1464, 1385, 1253, 1106, 1005, 836, 774, 668 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 5.85−5.68 (m, 1 H, C-7), 5.67−5.53 (m, 1 H, C-8), 5.35−5.28 (br s, 1 H, C-12), 4.04 (d, J = 5.6 Hz, 2 H, CH_2OH), 3.66 (dd, J = 10.2, 6.9 Hz, 1 H, C-2), 3.53 (t, J = 10.2 Hz, 1 H, C-2), 2.32−2.05 (m, 3 H), 2.00−1.50 (m, 6 H), 1.64 (d, J = 1.3 Hz, 3 H, C-17), 0.86 (s, 9 H, Si-^{t}Bu), 0.83 (d, J = 6.8 Hz, 3 H, C-19 or C-20), 0.76 (d, J = 6.7 Hz, 3 H, C-19 or C-20), 0.01 (s, 6 H, Si-CH$_3$); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 136.6, 134.0, 128.9, 121.5, 63.8, 62.2, 41.0, 39.1, 36.3, 32.3, 26.9, 25.9, 24.2, 23.1, 21.1, 18.2, 16.4, −5.4; HRMS (FAB) calcd for $C_{21}H_{40}$-NaO_3Si (M + Na$^+$) 375.2695, found 375.2704.

Synthesis of Epoxide 17 from Allylic Alcohol 16. To a suspension of diethyl L-tartrate (0.28 mL, 1.50 mmol, 0.2 equiv) and powdered 4 Å MS (6.8 g) in CH_2Cl_2 (90 mL) was added titanium(IV) isopropoxide (0.40 mL, 1.25 mmol, 0.2 equiv) at −20 °C followed by a 5.0 M CH_2-Cl_2 solution of *tert*-butyl hydroperoxide (2.7 mL, 13.5 mmol, 2.0 equiv). After the mixture was stirred for 40 min at the same temperature, a solution of allylic alcohol **16** (2.38 g, 6.75 mmol, 1.0 equiv) in CH_2Cl_2 (5 mL) was added dropwise via cannula. The reaction mixture was stirred for 8 h at the same temperature, further diluted with CH_2Cl_2 (150 mL), and quenched by addition of a saturated $NaHCO_3$ solution (100 mL). The mixture was then filtered through a Celite pad eluting with CH_2Cl_2 and the organic phase was separated, washed with water and brine, dried over Na_2SO_4, and concentrated. The residue was purified by flash chromatography (silica gel, 10% EtOAc in hexane) to furnish epoxy alcohol **17** (2.25 g, 91%) as a colorless oil: R_f = 0.47 (silica gel, EtOAc−hexane, 1:3); FT-IR (neat) ν_{max} 3442, 2927, 1465, 1387, 1253, 1104, 838, 775, 668 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.34 (br s, 1 H, C-12), 3.84 (br d, J = 12.4 Hz, 1 H), 3.72 (dd, J = 10.5, 5.1 Hz, 1 H, C-2), 3.60−3.45 (m, 2 H, CH*H*OH, C-2), 3.07, 3.02 (m, 1 H, C-7), 2.92−2.88 (m, 1 H, C-8), 2.43−2.33 (m, 1 H), 2.20−1.98 (m, 1 H), 1.95−1.70 (m, 5 H), 1.68 (s, 3 H), 1.56−1.47 (m 1 H), 0.85 (s, 9 H, TBS), 0.84 (d, J = 6.7 Hz, 3 H, C-19 or C-20), 0.76 (d, J = 6.7 Hz, 3 H, C-19 or C-20), 0.10 (s, 6 H, TBS); ^{13}C NMR (100.6 MHz, $CDCl_3$) 136.0, 121.8, 62.6, 62.0, 59.4, 55.9, 40.9, 37.5, 36.1, 31.6, 26.8, 25.9, 24.2, 22.6, 21.0, 18.1, 15.8, −5.3, −5.5; HRMS (FAB) calcd for $C_{21}H_{40}NaO_3Si$ (M + Na$^+$) 391.2644, found 391.2657.

Synthesis of Allylic Alcohol 19 through the Corresponding Mesylate. To a solution of epoxy alcohol **17** (1.05 g, 2.82 mmol, 1.0 equiv) and triethylamine (2.40 mL, 16.9 mmol, 6.0 equiv) in CH_2Cl_2 (28 mL) was added dropwise methanesulfonyl chloride (1.4 mL, 18.08

mmol, 4.9 equiv) at −20 °C. After 1 h (TLC monitoring), the reaction was quenched by addition of saturated NH_4Cl solution (20 mL), extracted with CH_2Cl_2 (2 × 50 mL), dried over Na_2SO_4, and concentrated. The residue was filtered through a short silica gel pad eluting with CH_2Cl_2, concentrated, and used immediately for the next step without further purification. A solution of the mesylate in THF (28 mL) was added via cannula to a 0.3 M THF solution of sodium naphthalenide (4.7 mL, 14.1 mmol, 5.0 equiv), generated in the same way described for the synthesis of allylic alcohol **13**, at 0 °C. After 10 min, the reaction was quenched by addition of saturated NH_4Cl solution (50 mL), extracted with ether (2 × 50 mL), washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by flash chromatography (silica gel, 5% EtOAc in hexane) to produce allylic alcohol **19** (895 mg, 90%) as a colorless oil: $R_f = 0.34$ (silica gel, EtOAc−hexane, 1:10); FT-IR (neat) ν_{max} 3420, 2955, 1464, 1387, 1254, 1073, 837, 775 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 5.98−5.80 (m, 1 H, C*H*═CH_2), 5.30−5.20 (m, 2 H, C-12, CH═C*H*H), 5.08 (dd, J = 10.4, 1.6 Hz, 1 H, CH═C*H*H), 4.37−4.26 (br s, 1 H, OH), 3.75 (dd, J = 10.9, 5.4 Hz, 1 H, C-2), 3.60 (t, J = 10.9 Hz, 1 H, C-2), 2.43−2.33 (m, 1 H), 1.97−1.60 (m, 6 H), 1.62 (s, 3 H, C-17), 1.60−1.40 (m, 2 H), 0.89 (s, 9 H, Si-^{t}Bu), 0.86 (d, J = 6.7 Hz, 3 H, C-19 or C-20), 0.78 (d, J = 6.7 Hz, 3 H, C-19 or C-20), 0.07 (s, 6 H, Si-CH_3); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 141.8, 137.5, 120.9, 113.6, 71.1, 63.1, 41.4, 37.0, 34.1, 26.9, 25.9, 24.2, 22.7, 21.0, 18.2, 16.2, −5.2, −5.4; HRMS (FAB) calcd for $C_{21}H_{41}O_2Si$ (M + H^+) 353.2876, found 353.2866.

Synthesis of PMB-ether 20. To a solution of allylic alcohol **19** (445 mg, 1.57 mmol, 1.0 equiv) and *p*-methoxybenzyl 2,2,2-trichloroacetimidate (2.22 g, 7.85 mmol, 5.0 equiv) in CH_2Cl_2 (8 mL) was added pyridinium *p*-toluenesulfonate (395 mg, 0.31 mmol, 0.2 equiv) at 25 °C. The reaction mixture was stirred for 48 h at the same temperature, and after the end of the reaction was established by TLC, the reaction was quenched by addition of saturated $NaHCO_3$ solution (10 mL). The organic phase was separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated. The residue was purified by flash chromatography (silica gel, EtOAc−pentane, 1:99) to produce PMB-ether **20** (240 mg, 89% based on 50% conversion) as a light yellow oil: $R_f = 0.61$ (silica gel, EtOAc−hexane, 1:3); FT-IR (neat) ν_{max} 2954, 1614, 1514, 1464, 1250, 1080, 837, 775 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.25 (d, J = 11.4 Hz, 2 H, ArH), 6.84 (dd, J = 11.4, 2.8 Hz, 2 H, ArH), 5.85−5.66 (m, 1 H, C*H*═CH_2), 5.30−5.17 (m, 3 H, C-12), 4.49 (d, J = 11.0 Hz, 1 H, C*H*H−Ar), 4.28 (d, J = 11.0 Hz, 1 H, C*H*H-Ar), 4.03−3.90 (m, 1 H, C-8), 3.78 (s, 3 H, OCH_3), 3.68−3.47 (m, 2 H, C-2), 2.50−2.40 (m, 1 H, C-10), 2.05−1.75 (m, 3 H), 1.60 (d, J = 2.4 Hz, 3 H, C-17), 1.65−1.45 (m, 4 H), 0.89 (s, 9 H, Si-^{t}Bu), 0.86 (d, J = 6.7 Hz, 3 H, C-10 or C-20), 0.82 (d, J = 6.6 Hz, 3 H, C-19 or C-20), 0.04 (s, 6 H, Si-CH_3); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 158.9, 139.8, 137.4, 131.0, 129.2, 120.8, 116.6, 113.6, 79.6, 70.1, 62.4, 55.2, 40.7, 36.9, 36.1, 34.6, 27.1, 26.0, 24.2, 22.6, 21.0, 18.3, 17.6, −5.2, −5.3; HRMS (FAB) calcd for $C_{29}H_{48}CsO_3Si$ (M + Cs^+) 605.2427, found 605.2446.

Synthesis of Methyl Ketone 21. A solution of PMB-ether **20** (135 mg, 0.285 mmol, 1.0 equiv) and mercuric acetate (100 mg, 3.4 mmol, 1.2 equiv) in methanol (2 mL) was stirred at 25 °C for 12 h. The reaction mixture was then transferred to a solution of LiCl (24.1 mg, 0.568 mmol, 2.0 equiv), $PdCl_2$ (50.5 mg, 0.285 mmol, 1.0 equiv), and $CuCl_2$ (0.115 mg, 0.855 mmol, 3.0 equiv) in methanol (1 mL) via cannula and was further stirred at 55 °C for another 3 h. Saturated $NaHCO_3$ (5 mL) was added, and the product was extracted with ether (20 × 3 mL). The organic extracts were dried over Na_2SO_4 and concentrated. The crude product was purified by flash chromatography (silica gel, 6% EtOAc in hexane) to furnish methyl ketone **21** (90.5 mg, 65%) as a colorless oil: $R_f = 0.34$ (silica gel, EtOAc−hexane, 1:15); FT-IR (neat) ν_{max} 2956, 1714, 1514, 1249, 1081, 836 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.26 (d, J = 6.6 Hz, 2 H, ArH), 6.85 (dd, J = 6.6, 2.1 Hz, 2 H, ArH), 5.33-5.25 (br s, 1 H, C-12), 4.41 (s, 2 H, OCH_2Ar), 4.04 (dd, J = 9.7, 3.6 Hz, 1 H, C-8), 3.79 (s, 3 H, OCH_3), 3.70 (dd, J = 9.3, 5.8 Hz, 1 H, C-2), 3.59 (t, J = 9.3 Hz, 1 H, C-2), 2.53-2.44 (m, 1 H, C-10), 2.13 (s, 3 H, $COCH_3$), 2.00−1.75 (m, 3 H), 1.65 (s, 3 H, C-17), 1.70−1.40 (m, 4 H), 0.89 (s, 9 H, Si-^{t}Bu), 0.84 (d, J = 6.7 Hz, 3 H, C-19 or C-20), 0.79 (d, J = 6.7 Hz, 3 H, C-19 or C-20), 0.03 (s, 6 H, Si-CH_3); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 212.3, 159.3, 136.8, 130.0, 129.5, 121.3, 113.8, 84.8, 72.7, 62.2, 55.3, 41.1, 36.6, 34.9, 32.6, 27.0, 26.1, 25.1, 24.3, 22.4, 21.1, 18.5, 17.0, −5.0, −5.2; HRMS (FAB) calcd for $C_{29}H_{48}CsO_4Si$ (M + Cs^+) 621.2376, found 621.2404.

