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Stereocontrolled and Convergent Total Synthesis of Amphidinolide T3

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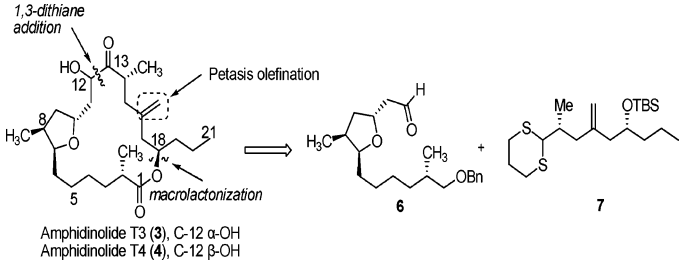

Stereocontrolled and convergent total synthesis of amphidinolide T3 has been described. A retrosynthetic scheme was constructed that led to the recognition of readily available and enantiomerically related compounds as starting materials for the total synthesis of amphidinolide T3. Thus, the two key building blocks **6** and **7** were defined as subtargets and synthesized in optically active forms. The C1−C12 fragment **6** was derived from commercially available D-glutamic acid or its synthetically equivalent (*R*)-5-hydroxymethyltetrahydrofuran-2-one **16** as starting material involving highly diastereoselective asymmetric allylation as a key step. The C13−C21 fragment **7** was efficiently synthesized in high yield through the dithiane coupling of the segment **10** and iodide **11**, followed by subsequent deprotection and Petasis olefination. Eventually, assembly of the fragment aldehyde **6** and dithiane **7** along with C−C bond formation, a two-step oxidation−reduction sequence, selective macrolactonization, and functional transformation furnished the convergent total and formal synthesis of amphidinolide T3 and T4, and this approach also provides a flexible and practical synthesis of amphidinolide T macrolides.

Introduction

A family of structurally diverse macrolides−amphidinolides were isolated from marine dinoflagellates of the genus *Amphidinium* living in symbiosis with Okinawan acoel flatworm *Amphiscolops* sp.[1,2] They have exhibited significant antitumor properties and cytotoxicity against a variety of National Cancer Institute (NCI) tumor cell lines as well as human epidermoid carcinoma KB cells.[1c,3] Amphidinolides display a common feature with one or more *exo*-methylene units, a highly oxygenated and stereochemically rich macrocycle ranging in size from 12 to 29 atoms. Due to their scarcity, biological activity, and challenging structure, amphidinolides represent attractive synthetic targets.[4]

Amphidinolide T class (Figure 1), a 19-membered macrolactone, has included five members (T1−T5) bearing a trisubstituted tetrahydrofuran ring, a hydroxyl ketone, and an exocyclic methylene group since the isolation of T1 in 2000.[5] Amphidinolide T2 is the only exception containing an additional hydroxymethyl substitution in the alkyl side chain. T3−T5 have very similar construction, only differing in their configuration at C12 and C14. Amphidinolide T1 possesses the reversed hydroxyl ketone moiety in contrast to T3−T5.

Synthetic studies on the amphidinolide T series have attracted a great deal of attention. So far, several groups have reported total syntheses of T1 and T3−5. The Fürstner group reported the first total syntheses of T4 in 2002 and T1, T3, T4, and T5 in 2003 by utilizing an efficient ring-closing metathesis (RCM) to obtain the macrocycles.[4h,j] Amphidinolide T1 was synthesized

* To whom correspondence should be addressed. Phone: 0086-21-54925182. Fax: 0086(21)64166128.

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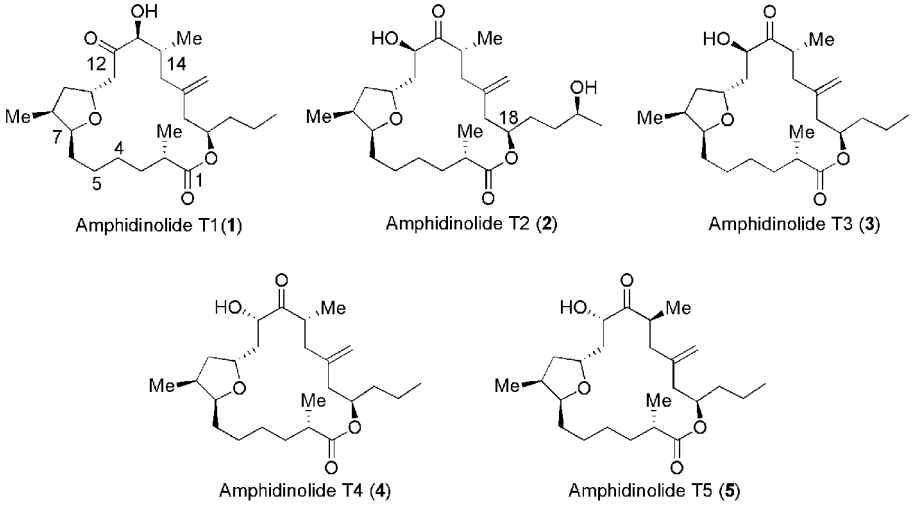
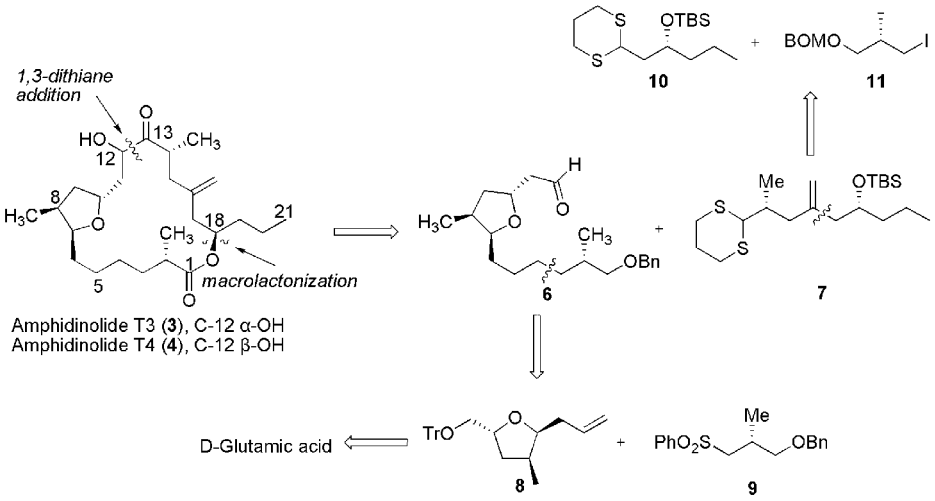


FIGURE 1. Amphidinolide T family.

SCHEME 1. Retrosynthetic Analysis



by the Ghosh group in 2003 through a Yamaguchi macrolactonization reaction.[4i] The syntheses of T1 and T4 were also reported by Jamison and co-wokers in 2004 and 2005 using a nickel-catalyzed, alkyne−aldehyde coupling reaction to form the 19-membered ring.[4o,p] In the present paper, we describe a full account of our efforts on total syntheses of amphidinolide T3 and T4.

Results and Discussion

Retrosynthetic Analysis and Synthetic Strategies. As shown in Scheme 1, our synthetic strategy for amphidinolides T3, T4 was highly convergent. We envisioned that the dithiane coupling reaction of C1−12 segment **6** and C13−21 segment **7** with stereogenic centers at C12 and C13; the selective formation of macrocycle would be furnished by Yamaguchi macrolactonization. The segment **7** could derive from components **10** and **11**. The synthesis of dithiane **10** involved a Noyori asymmetric hydrogenation of ethyl 3-oxohexanoate.[6] The subunit **11** was prepared from commercial methyl (*S*)-hydroxyl-2-methylpropionate. The aldehyde **6** could be disconnected at C3−4 and divided into subunits **8** and **9**; the subunit **9** was accessible by a diastereoselective alkylation of *N*-propionylox-

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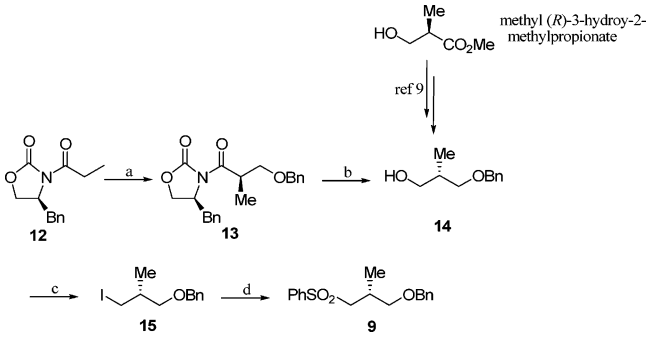
SCHEME 2. Synthesis of Sulfone 9[a]



[a] Reagents and conditions: (a) $TiCl_4$, *i*-$PrNEt_2$, CH_2Cl_2, 0 °C, then BOMCl, 99%, dr > 99:1; (b) $LiBH_4$, MeOH, THF, 0 °C, 99%; (c) I_2, PPh_3, imidazole, THF; (d) $PhSO_2Na$, DMF, 35 °C, 76% over two steps. BOMCl = benzyloxymethyl chloride.

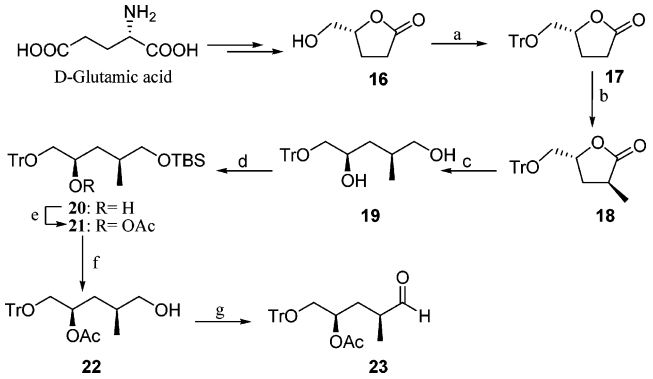
azolidinone with BOMCl. The trisubstituted and stereochemical tetrahydrofuran ring can be obtained from commercially available D-glutamic acid or its synthetically equivalent (*R*)-5-hydroxymethyltetrahydrofuran-2-one **16**.

Preparation of C1−C12 Fragment 6. As outlined in Scheme 2, the segment **9** was prepared via a sequence of high-yielding steps. The Lewis acid mediated alkylation of Evans oxazolidinone **12** with BOMCl[7] provided **13** in extremely high diastereomeric purity[8] on a multigram scale for a subsequent reduction with $LiBH_4$ to afford the primary alcohol **14**, which also can be prepared from the commercially available methyl (*R*)-3-hydroxyl-2-methylpropionate.[9] Alcohol **14** was then converted to iodide **15**; the derived iodide **15** was efficiently transformed into the sulfone **9** by displacement with sodium benzenesulfinate in DMF.[9]

The synthesis of the C7−C11 fragment was investigated using commercially available alcohol **16** as a starting material conveniently prepared via three steps by a known procedure[10] (Scheme 3). Protection of the hydroxyl group of **16** with trityl chloride and a subsequent methylation afforded compound **18** with high diastereoselectivity (dr = 11:1). Reduction of **18** with $LiAlH_4$ gave diol **19** quantitatively.[11] Selective protection of the primary hydroxyl group of **19** was achieved with TBSCl,[12] and then the secondary hydroxyl group in the resulting silyl ether **20** was acetylated to give ester **21**. After desilylation of **21** with TBAF, oxidation of the alcohol using the Dess−Martin periodinane gave the aldehyde **23**.[13] The overall yield from **16** to **23** was 55.5%.

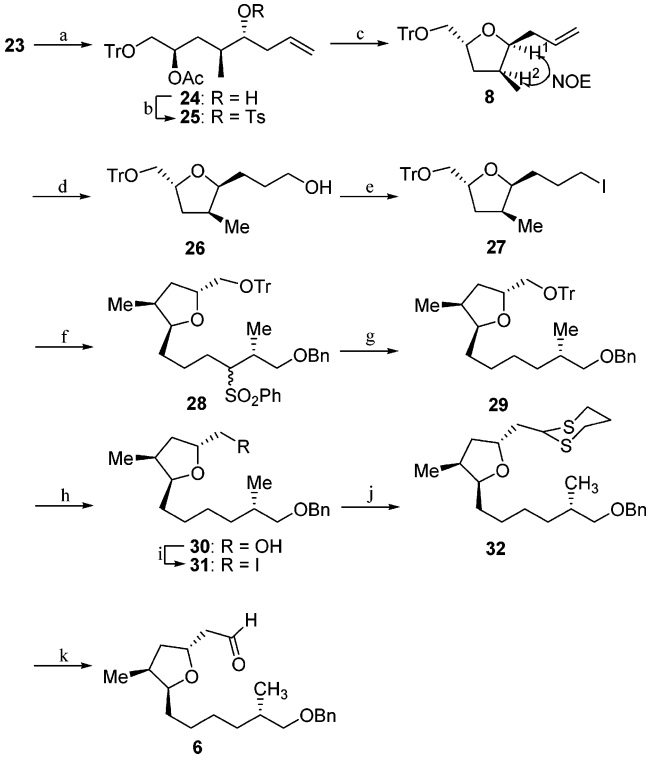
The stereocontrolled synthesis of the required trisubstituted tetrahydrofuran subunit **6** is a key to the total syntheses of

SCHEME 3. Synthesis of Aldehyde 23[a]



[a] Reagents and conditions: (a) TrCl, Py, CH_2Cl_2, reflux, 76%; (b) *n*-BuLi, *i*-Pr_2NH, −15 °C, then −78 °C, **17**, CH_3I, 81%, dr = 11:1; (c) $LiAlH_4$, THF, >99%; (d) TBSCl, imidazole, DMF, 0 °C, 99%; (e) Ac_2O, DMAP, Et_3N, 99%; (f) TBAF, THF, 96%; (g) DMP, CH_2Cl_2, 92%. TrCl = trityl chloride, TBS = *tert*-butyldimethylsilyl chloride, DMAP = 4-(dimethylamino) pyridine, TBAF = tetrabutylammonium fluoride, DMP = Dess−Martin periodinane.

