Synthesis of a *syn,syn,syn,syn*-Stereopentad Precursor of the Marine Sponge Polyketide Callystatin A

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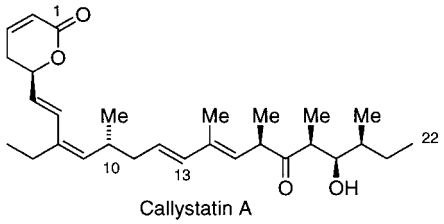
A C13−22 *syn,syn,syn,syn*-stereopentad precursor of the cytotoxic polyketide callystatin A has been prepared. The synthesis involved BF_3-promoted addition of the (*M*)-allenylstannane **28** to the α-methyl-*β*-OTBS aldehyde **8** to afford the *syn,syn* adduct homopropargylic alcohol **29**. Protection as the cyclic anisylidene acetal **31** and reduction of the acetylenic triple bond with Red-Al gave the (*E*)-allylic alcohol **32**. This was subjected to Sharpless asymmetric epoxidation and subsequent treatment with an ethylcopper reagent to yield diol **34**; hydrogenolysis of the derived tosylate **37** with $LiBEt_3H$ afforded **38**. Acetal hydrogenolysis with DIBAl-H and oxidation yielded aldehyde **40** which was subjected to Horner−Emmons homologation to afford ester **41**. This ester was converted to ester **44**, an intermediate in the Kobayashi synthesis, with which it was found to be identical.

Recently Kobayashi and co-workers reported the isolations,[1] structure elucidation,[1] and synthesis[2] of a marine sponge polyketide, callystatin A. Bioassay-guided purification by extraction and multiple chromatographic separations on silica gel, then HPLC on Cosmosil 5SL, followed by HPLC on $5C_{18}$-Ar columns afforded 1.0 mg of pure material. This substance shows remarkably high activity (IC_{50} = 0.01 ng/mL) against KB tumor cells.

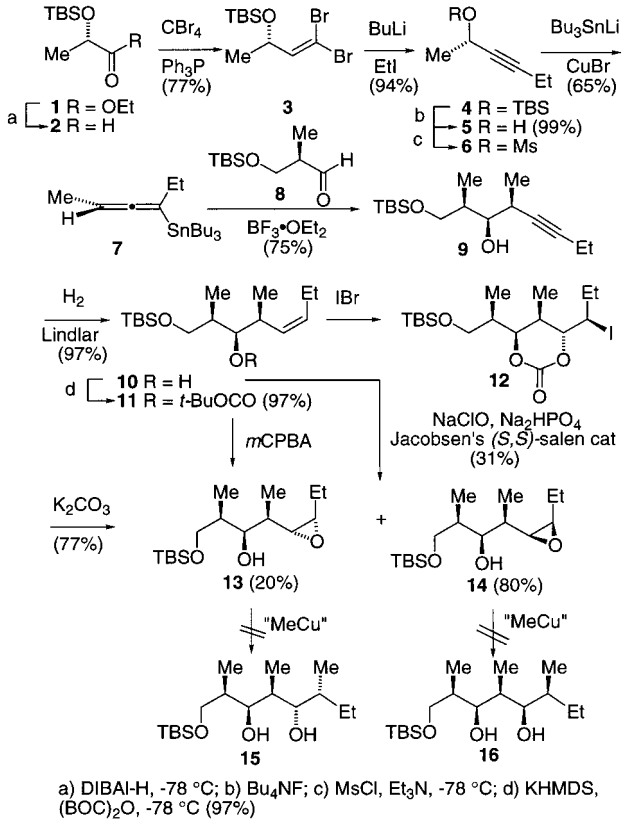


Callystatin A

The potent cytotoxicity of callystatin A and its extreme scarcity constitute a compelling case for total synthesis. We were attracted by these considerations and the presence of an *all-syn*-stereopentad array in a possible synthetic precursor.[2] We viewed the synthesis of this precursor as an opportunity to expand the scope of our synthetic approach to stereopentads by S_E2' additions of chiral allenylmetal reagents to aldehydes.[3] The *all-syn* diastereomer had not previously been prepared by this methodology.