Synthesis of Propargylic Alcohol 22. To a stirring solution of methyl ketone **21** (180 mg, 0.369 mmol, 1.0 equiv) in CH_2Cl_2−THF (3:1, 20 mL) at −78 °C was added ethynylmagnesium bromide (0.5 M in THF, 11.8 mL, 5.40 mmol, 14.6 equiv) via syringe over 15 min. The reaction was stirred for 6 h at that temperature after which it was allowed to warm to 25 °C. The reaction was quenched with saturated NH_4Cl solution (10 mL). The aqueous layer was separated and extracted with ether (3 × 20 mL), and the combined organic phase was dried over Na_2SO_4 and concentrated. The residue was taken up in THF (2 mL) and treated with 1.0 M THF solution of TBAF (1.47 mL, 1.47 mmol, 4.0 equiv) at 25 °C. After 2 h (TLC monitoring), the reaction was quenched with water and extracted with ethyl acetate (3 × 20 mL). The combined organic phase was dried over Na_2SO_4 and concentrated. The residue was purified by flash chromatography (silica gel, 50% EtOAc in hexane) to afford diol **22** (106 mg, 72%, two steps) as a colorless oil. $R_f = 0.24$ (silica gel, EtOAc−hexane, 1:1); FT-IR (neat) ν_{max} 3305, 2958, 1614,ied by flash chromatography (silica gel, 6% EtOAc, hexane) to afford 2*5* (0.12 g, 71%, three steps): R_f - 0.27 (silica gel, EtOAc−hexane, 1:3); FT-IR (neat) ν_{max} 2959, 22*3*1, 1730, 1614, 1513, 1248, 1078, 10*2*2, 842 cm^{-1}; 1H NMR (600 MHz, $CDCl_3$) δ 7.83 (d, J = 11.8 Hz, 1 H, C-2), 7.19 (d, J = 8.6 Hz, 2 H, ArH), 6.85 (d, J = 8.6 Hz, 2 H, ArH), 5.33 (s, 1 H, C-12), 4.81 (d, J = 11.3 Hz, 1 H, OCHHAr), 4.47 (d, J = 11.3 Hz, 1 H, OCHHAr), 4.30 (q, J = 7.2 Hz, 2 H, OCH_2CH_3), 3.80 (s, 3 H, OCH_3), 3.16 (d, J = 9.8 Hz); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 158.8, 137.5, 130.4, 129.1, 120.3, 113.3, 86.5, 83.2, 73.4, 72.3, 71.2, 61.7, 54.9, 40.8, 36.1, 34.7, 31.5, 26.6, 25.7, 23.9, 22.5, 20.8, 16.2.

Synthesis of Cyano Ester 25 through an Oxidation−Knoevenagel Condensation−Protection Sequence. A mixture of $NaHCO_3$ (504 mg, 5.99 mmol, 20.0 equiv), pyridine (0.485 mL, 5.99 mmol, 20.0 equiv), Dess−Martin periodinane (191 mg, 0.449 mmol, 1.5 equiv), and diol **22** (0.120 g, 0.300 mmol, 1.0 equiv) was stirred at 25 °C for 4 h. To the reaction was then added saturated $NaHCO_3$ solution (15 mL), and the product was extracted with ether (3 × 25 mL). The combined organic layers were dried over Na_2SO_4, filtered through Celite eluting with ether, and concentrated to afford aldehyde **23** that was used for the next step without futher purification. To a solution of aldehyde **23** in 95% ethanol (1.8 mL) were added ethyl cyanoacetate (0.963 mL, 9.00 mmol, 30 equiv) and β-alanine (107 mg, 1.20 mmol, 4.0 equiv). After 72 h at 25 °C, the reaction mixture was filtered through a pad of silica gel eluting with ether and concentrated to afford α,β-unsaturated cyano ester **24**, which was used for the next step without further purification. The residue of **24** was dissolved in CH_2Cl_2, and *N*,*N*-diisopropylethylamine (0.522 mL, 2.99 mmol, 10 equiv) was added. The reaction was cooled to −78 °C, and TMSOTf (0.288 mL, 1.49 mmol, 5.0 equiv) was added over 15 min. After 2 h, the reaction was quenched with excess methanol (10 mL) and concentrated. The resulting residue was purified by flash chromatography (silica gel, 6% EtOAc, hexane) to afford **25** (0.12 g, 71%, three steps): $R_f = 0.27$ (silica gel, EtOAc−hexane, 1:3); FT-IR (neat) ν_{max} 2959, 2231, 1730, 1614, 1513, 1248, 1078, 1022, 842 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.83 (d, J = 11.8 Hz, 1 H, C-2), 7.19 (d, J = 8.6 Hz, 2 H, ArH), 6.85 (d, J = 8.6 Hz, 2 H, ArH), 5.33 (s, 1 H, C-12), 4.81 (d, J = 11.3 Hz, 1 H, OC*H*HAr), 4.47 (d, J = 11.3 Hz, 1 H, OCH*H*Ar), 4.30 (q, J = 7.2 Hz, 2 H, OCH_2CH_3), 3.80 (s, 3 H, OCH_3), 3.16 (d, J = 9.8 Hz, 1 H, C-8), 3.02−2.97 (m, 1 H, C-10), 2.50 (s, 1 H, C-5), 2.10−2.05 (m, 1 H), 1.98−1.82 (m, 3 H), 1.73−1.67 (m, 1 H), 1.63 (d, J = 1.1 Hz, 3 H, C-17), 1.56−1.45 (m, 2 H), 1.47 (s, 3 H, C-17), 1.36 (t, J = 7.2 Hz), 3 H, OCH_2CH_3), 0.90 (d, J = 6.8 Hz, 3 H, C-19 or C-20), 0.76 (d, J = 6.7 Hz, 3 H, C-19 or C-20), 0.20 (s, 9 H, Si-^{t}Bu); ^{13}C NMR (150 MHz, $CDCl_3$) δ 167.9, 161.0, 159.2, 135.8, 130.5, 129.8, 120.8, 113.8, 113.7, 109.2, 86.2, 83.4, 74.5, 74.3, 73.3, 62.2, 55.1, 44.1, 39.7, 39.0, 32.6, 26.0, 23.9, 21.5, 20.9, 17.0, 14.2 1.8; HRMS (FAB) calcd for $C_{33}H_{47}CsNO_5Si$ (M + Cs^+) 698.2278, found 698.2289; $[\alpha]^{25}_D$ −23.3 (*c* 2.58, $CHCl_3$).

Synthesis of α,β-Unsaturated Aldehyde 27. To a solution of cyano ester **25** (280 mg, 0.497 mmol, 1.0 equiv) in hexanes (25 mL) at −78 °C was added dropwise a 1.0 M THF solution of DIBAL (5.0 mL, 5.0 mmol, 10.0 equiv). After 7 h at −78 °C and 1 h at −40 °C, EtOAc (5 mL) was added, and the reaction mixture was warmed to 25 °C. Addition of water (30 mL) and stirring for 1 h at ambient temperature completed the workup procedure. The reaction mixture was extracted with ether (3 × 50 mL), dried over Na_2SO_4, and concentrated. The product was purified by flash chromatography (silica gel, 10% EtOAc in hexane) to afford alcohol **26** (210 mg, 80%). To a solution of **26** (50.0 mg, 0.0949 mmol, 1.0 equiv) in CH_2Cl_2 (0.95 mL) was added *N*,*N*-diisopropylethylamine (0.33 mL, 1.90 mmol, 20.0 equiv), and the resulting mixture was cooled to −78 °C, after which TIPSOTf (0.26 mL, 0.95 mmol, 10.0 equiv) was added dropwise. After 1 h (TLC monitoring), the reaction was quenched by the addition of MeOH (0.2 mL). After 10 min, aqueous saturated NH_4Cl solution (5 mL) was added, and the mixture was warmed to 25 °C, extracted with ether (10 mL), and concentrated. The residue was purified by flash chromatography (silica gel, 2% EtOAc in hexane) to furnish TIPS ether **27** (58.8 mg, 91%) as a colorless oil: R_f = 0.33 (silica gel, EtOAc−hexane, 1:10); FT-IR (neat) ν_{max} 3470, 3300, 2957, 2360, 2337, 1672, 1613, 1513, 1418, 1370, 1302, 1250 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.10 (s, 1 H, CHO), 7.20 (d, J = 8.5 Hz, 2 H, ArH), 7.00 (d, J = 11.5 Hz, 1 H, C-2), 6.81 (d, J = 8.5 Hz, 2 H, ArH), 5.34 (s, 1 H, C-12), 4.86 (d, J = 11.0 Hz, 1 H, OC*H*HAr), 4.47 (d, J = 14.0 Hz, 1 H, C-15), 4.38 (d, J = 11.0 Hz, 1 H, OC*H*HAr), 4.33 (d, J = 14.0 Hz, 1 H, C-15), 3.48 (s, 3 H, OCH_3), 3.45−3.36 (m, 1 H, C-10), 3.36 (d, J = 10.0 Hz, 1 H, C-8), 2.44 (s, 1 H, C-5), 2.25−2.17 (m, 1 H), 2.02−1.94 (m, 1 H), 1.92−1.78 (m, 2 H), 1.72−1.62 (m, 1 H), 1.61 (s, 3 H, C-17), 1.60−1.50 (m, 3 H), 1.43 (s, 3 H, C-16), 1.15−1.05 (m, 3 H, TIPS), 1.04 (d, J = 7.8 Hz, 18 H, TIPS), 0.90 (d, J = 6.8 Hz, 3 H, C-19 or C-20), 0.72 (d, J = 6.6 Hz, 3 H, C-19 or C-20), 0.18 (s, 9 H, Si-CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 190.2, 159.0, 152.8, 138.3, 136.0, 131.2, 129.4, 120.8, 113.6, 86.6, 84.3, 74.7, 74.6, 73.5, 60.0, 55.2, 42.5, 38.1, 36.6, 31.7, 28.5, 25.5, 23.9, 21.8, 20.9, 18.0, 17.7, 12.0, 2.0; HRMS (FAB) calcd for $C_{40}H_{66}CsNO_5Si$ (M + Cs^+) 815.3503, found 815.3538; $[\alpha]^{25}_D$ −10.1 (*c* 0.98, $CHCl_3$).

Synthesis of Diastereoisomeric Diols 29. To a solution of ethyl vinyl ether (1.16 g, 16.0 mmol, 2.0 equiv) in THF (70.0 mL) at −78 °C was added 1.7 M *t*-BuLi in hexanes (8.5 mL, 14.4 mmol, 1.8 equiv), and the solution was warmed to 0 °C. The reaction was followed by the color change from yellow to colorless. The resulting vinyl anion solution was then cooled to −78 °C, and a solution of aldehyde **14** (2.60 g, 8.02 mmol, 1.0 equiv) in THF (25 mL) was added dropwise, after which the reaction mixture was stirred for an additional 30 min at −78 °C. The reaction was quenched by addition of saturated NH_4Cl solution (40 mL) and extracted with ether (3 × 150 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated. The crude product was then dissolved in ether and treated with concentrated H_2SO_4 in a separatory funnel while shaking vigorously. The progress of the hydrolysis was followed by TLC, and upon completion, the ether solution was washed with water (20 mL) and saturated $NaHCO_3$ solution (20 mL), dried over $MgSO_4$, and concentrated. The residue was purified by flash chromatography (silica gel, 10% to 15% Et_2O in hexane) to produce hydroxy ketones **28** as an inseparable mixture of stereoisomers (ca. 1.25:1 by NMR). To a solution of mixture **28** in THF (78 mL) at −78 °C was added ethynylmagnesium bromide (0.5 M in THF, 70.8 mL, 35.0 mmol, 4.4 equiv), and the solution was stirred at −78 °C for 6 h and then was allowed to slowly warm to −10 °C. The reaction was quenched by addition of saturated NH_4Cl solution (50 mL) and extracted with ether (3 × 100 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated, and the resulting residue was purified by flash chromatography (silica gel, 10% to 25% Et_2O in hexane) to afford the desired isomer **29** (1.39 g, 44%) along with its C-7, C-8 stereoisomer (1.04 g, 33%). For **29**: R_f = 0.40 (silica gel, Et_2O−hexane, 1:3); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.32 (br s, 1 H, C-12), 3.84−3.79 (m, 1 H, C-2), 3.72−3.67 (m, 1 H, C-2), 3.64 (dd, J = 10.5, 9.5 Hz, 1 H, C-8), 3.02 (d, J = 4.0 Hz, 1 H), 2.95 (br s, 1 H), 2.48−2.43 (m, 1 H), 2.43 (s, 1 H, C-5), 1.98−1.70 (m, 5 H), 1.68 (s, 3 H, C-17), 1.63−1.44 (m, 2 H), 1.42 (s, 3 H, C-16), 0.88 (s, 9 H, Si-^{t}Bu), 0.88 (d, J = 7.5 Hz, 3 H, C-19 or C-20), 0.81 (d, J = 7.0 Hz, 3 H, C-19 or C-20), 0.05 (s, 6 H, Si-CH_3); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 136.5, 121.2, 86.4, 74.6, 72.4, 70.9, 62.5, 40.5, 35.8, 35.0, 30.6, 26.8, 25.8, 24.0, 23.7, 22.2, 20.9, 18.7, 17.0, −5.4, −5.5.