SCHEME 4. Synthesis of Aldehyde 6[a]



[a] Reagents and conditions: (a) (*R*,*R*)-1,2-diamino-1,2-diphenylethanebis(sulfonamide), BBr_3, CH_2Cl_2, 0 °C, then allyltributylstannane, rt, 6 h, **23**, −78 °C, 2 h, 85%, dr >99:1; (b) TsCl, pyridine, rt, 99%; (c) KOH, diglyme, ethylene glycol, 40 °C, 99%; (d) BH_3·Me_2S, THF, then 30% H_2O_2, NaOH, 83%; (e) I_2, PPh_3, imidazole, THF, 95%; (f) *n*-BuLi, HMPA, THF, **9**, −78 °C, then **27**; (g) 6% Na−Hg, EtOH, 80% over two steps; (h) 80% HOAc, 35−40 °C, 95%; (i) PPh_3, I_2, imidazole, THF, 91%; (j) 1,3-dithiane, *t*-BuLi, THF/HMPA, then **31**, −78 °C, 83%; (k) $NaHCO_3$, CH_3I, CH_3CN−H_2O (v/v, 4:1), rt, 16 h, 95%. TsCl = *p*-toluenesulfony chloride.

amphidinolide T (Scheme 4).[14] Diastereomeric allylation of aldehyde **23** was first investigated using a catalytic system of

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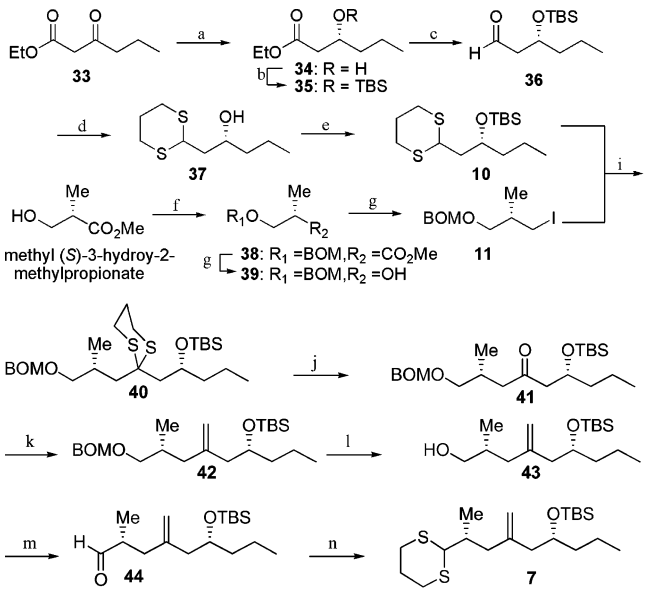
(14) For a review on the stereoselective synthesis of natural products with polysubstituted tetrahydrofuran moiety, see: Koert, U. *Synthesis* **1995**, 115−132.

titanium/(*R*)-BINOL.[15a−c] To our disappointment, yield and diastereoselectivity for this allylation turned out to be low (dr = 1:2.2, determined by ^{1}H NMR, 37% combined yield). Several aspects were tried in order to improve the yield and diastereoselectivity, including temperature, concentration, and reaction time, but no such efforts were successful. We assumed that the hindrance of α-methyl of aldehyde **23** resulted in the lack of success, which is in line with previous observations.[16] In addition, using *p*-nitrobenzoic acid as a promoter,[15d] we carried out the allylation reaction of aldehyde **23** with allytributyltin in CH_3CN to afford a quantitative yield of the corresponding homoallylic alcohol (dr = 1.2:1.0). Fortunately, asymmetric allylation of the aldehyde **23** was quite successful by the tin-to-boron transmetalation of allyltributylstannane using the boron bromide reagent generated in situ from (*R*,*R*)-1,2-diamino-1, 2-diphenylethane bis(sulfonamide) and boron tribromide,[17] furnishing the desired homoallylic alcohol **24** in 85% yield with excellent diastereoselectivity for the desired isomer (dr = >99:1, determined by ^{1}H NMR).[18] Subsequent O-protection with tosyl chloride[12] and treatment of **25** in the presence of potassium hydroxide in a mixed solvent of diglyme and ethylene glycol at 40 °C was successful in the formation of the trisubstituted tetrahydrofuan ring. Importantly, the "so-called" two-step reaction highly proceeded in favor of the desired 2,4,5-cis-trans single isomer **8** on the basis of the strong NOE effect indicated in Scheme 4.[19] After hydroboration−oxidation of **8**,[20] the resulting primary alcohol **26** was converted into the corresponding iodide **27** under standard conditions,[21] which was a suitable electrophile for the desired alkylation reaction. Alkylation of the carbanion generated from the sulfone **9** with iodide **27** in a solvent mixture of THF/HMPA and subsequent reductive removal of the sulfonyl group with 6% sodium amalgam (in situ) afforded benzyl ether **29** in 80% yield. Addition of HMPA as a cosolvent in this alkylation reaction remarkably improved the yield. Cleavage of trityl ether in **29** by exposure to 80% aqueous HOAc gave the primary alcohol **30** (95%), followed by conversion of the alcohol **30** to its corresponding iodide **31**. Elongation of the iodide **31** with 1, 3-dithiane/*t*-BuLi in 10% HMPA/THF at −78 °C provided the corresponding dithiane **32** (83%). Then, treatment of **32** with MeI /$NaHCO_3$ in aqueous acetonitrile led to the desired aldehyde **6** in excellent yield.[22]

Preparation of C13−C21 Fragment 7. The segment dithiane **7** was synthesized by a sequence of steps as outlined in Scheme 5. Thus, hydrogenation of ethyl-3-oxohexanote in the presence of [(*R*)-BINAP-$RuCl_2$](DMF)$_n$ as a catalyst provided **34** with high enantiomeric purity (ee > 99%).[23] The hydroxyl group in

SCHEME 5. Synthesis of Segment Dithiane 7[a]



[a] Reagents and conditions: (a) [(*R*)-BINAP-$RuCl_2$](DMF)n, H_2, MeOH, 20 atm, 100 °C, 92%; (b) TBSCl, imidazole, DMF, 91%; (c) DIBAL-H, CH_2Cl_2, −78 °C, 91%; (d) $HS(CH_2)_3SH$, $BF_3\cdot Et_2O$, 92%; (e) TBSOTf, 2,6-lutidine, CH_2Cl_2, 97%; (f) *i*-$PrNEt_2$, CH_2Cl_2; (g) $LiAlH_4$, Et_2O, 93%, over two steps; (h) PPh_3, I_2, imidazole, THF, 97%; (i) *t*-BuLi, HMPA, THF, **10**, −78 °C, then **11**; 83%; (j) I_2, $NaHCO_3$, acetone/H_2O (v/v, 5:1), 0 °C, 82%; (k) Cp_2TiMe_2, toluene, 110 °C, 86%; (l) Li, NH_3(l), THF, −78 °C, 99%; (m) DMP, CH_2Cl_2, 95%; (n) $ZnCl_2$, $TMSS(CH_2)_3SSTMS$, Et_2O, 0-rt, 92%. BINAP = 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl.

34 was protected with TBSCl to give silyl ether **35**, followed by reduction with DIBAL-H to give the corresponding aldehyde **36**. Then, treatment of the aldehyde **36** with 1,3-propanedithiol and boron trifluoride etherate furnished the dithiane. Unfortunately, the TBS group was removed simultaneously to give the dithiane **37**.[24] The resulting secondary alcohol was protected again with TBSOTf and 2,6-lutidine to afford the dithiane **10** in excellent yield.[12,25] It was noteworthy that the dithiane **10** can be readily prepared on a multigram scale. The synthesis of iodide **11** began with methyl (*S*)-3-hydroxy-2-methylpropionate, followed by protection and reduction with $LiAlH_4$ to afford the known alcohol **39**,[26] which underwent smooth iodination to give the iodide **11**. With the required two segments in hand, alkylation of dithiane **10** with iodide **11** gave the segment **40** in 83% yield. Deprotection of dithiane[12] provided ketone **41**, which was subject to Petasis olefination conditions[27] with Cp_2TiMe_2 in the presence of toluene at 110 °C to give the corresponding alkene **42**. Reductive removal of BOM group in resulting alkene **42** by using Li/NH_3 afforded the primary alcohol **43**. Aldehyde **44** was obtained by oxidation of **43** with Dess−Martin periodinane. A series of Lewis acid ($AlCl_3$, $TiCl_4$, $MgCl_2$, $SnCl_4$, and $ZnCl_2$) mediated dithioacetalizations of aldehyde **44** with 1,3-propanedithiol did not give

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(18) See the Supporting Information for details.

(19) NOE studies on compound **8** assigned the stereochemistry of the 2,4,5-cis-trans isomer. See the Supporting Information for details.

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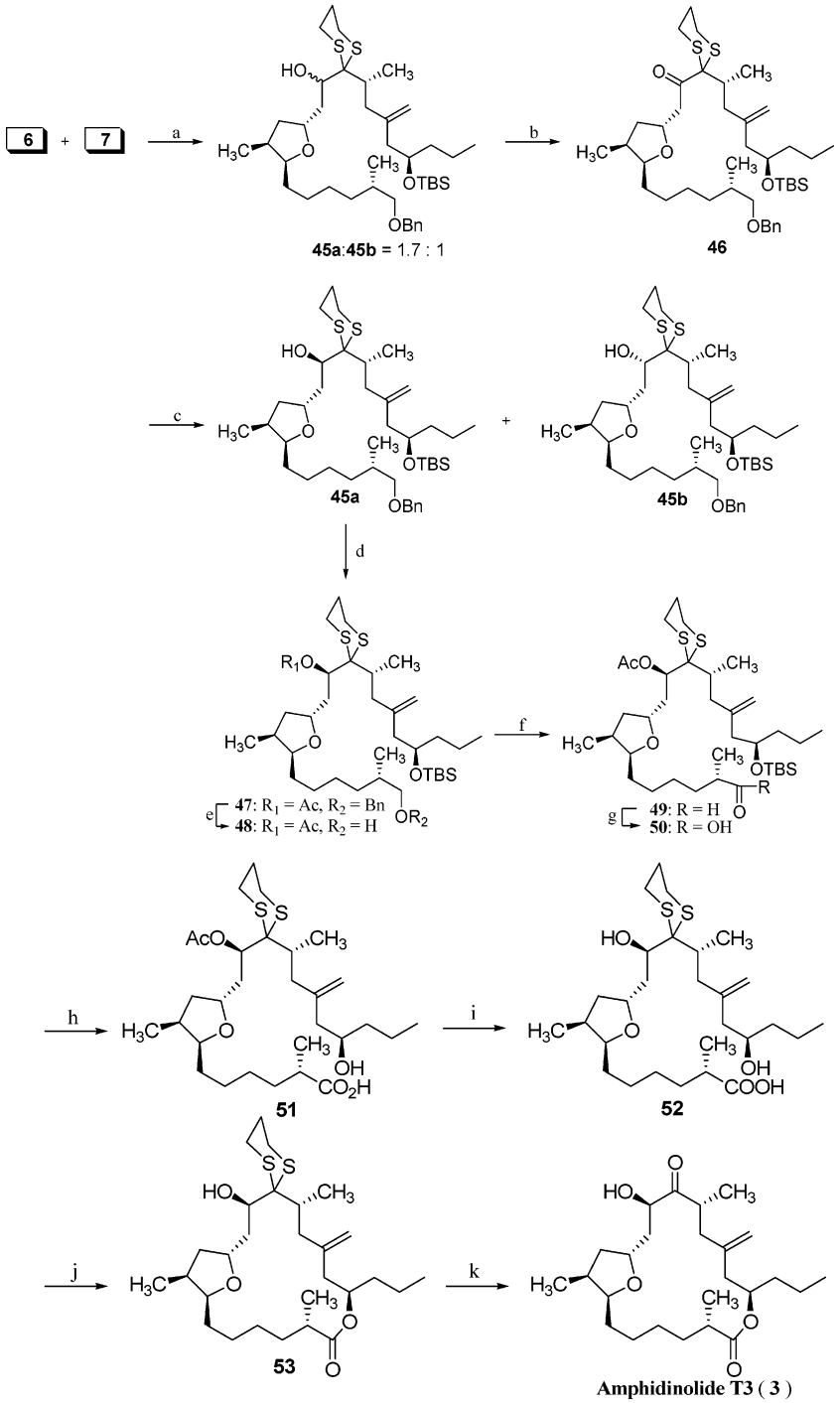
SCHEME 6. Completion of the Total Synthesis of Amphidinolide T3[a]