Allenylstannane **7** of >95% ee was obtained from TBS-protected ethyl lactate (**1**) by the sequence outlined in Scheme 1.[4] Addition of this stannane to aldehyde **8**,[5] in the presence of $BF_3{\cdot}OEt_2$, afforded the *syn,syn*-adduct **9**.

Scheme 1



a) DIBAl-H, -78 °C; b) Bu_4NF; c) MsCl, Et_3N, -78 °C; d) KHMDS, $(BOC)_2O$, -78 °C (97%)

Partial hydrogenation over Lindlar's catalyst[6] yielded the (*Z*) olefin **10**. Epoxidation of olefin **10** with *m*-ClC_6H_4-CO_3H (MCPBA) afforded a single diastereomer, subsequently identified as epoxide **13** through independent synthesis from the BOC derivative **11** via the iodocarbonate **12**.[7] Tirando and Prieto have shown that related (*Z*)-homoallylic alcohols afford *anti,syn*-iodocarbonates upon treatment with *n*-BuLi followed by CO_2 and I_2.[8] The

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(5) Roush, W. R.; Palkowitz, A. D.; Palmer, M. A. *J. Org. Chem.* **1987**, *52*, 316.

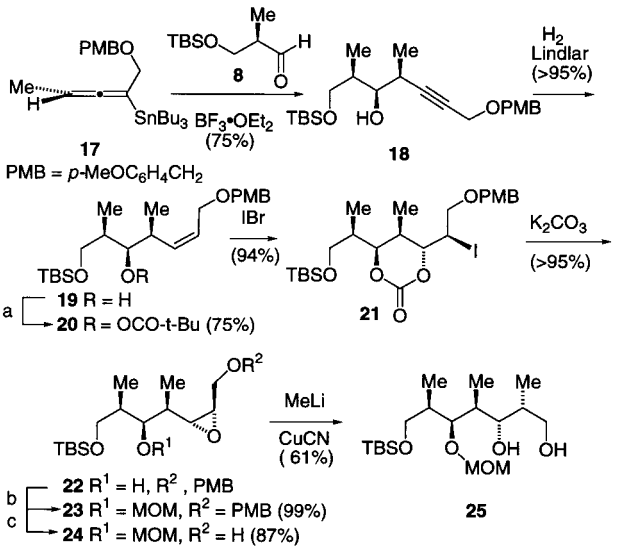
(6) Aldrich Chemical Co., Milwaukee, WI.

(7) Duan, J. J.-W.; Smith, A. B., III, *J. Org. Chem.* **1993**, *58*, 3703.

(8) Tirando, R.; Prieto, J. A. *J. Org. Chem.* **1993**, *58*, 5666.

10.1021/jo9902143 CCC: $18.00
Published on Web 05/15/1999

Scheme 2



a) BuLi, (*tert*-BuOCO)$_2$O, -78 °C; b) MOMCl, *i*-Pr$_2$NEt, Bu$_4$NI; c) 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, NaHCO$_3$

desired *syn*,*cis*-epoxide could be prepared through epoxidation of the (*Z*)-olefin **10** with Jacobsen's (*S*,*S*)-salen epoxidation catalyst (*S*,*S*)-*N*,*N*′-bis(3,5-di-*tert*-butylsalicylidene-1,2-cyclohexanediamino)manganese(III) chloride.[6] The resulting 4:1 mixture of *syn*,*syn*,*syn*,*cis*- and *syn*,*syn*,*anti*,*cis*-epoxides **14** and **13** could be separated by chromatography.

Attempts at S_N2 displacements on epoxide **14** with various cuprate reagents, including $Me_2CuCNLi_2$, MeCuCNLi, and MeMgBr·CuI, were unsuccessful.[9] Either starting material was recovered or multiple unidentified products were produced. The *syn*,*syn*,*anti*,*cis*-epoxide **13** was likewise unreactive.