Synthesis of Triol 30. To a solution of diol **29** (0.63 g, 1.59 mmol, 1.0 equiv) in THF (16 mL) at 0 °C was added TBAF (1.0M in THF, 3.18 mL, 3.18 mmol, 2.0 equiv), and the reaction mixture was allowed to warm to 25 °C over 1 h. After the end of the reaction was established by TLC, the reaction was quenched by addition of saturated NH_4Cl (50 mL) and extracted with ether (3 × 100 mL). The combined organic extracts were concentrated, and the residue was purified by filtration through silica gel to furnish triol **30** (0.45 g, 100%) as a light yellow oil: R_f = 0.12 (silica gel, Et_2O−hexane, 3:1); FT-IR (neat) ν_{max} 3385, 2958, 1448, 1368, 1078, 946 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.38 (br s, 1 H, C-12), 3.83 (dd, J = 10.0, 2.5 Hz, 1 H, C-2), 3.81 (dd, J = 10.0, 5.5 Hz, 1 H, C-2), 3.73 (dd, J = 11.0, 8.5 Hz, 1 H, C-8), 2.50 (s, 1 H, C-5), 2.49 (br s, 1 H), 2.01−1.92 (m, 3 H), 1.89−1.81 (m, 3 H), 1.80−1.71 (m, 1 H), 1.72 (d, J = 1.5 Hz, 3 H, C-17), 1.65−1.56 (m, 3 H), 1.48 (s, 3 H, C-16), 0.92 (d, J = 6.5 Hz, 3 H, C-19 or C-20), 0.83 (d, J = 6.5 Hz, 3 H, C-19 or C-20); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 136.5, 121.3, 86.2, 74.9, 72.9, 71.0, 62.2, 40.4, 36.1, 35.3, 31.2, 26.9, 24.2, 23.5, 22.3, 20.9, 16.7; HRMS (FAB) calcd for $C_{17}H_{28}NaO_3$ (M + Na^+) 303.1936, found 303.1944; $[\alpha]^{25}_D$ +43.5 (*c* 0.2, $CHCl_3$).

Synthesis of Trisilyl Ether 31. To a solution of triol **30** (0.45 g, 1.59 mmol, 1.0 equiv) in CH_2Cl_2 (16 mL) was added triethylamine (2.3 mL, 16.5 mmol, 10.3 equiv), and the solution was chilled to 0 °C. TESOTf (2.10 g, 8.00 mmol, 5.0 equiv) was then added, and the reaction mixture was allowed to warm to 25 °C. After the disappearance of the starting triol was established by TLC, the reaction was quenched by addition of saturated NH_4Cl (50 mL) and extracted with CH_2Cl_2 (3 × 100 mL). The organic extracts were combined, dried over $MgSO_4$, and concentrated. The residue was purified by filtration through silica gel (25% Et_2O in hexane) to produce trisilyl ether **31** (0.99 g, 100%) as a light yellow oil: R_f = 0.62 (silica gel, Et_2O−hexane, 1:9); FT-IR (neat) ν_{max} 3308, 2956, 2876, 1459, 1414, 1378, 1239, 1115, 1006 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.30 (br s, 1 H, C-12), 3.77 (d, J = 10.0, 7.5 Hz, 1 H, C-2), 3.60 (dd, J = 10.0, 7.5 Hz, 1 H, C-2), 2.43 (s, 1 H, C-5), 2.34 (br s, 1 H), 1.97−1.75 (m, 6 H), 1.67 (s, 3 H, C-17), 1.64−1.57 (m, 1 H), 1.39 (s, 3 H, C-16), 1.00−0.94 (m, 27 H, Si-CH_2CH_3), 0.91 (d, J = 7.0 Hz, 3 H, C-19 or C-20), 0.85 (d, J = 7.0 Hz, 3 H, C-19 or C-20), 0.81−0.57 (m, 18 H, Si-CH_2CH_3); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 137.8, 120.7, 87.2, 78.1, 73.9, 61.6, 42.7, 36.6, 35.1, 34.9, 29.9, 27.2, 25.3, 23.9, 22.0, 21.5, 17.1, 7.1, 6.9, 6.8, 6.0, 5.6, 4.3; HRMS (FAB) calcd for $C_{35}H_{70}CsO_3Si_3$ (M + Cs^+) 755.3687, found 755.3710; $[\alpha]^{25}_D$ +19.0 (*c* 0.8, $CHCl_3$).

Selective Deprotection of the Primary Hydroxide to Produce Alcohol 32. To a solution of trisilyl ether **31** (1.48 g, 2.37 mmol, 1.0 equiv) in 3:1 MeOH/CH_2Cl_2 (20 mL) was added a catalytic amount of PPTS (45 mg, 0.24 mmol, 0.1 equiv). After its completion (TLC monitoring), the reaction mixture was worked up by addition of saturated $NaHCO_3$ (50 mL) and extraction with ether (3 × 150 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated. The residue was purified by filtration through silica gel eluting with ether to provide alcohol **32** (1.18 g, 98%) as a colorless oil: R_f = 0.12 (silica gel, Et_2O−hexane, 1:9); FT-IR (neat) ν_{max} 3490, 3308, 2955, 2876, 1459, 1414, 1378, 1238, 1109, 1072, 1004 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.33 (br s, 1 H, C-12), 3.79 (dd, J = 9.5, 1.5 Hz, 1 H), 3.79−3.74 (m, 1 H), 3.70 (dd, J = 11.0, 4.5 Hz, 1 H, C-2), 2.46 (s, 1 H, C-5), 2.35 (br s, 1 H), 2.04 (ddd, J = 15.0, 9.0, 1.5 Hz, 1 H), 1.97−1.72 (m, 5 H), 1.69 (d, J = 1.5 Hz, 3 H, C-17), 1.69−1.52 (m, 2 H), 1.46 (s, 3 H, C-16), 0.97 (t, J = 7.5 Hz, 18 H, Si-CH_2CH_3), 0.92 (d, J = 6.5 Hz, 3 H), 0.83 (d, J = 6.5 Hz, 3 H), 0.80−0.65 (m, 12 H, Si-CH_2CH_3); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 137.4, 120.7, 86.4, 78.0, 74.0, 73.4, 62.5, 41.2, 36.9, 35.2, 33.9, 26.9, 26.4, 23.9, 22.3, 21.3, 17.1, 7.0, 6.9, 6.7, 6.3, 5.9, 5.6; HRMS (FAB) calcd for $C_{29}H_{56}CsO_3Si_2$ (M + Cs^+) 641.2822, found 641.2852; $[\alpha]^{25}_D$ +20.4 (*c* 2.0, $CHCl_3$).

Synthesis of Aldehyde 33. To a solution of alcohol **32** (1.24 g, 2.43 mmol, 1.0 equiv) and powdered activated 4 Å MS (0.5 g) in CH_2Cl_2 (16 mL) was added NMO (0.43 g, 3.64 mmol, 1.5 equiv), and the reaction mixture was stirred for 10 min. TPAP (0.043 g, 0.181 mmol,

0.07 equiv) was then added, and the reaction mixture was stirred at 25 °C for 30 min. The heterogeneous solution was then filtered through a short pad of silica gel and washed with CH_2Cl_2. After concentration, aldehyde **33** (1.20 g, 98%) was obtained as a colorless oil: $R_f = 0.42$ (silica gel, Et_2O−hexane, 1:9); FT-IR (neat) ν_{max} 3309, 2955, 2876, 1719, 1458, 1414, 1378, 1238, 1073, 1004 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.86 (d, $J = 6.7$ Hz, 1 H, C-2), 5.37 (br s, 1 H, C-12), 3.41 (d, $J = 12.0$ Hz, 1 H, C-8), 2.47−2.42 (m, 1 H), 2.43 (s, 1 H, C-5), 2.36−2.29 (m, 2 H), 2.09−1.97 (m 2 H), 1.86−1.67 (m, 2 H), 1.69 (d, $J = 1.7$ Hz, 3 H, C-17), 1.57−1.52 (m, 1 H), 1.39 (s, 3 H, C-16), 1.00−0.85 (m, 24 H), 0.80−0.59 (m, 12 H); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 207.8, 136.2, 121.2, 86.4, 78.7, 74.2, 72.9, 53.5, 37.2, 35.5, 33.9, 28.7, 25.8, 25.7, 23.6, 21.6, 21.1, 16.1, 7.0, 6.8, 6.4, 6.0, 5.6; HRMS (FAB) calcd for $C_{29}H_{54}NaO_3Si_2$ ($M + Na^+$) 529.3509, found 529.3487; $[\alpha]^{25}_D$ +18.5 (*c* 0.65, $CHCl_3$).

Formation of α,β-unsaturated Cyano Ester 34. A solution of aldehyde **33** (1.14 g, 2.25 mmol, 1.0 equiv), ethyl cyanoacetate (7.63 g, 67.0 mmol, 30 equiv), and β-alanine (0.080 g, 9.00 mmol, 4.0 equiv) in EtOH (15 mL) was stirred at 50 °C for 72 h. The reaction mixture was then concentrated and purified by filtration through a short pad of silica gel eluting with 10% Et_2O in hexanes to produce cyano ester **34** (1.28 g, 95%) as a colorless oil: $R_f = 0.40$ (silica gel, Et_2O−hexane, 1:9); FT-IR (neat) ν_{max} 3308, 2958, 2878, 2201, 1735, 1619, 1461, 1370, 1249, 1117, 1008 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.88 (d, $J = 12.0$ Hz, 1 H, C-2), 5.39 (br s, 1 H, C-12), 4.36−4.26 (m, 2 H, OCH_2CH_3), 3.34 (d, $J = 9.5$ Hz, 1 H, C-8), 3.06 (dd, $J = 7.0$, 5.0 Hz, 1 H, C-1), 2.47 (s, 1 H, C-5), 2.28−2.23 (m, 1 H), 2.13 (dd, $J = 15.0$, 9.0 Hz, 1 H, C-13), 1.99−1.74 (m, 5 H), 1.69 (s, 3 H, C-17), 1.38 (s, 3 H, C-16), 1.35 (t, $J = 7.0$ Hz, 3 H, OCH_2CH_3), 1.00−0.91 (m, 6 H, C-19 and C-20), 0.99 (t, $J = 8.0$ Hz, 9 H, $SiCH_2CH_3$), 0.94 (t, $J = 7.5$ Hz, 9 H), 0.81−0.58 (m, 12 H); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 168.3, 160.9, 136.2, 120.9, 113.8, 109.0, 86.4, 78.9, 74.2, 72.7, 62.2, 44.8, 40.1, 38.5, 34.3, 31.4, 30.2, 29.6, 25.8, 23.7, 21.6, 21.1, 15.9, 14.1, 7.1, 7.0, 6.1, 5.6; HRMS (FAB) calcd for $C_{34}H_{59}CsNO_4Si_2$ ($M + Cs^+$) 734.3037, found 734.3063; $[\alpha]^{25}_D$ +46.4 (*c* 1.2, $CHCl_3$).