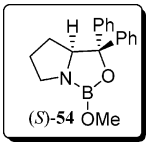
[a] Reagents and conditions: (a) *t*-BuLi, HMPA/THF (v/v, 1:9), **7**, −78 °C, 10 min, then −78 °C, **6**; 80%; isomers were easily separated by column chromatograph; (b) DMP, $NaHCO_3$, CH_2Cl_2, rt, 3 h, 91%; (c) see Table 1; (d) Ac_2O, DMAP, pyridine, 24 h, 92%; (e) DDQ, CH_2Cl_2/H_2O (v:v, 10:1), 30 h, 95%; (f) PCC, NaOAc, CH_2Cl_2; 4 Å MS, 0 °C, 12 h, 96%; (g) $AgNO_3$, NaOH, THF, H_2O, 0 °C, 2 h, 81%; (h) HF·Py, THF, rt, 24 h, 94%; (i) LiOH, MeOH/H_2O (v/v, 5:1), 40 °C, 15 h, 95%; (j) 2,4,6-Cl_3PhCOCl, *i*-PrNEt$_2$, 45 °C, 10 h, then DMAP, toluene, 10 h, 66%; (k) PhI$(CF_3CO_2)_2$, MeOH/H_2O (v/v, 10:1), 15 °C, 15 min, 82%. DDQ = 2, 3-dichloro-5, 6-dicyano-1, 4-benzoquinone, PCC = pyridium chlorochromate.

satisfactory results. Eventually, the dithiane **7** was accessible in excellent yield (92%) by anhydrous zinc chloride catalyzed thioacetalization using thiosilane ($TMSS(CH_2)_2STMS$) under mild conditions.[28]

Completion of the Total Synthesis of Amphidinolide T3. With the successful synthesis of two fragments **6** and **7**, our subsequent designed strategy called for the assembly of the aldehyde **6** and dithiane **7**. We applied Smith's protocol as shown in Scheme 6.[29] Treatment of the dithiane **7** with *tert*-butyllithium in 10% HMPA/THF at −78 °C followed by adding of the precooled aldehyde **6** led to a 1.7:1 mixture of C12 epimers **45a** and **45b** in 80% combined yield. Various attempts directed toward improving the diastereoseletivity of this reaction,

(28) Evans, D. A.; Truesdale, L. K.; Grimm, K. G.; Nesbitt, S. L. *J. Am. Chem. Soc.* **1977**, *99*, 5009−5017.

TABLE 1. Diastereoselective Reduction of Ketone 46



entry	reducing reagent	(isolated yield, %) 45a	45b
1	Li(*n*-Bu)BH_3	11	24
2	L-Selectride	NR	
3	$LiBH_4$	2	88
4	$NaBH_4$	49	46
5	(*S*)-**54**, BMS	68	

including addition of Lewis acid and changing the temperature and the addition rate of aldehyde **6**, completely failed.[30] However, for preparative purposes, it proved convenient to enhance the diasteromeric ratio in favor of **45a** (or **45b**) by a two-step oxidation−reduction sequence via the ketone **46**, which can be obtained in high yield by the oxidation of the mixture **45a** and **45b** with DMP (the stereochemistry of newly formed **45a** was confirmed according to amphidinolide T3 subsequently completed and also consistent with the mechanistic model by **CBS** catalyst (*S*)-**54**[31a]). Among the screened reagents (Table 1), reduction ketone **46** with $LiBH_4$ afforded **45b** as the major product (a precursor of synthesis of amphidinolide **T4**), whereas the use of oxazaborolidine-catalyzed borane reduction by (*S*)-**54**[31] gave the single isomer **45a**, which was used for subsequent synthetic investigations. Protection of hydroxyl group in **45a** with acetic anhydride followed by removal of benzyl group with DDQ provided the primary alcohol **48**. Next, the conversion of the primary hydroxyl moiety in **48** to the corresponding carboxylic acid was investigated, but the dithiane ring was liable to be oxidized. Our initial path using modified SmI_2-promoted Evans−Tischenko reduction, developed by Smith in the synthesis of (+)-13-deoxytedanolide,[32] did not afford a satisfactory yield. This transformation was achieved later via a two-step oxidation reaction under mild conditions, and the dithiane ring was not affected. Thus, the exposure of the resulting acid **50** to HF·Py complex, followed by hydrolysis in the presence of LiOH, gave the hydroxyl acid **52**. Selective macrocyclization carried out under Yamaguchi conditions,[33] as expected, provided macrolactone **53** with high chemoselectivity (73%). Removal of dithiane with bis(trifluoroacety) iodobenzene[34] led to the synthetic amphidinolide T3. Spectral data of a synthetic sample of **3** were identical with those of natural amphidinolide T3 (^{1}H NMR, ^{13}C NMR, HRMS, optical rotation).

In addition, it was noteworthy that the completion of the total synthesis of amphidinolide T3 (**3**) indicated T4 (**4**) might be synthesized from **45b** by the same routes to **3**. To some extent, the intermediate **46** should be also suitable for synthesis of amphidinolide T5 (**5**) as we changed the starting material in the preparation of iodide **11**.

Conclusion

In summary, we have achieved the total synthesis of T3 and formal synthesis of T4 via a highly flexible, concise, and convergent strategy using the readily available and inexpensive chiral building blocks. The fragment **6** was synthesized in 15 steps and 31% overall yield from the diol **19**; the other fragment **7** was prepared in 11 steps and 33% overall yield from **33**. We completed the synthesis of amphidinolide T3(**3**) in 25 steps for the longest linear sequence and 5.0% overall yield. Asymmetric allylation reactions of stannyl-derived allyldiazaborolanes proved to be a powerful protocol for the enantiocontrolled assembly of functional components in organic syntheses. A stereocontrolled and practical synthesis of the trisubstituted tetrahydrofuran ring has been demonstrated by a new approach. Mutual transformations of **45a** and **45b** could be conveniently accessed via the intermediate **46**. Efficient couplings of dithiane with electrophiles were featured in the approach.

Experimental Section

Ester 21. To a stirred solution of diol **19** (16.88 g, 45 mmol) in DMF (165 mL) cooled at 0 °C were added imidazole (7.65 g, 112 mmol) and *tert*-butyldimethylsilyl chloride (7.53 g, 50 mmol). After being stirred for 2 h at 0 °C, the reaction was quenched by addition of H_2O (90 mL), and the resulting solution was stirred at room temperature for another 30 min. The mixture was extracted with Et_2O (3 × 40 mL). The combined extracts were washed with brine (40 mL), dried over anhydrous Na_2SO_4, and concentrated on the rotary evaporator. The residue was purified by flash chromatography (hexane/ethyl acetate 5:1 v/v) to afford ether **20** (21.85 g, 99%) as a colorless oil. Ether **20** (21.85 g, 44.6 mmol) was dissolved in CH_2Cl_2 (210 mL). Ac_2O (10.7 mL, 111.7 mol), Et_3N (15.8 mL, 111.7 mmol), and DMAP (1.36 g, 11.2 mmol) were added to the solution, and the mixture was stirred at room temperature for 12 h and then quenched by addition of H_2O (100 mL). The resulting solution was stirred at room temperature for 1 h, and the aqueous phase was extracted with CH_2Cl_2 (3 × 30 mL). The combined extracts were washed with brine (50 mL), dried over anhydrous Na_2SO_4, and concentrated on the rotary evaporator. The residue was purified by flash chromatography (hexane/ethyl acetate 20:1 v/v) to afford ester **21** (28.9 g, 99%) as a white solid: R_f (hexane/ethyl acetate 15:1 v/v) 0.52; mp 82−83 °C; $[\alpha]^{24}_D$ +21.8 (*c* 1.06 $CHCl_3$); IR (neat, cm^{-1}) ν 2954, 2946, 1743, 1449, 1232, 1100, 767; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43−7.22 (m, 15H), 5.19(m, 1H), 3.39 (dd, J = 2.8, 2.4 Hz, 2H), 3.10 (m, 2H), 2.09 (s, 3H), 1.65−1.72 (m, 1H), 1.40 (ddd, J = 7.2, 6.7, 5.2 Hz, 2H), 0.87(d, J = 5.3 Hz, 3H), 0.85 (s, 9H), 0.07 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.6, 144.0, 128.7, 127.8, 127.0, 86.5, 71.9, 67.5, 65.3, 34.4, 32.4, 26.0, 21.3, 18.2, 17.4, −5.40, −5.42; MALDI-MS calcd for $C_{33}H_{44}O_4Si$ found 532, *m*/*z* [M + Na]$^+$ 555; HRMS (MALDI) *m*/*z* 555.2915, [M + Na]$^+$ calcd for $C_{33}H_{44}O_4SiNa^+$ 555.2901.

Alcohol 22. To a stirred solution of ester **21** (4.40 g, 8.3 mmol) in THF (80 mL) was added TBAF (16.6 mL of a 1.0 M solution in

(29) (a) Smith, A. B., III; Condon, S. M.; McCauley, J. A.; Leazer, J. L., Jr.; Leahy, J. W.; Maleczka, R. E., Jr. *J. Am. Chem. Soc.* **1997**, *119*, 947−961. (b) Smith, A. B., III; Condon, S. M.; Mccauler, J. A. *Acc. Chem. Res.* **1998**, *31*, 35−46.

(30) Typical examples of stereochemically controlled dithiane coupling reactions, see: (a) Nicolaou, K. C.; Baran, P. S.; Zhong, Y.-L.; Fong, K. C.; Choi, H.-S. *J. Am. Chem. Soc.* **2002**, *124*, 2190−2201. (b) Nicolaou, K. C.; Li, Y.-W.; Sugita, K.; Monenschein, H.; Guntupalli, P.; Mitchell, H. J.; Fylaktakidou, K. C.; Vourloumis, D.; Giannakakou, P.; O'Brate, A. *J. Am. Chem. Soc.* **2003**, *125*, 15443−15454. (c) See ref 29a.

(31) (a) Corey, E. J.; Helal, C. J. *Angew. Chem., Int. Ed.* **1998**, *37*, 1986−2012. (b) DeNinno, M. P.; Perner, R. J.; Lijewski, L. *Tetrahedron Lett.* **1990**, *31*, 7415−7418. (c) Kanematsu, K.; Nishizaki, A.; Sao, Y.; Shiro, M. *Tetrahedron Lett.* **1992**, *33*, 4967−4970. (d) Xu, J.-X.; Wei, T.-Z.; Zhang, Q.-H. *J. Org. Chem.* **2003**, *68*, 10146−10151.

(32) (a) Evans, D. A.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1990**, *112*, 6447−6449. (b) Smith, A. B., III; Lee, D.; Adams, C. M.; Kozlowski, M. C. *Org. Lett.* **2002**, *4*, 4539−4541. (c) Smith, A. B., III; Adams, C. M.; Barbosa, S. A. L.; Degnan, A. P. *J. Am. Chem. Soc.* **2003**, *125*, 350−351.

(33) Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989.

(34) Stork, G.; Zhao, K. *Tetrahedron Lett.* **1989**, *30*, 287−290.

THF, 16.6 mmol) at room temperature. After the solution was allowed to sit overnight, saturated aqueous NH_4Cl (50 mL) was added, and the mixture was extracted with Et_2O (3 × 25 mL). The combined extracts were washed with brine (25 mL), dried over anhydrous Na_2SO_4, and concentrated on the rotary evaporator. The residue was purified by flash chromatography (hexane/ethyl acetate 1:4 → 1:1 v/v) to afford alcohol **22** (3.32 g, 96%) as a viscous liquid: R_f (hexane/ethyl acetate 3:1 v/v) 0.39; $[\alpha]^{21}_D$ +19.9 (*c* 0.90 $CHCl_3$); IR (film, cm^{-1}) ν 3450, 3059, 2927, 1738, 1597, 1491, 1449, 1372, 1240, 706; ^1H NMR (300 MHz, $CDCl_3$) δ 7.43−7.23 (m, 15H), 5.20(m, 1H), 3.45 (dd, J = 2.7, 9.2 Hz, 2H), 3.08−3.18 (ddd, J = 3.3, 10.4, 14.4 Hz, 2H), 2.11 (s, 3H), 1.47−1.72 (m, 5H), 0.90 (d, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.0, 143.9, 128.7, 127.8, 127.1, 86.4, 71.9, 67.6, 65.2, 34.6, 32.3, 21.3, 17.3; ESI-MS calcd for $C_{27}H_{30}O_4Si$ found 418, *m*/*z* $[M + Na]^+$ 441; HRMS (ESI) *m*/*z* 441.2054 $[M + Na]^+$ calcd for $C_{27}H_{30}O_4SiNa^+$ 441.2036.