The failure of epoxides **13** and **14** to react with methyl cuprate reagents was surprising in view of previous successes with epoxides of (*E*)-allylic alcohols.[3,10] Molecular mechanics calculations indicate that the ethyl substituent of these epoxides tends to orient behind the epoxide ring, thereby blocking backside access.[11] It is also possible that the OH grouping of our previous examples provides assistance through coordination with the attacking cuprate reagent.[12,13] As a point of information it was of interest to examine the reactivity of the *cis*-epoxide **24** derived from the (*Z*)-allylic carbonate **20** (Scheme 2). Carbonate **20** was prepared from aldehyde **8** and the enantioenriched allenylstannane **17**, as outlined in Scheme 2. Iodolactonization[7] proceeded in high yield to afford iodocarbonate **21** as the sole product. Base treatment led to the epoxide **22**, also in high yield. Protection as the MOM derivative **23** and removal of the PMB protecting group yielded the epoxy alcohol **24**. Treatment of this intermediate with the higher order methyl cyanocuprate[9] afforded the diol **25** in 61% yield (unoptimized). It therefore seems likely that a combination of unfavorable steric effects and the absence of a directing OH group may be responsible for the unreactivity of epoxides **13** and **14** toward cuprate reagents. To make the comparison more exact, we also prepared the MOM derivative of epoxy alcohol **13** and subjected it to the higher order methyl cyanocuprate without success. No diol product was obtained from this reaction.

To confirm that the diol **25** was indeed the *syn*,*syn*,*anti*,*syn* isomer and not the all *syn* adduct, we converted it to the symmetric bis-TBS, MOM ether **27** (eq 1). The ^{1}H NMR spectrum and optical rotation confirmed our assumption that this product was not the *all-syn* (meso) compound.

(1)

Given the apparent need for an allylic OH directing group to facilitate epoxide opening and in view of our previous success with epoxides of (*E*)-allylic alcohols, the sequence outlined in Scheme 3 was formulated, in which addition of an ethylcopper reagent to epoxide **33** would produce the adduct **34** which, after protection and reduction, would be converted to the *all-syn* product **38**. The approach was particularly appealing since we had carried out the synthesis of the enantiomer of epoxy alcohol **33** in connection with our recent synthesis of discodermolide.[10]

The conversion of the (*M*)-allenylstannane **28** to epoxy alcohol **33** was effected as reported for the enantiomeric series.[10] Addition of EtMgBr−CuI to this epoxide afforded diol **34** as the sole product. Selective tosylation led to the monotosylate **35**. Protection of the secondary alcohol of **35** with TBSOTf proceeded slowly and afforded the silyl ether **36** in <50% yield. The formation of polar byproducts suggested that the sensitive PMP acetal grouping was being cleaved by the 2,6-lutidinium triflate produced in the silylation reaction. Silylation with Et_3SiOTf proceeded more rapidly, affording the silyl ether **37** in 90% yield.

Hydrogenolysis of the tosylate function of **37** was effected with $LiBEt_3H$. Selective cleavage of the anisylidene acetal **38** with DIBAl-H yielded the primary alcohol **39** which was converted to aldehyde **40** by treatment with the Dess−Martin periodinane reagent.[14] Wittig condensation of aldehyde **40** with the phosphorylidene propionate reagent yielded the (*E*)-adduct **41**, an analogue of the TBS counterpart **44** previously reported by Kobayashi and co-workers.[2] For comparison purposes, the silyl ether was cleaved with Bu_4NF and the alcohol **42** was silylated with TBSOTf. Cleavage of the PMB ether **43** with DDQ afforded hydroxy ester **44**. Compari-

(9) Cf. Lipschutz, B. Synthetic Procedures Involving Organocopper Reagents. In *Organometallics in Synthesis*; Schlosser, M., Ed.; John Wiley and Sons: Chichester, 1994; p 283.

(10) Marshall, J. A.; Lu, Z.-H.; Johns, B. A. *J. Org. Chem.* **1998**, *63*, 817. Marshall, J. A.; Johns, B. A. *J. Org. Chem.* **1998**, *63*, 7885.