Synthesis of Hydroxy Aldehyde 35. To a solution of cyanoester **34** (101 mg, 0.168 mmol, 1.0 equiv) in hexanes (8.4 mL) at −78 °C was added DIBAL (1.0M in toluene, 1.7 mL, 1.70 mmol, 10.0 equiv). The reaction mixture was stirred for 6 h at −78 °C and then slowly warmed to −10 °C for 2 h. The reaction was then quenched with ethyl acetate (0.2 mL), saturated NH_4Cl (10 mL) solution was added, and the reaction was stirred for 2 h, after which it was filtered through a short Celite pad eluting with ether and extracted with ethyl acetate (3 × 10 mL). The combined organic extracts were concentrated and purified by flash chromatography (silica gel, 10% Et_2O in hexanes) to produce hydroxyaldehyde **35** (79.8 mg, 90%) as a light yellow oil: $R_f = 0.42$ (silica gel, Et_2O−hexane, 1:1); FT-IR (neat) ν_{max} 3447, 3307, 2957, 2877, 1677, 1459, 1414, 1380, 1239, 1117, 1008 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 10.18 (s, 1 H, C-4), 6.89 (d, $J = 12.0$ Hz, 1 H, C-2), 5.39 (br s, 1 H, C-12), 4.35 (dd, $J = 13.0$, 5.0 Hz, 1 H, C-15), 4.17 (dd, $J = 13.0$, 7.0 Hz, 1 H, C-15), 3.47 (d, $J = 10.0$ Hz, 1 H, C-8), 3.37−3.29 (m, 1 H, C-1), 2.49 (s, 1 H, C-5), 2.23−2.12 (m, 3 H), 2.01−1.68 (m, 4 H), 1.68 (d, $J = 1.0$ Hz, 3 H, C-17), 1.58 (s, 1 H), 1.37 (s, 3 H, C-16), 0.98−0.88 (m, 6 H, C-19 and C-20), 0.97 (t, $J = 8.0$ Hz, 9 H, $SiCH_2CH_3$), 0.89 (t, $J = 8.0$ Hz, 9 H, $SiCH_2CH_3$), 0.81−0.62 (m, 12 H, $SiCH_2CH_3$); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 191.2. 154.8, 138.1, 136.6, 120.9, 86.8, 79.3, 74.5, 72.9, 62.8, 40.9, 38.4, 38.3, 34.2, 29.7, 28.5, 25.6, 23.5, 21.7, 21.1, 15.4, 7.1, 7.0, 6.0, 5.6; HRMS (FAB) calcd for $C_{32}H_{58}O_4Si_2$ ($M + Cs^+$) 695.2928, found 695.2951; $[\alpha]^{25}_D$ +66.0 (*c* 3.0 $CHCl_3$).

Synthesis of Trisilyl Ether 36. To a solution of hydroxy aldehyde **35** (930.0 mg, 1.65 mmol, 1.0 equiv) and $^iPr_2NEt$ (2.8 mL, 16.07 mmol, 9.7 equiv) in CH_2Cl_2 (8 mL) at −78 °C was added TIPSOTf (2.2 mL, 8.25 mmol, 5.0 equiv), and the solution was stirred at that temperature for 1 h. The reaction mixture was quenched by addition of MeOH (0.5 mL) followed by addition of saturated NH_4Cl (10 mL). The mixture was then extracted with ether (10 mL), and the organic extracts were combined, dried over Na_2SO_4, and concentrated. The resulting residue was purified by flash chromatography (silica gel, 2% EtOAc−hexane) to furnish trisilyl ether **36** (1.10 g, 93%) as a light yellow oil: $R_f = 0.33$ (silica gel, hexane); FT-IR (neat) ν_{max} 3309, 2957, 2872, 2361, 1675, 1462, 1381, 1239, 1167, 1117, 1007, 882, 819, 741 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 10.14 (s, 1 H, C-4), 6.98 (d, $J = 11.6$ Hz, 1 H, C-2), 5.37 (br s, 1 H, C-12), 4.52 (dd, $J = 14.0$, 1.2 Hz, 1 H, C-15), 4.21 (dd, $J = 14.0$, 1.6 Hz, 1 H, C-15), 3.53 (d, $J = 9.3$ Hz, 1 H, C-8), 3.45−3.38 (m, 1 H, C-1), 2.39 (s, 1 H, C-5), 2.28−2.23 (m, 1 H), 2.04−1.92 (m, 2 H), 1.90−1.82 (m, 1 H), 1.78−1.70 (m, 1 H), 1.65−1.54 (m, 1 H), 1.67 (d, $J = 1.2$ Hz, 3 H, C-17), 1.45−1.38 (m, 1 H), 1.33 (s, 3 H, C-16), 1.03−1.00 (m, 24 H, TIPS, C19 or C20), 0.93−0.87 (m, 21 H, $Si\text{-}CH_2CH_3$ and C19 or C20), 0.72−0.50 (m, 12 H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 190.1, 153.0, 138.4, 136.5, 120.8, 86.9, 78.6, 74.6, 72.8, 60.5, 40.8, 39.2, 37.2, 33.9, 29.7, 28.4, 25.0, 23.7, 21.9, 21.2, 18.0, 16.7, 11.9, 7.1, 6.1, 5.9, 5.6; HRMS (FAB) calcd for $C_{41}H_{78}NaO_4Si_3$ ($M + Na^+$) 741.5105, found 741.5136; $[\alpha]^{25}_D$ +33.7 (*c* 1.4, $CHCl_3$).

Synthesis of Alkynone 37 by Intramolecular Acetylide Addition to Aldehyde 27. A solution of LiHMDS (1.0M in THF, 0.037 mL, 0.037 mmol, 1.5 equiv) was added dropwise to a solution of aldehyde **27** (17.0 mg, 0.025 mmol, 1.0 equiv) in THF (1.2 mL) at 25 °C. After 10 min (TLC monitoring), the reaction mixture was quenched by the addition of aqueous saturated NH_4Cl solution (5 mL), extracted with ether (2 × 10 mL), dried over Na_2SO_4, and concentrated. The residue was redissolved in CH_2Cl_2 (1.0 mL) and $NaHCO_3$ (41.8 mg, 0.497 mmol, 20 equiv) was added to the solution at 0 °C. After 40 min, Dess−Martin periodinane (10.6 mg, 0.025 mmol, 1.0 equiv) was added to the reaction mixture at the same temperature, and the solution was warmed to 25 °C. After 4 h of stirring at ambient temperature, the reaction was diluted with ether (5 mL) and quenched by the consecutive addition of saturated aqueous $NaHCO_3$ solution (5 mL) and sodium thiosulfate pentahydrate ($Na_2S_2O_3 \cdot 5H_2O$, 65 mg, 0.261 mmol, 10.4 equiv). The resulting solution was extracted with ether (2 × 10 mL), and the combined organic extracts were dried over Na_2SO_4 and concentrated. The crude product was purified by flash chromatography (silica gel, 1% EtOAc in hexane) to provide enyneone **37** (14.4 mg, 85%, two steps) as a colorless oil: $R_f = 0.46$ (silica gel, EtOAc−hexane, 1:10); FT-IR (neat) ν_{max} 2961, 2361, 2197, 1650, 1611, 1512, 1461, 1384, 1461, 1384, 1248, 1175, 1095, 1035, 841, 760, 685 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.25 (d, $J = 8.3$ Hz, 2 H, Ar−H), 6.84 (d, $J = 8.3$ Hz, 2 H, Ar−H), 6.27 (d, $J = 12.0$ Hz, 1 H, C-2), 5.33 (br s, 1 H, C-12), 4.80 (d, $J = 12.0$ Hz, 1 H OCH*H*-Ar), 4.65 (d, $J = 12.0$ Hz, 1 H, OC*H*H−Ar), 4.34 (d, $J = 14.2$ Hz, 1 H, C-15), 4.30 (d, $J = 14.2$ Hz, 1 H, C-15), 3.78 (s, 3 H, OCH_3), 3.39 (d, $J = 2.8$ Hz, 1 H, C-8), 3.36 (d, $J = 12.0$ Hz, 1 H, C-1), 2.18−2.05 (m, 1 H), 1.98−1.80 (m, 2 H), 1.67 (s, 3 H, C-17), 1.62−1.53 (m, 1 H), 1.45 (s, 3 H, C-16), 1.20−1.10 (m, 1 H, C-14), 1.08−0.94 (m, 21 H, TIPS), 0.81 (d, $J = 6.4$ Hz, 3 H, C-19 or C-20), 0.64 (d, $J = 6.5$ Hz, 3 H, C-19 or C-20), 0.24 (s, 9 H, $Si\text{-}CH_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 181.2, 159.2, 142.0, 139.5, 133.6, 130.9, 129.7, 121.4, 113.7, 103.2, 88.6, 87.2, 73.7, 73.5, 63.5, 55.2, 44.8, 38.3, 37.8, 33.4, 29.6, 25.7, 21.9, 21.9, 21.5, 20.3, 17.9, 11.9, 1.7; HRMS (FAB) calcd for $C_{40}H_{64}CsO_5Si_2$ ($M + Cs^+$) 813.3347, found 813.3314; $[\alpha]^{25}_D$ +22.7 (*c* 1.8, $CHCl_3$).

Synthesis of Propargylic Alcohol 38. To a solution trimethylsilyl ether **37** (3.2 mg, 0.0047 mmol, 1.0 equiv) in MeOH (1 mL) was added, at 25 °C, PPTS (1.18 mg, 0.0047 mmol, 1.0 equiv), and the reaction mixture was allowed to stir at ambient temperature for 30 min. The reaction was quenched by addition of saturated $NaHCO_3$ solution (1 mL) and extracted with ether (2 × 10 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated. The crude product was purified by flash chromatography (silica gel, 15% EtOAc in hexane) to provide alcohol **38** (2.7 mg, 94%) as a colorless oil: $R_f = 0.45$ (silica gel, EtOAc−hexane, 1:3); ^1H NMR (600 MHz, $CDCl_3$) δ 7.22 (d, $J = 6.7$ Hz, 2 H, Ar*H*), 6.85 (dd, $J = 6.7$, 2.3 Hz, 2 H, Ar*H*), 6.28 (d, $J = 11.7$ Hz, 1 H, C-2), 5.39 (s, 1 H, C-12), 4.70 (d, $J = 11.6$ Hz, 1 H, OC*H*HAr), 4.59 (d, $J = 11.6$ Hz, 1 H, OCH*H*Ar), 4.34 (s, 2 H, C-15), 3.78 (s, 3 H, OCH_3), 3.52 (s, 1 H, C-8), 3.44 (d, $J = 11.6$ Hz, 1 H, C-1), 2.48 (br s, 1 H, OH), 2.22−2.10 (m, 2 H), 2.01 (d, $J = 14.1$ Hz, 1 H), 1.92 (d, $J = 18.3$ Hz, 1 H), 1.72 (s, 3 H, C-17), 1.70−1.66 (m, 1 H), 1.47 (s, 3 H, C-16), 1.40−1.30 (m, 2 H), 1.10−1.02 (m, 21 H, TIPS), 0.85 (d, $J = 6.7$ Hz, 3 H, C-19 or C-20), 0.74 (d, $J = 6.7$ Hz, 3 H, C-19 or C-20); ^{13}C NMR (150 MHz, $CDCl_3$) δ 181.0, 159.5, 142.7, 139.3, 133.1, 129.8, 129.5, 122.0, 114.0, 102.2, 87.6, 86.1, 72.5, 71.7, 63.5, 55.3, 45.1, 38.7, 37.8, 32.6, 29.7, 25.7, 21.9, 21.5, 21.4, 20.5,

17.9, 11.9; HRMS (FAB) calcd for $C_{37}H_{56}CsO_5Si$ (M + Cs^+) 741.2951, found 741.2979; $[\alpha]^{25}_D$ +39.3 (*c* 0.68, $CHCl_3$).