Aldehyde 23. To a solution of alcohol **22** (1.67 g, 4 mmol) in CH_2Cl_2 (33 mL) was added DMP (2.71 g, 6.4 mmol) in one portion at room temperature. After being stirred for 30 min, the reaction was diluted with Et_2O (20 mL) and quenched by addition of saturated aqueous $Na_2S_2O_3$ (20 mL) and $NaHCO_3$ (5 mL). The aqueous phase was extracted with Et_2O (3 × 10 mL). The combined extracts were washed with brine (20 mL), dried over anhydrous Na_2SO_4, and concentrated on the rotary evaporator to give a pale yellow-white product. Recrystallization from hexane afforded **23** (1.54 g, 92%) as white needles: R_f (hexane/ethyl acetate 8:1 v/v) 0.48; mp 87−88 °C; $[\alpha]^{21}_D$ +30.6 (*c* 0.70 $CHCl_3$); IR (neat, cm^{-1}) ν 3059, 3033, 2934, 1742, 1701, 1590, 1491, 1449, 1373, 1237; ^1H NMR (300 MHz, $CDCl_3$) δ 9.61 (d, J = 1.4 Hz, 1H), 7.44−7.22 (m, 15H); 5.16−5.09 (m, 1H), 3.16 (ddd, J = 4.4, 10.4, 12.8 Hz, 2H), 2.43−2.34 (m, 1H), 2.08 (s, 3H), 2.01 (ddd, J = 3.7, 6.9, 11.5 Hz, 1H), 1.86 (ddd, J = 4.9, 9.1, 14.1 Hz, 1H), 1.08 (d, J = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.6, 170.4, 203.6, 170.4, 143.8, 128.7, 127.9, 127.1, 86.6, 70.8, 64.8, 42.9, 31.7, 21.1, 13.5; ESI-MS calcd for $C_{27}H_{28}O_4$ found 416, *m*/*z* $[M + Na]^+$ 439; HRMS (ESI) *m*/*z* 439.1867, $[M + Na]^+$ calcd for $C_{27}H_{28}O_4Na^+$ 439.1879.

Alcohol 24. To a three-necked flask (50 mL) containing (*R*,*R*)-1,2-bis-*p*-toluenesulfonyl-1, 2-diphenylethane (242.5 mg, 0.47 mmol) in CH_2Cl_2 (4.5 mL) cooled to 0 °C was added boron tribromide (0.47 mL of a 1 M solution in CH_2Cl_2, 0.47 mmol). The mixture was stirred at 0 °C for 10 min, warmed to room temperature, and stirred for 2 h. After the solvent and HBr (this was key to yield) were completely removed under reduced pressure, the resulting solid was diluted with CH_2Cl_2 (4.5 mL) and cooled to 0 °C. Allyltributylstannane (172 mg, 0.52 mmol) was added dropwise. After the mixture was stirred for 6 h at room temperature, the reaction was cooled to −78 °C, and a solution of aldehyde **23** (137 mg, 0.33 mmol) in CH_2Cl_2 (1 mL) was added. After being stirred for 2 h at −78 °C, the reaction was quenched with pH = 7 buffer solution (5 mL) and warmed to room temperature. The mixture was diluted with CH_2Cl_2 (50 mL). The organic phase was washed with brine (30 mL). The combined aqueous phases were extracted with CH_2Cl_2 (15 mL). The combined organic phases were dried over anhydrous Na_2SO_4 and concentrated on the rotary evaporator. The resulting solid was washed with ether to recover the bissulfonamide chiral auxiliary. The filtrate was concentrated in vacuo and purified by flash chromatography (hexane/ethyl acetate 10:1 v/v) to afford alcohol **24** (128 mg, 85%) as a colorless oil and recover **23** (10 mg) simultaneously: R_f(hexane/ethyl acetate 6:1 v/v) 0.40; $[\alpha]^{21}_D$ +33.0 (*c* 0.63 $CHCl_3$); IR (neat, cm^{-1}) ν 3511, 3052, 2926, 1734, 1638, 1490, 1446, 1240, 703; ^1H NMR (300 MHz, $CDCl_3$) δ 7.46−7.23 (m, 15H), 5.85−5.71 (m, 1H), 5.18−5.15 (m, 1H), 5.13 (s, 1H), 5.09 (s, 1H), 3.43(br,1H), 3.13 (ddd, J = 3.3, 10.1, 14.3 Hz, 2H), 2.23−2.28 (m, 1H), 2.14 (s, 3H), 2.00−2.10 (m, 1H), 1.84−1.89 (m, 1H), 1.71 (m, 1H), 1.47−1.49 (m, 2H), 0.88 (d, J = 6.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.7, 143.9, 135.1, 128.7, 127.8, 127.0, 118.1, 86.5, 74.4, 72.5, 64.9, 38.3, 35.2, 33.6, 21.4, 13.3; ESI-MS calcd for $C_{30}H_{34}O_4$, found 458 *m*/*z* $[M + Na]^+$ 481; HRMS (ESI) *m*/*z* 481.2347, $[M + Na]^+$ calcd for $C_{30}H_{34}O_4Na^+$ 481.2349.

Alkene 8. To a solution of **24** (6.29 g, 13.7 mmol) in pyridine (32 mL) cooled to 0 °C was added TsCl (6.54 g, 34.3 mmol). After being stirring for 5 min, the reaction mixture was warmed to room temperature, stirred for 48 h, and then quenched with ice−water. The resulting solution was stirred at room temperature for 0.5 h; the mixture was extracted with Et_2O (3 × 20 mL). The combined extracts were successively washed with 2 M HCl (3 × 15 mL), saturated $NaHCO_3$ (15 mL), and brine (50 mL), dried over anhydrous Na_2SO_4, and concentrated on the rotary evaporator. The residue was purified by flash chromatography (hexane/ethyl acetate 20:1 v/v) to afford tosylate **25** (8.36 g, 99%) as a colorless oil: R_f (hexane/ethyl acetate 8:1 v/v) 0.45; $[\alpha]^{21}_D$ +22.5 (*c* 1.45 $CHCl_3$); IR (neat, cm^{-1}) ν 3052, 2919, 1738, 1597, 1486, 1449, 1365, 1238, 1177, 901, 708; ^1H NMR (300 MHz, $CDCl_3$) δ 7.74 (d, J = 8.4 Hz, 2H), 7.23−7.43 (m, 17H), 5.46−5.33 (m, 3H), 5.05 (m, 1H), 4.94−4.83 (m, 2H), 4.43 (m, 2H), 3.10 (ddd, J = 3.9, 10.5, 14.4 Hz, 2H), 2.42 (s, 3H), 2.28−2.25 (m, 2H), 2.11 (s, 3H), 1.92 (m, 1H), 1.67−1.76 (m, 1H), 1.41−1.48 (m, 1H), 0.85 (d, J = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.5, 144.4, 143.8, 134.4, 132.5, 129.6, 128.6, 127.9, 127.8, 127.1, 118.3, 86.6, 85.8, 71.1, 64.7, 34.7, 33.0, 32.9, 32.7, 29.7, 21.6, 21.2, 15.3; ESI-MS calcd for $C_{37}H_{40}O_6S$ found 612, *m*/*z* $[M + NH_4]^+$ 630; HRMS (ESI) *m*/*z* 635.2439 $[M + Na]^+$, calcd for $C_{37}H_{40}O_6SNa^+$ 635.2437. A solution of KOH (2.02 g, 36 mmol) in ethylene glycol (20 mL) was added to a solution of **25** (1.11 g, 1.8 mmol) in diglyme (10 mL). The mixture was warmed to 40 °C for 90 min. The solution was then cooled and quenched with water (20 mL). The aqueous phase was extracted with Et_2O (3 × 15 mL), and the combined organic phases were washed with water (15 mL) and brine (30 mL), dried over anhydrous Na_2SO_4, and concentrated on the rotary evaporator. The residue was purified by flash chromatography (hexane/ethyl acetate 50:1 v/v) to afford alkene **8** (0.71 g, 99%) as a colorless oil: R_f (hexane/ethyl acetate 40:1 v/v) 0.32; $[\alpha]^{21}_D$ +4.37 (*c* 0.84 $CHCl_3$); IR (film, cm^{-1}) ν 3059, 2962, 2928, 1638, 1594, 1491, 1448, 1089, 704, 632; ^1H NMR (300 MHz, $CDCl_3$) δ 7.42−7.14 (m, 15H), 5.76−5.89 (m, 1H), 4.99−5.11 (m, 2H), 4.26 (m, 1H), 3.88 (m, 1H), 3.05 (dd, J = 5.7, 9.3 Hz, 1H), 2.89 (dd, J = 5.1, 9.9 Hz, 1H), 2.15−2.33 (m, 3H), 1.78−1.87 (m, 1H), 1.58−1.66 (ddd, J = 2.7, 7.5, 10.2 Hz, 1H), 0.87 (d, J = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.3, 135.7, 128.8, 127.7, 126.9, 116.3, 86.4, 80.9, 76.1, 66.8, 36.7, 35.7, 35.3, 14.1; ESI-MS calcd for $C_{28}H_{30}O_2$ found 398, *m*/*z* $[M + Na]^+$ 421; HRMS (ESI) *m*/*z* 421.2139, $[M + Na]^+$ calcd for $C_{28}H_{30}O_2Na^+$ 421.2138.

Alcohol 26. A solution of borane−dimethyl sulfide (16 mL of a 2.0 M solution in THF, 32 mmol) was added to a solution of **8** (3.54 g, 8.9 mmol) in dry THF (100 mL) and cooled to 0 °C. After being warmed to room temperature and stirred, the mixture was again cooled to 0 °C and carefully quenched by successively addition of EtOH (60 mL), NaOH aq (60 mL, 3.0 M), and 30% H_2O_2 (60 mL). The mixture was stirred for 2 h at room temperature. The aqueous phase was extracted with Et_2O (3 × 40 mL), and the combined organic phases were washed with brine (40 mL), dried over anhydrous Na_2SO_4, and concentrated on the rotary evaporator. The residue was purified by flash chromatography (hexane/ethyl acetate, 8:1 → 6:1 v/v) to afford alcohol **26** (3.2 g, 83%) as a colorless oil: R_f (hexane/ethyl acetate 4:1 v/v): 0.17; $[\alpha]^{20}_D$ +8.77 (*c* 1.10 $CHCl_3$); IR (film, cm^{-1}) ν 3400, 2935, 1594, 1491, 1448, 1071, 749, 704; ^1H NMR (300 MHz, $CDCl_3$) δ 7.51−7.21 (m, 15H), 4.37−4.29 (m, 1H), 3.92 (td, J = 4.8, 8.7 Hz, 1H), 3.72 (ddd, J = 6.0, 10.8, 6.3 Hz, 2H), 3.13 (dd, J = 5.7, 9.3 Hz, 1H), 3.00 (dd, J = 4.5, 9.9 Hz, 1H), 2.56 (br. s, 1H), 2.24 (m, 1H), 1.94−1.85 (m, 1H), 1.53−1.80 (m, 5H), 0.94(d, J = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.2, 128.8, 128.73 127.9, 127.7, 126.9, 81.9, 76.2, 66.7, 63.0, 36.6, 36.2, 30.6, 27.8, 14.2; ESI-MS calcd for $C_{28}H_{32}O_3$, found 416 *m*/*z* $[M + Na]^+$ 439; HRMS (ESI) *m*/*z* 439.2246, $[M + Na]^+$ calcd for $C_{28}H_{32}O_3\ Na^+$ 439.2243.

Iodide 27. PPh_3 (6.03 g, 23.0 mmol) and imidazole (3.13 g, 46.0 mmol) were added sequentially to a solution of alcohol **26** (3.19 g, 7.67 mmol) in THF (105 mL) at 0 °C. After the solution was stirred for 10 min, I_2 (5.84 g, 23 mmol) was added in three portions and the mixture maintained at this temperature for 10 min. The reaction mixture was warmed to room temperature, stirred for another 2 h, and then quenched with saturated aqueous $Na_2S_2O_3$ (45 mL). The aqueous phase was extracted with Et_2O (3 × 15 mL), and the combined organic phases were washed with brine (30 mL), dried over anhydrous Na_2SO_4, and concentrated on the rotary evaporator. The residue was purified by flash chromatography (hexane/ethyl acetate 100:1 v/v) to afford iodide **27** (3.81 g, 95%) as a colorless oi: R_f (hexane/ethyl acetate 30:1 v/v) 0.48; $[\alpha]^{20}_D$ +12.8 (*c* 0.88 in $CHCl_3$); IR (film, cm^{-1}) ν 3052, 2960, 1594, 1490, 1448, 1224, 1075, 703; ^1H NMR (300 MHz, $CDCl_3$) δ 7.52−7.22 (m, 15H), 4.29 (m, 1H), 3.88 (m, 1H), 3.34−3.19 (m, 2H), 3.10 (dd, J = 5.4, 9.3 Hz, 1H), 2.97 (dd, J = 4.2, 9.6 Hz, 1H), 2.20(m, 1H), 1.89 (dt, J = 6.9, 19.8 Hz, 2H), 1.67 (ddd, J = 3.3, 7.5, 10.2 Hz, 1H), 1.57 (dd, J = 7.2, 14.4 Hz, 3H), 0.92(d, J = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.2, 128.8, 127.7, 126.9, 86.4, 80.5, 76.0, 66.9, 36.5, 36.0, 31.7, 31.2, 14.2, 7.2. Anal. Calcd for $C_{28}H_{31}IO_2$: C, 63.88; H, 5.94. Found: C, 63.67; H, 5.82.