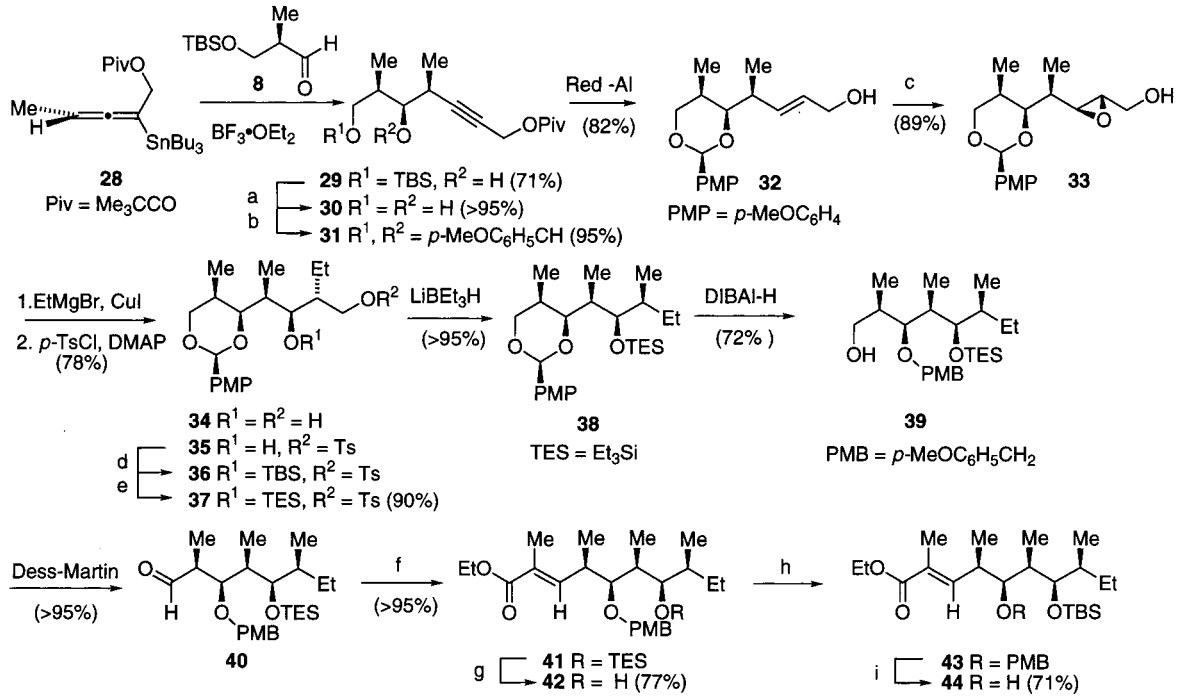
(11) The program Macromodel V4.5 was employed for these calculations. Global minimum multiple conformer searching was achieved with the Monte Carlo subroutine in BATCHMIN through multiple step interations (typically 1000) until the minimum energy conformer was found multiple times. For a description of the program, see: (a) Mohamadi, F.; Richards, N. G. J.; Guida, W. C.; Liskamp, R.; Lipton, M.; Caufield, C.; Chang, G.; Hendrickson, T.; Still, W. C. *J. Comput. Chem.* **1990**, *11*, 440. (b) Chang, G.; Guida, W. C.; Still, W. C. *J. Am. Chem. Soc.* **1989**, *111*, 4379.

(12) For the use of vinyl cuprates in the opening of methyl-substituted *cis*-epoxides, see: Lipshutz, B. H.; Barton, J. C. *J. Org. Chem.* **1988**, *53*, 4495.

(13) For additional evidence on this point, see: Marshall, J. A.; Trometer, J. D.; Cleary, D. G. *Tetrahedron* **1989**, *45*, 391.

(14) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155. Meyer, S. D.; Schreiber, S. L. *J. Org. Chem.* **1994**, *59*, 7549.

Scheme 3



a) Bu_4NF; b) *p*-$MeOC_6H_5CH(OMe)_2$, *dl*-camphorsulfonic acid; c) L-(+)-diisopropyl tartrate, Ti(O-*i*-Pr)$_4$, *tert*-BuOOH, -30 °C; d) TBSOTf, 2,6-lutidine, 0 °C; e) TESOTf, 2,6-lutidine, 0 °C; f) $Ph_3P{=}C(Me)CO_2Et$; g) Bu_4NF; h) TBSOTf, 2,6-lutidine; i) DDQ, CH_2Cl_2, H_2O

son of the ^{1}H NMR spectrum of this material with that of an authentic sample confirmed their identity.

The present findings provide a route to the *all-syn*-stereopentad **39**. The unreactivity of the *cis*-epoxides **13** and **14** toward various cuprate reagents is unexpected. The successful opening of the *cis*-epoxy alcohol **24** with cuprate reagents suggests that a neighboring hydroxyl function may be required to activate the cuprate or the epoxide. If so, this effect will have a bearing on future synthetic applications of this methodology.