Synthesis of the Basic Tricyclic Core 40. To a solution of alkynone **38** (6.2 mg, 0.0135 mmol, 1.0 equiv) in toluene (1 mL) was added 5% Pd on $CaSO_4$ treated with Pb (Lindlar catalyst, 14.0 mg, 0.00675 mmol, 0.5 equiv) at 25 °C under argon. This suspension was then stirred under a H_2 atmosphere (1 atm) at the same temperature for 20 min, and the reaction mixture was filtered through Celite and concentrated. The crude residue was purified by flash chromatography (silica gel, 10% EtOAc−hexanes) to produce hemiketal **40** (6.2 mg, 75%) as a colorless oil, along with its 5,6-dihydro analogue (1.5 mg, 15%): R_f = 0.55 (silica gel, EtOAc−hexane, 1:3); FT-IR (neat) ν_{max} 3418, 2866, 1615, 1515, 1463, 1248, 1017 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.24 (d, *J* = 8.5 Hz, 2 H, Ar*H*), 6.85 (dd, *J* = 8.5, 2.3 Hz, 2 H, Ar*H*), 6.04 (s, 2 H, C-5, C-6), 5.40 (d, *J* = 9.3 Hz, 1 H, C-2), 5.25 (s, 1 H, C-12), 4.89 (s, 1 H, OH), 4.56 (d, *J* = 11.3 Hz, 1 H, C-15), 4.37 (d, *J* = 11.3 Hz, 1 H, OC*H*H-Ar), 4.36 (d, *J* = 11.6 Hz, 1 H, C-15), 4.05 (d, *J* = 11.6 Hz, 1 H, C-15), 3.95−3.90 (m, 1 H, C-1), 3.78 (s, 3 H, OCH_3), 3.31 (d, *J* = 7.1 Hz, 1 H, CHC═C), 2.27 (br d, *J* = 16.4 Hz, 1 H), 2.16 (br d, *J* = 11.5 Hz, 1 H), 1.98 (br d, *J* = 17.9 Hz, 1 H), 1.74 (d, *J* = 13.9 Hz, 1 H), 1.57 (s, 3 H, C═CCH_3), 1.54 (s, 3 H, $OCCH_3$), 1.48−1.40 (m, 1 H), 1.28−1.20 (m, 2 H), 1.15−1.05 (m, 3 H, Si-C*H*$(CH_3)_2$), 1.03 (d, *J* = 6.4 Hz, 18 H, Si-CH(C*H*$_3)_2$), 0.91 (d, *J* = 6.7 Hz, 3 H, C-19 or C-20), 0.87 (d, *J* = 6.7 Hz, 3 H, C-19 or C-20); ^{13}C NMR (150 MHz, $CDCl_3$) δ 159.4, 136.2, 134.6, 133.9, 133.4, 131.2, 130.3, 129.8, 121.5, 113.8, 112.2, 91.4, 86.6, 71.3, 68.3, 55.3, 42.0, 39.2, 33.7, 29.5, 29.0, 25.8, 24.4, 22.2, 22.1, 20.3, 17.8, 11.6; HRMS (FAB) calcd for $C_{37}H_{58}CsO_5Si$ (M + Cs^+) 743.3108, found 743.3132; $[\alpha]^{25}_D$ +38.1 (*c* 0.28, $CHCl_3$).

Synthesis of Methyl Ketal 41. To a solution of hemiketal **40** (4.0 mg, 0.0066 mmol, 1.0 equiv) in MeOH (0.5 mL) was added PPTS (1.65 mg, 0.0066 mmol, 1.0 equiv). After 10 min, the reaction was quenched by addition of saturated $NaHCO_3$ solution (5 mL). The biphasic system was then extracted with CH_2Cl_2,(3 × 10 mL), and the organic extracts were combined, dried over Na_2SO_4, and concentrated. The product was purified by flash chromatography (silica gel, 5% EtOAc in hexane) to furnish ketal **41** (4.5 mg, 100%) as a light yellow oil: R_f = 0.68 (silica gel, EtOAc−hexane, 1:3); FT-IR (neat) ν_{max} 2957, 2866, 1614, 1514, 1463, 1250, 1064 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.24 (d, *J* = 8.5 Hz, 2 H, ArH), 6.86 (d, *J* = 8.5 Hz, 2 H, ArH), 6.06 (d, *J* = 5.8 Hz, 1 H, C-5 or C-6), 5.91 (d, *J* = 5.8 Hz, 1 H, C-5 or C-6), 5.65 (d, *J* = 9.5 Hz, 1 H, C-2), 5.22 (s, 1 H, C-12), 4.57 (d, *J* = 11.4 Hz, 1 H, OC*H*HAr), 4.36 (d, *J* = 11.4 Hz, 1 H, OC*H*HAr), 4.17 (d, *J* = 13.5 Hz, 1 H, C-15), 4.12 (d, *J* = 13.5 Hz, 1 H, CH*H*OSi), 3.83−3.80 (m, 1 H, C-8), 3.79 (s, 3 H, $ArOCH_3$), 3.28 (d, *J* = 7.0 Hz, 1 H, C-1), 3.15 (s, 3 H, OCH_3), 2.34 (br d, *J* = 19.4 Hz, 1 H), 2.14 (br d, *J* = 8.6 Hz, 1 H), 1.95 (br d, *J* = 17.9 Hz, 1 H), 1.73 (d, *J* = 14.9 Hz, 1 H), 1.56 (s, 3 H, C-17), 1.45 (s, 3 H, C-16), 1.38−1.30 (m, 1 H), 1.25−1.17 (m, 2 H), 1.07−1.00 (m, 3 H, Si-C*H*$(CH_3)_2$), 1.01 (d, *J* = 6.4 Hz, 18 H, Si-^{t}Bu), 0.90 (d, *J* = 6.7 Hz, 3 H, C-19 or C-20), 0.85 (d, *J* = 6.7 Hz, 3 H, C-19 or C-20); ^{13}C NMR (150 MHz, $CDCl_3$) δ 159.4, 136.5, 135.1, 134.3, 130.3, 129.9, 129.7, 128.5, 121.5, 115.7, 113.8, 91.0, 86.7, 71.1, 64.7, 55.2, 49.4, 42.3, 39.3, 33.2, 29.3, 29.1, 24.6, 24.5, 22.1, 20.4, 17.9, 11.8; HRMS (FAB) calcd for $C_{38}H_{60}CsO_5Si$ (M + Cs^+) 757.3264, found 757.3294; $[\alpha]^{25}_D$ +43.9 (*c* 0.20, $CHCl_3$).

Synthesis of Alcohol 42 from PMB-ether 41. A solution of ether **41** (5.0 mg, 0.0080 mmol, 1.0 equiv) in THF (1 mL) and EtOH (2 drops) was added to liquid NH_3 (2 mL) at −78 °C. Sodium (1.8 mg, 0.078 mmol, 9.8 equiv) was then added, and the reaction was stirred at −78 °C for 20 min. After the end of the deprotection was established by TLC, the reaction was quenched by addition of solid NH_4Cl (50 mg), warmed to ambient temperature to evaporate the NH_3, extracted with ether (3 × 10 mL), dried with Na_2SO_4, concentrated, and purified by flash chromatography (silica gel, 15% EtOAc in hexane) to provide alcohol **42** along with its 5,6-dihydro analogue **43** as an inseparable mixture (ca. 2:1, 3.8 mg, 95%).

Synthesis of Alcohol 42 from Hydroxy Alkynone 45. To a solution of α,*β*-alkynone **45** (26.8 mg, 0.055 mmol, 1.0 equiv) in acetone (3 mL) was added [Rh(nbd)(dppb)]BF_4 (1.9 mg, 0.0027 mmol, 0.05 equiv) at 25 °C under argon. The reaction flask was then evacuated and treated with hydrogen gas (1 atm). After 10 min, the reaction was quenched by addition of saturated $NaHCO_3$ (10 mL), extracted with ether (3 × 10 mL), dried over Na_2SO_4, and concentrated to a crude residue. To a solution of this residue in MeOH (6 mL) was added PPTS (6.9 mg, 0.027 mmol, 0.5 equiv) at 25 °C. After 10 min, the reaction was quenched by addition of saturated $NaHCO_3$, (10 mL), extracted with ether (3 × 20 mL), dried over Na_2SO_4 and concentrated. The residue was purified by flash chromatography (silica gel, 15% EtOAc in hexane) to produce methyl ketal **42** (22.2 mg, 80%, two steps) as a colorless oil: R_f = 0.43 (silica gel, EtOAc−hexane, 1:3); FT-IR (neat) ν_{max} 3456, 2940 2866, 1466, 1366, 1047, 881 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 6.03 (d, *J* = 5.8 Hz, 1 H, C-5 or C-6), 5.95 (d, *J* = 9.5 Hz, 1 H, C-2), 5.92 (d, *J* = 5.8 Hz, 1 H, C-5 or C-6), 5.37 (br s, 1 H, C-12), 4.43 (d, *J* = 14.0 Hz, 1 H, C-5), 4.41 (d, *J* = 14.0 Hz, 1 H, C-5), 4.20−4.10 (m, 1 H, C-8), 3.53 (d, *J* = 7.0 Hz, 1 H, C-1), 3.16 (s, 3 H, OCH_3), 2.53 (br d, *J* = 18.5 Hz, 1 H, C-13), 2.34 (br d, *J* = 10.5 Hz, 1 H, C-10), 2.04 (d, *J* = 18.5 Hz, 1 H, C-13), 1.75−1.66 (m, 1 H), 1.63 (s, 3 H, C-17), 1.60−1.53 (m, 2 H), 1.52 (s, 3 H, C-16), 1.36−1.28 (m, 1 H), 1.25−1.18 (m, 1 H), 1.15−1.05 (m, 21 H, TIPS), 0.96 (d, *J* = 6.5 Hz, 3 H, C-19 or C-20), 0.93 (d, *J* = 6.5 Hz, 3 H, C-19 or C-20); ^{13}C NMR (125 MHz, C_6D_6) δ 137.3, 134.6, 134.5, 130.1, 129.5, 121.9, 116.2, 91.6, 80.8, 65.2, 49.4, 43.2, 39.6, 35.0, 33.8, 29.6, 25.3, 24.9, 22.6, 22.4, 20.7, 18.3, 12.4; HRMS (FAB) calcd for $C_{30}H_{52}NaO_4Si$ (M + Na^+) 527.3532, found 527.3548; $[\alpha]^{25}_D$ +75.7 (*c* 2.3, benzene).