Benzyl Ether 29. To a stirred solution of the sulfone **9** (2.64 g, 8.69 mmol) in THF (20 mL) and HMPA (7.8 mL) cooled at −78 °C was added *n*-BuLi (6.5 mL of a 1.6 M solution in THF, 10.4 mmol) dropwise. The mixture gradually turned amaranth and was warmed to −30 °C for 30 min and then recooled to −78 °C. A solution of iodide **27** (3.81 g, 7.24 mmol) in THF (28 mL) was added dropwise. After being stirred for 2 h, the reaction was quenched by addition of saturated aqueous NH_4Cl (10 mL) and then warmed to room temperature. The mixture was extracted with Et_2O (3 × 10 mL), and the combined extracts were washed with brine (10 mL), dried over anhydrous Na_2SO_4, and concentrated on the rotary evaporator. The residue was purified by flash chromatography (hexane/ethyl acetate 20:1 → 10:1 → 6:1 v/v) to afford a diastereomeric mixture of sulfones (4.89 g) as a colorless oil, which was employed in the next experiment without separation of the diastereomers. To a vigorously stirred solution of the diastereomeric mixture of sulfones (4.89 g, 6.97 mmol) in EtOH (93 mL) cooled at 0 °C was added 6% sodium amalgam (50 g, 130 mmol) in one portion. After 5 min, the mixture was warmed to room temperature, stirred for 2−3 h, diluted with saturated aqueous NH_4Cl (30 mL), and stirred at room temperature for 2 h. The aqueous phase was extracted with Et_2O (3 × 15 mL), and the combined organic phases were washed with brine (15 mL), dried over anhydrous Na_2SO_4, and concentrated on the rotary evaporator. The residue was purified by flash chromatography (hexane/ethyl acetate 50:1 → 10: 1 v/v) to afford benzyl ether **29** (3.26 g, 80%) as a colorless oil: R_f (hexane/ethyl acetate 15:1 v/v) 0.56; $[\alpha]^{20}_D$ +14.6 (*c* 0.51 $CHCl_3$); IR (film, cm^{-1}) ν 3052, 3022, 2929, 1594, 1491, 1449, 1095, 698; ^1H NMR (300 MHz, $CDCl_3$) δ 7.50−7.19 (m, 20H), 4.48 (s, 2H), 4.29 (m, 1H), 3.83 (m, 1H), 3.32 (dd, J = 6.3, 9.0 Hz, 1H), 3.22 (dd, J = 6.6, 9.0 Hz, 1H), 3.11 (dd, J = 6.3, 9.6 Hz, 1H), 2.95 (dd, J = 4.5, 9.9 Hz, 1H), 2.17 (m, 1H), 1.91−1.82 (m, 1H), 1.77−1.75 (m, 1H), 1.66 (ddd, J = 2.4, 7.2, 9.6 Hz, 1H), 1.29−1.63 (m, 7H), 1.12−1.16 (m, 1H), 0.89−0.93 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.3, 138.9, 128.8, 128.3, 127.9, 127.7, 127.5, 127.4, 127.3,126.8, 86.3, 81.5, 76.0, 75.8, 72.9, 66.9, 36.7, 35.8, 33.7, 33.5, 30.7, 27.3, 27.3, 17.2, 14.1; ESI-MS calcd for $C_{39}H_{46}O_3$ found 562, m/z $[M + NH_4]^+$ 580; HRMS (ESI) m/z 585.3336 $[M + Na]^+$ calcd for $C_{39}H_{46}O_3Na^+$ 585.3339.

Alcohol 30. A mixture of ether **29** (5.36 g, 9.54 mmol) in 80% (v/v) aqueous HOAc (64 mL) was warmed at 50−55 °C for 3 h under stirred. The mixture was cooled to room temperature and quenched with saturated aqueous $NaHCO_3$ (50 mL). The aqueous phase was extracted with Et_2O (3 × 20 mL), and the combined organic phases were washed with brine (25 mL), dried over anhydrous Na_2SO_4, and concentrated on the rotary evaporator. The residue was purified by flash chromatography (hexane/ethyl acetate 10:1 → 5:1 v/v) to afford alcohol **30** (2.92 g, 95%) as a colorless oil: R_f (hexane/ethyl acetate 3:1 v/v) 0.28; $[\alpha]^{20}_D$ −9.9 (*c* 1.57 $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.35−7.27 (m, 5H), 4.50 (s, 3H), 4.17 (tdd, J = 7.1, 7.1, 3.2 Hz, 1H), 3.85 (m, 1H), 3.61 (m, 1H), 3.46 (dt, J = 11.6, 5.8 Hz, 1H), 3.32 (dd, J = 9.0, 6.1 Hz, 1H), 2.24 (m, 1H), 2.03 (t, J = 6.6 Hz, 1H), 1.85 (dd, J = 12.4, 7.6 Hz, 1H), 1.76 (dd, J = 12.4, 6.6 Hz, 1H), 1.65 (ddd, J = 12.4, 7.3, 3.3 Hz, 1H), 1.40−1.36 (m, 7H), 1.10 (m, 1H), 0.92 (d, J = 6.6 Hz, 3H), 0.92 (d, J = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.7, 128.3, 127.5, 127.3, 81.7, 77.4, 75.9, 72.9, 65.5, 35.8, 35.4, 33.5, 33.4, 30.3, 27.1, 26.8, 17.1, 13.9; IR (film, cm^{-1}) 3430, 2931, 2858, 1454, 1205, 1096; ESI-MS calcd for $C_{20}H_{32}O_3$ found 320, m/z $[M + H]^+$ 321; HRMS (ESI) m/z 343.2249, $[M + Na]^+$ calcd for $C_{20}H_{32}O_3Na^+$ 343.2244.

Iodide 31. Iodide **31** was prepared as the same approach to **27**: R_f (hexane/ethyl acetate 25:1 v/v) 0.38; $[\alpha]^{20}_D$ +20.6 (*c* 0.25 $CHCl_3$); IR (neat, cm^{-1}) ν 2961, 2856, 1496, 1454, 1362, 1096; ^1H NMR (300 MHz, $CDCl_3$) δ 7.36−7.27 (m, 5H), 4.51 (s, 2H), 4.12 (tdd, J = 7.5, 7.5, 4.6 Hz, 1H), 3.98 (m, 1H), 3.28 (dd, J = 9.6, 4.5 Hz, 1H), 3.29 (m, 2H), 3.17 (dd, J = 9.5, 7.6 Hz, 1H), 2.29 (m, 1H), 1.90 (ddd, J = 12.4, 7.1, 3.7 Hz, 2H), 1.79 (m, 1H), 1.49−1.26 (m, 7H), 1.14 (m, 1H), 0.93 (d, J = 6.5 Hz, 3H), 0.92 (d, J = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.8, 128.3, 127.5, 127.4, 82.5, 77.4, 75.9, 72.9, 40.5, 36.3, 33.5, 33.4, 30.4, 27.1, 26.7, 17.1, 13.9, 12.1; ESI-MS calcd for $C_{20}H_{31}IO_2$ found 430, m/z $[M + NH_4]^+$ 448; HRMS (ESI) m/z 453.1266 $[M + Na]^+$ calcd for $C_{20}H_{31}IO_2Na^+$ 453.1261.

2-Substituted Dithiane 32. 1,3-Dithiane (3.67 g, 30.6 mmol) was dissolved in 10% HMPA/THF (32 mL, v/v) cooled to −78 °C. After the solution was stirred for 20 min, a solution of iodide **31** (4.37 g, 10.2 mmol) in 10% HMPA/THF (16 mL) was added dropwise. The mixture was stirred for 1.5 h and quenched with saturated aqueous NH_4Cl (10 mL). The aqueous phase was extracted with Et_2O (2 × 10 mL), and the combined organic phases were washed with brine (10 mL), dried over anhydrous Na_2SO_4, and concentrated on the rotary evaporator. The residue was purified by flash chromatography (hexane/ethyl acetate 100:1 → 50:1) to afford dithiane **32** (3.59 g, 83%) as a colorless oil: R_f (hexane/ethyl acetate 15:1 v/v) 0.49; $[\alpha]^{20}_D$ −26.4 (*c* 0.35 $CHCl_3$); IR (neat, cm^{-1}) ν 2931, 2855, 1454, 1268, 1091, 998, 735; ^1H NMR (300 MHz, $CDCl_3$) δ 7.35−7.27 (m, 5H), 4.50 (s, 2H), 4.35 (ddd, J = 15.7, 7.6, 4.1 Hz, 1H), 4.21 (dd, J = 9.2, 5.0 Hz, 1H), 3.80 (dt, J = 7.5, 4.9 Hz, 1H), 3.32 (dd, J = 9.1, 5.9 Hz, 1H), 3.23 (dd, J = 9.2, 6.9 Hz, 1H), 2.97−2.78 (m, 4H), 2.20 (m, 2H), 1.94−1.75 (m, 6H), 1.67−1.37 (m, 7H), 1.13 (m, 1H), 0.92 (d, J = 6.5 Hz, 3H), 0.89 (d, J = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.7, 128.2, 127.4, 127.3, 80.8, 75.9, 72.8, 72.7, 44.5, 42.5, 40.1, 35.7, 33.5, 33.3, 30.4, 30.3, 30.0, 27.1, 26.8, 25.9, 17.0, 13.9; ESI-MS calcd for $C_{24}H_{38}O_2S_2$ found 422, m/z $[M + NH_4]^+$ 440; HRMS (ESI) m/z 445.2211, $[M + Na]^+$ calcd for $C_{24}H_{38}O_2S_2Na^+$ 445.2205.

Aldehyde 6. $NaHCO_3$ (383 mg, 4.6 mmol) and CH_3I (457 μL, 7.36 mmol) were successively added to a solution of dithiane **32** (193 mg, 0.46 mmol) in 80% CH_3CN/H_2O (6 mL). The mixture was stirred for 16 h at room temperature and diluted by addition of water (5 mL). The aqueous layer was extracted with Et_2O (3 × 5 mL), and the combined organic phases were washed with brine (8 mL), dried over anhydrous Na_2SO_4, and concentrated on the rotary evaporator. The residue was purified by flash chromatography (hexane/ethyl acetate 20:1 → 10:1 v/v) to afford aldehyde **6** (150 mg, 95%) as a colorless oil: R_f (hexane/ethyl acetate 8:1 v/v): 0.25; $[\alpha]^{20}_D$ −6.5 (*c* 1.95 $CHCl_3$); IR (film, cm^{-1}) ν 3030, 2929, 2854, 1726, 1454, 1376, 1096, 736, 698; ^1H NMR (300 MHz, $CDCl_3$) δ 9.82 (d, J = 2.2 Hz, 1H), 7.36−7.27 (m, 5H), 4.54 (m, 1H), 4.5 (m, 1H), 3.89 (m, 1H), 3.32 (dd, J = 9.1, 6.2 Hz, 1H), 3.24 (dd, J = 9.1, 7.2 Hz, 1H), 2.68 (ddd, J = 16.3, 7.4, 2.7 Hz, 1H), 2.55 (ddd, J = 16.0, 5.1, 1.7 Hz, 1H), 2.26 (m, 1H), 1.88 (m, 1H), 1.77 (dt, J = 12.2, 7.1 Hz, 1H), 1.39−1.26 (m, 7H), 1.13 (m, 1H), 0.93 (d, J = 7.1 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.7, 138.7, 128.2, 127.4, 127.3, 81.5, 75.9, 72.9, 71.4, 50.5, 40.4, 35.7, 33.5,

33.3, 30.2, 27.1, 26.7, 17.0, 13.8; ESI-MS calcd for $C_{21}H_{32}O_3$ found 332, *m/z* $[M + H]^+$ 333; HRMS (ESI) *m/z* 355.2249, $[M + Na]^+$ calcd for $C_{21}H_{32}O_3Na^+$ 355.2244.