Experimental Section

(*M*)-4-(Tributylstannyl)-2,3-hexadiene (7). To a solution of 5.18 g (52.73 mmol) of alcohol **5** in 200 mL of CH_2Cl_2 were added 18.4 mL (131.8 mmol) of Et_3N and 8.15 mL (105.5 mmol) of CH_3SO_2Cl at −78 °C. The solution solidified after 5 min of stirring. The solid was warmed enough to free the stir bar, and the suspension was cooled back to −78 °C. After stirring for 1 h, the reaction was quenched with 50 mL of saturated $NaHCO_3$. The layers were separated, and the aqueous layer was extracted with ether. The combined organic extracts were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure to afford crude mesylate **6** as a clear oil. Mesylate **6** was used without further purification.

To a solution of 14.78 mL (105.5 mmol) of *i*-Pr_2NH in 130 mL of THF was added 42.18 mL (105.46 mmol) of *n*-BuLi (2.5 M in hexanes) at 0 °C. The solution was stirred at 0 °C for 15 min, and 28.36 mL (105.5 mmol) of *n*-Bu_3SnH was added dropwise. After 30 min, the solution was cooled to −78 °C and 21.68 g (105.5 mmol) of $CuBr{\cdot}SMe_2$ was added. The solution was stirred for an additional 30 min followed by the addition of 9.28 g (52.73 mmol) of mesylate **6** in 20 mL of THF. The solution was stirred for 10 min and quenched with 1.5 L of 9:1 NH_4Cl:NH_4OH. The resultant mixture was stirred for 2 h, and the layers were separated. The aqueous layer was extracted with ether, and the combined organic extracts were washed with brine. The solution was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was distilled to afford 12.5 g (65%) of allenylstannane **7** as a faint yellow oil, bp 119−122 °C at 0.05 mmHg: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.60 (m, 1 H), 2.14−2.00 (m, 2 H), 1.60 (d, J = 6.9 Hz, 3 H), 1.54−1.44 (m, 6 H), 1.35−1.25 (m, 6 H), 1.02 (t, J = 7.3 Hz, 3 H), 0.94−0.86 (m, 15 H).

(4*S*,5*R*,6*R*)-7-(*tert*-Butyldimethylsilyloxy)-4,6-dimethyl-5-hydroxy-2-heptynyl Pivalate (29). To a solution of 8.0 g (17.5 mmol) of allenylstannane **28**[10] and 4.60 g (22.75 mmol) of aldehyde **8**[5] in 50 mL of CH_2Cl_2 was added 5.40 mL (43.75 mmol) of $BF_3{\cdot}OEt_2$ at −78 °C. The mixture was stirred at −78 °C for 6 h, quenched with saturated $NaHCO_3$, and stirred for 30 min. The aqueous layer was extracted with ether, and the combined organic extracts were dried over Na_2SO_4. The solution was filtered and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (elution with 10% EtOAc in hexanes) to give 4.58 g (71%) of pivalate **29** as a clear oil: $[\alpha]_D$ = −0.3 (*c* 3.67, $CHCl_3$); IR (neat) 3500, 2957, 2930, 2240, 1738 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.63 (d, J = 2.1 Hz, 2 H), 3.87 (dd, J = 9.9, 3.0 Hz, 1 H), 3.73−3.67 (m, 2 H), 3.51 (d, J = 1.8 Hz, 1 H), 2.4 (m, 1 H), 2.1 (m, 1 H), 1.27 (d, J = 6.9 Hz, 3 H), 1.21 (s, 9 H), 0.99 (d, J = 6.9 Hz, 3 H), 0.90 (s, 9 H), 0.078 (s, 6 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 177.7, 88.6, 78.3, 77.2, 76.2, 69.4, 52.6, 38.7, 36.3, 30.4, 27.0, 25.8, 18.1, 17.5, 9.4, −5.63, −5.7. Anal. Calcd for $C_{20}H_{38}O_4Si$: C, 64.82; H, 10.34. Found: C, 64.75; H, 10.39.