Synthesis of 5,6-Dihydro Analogue 43 from Hydroxy Alkynone 45. To a solution of ketone **45** (4.5 mg, 0.0092 mmol, 1.0 equiv) in ethyl acetate (0.5 mL) was added 5% Pd on $BaSO_4$ (19.6 mg, 0.0092 mmol, 1.0 equiv). This suspension was stirred under a hydrogen atmosphere (1 atm) at 25 °C for 1 h. The reaction mixture was then filtered through Celite and concentrated by evaporation. To a solution of the crude residue in MeOH (0.5 mL) was added PPTS (4.6 mg, 0.018 mmol, 2.0 equiv), and the mixture was stirred for 6 h at 25 °C. A saturated solution of $NaHCO_3$ (5 mL) was added, and the reaction mixture was extracted with ether (3 × 10 mL), dried over Na_2SO_4, and concentrated. The crude residue was purified by flash chromatography (silica gel, 15% EtOAC−hexane) to provide 5,6-dihydro methyl ketal analogue **43** (3.0 mg, 64%, two steps): R_f = 0.50 (silica gel, EtOAc−hexane, 1:3); FT-IR (neat) ν_{max} 3422, 2961, 2865, 2361, 1464, 1383, 1122, 1047, 882, 684 cm^{-1}; ^1H NMR (400 MHz, C_6D_6) δ 6.05 (d, *J* = 9.7 Hz, 1 H, C-2), 5.41 (br s, 1 H, C-12), 4.31 (dd, *J* = 13.7, 1.0 Hz, 1 H, C-15), 4.26 (dd, *J* = 13.7, 1.5 Hz, 1 H, C-15), 4.16−4.12 (m, 1 H, C-1), 3.38 (d, *J* = 16 Hz, 1 H, C-8), 3.23 (s, 3 H, OCH_3), 2.63−2.52 (m, 1 H), 2.41−2.26 (m, 3 H), 2.19−2.11 (m, 2H), 1.85−1.79 (m, 1 H), 1.70−1.58 (m, 3 H), 1.66 (s, 3 H, C-17), 1.45 (s, 3 H, C-16), 1.35−1.30 (m, 2 H), 1.15−1.01 (m, 21 H, TIPS), 1.01 (d, *J* = 6.6 Hz, 3 H, C-19 or C-20), 0.96 (d, *J* = 6.4 Hz, 3 H, C-19 or C-20); ^{13}C NMR (100.6 MHz, C_6D_6) δ 137.7, 134.5, 130.3, 121.9, 112.9, 87.4, 80.2, 64.7, 49.8, 43.8, 39.7, 38.9, 35.4, 33.8, 29.6, 29.3, 28.9, 25.1, 22.6, 22.3, 20.8, 18.3, 12.3; HRMS (FAB) calcd for $C_{30}H_{54}NaO_4Si$ (M + Na^+) 529.3689, found 529.3708; $[\alpha]^{25}_D$ +32.6 (*c* 0.83, 1,4-dioxane).

Synthesis of Bicyclic Alcohol 44. To a solution of PMB-ether **37** (31.0 mg, 0.045 mmol, 1.0 equiv) in CH_2Cl_2 (4.6 mL) and H_2O (0.3 mL) was added DDQ (21.0 mg, 0.091 mmol, 2.0 equiv), and the reaction was stirred at 25 °C for 30 min. After the disappearance of starting ether was established by TLC, the reaction was quenched by addition of saturated $NaHCO_3$ (3 mL), extracted with ether (3 × 10 mL), and dried over Na_2SO_4. The crude residue was purified by flash chromatography (silica gel, EtOAc−hexane, 1:99) to yield alcohol **44** (20.4 mg, 80%) as a colorless oil: R_f = 0.57 (silica gel, EtOAc−hexane, 1:10); FT-IR (neat) ν_{max} 3490, 2959, 2866, 2197, 1651, 1464, 1384, 1252, 1122, 1095, 1021, 864, 843 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.32 (d, *J* = 12.0 Hz, 1 H, C-2), 5.41 (br s, 1 H, C-12), 4.37 (s, 2 H, C-15), 3.66 (d, *J* = 2.9 Hz, 1 H, C-8), 3.49 (d, *J* = 12.0 Hz, 1 H, C-1), 2.57 (br s, 1 H, OH), 2.41 (br d, *J* = 11.0 Hz, 1 H, C-10), 2.22 (br d, *J* = 17.0 Hz, 1 H, C-13), 1.89 (br d, *J* = 17.0 Hz, 1 H, C-13), 1.86 (dd, *J* = 14.4, 4.1 Hz, 1 H), 1.71 (s, 3 H, C-17), 1.62−1.52 (m, 3 H), 1.37 (s, 3 H, C-16), 1.11−1.02 (m, 21 H, TIPS), 0.92 (d, *J* = 6.1 Hz, 3 H, C-19 or C-20), 0.91 (d, *J* = 6.2 Hz, 3 H, C-19 or C-20), 0.24 (s, 9 H, TMS); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 181.2, 142.5, 139.3, 133.6, 121.7, 102.4, 89.2, 81.8, 72.2, 63.7, 45.0, 38.8, 32.0, 29.8, 25.9,

21.8, 21.6, 20.8, 20.2, 17.9, 11.9, 1.5; HRMS (FAB) calcd for $C_{32}H_{56}CsO_4Si_2$ (M + Cs^+) 693.2772, found 693.2745; $[\alpha]^{25}_D$ +45.2 (*c* 0.44, $CHCl_3$).

Synthesis of Alkynone 49. To a solution of aldehyde **36** (243.0 mg, 0.338 mmol, 1.0 equiv) in THF (17 mL) was added dropwise a 1.0 M THF solution of LiHMDS (0.68 mL, 0.68 mmol, 2.0 equiv) at −20 °C. The reaction mixture was stirred for 20 min at that temperature, and the reaction was then quenched with saturated NH_4Cl solution (30 mL), extracted with ether (2 × 50 mL), dried over Na_2SO_4, and concentrated to a crude residue. A solution of this residue in CH_2Cl_2 (9 mL) was added to a solution of $NaHCO_3$ (170.0 mg, 2.0 mmol, 5.9 equiv), pyridine (0.16 mL, 2.0 mmol, 5.9 equiv), and Dess−Martin reagent (286.0 mg, 0.67 mmol, 2.0 equiv) in CH_2Cl_2 (9 mL) at 0 °C. The reaction was stirred for 1 h at the same temperature and then quenched by consecutive addition of saturated $NaHCO_3$ (20 mL) and $Na_2S_2O_3·5H_2O$ (1.17 g, 4.7 mmol, 13.9 equiv). The resulting solution was stirred for an additional 30 min, extracted with ether (2 × 50 mL), dried over Na_2SO_4, and concentrated. This crude residue was then purified by flash chromatography (silica gel, 0.5% EtOAc in hexane) to produce bicyclic alkynone **49** (216 mg, 89%, two steps) as a light yellow oil: R_f = 0.74 (silica gel, EtOAc−hexane, 1:10); FT-IR (neat) ν_{max} 2957, 2362, 1652, 1460, 1383, 1212, 1114, 1004, 883, 732, 684 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.33 (d, *J* = 11.8 Hz, 1 H, C-2), 5.39 (br s, 1 H, C-12), 4.38 (d, *J* = 14.2 Hz, 1 H, C-15), 4.32 (d, *J* = 14.2 Hz, 1 H, C-15), 3.71 (s, 1 H, C-1), 3.55 (d, *J* = 11.8 Hz, 1H, C-8), 2.36 (br d, *J* = 8.8 Hz, 1 H, C-10), 2.20 (br d, *J* = 18.0 Hz, 1 H, C-13), 1.98 (br d, *J* = 18.0 Hz, 1 H, C-13), 1.80−1.70 (m, 3 H), 1.67 (s, 3 H, C-17), 1.57−1.50 (m, 1 H), 1.36 (s, 3 H, C-16), 1.07−0.90 (m, 45 H), 0.77−0.53 (m, 12 H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 181.2, 141.9, 139.7, 133.8, 121.8, 103.8, 87.7, 83.3, 72.5, 63.4, 44.8, 38.9, 38.0, 36.0, 30.0, 25.9, 21.9, 21.5, 21.2, 20.2, 17.9, 11.9, 7.0, 6.9, 5.8, 5.2; HRMS (FAB) calcd for $C_{41}H_{76}CsO_4Si_3$ (M + Cs^+) 849.4106, found 849.4139; $[\alpha]^{25}_D$ +50.3 (*c* 3.87, $CHCl_3$).

Synthesis of Diol 45. To a solution of trisilyl ether **49** (200 mg, 0.28 mmol, 1.0 equiv) in THF (1 mL) was added $Et_3N·3HF$ (0.23 mL, 1.40 mmol, 5.0 equiv) at 25 °C. After 1.5 h, the reaction was cooled to 0 °C, quenched by addition of $NaHCO_3$ (10 mL), extracted with ether (3 × 10 mL), dried over Na_2SO_4, and concentrated. The residue was purified by flash chromatography (silica gel, 25% EtOAc in hexane) to produce diol **45** (107 mg, 78%) as a colorless oil: R_f = 0.26 (silica gel, EtOAc−hexane, 1:3); FT-IR (neat) ν_{max} 3411, 2941, 2867, 2202, 1650, 1465, 1385, 1207, 1089, 1018, 883, 757, 685 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.32 (d, *J* = 12.0 Hz, 1 H, C-2), 5.40 (br s, 1 H, C-12), 4.35 (s, 2 H, C-15), 3.75 (s, 1 H, C-1), 3.47 (d, *J* = 12.0 Hz, 1 H, C-8), 2.47 (s, 1 H), 2.42 (br d, *J* = 11.5 Hz, 1 H), 2.38 (s, 1 H), 2.23−2.17 (m, 1 H), 1.98 (d, *J* = 18.4 Hz, 1 H), 1.88 (dd, *J* = 14.6, 4.2 Hz, 1 H), 1.70 (s, 3 H, C-17), 1.64 (t, *J* = 13.1 Hz, 1 H), 1.56−1.49 (m, 2 H), 1.43 (s, 3 H, C-16), 1.09−1.03 (m, 3 H), 1.01 (d, *J* = 6.5 Hz, 18 H), 0.90 (d, *J* = 6.9 Hz, 3 H, C-19 or C-20), 0.89 (d, *J* = 6.9 Hz, 3 H, C-19 or C-20); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 181.4, 142.6, 139.5, 133.4, 121.8, 102.5, 87.8, 80.6, 71.2, 63.7, 45.0, 38.8, 38.3, 33.0, 29.8, 25.9, 21.8, 21.6, 20.4, 19.8, 17.9, 11.9; HRMS (FAB) calcd for $C_{29}H_{48}CsO_4Si$ (M + Cs^+) 621.2376, found 621.2345; $[\alpha]^{25}_D$ +30.2 (*c* 1.49, $CHCl_3$).

Synthesis of Mixed Anhydride of the Aromatic Side Chain 52. To a solution of ethyl ester **50** (750 mg, 4.16 mmol, 1.0 equiv) in (1:1) THF−water (32.0 mL) at 25 °C was added $LiOH·H_2O$ (192 mg, 4.57 mmol, 1.1 equiv), and the resulting reaction mixture was stirred at the same temperature for 12 h. The solvent was removed under reduced pressure, and the solid was azeotroped with benzene (5 mL × 5) and finally dried under high vacuum. The acid salt **51** was used without further purification. To a solution of **51** in THF (40 mL) at 25 °C was added Piv-Cl (0.54 mL, 4.58 mmol, 1.1 equiv), and the reaction mixture was stirred at the same temperature for 12 h. Once complete by TLC, the reaction mixture was filtered, and the filtrate was concentrated under reduced pressure and dried under high vacuum to give anhydride **52** (698 mg, 75%). The anhydride was stored as a 0.2 M solution in CH_2Cl_2 and used in this form for the esterification: ^1H NMR (400 MHz, $CDCl_3$) δ 7.61 (d, *J* = 19.4 Hz, 1 H, C-2′), 7.46 (s, 1 H, C-5′), 7.14 (s, 1 H, C-7′), 6.58 (d, *J* = 19.3 Hz, 1 H, C-3′), 3.73 (s, 3 H, C-9′), 1.27 (s, 9 H, Me); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 174.2, 163.2, 139.4, 139.1, 138.0, 125.0, 114.6, 39.9, 33.8, 26.6, 26.6, 26.6.