Disubstituted Dithiane 40. To a solution of **10** (4.34 g, 13.5 mmol) in dry THF (45 mL) cooled to −78 °C were added *t*-BuLi (9.0 mL of a 1.5 M soln in THF, 13.5 mL) over a period of 10 min and HMPA (4.9 mL). After the solution was stirred for 30 min, a solution of the iodide **11** (3.1 g, 9.7 mmol) in THF (30 mL) was added dropwise. The resulting solution was stirred at −78 °C for 1 h and quenched with saturated aqueous NH_4Cl (25 mL). The aqueous phase was extracted with Et_2O (3 × 10 mL). The combined extracts were washed with brine (25 mL), dried over anhydrous Na_2SO_4, and concentrated on the rotary evaporator. The residue was purified by flash chromatography (hexane/ethyl acetate 100:1 v/v) to afford **40** (4.1 g, 83%) as a colorless oil: R_f (hexane/ethyl acetate 50:1 v/v) 0.25; $[\alpha]^{20}_D$ −4.7 (*c* 0.97 $CHCl_3$); IR (neat, cm^{-1}) ν 2957, 1380, 1255, 1110, 1047; ^1H NMR (300 Hz, $CDCl_3$) δ 7.38−7.27 (m, 5H), 4.78 (s, 2H), 4.63 (s, 2H), 4.10 (m, 1H), 3.57 (dd, *J* = 9.3, 5.5 Hz, 1H), 3.42 (dd, *J* = 9.0, 7.0 Hz, 1H), 2.83 (m, 4H), 2.20 (dd, *J* = 15.1, 4.1 Hz, 2H), 2.03−1.98 (m, 2H), 1.90 (m, 2H), 1.82 (dd, *J* = 15.3, 5.7 Hz, 1H), 1.62 (m, 1H), 1.51−1.30 (m, 3H), 1.10 (d, *J* = 6.8 Hz, 3H), 0.94 (d, *J* = 7.1 Hz, 3H), 0.89 (s, 9H), 0.12 (s, 3H), 0.10 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.9, 128.4, 127.9, 127.6, 94.5, 73.9, 69.8, 69.2, 53.6, 46.8, 43.4, 41.4, 30.3, 26.5, 26.2, 26.1, 24.9, 20.1, 18.1, 17.9, 14.3, −3.8, −4.0; ESI-MS calcd for $C_{27}H_{48}O_3S_2Si$ found 512, *m/z* $[M + NH_4]^+$ 530; HRMS (ESI) *m/z* 535.2712, $[M + Na]^+$ calcd for $C_{27}H_{48}O_3S_2SiNa^+$ 535.2706.

Ketone 41. $NaHCO_3$ (5.94 g, 70.7 mmol) and I_2 (7.98 g, 31.4 mmol) were successively added to a solution of **40** (4.03 g, 7.86 mmol) in acetone/H_2O (130 mL, 5:1, v/v) cooled to 0 °C. After being stirred for 1 h, the reaction mixture was quenched with saturated aqueous $Na_2S_2O_3$ (30 mL) and extracted with Et_2O (3 × 20 mL). The combined extracts were washed with brine (15 mL), dried over anhydrous Na_2SO_4, and concentrated on the rotary evaporator. The residue was purified by flash chromatography (hexane/ethyl acetate 100:1 → 50:1 v/v) to afford **41** (2.75 g, 83%) as a colorless oil: R_f (hexane/ethyl acetate 40:1 v/v) 0.28; $[\alpha]^{20}_D$ −13.8 (*c* 0.97 $CHCl_3$); IR (neat, cm^{-1}) ν 2958, 1716, 1462, 1387, 1257, 1048; ^1H NMR (300 Hz, $CDCl_3$) δ 7.37−7.27 (m, 5H), 4.74 (s, 2H), 4.59 (s, 2H), 4.18 (dt, *J* = 12.2, 5.6 Hz, 1H), 3.47 (dd, *J* = 9.4, 5.8 Hz, 1H), 3.38 (dd, *J* = 9.5, 6.4 Hz, 1H), 2.64−2.56 (m, 2H), 2.45 (dd, *J* = 15.4, 5.2 Hz, 1H), 2.34 (m, 1H), 2.25 (dd, *J* = 15.8, 7.7 Hz, 1H), 1.44−1.26 (m, 4H), 0.93 (dd, *J* = 13.7, 6.9 Hz, 3H), 0.87 (s, 12H), 0.07 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 209.1, 137.8, 128.4, 127.8, 127.7, 94.6, 72.5, 69.3, 68.6, 50.6, 48.4, 39.9, 29.3, 25.8, 18.3, 18.0, 17.2, 14.2, −4.6, −4.7; ESI-MS calcd for $C_{24}H_{42}O_4Si$ found 422, *m/z* $[M + H]^+$ 423; HRMS (ESI) *m/z* 445.2750, $[M + Na]^+$ calcd for $C_{24}H_{42}O_4Si\ Na^+$ 445.2745.

Alkene 42. To a solution of **41** (1.73 g, 4.08 mmol) in toluene (40 mL) was added Cp_2TiMe_2 (24.5 mL of a 0.5 M soln in toluene, 12.24 mmol). The resulting mixture shielded from light was stirred vigorously and refluxed for 3 h. After being cooled to room temperature, the solvent was removed under reduced pressure and diluted with petroleum ether. The resulting yellow-orange precipitate was removed by filtration, and the filtration was concentrated. The residue was purified by flash chromatography (hexane) to afford **42** (1.53 g, 86%) as a colorless oil: R_f (hexane/ethyl acetate 50:1 v/v) 0.63; $[\alpha]^{20}_D$ +4.8 (*c* 1.00 $CHCl_3$); IR (neat, cm^{-1}) ν 3070, 2958, 1643, 1463, 1255, 1107, 1047, 774; ^1H NMR (300 Hz, $CDCl_3$) δ 7.37−7.27 (m, 5H), 4.80 (d, *J* = 4.3 Hz, 2H), 4.77 (s, 2H), 3.79 (m, 1H), 3.47 (dd, *J* = 9.5, 5.7 Hz, 1H), 3.40 (dd, *J* = 9.0, 6.4 Hz, 1H), 2.20 (dd, *J* = 13.3, 5.6 Hz, 2H), 2.12 (dd, *J* = 13.7, 7.3 Hz, 1H), 1.93 (m, 1H), 1.81(dd, *J* = 13.5, 8.5 Hz, 1H), 1.45−1.25 (m, 4H), 0.94 (d, *J* = 6.4 Hz, 3H), 0.89 (s, 12H), 0.06 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.8, 137.9, 128.4, 127.9, 127.6, 113.5, 94.7, 73.2, 70.8, 69.2, 43.9, 40.7, 39.0, 31.5, 25.9, 18.5, 18.1, 17.0, 14.2, −4.4, −4.6; ESI-MS calcd for $C_{25}H_{44}O_3Si$ found 420, *m/z* $[M + Na]^+$ 443; HRMS (ESI) *m/z* 443.2957, $[M + Na]^+$ calcd for $C_{25}H_{44}O_3SiNa^+$ 443.2952.

Alcohol 43. To a solution of lithium (347 mg, 49.6 mmol) in liquid ammonia (220 mL) cooled to −78 °C was added alkene **42** (1.94 g, 4.6 mmol) in THF (22 mL). The resulting dark blue mixture was stirred for 1.5 h. Solid NH_4Cl was then added until the blue disappeared. After the liquid was evaporated at room temperature, water and diethyl ether were added. The aqueous phase was extracted with Et_2O (3 × 10 mL). The combined extracts were washed with brine (10 mL), dried over anhydrous Na_2SO_4, and concentrated on the rotary evaporator. The residue was purified by flash chromatography (hexane/ethyl acetate 20:1 → 10:1 v/v) to afford **43** (1.36 g, 99%) as a colorless oil: R_f (hexane/ethyl acetate 8:1 v/v) 0.46; $[\alpha]^{20}_D$ +14.9 (*c* 1.00 $CHCl_3$); IR (neat, cm^{-1}) ν 3347, 2959, 1644, 1463, 1362, 1255, 1126, 1040; ^1H NMR (300 Hz, $CDCl_3$) δ 4.82 (s, 2H), 3.80 (m, 1H), 3.50 (m, 2H), 2.17 (m, 3H), 1.86 (dd, *J* = 16.1, 7.3 Hz, 2H), 1.48−1.27 (m, 5H), 0.91 (d, *J* = 6.5 Hz, 3H), 0.89 (s, 12H), 0.05 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.2, 113.5, 70.9, 68.2, 43.7, 40.7, 39.1, 33.8, 25.9, 18.5, 18.1, 16.7, 14.2, −4.4, −4.6; ESI-MS calcd for $C_{17}H_{36}O_2Si$ found 300, *m/z* $[M + H]^+$ 301; HRMS (ESI) *m/z* 323.2382, $[M + Na]^+$ calcd for $C_{17}H_{36}O_2SiNa^+$ 323.2377.

Aldehyde 44. Aldehyde **44** (94%) was prepared from alcohol **43** using the above procedure for aldehyde **23**: R_f (hexane/ethyl acetate 40:1 v/v) 0.52; $[\alpha]^{20}_D$ +1.6 (*c* 1.07 $CHCl_3$); IR (neat, cm^{-1}) ν 3077, 2959, 1731, 1645, 1463, 1362, 1126, 1092; ^1H NMR (300 Hz, $CDCl_3$) δ 9.64 (d, *J* = 2.0 Hz, 1H), 4.84 (d, *J* = 11.7 Hz, 2H), 3.79 (m, 1H), 2.56 (td, *J* = 6.8, 1.9 Hz, 1H), 2.49 (m, 1H), 2.16 (d, *J* = 6.6 Hz, 2H), 2.04 (m, 1H), 1.41−1.26 (m, 4H), 1.09 (d, *J* = 7.3 Hz, 3H), 0.88 (m, 12H), 0.05 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 204.7, 143.4, 114.3, 71.0, 44.3, 43.7, 39.1, 37.5, 25.9, 18.5, 18.1, 14.2, 13.4, −4.4, −4.6; ESI-MS calcd for $C_{17}H_{34}O_4Si$ found 298, *m/z* $[M + Na]^+$ 321; HRMS (ESI) *m/z* 321.2226, $[M + Na]^+$ calcd for $C_{17}H_{34}O_4SiNa^+$ 321.2220.

Dithiane 7. To a 100-mL, three-necked flask containing $ZnCl_2$ (730 mg, 5.36 mmol) in Et_2O (55 mL) cooled to 0 °C was added 1, 3-propanedithiobis(trimethylsilane) (1.13 mL, 5.36 mmol). After 5 min, the solution of aldehyde **44** (805 mg, 2.68 mmol) in Et_2O (26 mL) was added dropwise. The reaction mixture was then warmed to room temperature and stirred for 1 h. The reaction was quenched by addition of aqueous ammonia (20 mL) and water (30 mL). The aqueous phase was extracted with Et_2O (3 × 15 mL). The combined extracts were washed with brine (15 mL), dried over anhydrous Na_2SO_4, and concentrated on the rotary evaporator. The residue was purified by flash chromatography (hexane) to afford **7** (944 mg, 91%) as a colorless oil: R_f (hexane/ethyl acetate 60:1) 0.54; $[\alpha]^{20}_D$ +13.4 (*c* 0.95 $CHCl_3$); IR (neat, cm^{-1}) ν 3074, 2958, 1643, 1255, 1125, 1041; ^1H NMR (300 Hz, $CDCl_3$) δ 4.84 (s, 2H), 4.47 (d, *J* = 3.1 Hz, 2H), 3.80 (m, 1H), 2.89 (m, 4H), 2.40 (dd, *J* = 13.2, 5.2 Hz, 2H), 2.21 (dd, *J* = 13.7, 6.0 Hz, 1H), 2.16−2.02 (m, 3H), 1.96 (dd, *J* = 13.3, 8.8 Hz, 1H), 1.86 (m, 1H), 1.44−1.28 (m, 4H), 1.07(d, *J* = 6.9 Hz, 3H), 0.89 (m, 12H), 0.07 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.2, 114.3, 70.6, 54.9, 40.7, 38.9, 36.5, 31.1, 30.7, 26.3, 25.9, 18.5, 18.0, 16.7, 14.2, −4.3, −4.6; ESI-MS calcd for $C_{20}H_{40}OS_2Si$ found 388, *m/z* $[M + H]^+$ 389; HRMS (ESI) *m/z* 411.2187, $[M + Na]^+$ calcd for $C_{20}H_{40}OS_2SiNa^+$ 411.2182.