Synthesis of 53 by Attachment of the Aromatic Side Chain. A mixture of alcohol **42** (61.0 mg, 0.120 mmol, 1.0 equiv), DMAP (14.7 mg, 0.120 mmol, 1.0 equiv), triethylamine (0.3 mL, 2.15 mmol, 17.9 equiv), and mixed anhydride **52** (6.0 mL of 0.2 M solution in CH_2Cl_2, 1.22 mmol, 10.0 equiv) was stirred at 25 °C for 22 h. The reaction mixture was then concentrated and purified by flash chromatography (silica gel, 10:10:1, EtOAc−CH_2Cl_2−MeOH) to yield ester **53** (75.0 mg, 98%): R_f = 0.42 (silica gel, 10:10:1, EtOAc−CH_2Cl_2−MeOH); FT-IR (neat) ν_{max} 2940, 2864, 1704, 1639, 1465, 1384, 1269, 1154, 1060, 994 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.51 (d, *J* = 15.6 Hz, 1 H, C-3′), 7.48 (s, 1 H, C-5′), 7.07 (s, 1 H, C-7′), 6.56 (d, *J* = 15.6 Hz, 1 H, C-2′), 6.10 (d, *J* = 5.8 Hz, 1 H, C-5 or C-6), 6.02 (d, *J* = 5.8 Hz, 1 H, C-5 or C-6), 5.70 (d, *J* = 9.6 Hz, 1 H, C-2), 5.20 (br s, 1 H, C-12), 4.80 (d, *J* = 7.2 Hz, 1 H, C-8), 4.20 (d, *J* = 13.2 Hz, 1 H, C-8), 4.12 (d, *J* = 13.2 Hz, 1 H, C-15), 3.95−3.92 (m, 1 H, C-1), 3.69 (s, 3 H, C-9′), 3.19 (s, 3 H, OCH_3), 2.58 (br d, *J* = 10.0 Hz, 1 H, C-10), 2.33 (br d, *J* = 18.5 Hz, 1 H, C-13), 1.95 (br d, *J* = 18.5 Hz, 1 H, C-13), 1.57−1.53 (m, 2 H, C-9), 1.52−1.49 (m, 1 H, C-18), 1.47 (s, 3 H, C-17 Hz), 1.42 (s, 3 H, C-16), 1.25−1.18 (m, 1 H, C-14), 1.08−1.00 (m, 21 H), 0.97 (d, *J* = 6.6 Hz, 3 H, C-19 or C-20), 0.90 (d, *J* = 6.4 Hz, 3 H, C-19 or C-20); ^{13}C NMR (150 MHz, $CDCl_3$) δ 166.3, 139.1, 136.1, 136.0, 134.1, 134.0, 130.6, 130.4, 122.6, 121.1, 116.2, 116.0, 89.8, 81.6, 64.9, 49.6, 42.6, 38.7, 33.6, 31.5, 29.1, 24.7, 24.4, 22.2, 22.0, 20.6, 18.0, 12.0; HRMS (FAB) calcd for $C_{37}H_{58}CsN_2O_5Si$ (M + Cs^+) 771.3169, found 771.3191; $[\alpha]^{25}_D$ +5.6 (*c* 1.6, $CHCl_3$).

Synthesis of Alcohol 54. To a solution of silyl ether **53** (75.0 mg, 0.117 mmol, 1.0 equiv) in THF (2 mL) was added 1.0 M TBAF in THF (0.22 mL, 0.22 mmol, 1.9 equiv), and the reaction was stirred for 1 h at 25 °C. After completion (thin-layer chromatography monitoring), the reaction mixture was concentrated and purified by flash chromatography (silica gel, 10:10:1, EtOAc−CH_2Cl_2−MeOH) to provide alcohol **54** (50.0 mg, 89%): R_f = 0.23 (silica gel, 10:10:1, EtOAc−CH_2Cl_2−MeOH); FT-IR (neat) ν_{max} 3380, 2961, 2361, 1700, 1636, 1450, 1382, 1269, 1156, 1036, 731 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.51 (d, *J* = 15.6 Hz, 1 H, C-3′), 7.42 (s, 1 H, C-5′), 7.06 (s, 1 H, C-7′), 6.54 (d, *J* = 15.6 Hz, 1 H, C-2′), 6.20 (d, *J* = 6.0 Hz, 1 H, C-5 or C-6), 6.01 (d, *J* = 5.9 Hz, 1 H, C-5 or C-6), 5.53 (d, *J* = 9.6 Hz, 1 H, C-2), 5.24 (br s, 1 H, C-12), 4.79 (d, *J* = 7.2 Hz, C-8), 4.13 (d, *J* = 12.0 Hz, 1 H, C-15), 3.94−3.85 (m, 2 H, C-15, C-1), 3.68 (s, 3 H, N−CH_3), 3.21 (s, 3 H, OCH_3), 2.67 (br d, *J* = 8.6 Hz, 1 H, C-10), 2.57 (br s, 1 H, OH), 2.30 (br d, *J* = 10.0 Hz, 1 H, C-13), 1.97 (br d, *J* = 18.0 Hz, 1 H, C-13), 1.65−1.50 (m, 3 H, C-9, C-18), 1.57 (s, 3 H, C-17), 1.49 (s, 3 H, C-16), 1.28−1.25 (m, 1 H, C-14), 0.96 (d, *J* = 6.6 Hz, 3 H, C-19 or C-20), 0.90 (d, *J* = 6.4 Hz, 3 H, C-19 or C-20); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.6, 139.2, 138.4, 136.8, 136.4, 135.6, 135.0, 134.0, 129.16, 122.7, 121.4, 117.0, 115.8, 90.3, 81.4, 67.3, 49.6, 42.0, 38.7, 33.9, 33.6, 31.5, 29.0, 24.3, 22.2, 22.1, 20.5; HRMS (FAB) calcd for $C_{28}H_{38}NaN_2O_5$ (M + Na^+) 505.2678, found 505.2661; $[\alpha]^{25}_D$ −44.7 (*c* 0.49, $CHCl_3$).

Synthesis of Aldehyde 55. To a solution of allylic alcohol **54** (50 mg, 0.104 mmol, 1.0 equiv) in CH_2Cl_2 (2 mL) was added $NaHCO_3$ (88.0 mg, 0.595 mmol, 10.0 equiv) and Dess−Martin reagent (84.8 mg, 0.20 mmol, 2.0 equiv), and the reaction was stirred for 30 min at ambient temperature, after which 2-propanol (0.1 mL) was added followed by ethyl acetate (10 mL). The precipitate was filtered off, and the filtrate was concentrated and purified by flash chromatography (silica gel, 10:10:1, EtOAc−CH_2Cl_2−MeOH) to yield aldehyde **55** (49.5 mg, 100%): R_f = 0.43 (silica gel, 10:10:1, EtOAc−CH_2Cl_2−MeOH); FT-IR (neat) ν_{max} 2961, 1694, 1636, 1269, 1156, 1051 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.28 (s, 1 H, C-15), 7.53 (d, *J* = 15.6 Hz, 1 H, C-3′), 7.47 (s, 1 H, C-5′), 7.09 (s, 1 H, C-7′), 6.56 (d, *J* = 15.6 Hz, 1 H, C-2′), 6.48 (d, *J* = 9.9 Hz, 1 H, C-2), 6.30 (d, *J* = 5.9 Hz, 1 H, C-5 or C-6), 6.19 (d, *J* = 5.9 Hz, 1 H, C-5 or C-6), 5.34 (br s, 1 H, C-12), 4.80 (d, *J* = 7.4 Hz, 1 H, C-8), 4.30−4.28 (m, 1 H, C-1), 3.70 (s, 3 H, C-9′), 3.25 (s, 3 H, OCH_3), 2.77 (br d, *J* = 9.4 Hz, 1 H, C-10), 2.41 (br d, *J* = 18.8 Hz, 1 H, C-13), 2.10 (br d, *J* = 18.8 Hz, 1 H, C-13), 1.67−1.56 (m, 3 H, C-9, C-18), 1.53 (s, 3 H, C-17), 1.46 (s, 3 H, C-16), 1.38−1.36 (m, 1 H, C-14), 1.01 (d, *J* = 6.6 Hz, 3 H, C-19 or C-20), 0.96 (d, *J* = 6.4 Hz, 3 H, C-19 or C-20); ^{13}C NMR (125 MHz,

$CDCl_3$) δ 193.9, 166.7, 159.4, 142.0, 139.3, 138.3, 136.5, 135.6, 134.1, 129.7, 122.8, 121.5, 115.8, 114.5, 89.4, 81.2, 50.2, 41.4, 39.0, 35.6, 33.6, 31.6, 28.9, 24.3, 24.3, 22.1, 22.0, 20.5; HRMS (FAB) calcd for $C_{28}H_{37}N_2O_5$ ($M + H^+$) 481.2702, found 481.2714; $[\alpha]^{25}_D$ +72.7 (*c* 0.4, $CHCl_3$).

Synthesis of Methyl Ester 57 with the Intermediacy of Acid 56. To a solution of aldehyde **55** (14.0 mg, 0.0291 mmol, 1.0 equiv) in ^{t}BuOH−H_2O (5:1, 1.2 mL total) were added 2.0 M 2-methyl-2-butene in THF (1 mL, 2.0 mmol, 68.7 equiv), NaH_2PO_4 (10.5 mg, 0.087 mmol, 2.9 equiv), and $NaClO_2$ (15.7 mg, 0.174 mmol, 6.0 equiv) at 0 °C. The reaction was stirred at the same temperature for 2 h, after which an ether solution of CH_2N_2 (excess) was added and the reaction was stirred for an additional 10 min at 25 °C. The excess CH_2N_2 was removed by an argon stream, the reaction was extracted with ethyl acetate (3 × 15 mL), dried over Na_2SO_4, and concentrated. The crude residue was purified by flash chromatography (silica gel, 10:10:1 EtOAc−CH_2Cl_2−MeOH) to furnish methyl ester **57** (13.1 mg, 88%, two steps): R_f = 0.42 (silica gel, 10:10:1 EtOAc−CH_2Cl_2−MeOH); FT-IR (neat) ν_{max} 3410, 2960, 1711, 1637, 1435, 1384, 1269, 1155, 1048, 732 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51 (d, J = 15.6 Hz, 1 H, C-3′), 7.44 (s, 1 H, C-5′), 7.07 (s, 1 H, C-7′), 6.72 (d, J = 9.9 Hz, 1 H, C-2), 6.55 (d, J = 15.6 Hz, 1 H, C-2′), 6.48 (d, J = 5.9 Hz, 1 H, C-5), 6.17 (d, J = 5.9 Hz, 1 H, C-6), 5.28 (br s, 1 H, C-12), 4.78 (d, J = 7.4 Hz, 1 H, C-8), 4.15−4.12 (m, 1 H, C-1), 3.70 (s, 3 H, OCH_3), 3.69 (s, 3 H, C-9′), 3.22 (s, 3 H, OCH_3), 2.67 (br d, J = 10.8 Hz, 1 H, C-10), 2.38 (br d, J = 16.4 Hz, 1 H, C-13), 2.03 (br d, J = 16.4 Hz, 1 H, C-13), 1.66−1.53 (m, 3 H, C-9, C-18), 1.51 (s, 3 H, C-17), 1.44 (s, 3 H, C-16), 1.37−1.28 (m, 1 H, C-14), 0.97 (d, J = 6.6 Hz, 3 H, C-19 or C-20), 0.92 (d, J = 6.4 Hz, 3 H, C-19 or C-20); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.1, 166.7, 146.4, 139.2, 138.4, 136.4, 134.9, 134.0, 132.0, 131.0, 122.7, 121.4, 115.9, 115.5, 89.6, 81.4, 51.8, 50.2, 41.7, 38.7, 34.7, 33.6, 31.5, 28.9, 24.4, 24.3, 22.2, 22.0, 20.5; HRMS (FAB) calcd for $C_{29}H_{38}CsN_2O_6$ ($M + Cs^+$) 643.1784, found 643.1762; $[\alpha]^{25}_D$ −44.7 (*c* 0.5, $CHCl_3$).