Alcohols 45a and 45b. To a solution of dithiane **7** (1.54 g, 3.99 mmol) in 10% HMPA/THF (15 mL) cooled to −78 °C was added *t*-BuLi (2.67 mL of a 1.5 M soln in pentane, 4.0 mmol) over a period 3 min. The precooled (−78 °C) aldehyde **6** (442 mg, 1.33 mmol) in 10% HMPA/THF (12 mL) was immediately added to the dark orange anion mixture, and the reaction was stirred at −78 °C for 1 h. Then, it was quenched with saturated aqueous NH_4Cl (10 mL). The organic phase was separated, and the aqueous phase was extracted with Et_2O (3 × 10 mL). The combined organic phases were washed with water (10 mL) and brine (15 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated. The residue was purified by flash chromatography (hexanes−ethyl acetate, 50:1−25:1) to recover **7** (750 mg, 73%) and afford **45a** (488 mg, 51%)

as a colorless oil and **45b** (277 mg, 29%). **45a**: R_f (hexane/ethyl acetate 8:1 v/v) 0.53; $[\alpha]^{20}_D$ +16.4 (*c* 1.03 $CHCl_3$); IR (neat, cm^{-1}) ν 3461, 2929, 1641, 1255, 1095; ^1H NMR (300 Hz, $CDCl_3$) δ 7.34−7.27 (m, 5H), 4.80 (d, J = 8.4 Hz, 2H), 4.50 (s, 2H), 4.34 (m, 1H), 4.23 (d, J = 9.7 Hz, 1H), 4.05 (s, 1H), 3.89 (m, 2H), 3.32 (dd, J = 9.1, 6.2 Hz, 1H), 3.23 (dd, J = 9.3, 6.7 Hz, 1H), 2.91 (m, 3H), 2.71 (m, 2H), 2.23 (m, 3H), 2.04 (m, 4H), 1.92−1.71(m, 5H), 1.44−1.26 (m, 11H), 1.13 (d, J = 6.1 Hz, 3H), 1.13 (m, 1H), 0.90 (m, 9H), 0.89 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.2, 138.7, 128.2, 127.4, 127.3, 114.1, 81.4, 77.4, 75.9, 74.0, 72.9, 70.3, 62.4, 43.7, 40.5, 39.5, 38.5, 37.7, 37.6, 35.5, 33.5, 33.4, 30.4, 27.1, 26.9, 25.9, 25.4, 24.7 18.3, 18.0, 17.0, 15.2, 14.2, 13.9, −4.2, −4.5; ESI-MS calcd for $C_{41}H_{72}O_4S_2Si$ found 720, *m/z* $[M + Na]^+$ 743; HRMS (ESI) *m/z* 743.4539, $[M + Na]^+$ calcd for $C_{41}H_{72}O_4S_2SiNa^+$ 743.4533. **45b**: R_f (hexane/ethyl acetate 8:1 v/v) 0.40; $[\alpha]^{20}_D$ −4.5 (*c* 0.61 $CHCl_3$); IR (neat, cm^{-1}) ν 3461, 2931, 1641, 1463, 1254, 1095; ^1H NMR (300 Hz, $CDCl_3$) δ 7.35−7.27 (m, 5H), 4.78 (d, J = 10.3 Hz, 2H), 4.50 (s, 2H), 4.44 (m, 2H), 3.82 (m, 2H), 3.31 (dd, J = 9.1, 6.3 Hz, 1H), 3.23 (dd, J = 9.2, 6.9 Hz, 1H), 3.14 (m, 2H), 3.01 (s, 1H), 2.86 (d, J = 12.2 Hz, 1H), 2.61 (m, 2H), 2.21 (m, 3H), 2.02−1.69 (m, 9H), 1.45−1.26 (m, 11H), 1.08 (d, J = 6.2 Hz, 3H), 1.08 (m, 1H), 0.90 (m, 9H), 0.88 (s, 9H), 0.06 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.2, 138.8, 128.3, 127.5, 127.4, 113.7, 82.0, 80.5, 76.0, 74.4, 73.0, 70.5, 63.1, 43.9, 40.4, 39.4, 38.8, 37.8, 37.7, 36.2, 33.7, 33.5, 30.6, 27.2, 26.4, 25.9, 25.7, 24.6, 18.4, 18.1, 17.2, 14.8, 14.3, 14.2, −4.2, −4.5; ESI-MS calcd for $C_{41}H_{72}O_4S_2Si$ found 720, *m/z* $[M + Na]^+$ 743; HRMS (ESI) *m/z* 743.4539, $[M + Na]^+$ calcd for $C_{41}H_{72}O_4S_2SiNa^+$ 743.4533.

Ketone 46. To a mixture of alcohol isomers **45a/45b** (250 mg, 0.35 mmol) in CH_2Cl_2 (15 mL) were added DMP (295 mg, 0.69 mmol) and $NaHCO_3$ (35 mg, 0.42 mmol) at room temperature. After being stirred for 2 h, the reaction was diluted with Et_2O (10 mL) and quenched by addition of saturated aqueous $Na_2S_2O_3$ (10 mL) and $NaHCO_3$ (3 mL). The aqueous phase was extracted with Et_2O (2 × 10 mL). The combined extracts were washed with brine (15 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated. The residue was purified by flash chromatography (hexane/ethyl acetate 50:1 → 30:1 v/v) to afford **46** (229 mg, 91%) as a colorless oil: R_f (hexane/ethyl acetate 8:1 v/v) 0.61; $[\alpha]^{25}_D$ −5.3 (*c* 0.50 $CHCl_3$); IR (neat, cm^{-1}) ν 2927, 1705, 1640, 1462, 1254, 1097, 1040, 836, 774; ^1H NMR (300 Hz, $CDCl_3$) δ 7.34−7.26 (m, 5H), 4.85 (s, 1H), 4.81 (s, 1H), 4.62 (m, 1H), 4.49 (s, 2H), 3.83 (m, 2H), 3.29 (dd, J = 9.0, 6.0 Hz, 1H), 3.21 (dd, J = 9.0, 6.3 Hz, 1H), 3.09 (m, 2H), 2.86−2.50 (m, 5H), 2.23−1.98 (m, 7H), 1.92−1.63 (m, 4H), 1.45−1.26 (m, 10H), 1.02 (d, J = 6.3 Hz, 3H), 0.91 (m, 9H), 0.89 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.9, 144.2, 138.8, 128.3, 127.5, 127.4, 114.5, 81.2, 76.0, 73.3, 73.0, 70.7, 68.5, 43.7, 42.8, 40.0, 38.9, 37.1, 36.0, 33.7, 33.5, 30.5, 27.7, 27.2, 27.0, 26.0, 24.9, 18.3, 18.1, 17.2, 14.6, 14.3, 14.0, −4.1, −4.4; MALDI-MS calcd for $C_{41}H_{70}O_4S_2Si$ found 718, *m/z* $[M + Na]^+$ 741; HRMS (MALDI) *m/z* 741.4362, $[M + Na]^+$ calcd for $C_{41}H_{70}O_4S_2SiNa^+$ 741.4377.

Reduction of Ketone 46 with $LiBH_4$. To a stirring solution of ketone **46** (85 mg, 0.12 mmol) in THF (5 mL) and MeOH (25 μL) at 0 °C was added lithium borohydride (300 μL of a 1.0 M soln in THF, 0.3 mmol) dropwise. After being stirred at 0 °C for 30 min, the reaction mixture was warmed to 25 °C, maintained at this temperature for 2 h, and then quenched with water, The aqueous phase was extracted with Et_2O (3 × 5 mL), and the combined organic phases were washed with brine (5 mL), dried over anhydrous Na_2SO_4, and concentrated on the rotary evaporator. The residue was purified by flash chromatography (hexane/ethyl acetate 20:1 v/v) to afford alcohol **45b** (75 mg, 88%) as a colorless oil and small amounts of **45a**.

Reduction of Ketone 46 Using (*S*)-54. To a solution of ketone **46** (64 mg, 0.09 mmol) and (*S*)-**54**[31d] (900 μL of a 0.2 M soln in THF, 0.18 mmol) in THF (2 mL) was added borane−dimethyl sulfide (100 μL of a 2.0 M soln in THF, 0.20 mmol) at 15 °C. The reaction mixture was stirred for 12 h and quenched with MeOH (100 μL). After the mixture was stirred for 2 h, 1 M HCl (200 μL) was added, and the resulting mixture was diluted with Et_2O (15 mL), washed with water (2 mL) and brine (3 mL), dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by flash chromatography (hexane/ethyl acetate 20:1 v/v) to afford single alcohol **45a** (43.6 mg, 68%) as a colorless oil.

Alcohol 48. To a solution of **45a** (300 mg, 0.42 mmol) in pyridine (4 mL) were successively added DMAP (18 mg, 0.15 mmol) and Ac_2O (325 μL, 3.42 mmol). After being stirred at room temperature for 24 h, the mixture was quenched by addition of ice−water (10 mL), stirred for an additional 30 min, and extracted with Et_2O (3 × 6 mL). The combined extracts were washed with brine (50 mL), dried over anhydrous Na_2SO_4, and concentrated on the rotary evaporator. The residue was purified by flash chromatography (hexane/ethyl acetate 20:1 v/v) to afford ester **47** (293 mg, 92%) as a colorless oil: R_f (hexane/ethyl acetate 8:1 v/v) 0.56; $[\alpha]^{20}_D$ +36.4 (*c* 1.68 $CHCl_3$); IR (neat, cm^{-1}) ν 2933, 1741, 1643, 1371, 1236, 1097; ^1H NMR (300 MHz, $CDCl_3$) δ 7.36−7.27 (m, 5H), 5.47 (d, J = 10.2 Hz, 1H), 4.82 (s, 1H), 4.77 (s, 1H), 4.50 (s, 2H), 4.05 (m, 1H), 3.86 (m, 2H), 3.32 (dd, J = 9.1, 6.0 Hz, 1H), 3.23 (dd, J = 9.0, 6.4 Hz, 1H), 3.05 (m, 2H), 2.92 (d, J = 12.9 Hz, 1H), 2.66 (d, J = 4.4 Hz, 1H), 2.51 (d, J = 5.1 Hz, 1H), 2.26 (m, 3H), 2.11(s, 3H), 2.09−1.81(m, 9H), 1.47−1.26 (m, 11H), 1.05 (m, 1H), 1.04 (d, J = 6.3 Hz, 3H), 0.92 (m, 9H), 0.89 (s, 9H), 0.09 (s, 3H), 0.07 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.7, 145.0, 138.7, 128.2, 127.4, 127.3, 114.4, 81.2, 75.9, 74.8, 72.9, 71.6, 70.2, 61.1, 43.7, 39.8, 38.5, 37.5, 36.5, 35.9, 33.6, 33.4, 30.5, 27.2, 27.0, 26.8, 25.9, 25.6, 24.6, 21.2, 18.3, 18.1, 17.1, 14.4, 14.2, 14.0, −4.1, −4.5; ESI-MS calcd for $C_{43}H_{74}O_5S_2Si$ found 762, *m/z* $[M + Na]^+$ 785; HRMS (ESI) *m/z* 785.4645, $[M + Na]^+$ calcd for $C_{43}H_{74}O_5S_2SiNa^+$ 785.4639.

DDQ (1.3 g, 5.75 mmol) was added to the solution of ester **47** (146 mg, 0.19 mmol) in CH_2Cl_2/H_2O (17.6 mL 10:1 v/v). The reaction mixture was stirred for 18 h at room temperature and quenched with saturated aqueous $NaHCO_3$ (30 mL). The aqueous phase was extracted with Et_2O (3 × 15 mL). The combined extracts were washed with saturated aqueous $NaHCO_3$ (15 mL) and brine (20 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated. The residue was purified by flash chromatography (hexane/ethyl acetate 6:1 v/v) to afford alcohol **48** (122 mg, 95%) as a colorless oil: R_f (hexane/ethyl acetate 7:3 v/v) 0.63; $[\alpha]^{20}_D$ +33.5 (*c* 0.50 $CHCl_3$); IR (neat, cm^{-1}) ν 3454, 2931, 1741, 1641, 1463, 1236, 1040; ^1H NMR (300 MHz, $CDCl_3$) δ 5.40 (d, J = 9.9 Hz, 1H), 4.75 (s, 1H), 4.69 (s, 1H), 3.98 (m, 1H), 3.81(d, J = 4.7 Hz, 2H), 3.44 (dd, J = 10.4, 5.7 Hz, 1H), 3.35 (dd, J = 10.2, 6.4 Hz, 1H), 2.98 (m, 2H), 2.85 (d, J = 12.9 Hz, 1H), 2.58 (dd, J = 14.0, 3.7 Hz, 1H), 2.44 (d, J = 14.3 Hz, 1H), 2.27−2.12 (m, 3H), 2.10 (s, 3H), 2.08−1.95 (m, 8H), 1.68 (m, 2H), 1.46−1.26 (m, 11H), 1.16 (m, 1H), 1.05 (d, J = 6.6 Hz, 3H), 0.92 (d, J = 6.9 Hz, 3H), 0.90 (s, 15H), 0.09 (s, 3H), 0.07 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.7, 145.2, 114.2, 81.3, 75.0,72.1, 70.4, 68.3, 61.4, 43.8, 40.3, 39.9, 38.6, 37.8, 36.7, 36.0, 33.1, 30.5, 27.2, 27.0, 26.8, 26.0, 25.6, 24.6, 21.3, 18.3, 18.1, 16.6, 14.6, 14.3, 14.1, −4.1, −4.4; ESI-MS calcd for $C_{36}H_{68}O_5S_2Si$ found 672, *m/z* $[M + Na]^+$ 695; HRMS (ESI) *m/z* 695.4175, $[M + Na]^+$ calcd for $C_{36}H_{68}O_5S_2SiNa^+$ 695.4169.