Completion of the Synthesis for Sarcodictyin A (7). To a solution of methyl ester **57** (6.0 mg, 0.0117 mmol, 1.0 equiv) in 10:1 CH_2Cl_2−H_2O (1.1 mL) was added CSA (10 mg, 0.043 mmol, 6.4 equiv) and the reaction was stirred at 25 °C for 16 h, after which triethylamine was added and the reaction mixture was concentrated. The crude mixture was purified by flash chromatography (silica gel, 10:10:1, EtOAc−CH_2Cl_2−MeOH) to yield sarcodictyin A (**7**) (4.6 mg, 79%) as a white solid: R_f = 0.32 (silica gel, 10:10:1, EtOAc−CH_2Cl_2−MeOH); FT-IR (neat) ν_{max} 2958, 2361, 1711, 1636, 1244, 1153, 1050 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51 (d, J = 16.0 Hz, 1 H, C-3′), 7.43 (s, 1 H, C-5′), 7.07 (s, 1 H, C-7′), 6.80 (d, J = 15.6 Hz, 1 H, C-5′), 6.33 (d, J = 5.6 Hz, 1 H, C-5 or C-6), 6.09 (d, J = 5.6 Hz, 1 H, C-5 or C-6), 5.30 (br s, 1 H, C-12), 4.79 (d, J = 7.3 Hz, 1 H, C-8), 4.20−4.17 (m, 1 H, C-1), 4.03 (s, 1 H, OH), 3.74 (s, 3 H, OCH_3), 3.68 (s, 3 H, OCH_3), 2.71 (d, J = 9.9 Hz, 1 H, C-10), 2.37 (br d, J = 16.4 Hz, 1 H, C-13), 2.05 (br d, J = 17.2 Hz, 1 H, C-13), 1.68−1.55 (m, 3 H, C-9, C-18), 1.52 (s, 3 H, C-17), 1.48 (s, 3 H, C-16), 1.35−1.30 (m, 1 H, C-14), 0.98 (d, J = 6.7 Hz, 3 H, C-19 or C-20), 0.92 (d, J = 6.4 Hz, 3 H, C-19 or C-20); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.1, 166.7, 147.2, 139.2, 138.4, 136.5, 134.1, 133.3, 132.8, 131.8, 122.7, 121.4, 115.8, 110.9, 90.8, 81.0, 52.1, 41.8, 39.0, 35.0, 33.6, 31.8, 28.9, 25.6, 24.4, 22.2, 22.0, 20.5; HRMS (FAB) calcd for $C_{28}H_{36}CsN_2O_6$ ($M + Cs^+$) 629.1628, found 629.1648; $[\alpha]^{25}_D$ −19.1 (*c* 0.11, EtOH).

Synthesis of Ethyl Ester 58. To a solution of aldehyde **55** (27.8 mg, 0.058 mmol, 1.0 equiv) in ^{t}BuOH−H_2O (5:1, 1.2 mL total) were added 2.0 M 2-methyl-2-butene in THF (1 mL, 2.0 mmol, 34.4 equiv), NaH_2PO_4 (20.9 mg, 0.174 mmol, 3.0 equiv) and $NaClO_2$ (31.5 mg, 0.340 mmol, 2.9 equiv) at 0 °C. The reaction was stirred at the same temperature for 2 h, after which an ether solution of excess CH_3CHN_2 was added and the reaction was stirred for an additional 10 min at 25 °C. The excess CH_3CHN_2 was removed by an argon stream, and the reaction mixture was extracted with ether (2 × 15 mL), dried over Na_2SO_4, and concentrated. The crude residue was purified by flash chromatography (silica gel, 10:10:1 EtOAc−CH_2Cl_2−MeOH) to yield ethyl ester **58** (27.0 mg, 89%, two steps); R_f = 0.41 (silica gel, 10:10:1 EtOAc−CH_2Cl_2−MeOH); FT-IR (neat) ν_{max} 2963, 1708, 1636, 1269, 1154, 1048 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52 (d, J = 15.6 Hz, 1 H, C-3′), 7.44 (s, 1 H, C-5′), 7.08 (s, 1 H, C-7′), 6.72 (d, J = 9.8 Hz, 1 H, C-2), 6.56 (d, J = 15.6 Hz, 1 H, C-2′), 6.49 (d, J = 5.9 Hz, 1 H, C-5), 6.17 (d, J = 5.9 Hz, 1 H, C-6), 5.28 (br s, 1 H, C-12), 4.79 (d, J = 7.4 Hz, 1 H, C-14, C-8), 4.15 (q, J = 7.6 Hz, 2 H, OCH_2CH_3), 4,14−4.11 (m, 1 H, C-1), 3.69 (s, 3 H, C-9′), 3.23 (s, 3 H, OCH_3), 2.67 (br d, J = 8.1 Hz, 1 H, C-10), 2.37 (br d, J = 17.4 Hz, 1 H, C-13), 2.03 (br d, J = 17.4 Hz, 1 H, C-13), 1.63 (d, J = 15.0 Hz, 1 H, C-9), 1.62−1.60 (m, 2 H, C-9, C-18), 1.51 (s, 3 H, C-17), 1.44 (s, 3 H, C-16), 1.36−1.30 (m, 1 H, C-14), 1.26 (t, J = 7.6 Hz, 3 H, OCH_2CH_3, 0.97 (d, J = 6.6 Hz, 3 H, C-19 or C-20), 0.93 (d, J = 6.4 Hz, 3 H, C-19 or C-20); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.8, 166.7, 146.1, 139.2, 138.4, 136.4, 134.8, 134.0, 132.3, 131.1, 122.7, 121.4, 115.9, 115.6, 89.53, 81.43, 60.6, 50.1, 41.7, 38.8, 34.7, 33.6, 31.5, 28.9, 24.4, 24.3, 22.2, 22.0, 20.5, 14.1; HRMS (FAB) calcd for $C_{30}H_{40}CsN_2O_6$ ($M + Cs^+$) 657.1941, found 657.1959; $[\alpha]^{25}_D$ −12.0 (*c* 0.4, $CHCl_3$).

Completion of the Synthesis of Sarcodictyin B (8). To a solution of ethyl ester **58** (3.5 mg, 0.0067 mmol, 1.0 equiv) in 10:1 CH_2Cl_2−H_2O (1.1 mL) was added CSA (10.0 mg, 0.043 mmol, 6.4 equiv). The reaction was then stirred at 25 °C for 24 h, after which triethylamine was added and the reaction mixture was concentrated. The crude mixture was purified by flash chromatography (silica gel, 10:10:1 EtOAc−CH_2Cl_2−MeOH) to yield sarcodictyin B (**8**) (3.0 mg, 86%) as a white solid: R_f = 0.32 (silica gel, 10:10:1 EtOAc−CH_2Cl_2−MeOH); FT-IR (neat) ν_{max} 3348, 2926, 2855, 1708, 1637, 1458, 1383, 1299, 1271, 1244, 1156, 1051; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52 (d, J = 15.6 Hz, 1 H, C-3′), 7.44 (s, 1 H, C-5′), 7.08 (s, 1 H, C-7′), 6.81 (d, J = 9.8 Hz, 1 H, C-2), 6.55 (d, J = 15.5 Hz, 1 H, C-2′), 6.32 (d, J = 5.8 Hz, 1 H, C-5 or C-6), 6.09 (d, J = 5.8 Hz, 1 H, C-5 or C-6), 5.30 (br s, 1 H, C-12), 4.80 (d, J = 7.4 Hz, 1 H, C-8), 4.24−4.15 (m, 3 H, C-1 and OCH_2CH_3), 4.04 (s, 1 H, OH), 3.69 (s, 3 H, N−CH_3), 2.71 (br d, J = 11.7 Hz, 1 H, C-10), 2.37 (br d, J = 11.0 Hz, 1 H, C-13), 2.05 (br d, J = 11.3 Hz, 1 H, C-13), 1.65 (d, J = 14.7 Hz, 1 H, C-9), 1.64−1.55 (m, 2 H, C-9, C-18), 1.52 (s, 3 H, C-17), 1.49 (s, 3 H, C-16), 1.28 (t, J = 7.0 Hz, 3 H, OCH_2CH_3), 1.23−1.21 (m, 1 H, C-14), 0.98 (d, J = 6.6 Hz, 3 H, C-19 or C-20), 0.93 (d, J = 6.4 Hz, 3 H, C-19 or C-20); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.8, 166.7, 147.0, 139.2, 138.4, 136.5, 134.1, 133.2, 132.8, 131.9, 122.7, 121.4, 115.9, 111.0, 90.9, 81.1, 61.1, 41.8, 39.1, 35.0, 33.6, 31.8, 28.9, 25.6, 24.4, 22.2, 22.1, 20.5, 14.1; HRMS (FAB) calcd for $C_{29}H_{38}CsN_2O_6$ ($M + Cs^+$) 643.1784, found 643.1804; $[\alpha]^{25}_D$ −4.0 (*c* 0.15, EtOH).

Synthesis of C5,C6-Saturated Analogue 61. Analogue **61** was synthesized by the same reaction sequence followed for the two natural products (**53**, **54**, **55**, **56**, **57**, **58**) from alcohol **43**: R_f = 0.32 (silica gel, 10:10:1, EtOAc−CH_2Cl_2−MeOH); FT-IR (neat) ν_{max} 2959, 1711, 1638, 1451, 1247, 1159, 1043 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52 (d, J = 15.6 Hz, 1 H), 7.45 (s, 1 H), 7.07 (s, 1 H), 6.77 (d, J = 10.2 Hz, 1 H), 6.51 (d, J = 5.6 Hz, 1 H), 5.34 (br s, 1 H, C-12), 4.64 (d, J = 8.0 Hz, 1 H, C-8), 4.11 (m, 1 H, C-1), 3.70 (s, 3 H, CO_2Me), 3.69 (s, 3 H, N-Me), 3.20 (s, 3 H, OMe), 2.62−2.53 (m, 2 H, C-10, C-5 or C-6), 2.49 (m, 1 H, C-5 or C-6), 2.35 (br dd, J = 16.5, 2.0 Hz, 1 H, C-13), 2.20 (m, 1 H, C-5 or C-6), 2.06 (br dd, J = 18.7, 2.0 Hz, 1 H, C-13), 1.82−1.75 (m, 2 H, C-5 or C-6, C-9), 1.56 (s, 3 H, Me), 1.55−1.46 (m, 1 H, C-9), 1.35 (s, 3 H, Me), 20 (m, 1 H, C-14), 0.95 (d, J = 6.6 Hz, 3 H, C-19 or C-20), 0.92 (d, J = 6.4 Hz, 3 H, C-19 or C-20); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.5, 166.8, 148.0, 139.1, 138.4, 136.1, 133.9, 132.7, 122.6, 121.6, 116.3, 112.0, 85.4, 80.9, 51.8, 50.4, 42.4, 39.5, 37.9, 34.9, 33.6, 32.1, 30.6, 28.6, 28.1, 24.1, 22.1, 22.1, 20.6; HRMS (FAB) calcd for $C_{29}H_{40}CsN_2O_6$ ($M + Cs^+$) 645.1941, found 645.1962; [ga]$^{25}_D$ +41.7 (*c* 0.2, $CHCl_3$).

Acknowledgment. This work was supported by The Skaggs Institute for Chemical Biology, the National Institutes of Health USA, Novartis and CaP CURE, and by fellowships from Novartis (to D.V.), the Japanese Society for the Promotion of Science for Young Scientists (to S.H.), and the Department of Defense, USA (to J.P.)

Supporting Information Available: Selected physical data for intermediates **10**−**13** (5 pages, print/PDF). See any current masthead page for ordering information and Web access instructions.

JA981062G