Aldehyde 49. To a solution of **48** (46 mg, 0.068 mmol) in CH_2Cl_2 (6 mL) were added 4 Å MS (29 mg) and NaOAc (5.6 mg, 0.068 mmol). The mixture was cooled to 0 °C, and PCC (44 mg, 0.204 mmol) was added. The resulting solution was stirred for 24 h at 0 °C and diluted with petroleum ether (12 mL). The resulting precipitate was removed by filtration, and the filtrate was concentrated. The residue was purified by flash chromatography (hexane) to afford **49** (44 mg, 96%) as a colorless oil: R_f (hexane/ethyl acetate 15:1 v/v) 0.42; $[\alpha]^{20}_D$ +28.6 (*c* 1.15 $CHCl_3$); IR (neat, cm^{-1}) ν 2934, 1740, 1641, 1463, 1372, 1236, 1040; ^1H NMR (300 MHz, $CDCl_3$) δ 9.62 (d, J = 1.8 Hz, 1H), 5.47 (d, J = 10.1 Hz, 1H), 4.82 (s, 1H), 4.77 (s, 1H), 4.05 (m, 1H), 3.88 (m, 2H), 3.05 (m,

2H), 2.92 (d, J = 13.0 Hz, 1H), 2.66 (d, J = 14.2 Hz, 1H), 2.51(d, J = 14.6 Hz, 1H), 2.36−2.20 (m, 4H), 2.08 (s, 3H), 2.10−1.72 (m, 10H), 1.45−1.26 (m, 10H), 1.10 (d, J = 7.0 Hz, 3H), 1.04 (d, J = 6.3 Hz, 3H), 0.90 (s, 15H), 0.09 (s, 3H), 0.07 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 205.1, 170.7, 145.11, 114.3, 81.2, 74.9, 71.9, 70.4, 61.3, 46.2, 43.8, 40.2, 39.8, 38.6, 37.7, 36.0, 30.5, 27.2, 26.82, 26.8, 26.0, 21.2, 18.3, 18.1, 14.5, 14.2, 14.1, 13.3, −4.1, −4.5; ESI-MS calcd for $C_{36}H_{66}O_5S_2Si$ found 670, m/z [M + Na]$^+$ 693; HRMS (ESI) m/z 693.4019 [M + Na]$^+$, calcd for $C_{36}H_{66}O_5S_2SiNa^+$ 693.4013.

Acid 50. To a solution of silver nitrate (41.4 mg, 0.244 mmol) in water (1.6 mL) cooled to 0 °C was added a solution of aldehyde **49** (69 mg, 0.103 mmol) in THF (3.2 mL) followed by a solution of NaOH (1.6 mL of a 0.3 M soln in water) over a period of 5 min. The mixture was stirred intensively for 1.5 h at 0 °C, and the deposited silver was filtered off and washed with water. The filtrate was cooled and acidified with aq HCl (1.0 M) to pH = 5. The mixture was extracted with Et_2O (3 × 6 mL). The combined extracts were washed with brine (5 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated. The residue was purified by flash chromatography (hexane/ethyl acetate 5:1 → 3:1 v/v) to afford acid **50** (57.6 mg, 81%) as a colorless oil: R_f (hexane/ethyl acetate 2:1 v/v) 0.53; $[\alpha]^{24}_D$ +22.7 (c 1.27 $CHCl_3$); IR (neat, cm^{-1}) ν 2926, 1741, 1708, 1640, 1463, 1372, 1235, 1040, 836; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.48 (d, J = 10.1 Hz, 1H), 4.83 (s, 1H), 4.77 (s, 1H), 4.06 (m, 1H), 3.88 (m, 2H), 3.05 (m, 2H), 2.92 (d, J = 13.2 Hz, 1H), 2.66 (d, J = 13.8 Hz, 1H), 2.55−2.42 (m, 2H), 2.36−2.21 (m, 3H), 2.09 (s, 3H), 2.08−1.69 (m, 10H), 1.45−1.26 (m, 10H), 1.18 (d, J = 7.2 Hz, 3H), 1.04 (d, J = 6.2 Hz, 3H), 0.90 (s, 15H), 0.09 (s, 3H), 0.07 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 182.4, 170.8, 145.1, 114.4, 81.3, 75.0, 71.9, 70.4, 61.3, 43.8, 40.3, 39.9, 39.3, 38.6, 37.7, 36.6, 36.0, 33.5, 30.4, 27.4, 26.7, 26.0, 25.7, 24.7, 21.3, 18.4, 18.1, 14.6, 14.3, 14.1, −4.1, −4.4; MALDI-MS calcd for $C_{36}H_{66}O_6S_2Si$ found 686, m/z [M + H]$^+$ 687; HRMS (MALDI) m/z 709.4078, [M + Na]$^+$ calcd for $C_{36}H_{66}O_6S_2SiNa^+$ 709.4083.

Hydroxyl Acid 52. To a solution of **50** (55 mg, 0.08 mmol) in THF (3 mL) was added HF·Py complex (3.2 mL of a 1.0 M soln in THF, 3.2 mmol) at room temperature. The mixture was stirred for 24 h and quenched with ice−water (6 mL). The resulting mixture was diluted with Et_2O (30 mL). The organic phase was successively washed with saturated aqueous $NaHCO_3$ (5 mL) and brine (5 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated. The residue was purified by flash chromatography (hexane/ethyl acetate 3:1 → 1: 1 v/v) to afford alcohol **51** (43 mg, 94%) as a colorless oil: R_f (hexane/ethyl acetate 1:1 v/v) 0.47; $[\alpha]^{24}_D$ +29.7 (c 0.95 $CHCl_3$); IR (neat, cm^{-1}) ν 3424, 3072, 2927, 1738, 1709, 1642, 1463, 1373, 1222, 733; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.46 (d, J = 10.8 Hz, 1H), 4.91 (s, 1H), 4.88 (s, 1H), 4.04 (m, 1H), 3.86 (m, 2H), 3.08−3.00 (m, 3H), 2.65 (d, J = 14.1 Hz, 1H), 2.53−2.45 (m, 2H), 2.34−2.24 (m, 2H), 2.16 (d, J = 6.3 Hz, 1H), 2.09 (s, 3H), 2.08−1.69 (m, 10H), 1.48−1.28 (m, 13H), 1.18 (d, J = 6.9 Hz, 3H), 1.07 (d, J = 5.2 Hz, 3H), 0.96−0.89 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 181.2, 170.8, 145.4, 113.8, 81.1, 74.9, 71.8, 69.4, 61.3, 44.5, 40.6, 39.8, 39.2, 39.0, 38.1, 36.6, 36.0, 33.6, 30.3, 27.3, 26.5, 25.7, 24.7, 21.3, 18.8, 16.9, 15.0, 14.2, 14.1; ESI-MS calcd for $C_{30}H_{53}O_6S_2$ found 572. m/z [M + Na]$^+$ 595; HRMS (ESI) m/z 573.3279, [M + H]$^+$ calcd for $C_{30}H_{53}O_6S_2H^+$ 573.3278.

To a solution of acid **51** (42 mg, 0.073 mmol) in MeOH/H_2O (3 mL, 5:1) was added hydrate LiOH (30 mg, 0.71 mmol). After the mixture was warmed to 40−50 °C and stirred for 12 h, 1 M HCl was added and acidified to pH = 5. The mixture was extracted with Et_2O (3 × 5 mL). The combined extracts were washed with brine (5 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated. The residue was purified by flash chromatography (hexane/ethyl acetate 3:2 v/v) to afford **52** (37 mg, 95%) as a colorless oil: R_f (hexane/ethyl acetate 1:1 v/v) 0.36; $[\alpha]^{20}_D$ +26.9 (c 0.31 $CHCl_3$); IR (neat, cm^{-1}) ν 3443, 2935, 1708, 1642; ^{1}H NMR (300 Hz, $CDCl_3$) δ 4.90 (s, 2H), 4.31 (m, 1H), 4.19 (d, J = 10.1 Hz, 1H), 3.92 (m, 1H), 3.81 (m, 1H), 3.01−2.88 (m, 3H), 2.78−2.69 (m, 2H), 2.46 (m, 1H), 2.30−1.80 (m, 12 H), 1.68 (m, 1H), 1.58−1.27 (m, 11H), 1.18 (d, J = 7.1 Hz, 3H), 1.16 (d, J = 5.8 Hz, 3H), 0.96−0.91 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 180.5, 145.7, 113.6, 81.4, 77.2, 74.5, 69.4, 62.5, 44.6, 40.5, 39.9, 39.1, 38.3, 38.0, 35.7, 33.5, 30.1, 29.7, 27.2, 26.6, 25.7, 24.7, 18.9, 17.0, 15.6, 14.1, 14.0; ESI-MS calcd for $C_{28}H_{50}O_5S_2$ found 530, m/z [M − H]$^-$ 529; HRMS (ESI) m/z 553.2997, [M + Na]$^+$ calcd for $C_{28}H_{50}O_5S_2Na^+$ 553.2992.

Macrolactone 53. To a solution of the hydroxyl acid **52** (22.4 mg, 0.042 mmol) in toluene (5 mL) were added 2,4,6-tirchlorobenzoyl chloride (222 μL, 1.46 mmol) and diisopropylethylamine (444 μL, 2.92 mmol). The mixture was stirred for 12 h at room temperature. Then, the solution was diluted by addition of toluene (5 mL) and added by a syringe pump slowly to a solution of DMAP (192 mg, 1.56 mmol) in toluene (110 mL) at 45 °C over 12 h. The reaction was stirred for an additional 10 h at 45 °C and quenched with saturated aqueous NH_4Cl (50 mL). The aqueous phase was extracted with EtOAc (3 × 20 mL). The combined extracts were washed with brine (30 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated. The residue was purified by flash chromatography (hexane/ethyl acetate 20:1 v/v) to afford macrolactone **53** (15.4 mg, 70%) as a colorless oil: R_f (hexane/ethyl acetate 8:1 v/v) 0.50; $[\alpha]^{20}_D$ +17.7 (c 0.32 $CHCl_3$); IR (neat, cm^{-1}) ν 3474, 2929, 1725, 1638, 1462, 1054, 899; ^{1}H NMR (300 Hz, $CDCl_3$) δ 5.00 (m, 1H), 4.85 (s, 1H), 4.82 (s, 1H), 4.38 (m, 1H), 4.18 (d, J = 10.2 Hz, 1H), 4.05 (m, 1H), 3.43 (s, 1H), 3.08−2.99 (m, 2H), 2.78−2.67 (m, 3H), 2.47−1.76 (m, 13 H), 1.63 (m, 11H), 1.15 (d, J = 7.1 Hz, 3H), 1.14 (d, J = 6.4 Hz, 3H), 0.93−0.88 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.8, 144.1, 114.7, 77.7, 75.3, 73.1, 72.1, 63.3, 39.9, 39.6, 39.1, 38.5, 37.9, 36.9, 36.2, 35.3, 32.7, 27.0, 26.9, 25.7, 24.9, 24.5, 18.6, 17.2, 15.2, 14.8, 14.1; ESI-MS calcd for $C_{28}H_{48}O_4S_2$ found 512, m/z [M + Na]$^+$ 535; HRMS (ESI) m/z 535.2886, [M + Na]$^+$ calcd for $C_{28}H_{48}O_4S_2Na^+$ 535.2886.

Amphidinolide T3. A solution of macrolactone **53** (15 mg, 0.03 mmol) in MeOH/H_2O (2.75 mL, 10:1) was cooled to 0 °C and treated with PhI $(O_2CCF_3)_2$ (24 mg, 0.06 mmol). After 15 min, the reaction was diluted with Et_2O (20 mL) and quenched with saturated aqueous $NaHCO_3$ (5 mL). The organic phase was separated, washed with brine (5 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated. The residue was purified by flash chromatography (hexane/ethyl acetate 30:1 v/v) to afford synthetic amphidinolide T3 (10.1 mg, 82%) as a colorless oil: R_f (hexane/ethyl acetate 8:1 v/v) 0.28; $[\alpha]^{20}_D$ −39.9 (c 0.16 $CHCl_3$) (lit.[4j] $[\alpha]^{20}_D$ −40.0 (c 0.075 $CHCl_3$); IR (neat, cm^{-1}) 3450, 2932, 1729; ^{1}H NMR (500 Hz, C_6D_6) δ 5.19 (m, 1H), 4.87 (m, 1H), 4.85 (m, 1H), 4.51 (d, J = 2.8 Hz, 1H), 4.37 (dt, J = 9.2, 2.8 Hz, 1H), 4.04 (ddd, J = 10.6, 7.9, 2.8 Hz, 1H), 3.78 (dt, J = 10.0, 3.8 Hz, 1H) 3.53 (m, 1H), 2.60 (dd, J = 13.4, 5.4 Hz, 1H), 2.55 (dd, J = 13.4, 5.4 Hz, 1H), 2.44 (m, 1H), 2.16 (dd, J = 13.5, 8.5 Hz, 1H), 1.94 (dt, J = 14.5, 2.4 Hz, 1H), 1.87 (dd, J = 13.5, 8.9 Hz, 1H), 1.77−1.20 (m, 15H), 1.67 (dt, J = 14.8, 7.8 Hz, 1H), 1.13 (d, J = 6.6 Hz, 3H), 1.12 (d, J = 7.0 Hz, 3H), 0.86 (t, J = 7.6 Hz, 3H), 0.67 (d, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 215.7, 174.8, 143.3, 114.7, 79.2, 76.2, 76.1, 72.1, 41.4, 41.2, 40.6, 39.9, 39.3, 38.4, 36.3, 35.9, 34.6, 29.7, 26.5, 26.5, 18.8, 17.7, 15.5, 14.2, 14.1; ESI-MS calcd for $C_{25}H_{42}O_5$ found 422, m/z [M + Na]$^+$ 445; HRMS (ESI) m/z 445.2930 [M + Na]$^+$ calcd for $C_{25}H_{42}O_5Na^+$ 445.2925.

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Supporting Information Available: Experimental general information, procedures, and ^{1}H NMR and ^{13}C NMR spectra for compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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