***syn,syn-p*-Anisylidene Acetal 30.** To a solution of 3.0 g (8.1 mmol) of pivalate **29** in 30 mL of THF was added 10.5 mL (10.5 mmol) of TBAF (1.0 M in THF) dropwise at 0 °C. The solution was warmed to room temperature and stirred for 1 h. The mixture was poured into brine, extracted with ether, and dried over Na_2SO_4. After filtration and concentration under reduced pressure, the crude diol **30** was dissolved in 50 mL of benzene and 1.90 mL (12.15 mmol) of *p*-anisaldehyde dimethyl acetal was added followed by addition of a catalytic amount of *dl*-camphorsulfonic acid (ca. 15 mg). The solution was refluxed with azeotropic removal of methanol for 12 h. The solution was cooled to rt, and 2 mL of Et_3N was added followed by removal of solvent under reduced pressure. The residue was purified by column chromatography on silica gel (elution with 30% EtOAc in hexanes containing 1% Et_3N) to afford 3.00 g (95%) of acetal **31** as a colorless oil: $[\alpha]_D$ = −2.51 (*c* 1.04, $CHCl_3$); IR (neat) 2972, 2934, 2220 cm^{-1}; ^{1}H NMR

($CDCl_3$, 300 MHz) δ 7.40 (d, J = 8.7 Hz, 2 H), 6.89 (d, J = 8.7 Hz, 2 H), 5.43 (s, 1 H), 4.65 (d, J = 2.1 Hz, 2 H), 4.06−4.04 (m, 2 H), 3.80 (s, 3 H), 3.67 (dd, J = 9.9, 2.1 Hz, 1 H), 2.63 (m, 1 H), 1.96 (m, 1 H), 1.27 (d, J = 6.6 Hz, 3 H), 1.22 (s, 9 H), 1.19 (d, J = 7.2 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 177.7, 159.9, 131.2, 127.2, 113.6, 101.5, 86.8, 82.6, 76.37, 73.8, 55.3, 52.5, 38.7, 30.5, 28.8, 27.0, 17.5, 11.1. Anal. Calcd for $C_{22}H_{30}O_5$: C, 70.56; H, 8.07. Found: C, 70.6; H, 8.23.

***syn,syn*-Allylic Alcohol 32.** To a solution of 2.01 g (5.37 mmol) of propargylic pivalate **31** in 50 mL of THF was added 7.9 mL (40.3 mmol) of Red-Al (65 wt % in toluene) dropwise at 0 °C. The mixture was stirred at 0 °C for 14 h and quenched with 50 mL of saturated potassium sodium tartrate. After the mixture was stirred for 1 h, the layers were separated, and the aqueous layer was extracted with EtOAc. The combined organic extracts were washed with brine and dried over Na_2SO_4. After filtration and removal of solvent under reduced pressure, the residue was purified by column chromatography on silica gel (elution with 30% EtOAc in hexanes containing 1% Et_3N) to produce allylic alcohol **32** (1.30 g, 85%) as a white solid: mp 77−78 °C; $[\alpha]_D$ = −8.8 (*c* 1.00, $CHCl_3$); IR (neat) 3432, 2960, 2916, 2837 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.42 (d, J = 8.7 Hz, 2 H), 6.89 (d, J = 9.0 Hz, 2 H), 5.75 (dt, J = 15.3, 5.4 Hz, 1 H), 5.51 (dd, J = 15.6, 8.7 Hz, 1 H), 5.44 (s, 1 H), 4.15−4.11 (m, 2 H), 4.0 (m, 2 H), 3.80 (s, 3 H), 3.52 (dd, J = 10.2, 2.4 Hz, 1 H), 2.43 (m, 1 H), 1.62 (m, 1 H), 1.49 (s broad, 1 H), 1.16 (d, J = 6.9 Hz, 3 H), 1.11 (d, J = 6.6 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 159.7, 132.7, 131.48, 130.0, 127.2, 113.5, 101.7, 83.4, 73.9, 63.4, 55.2, 38.6, 30.4, 17.4, 11.1. Anal. Calcd for $C_{17}H_{24}O_4$: C, 69.84; H, 8.27. Found: C, 69.75; H, 8.24.

***syn,syn*-Epoxy Alcohol 33.** To a suspension of 4 Å MS (500 mg) in 50 mL of CH_2Cl_2 was added 1.25 mL (5.9 mmol) of L-(+)-diisopropyltartrate followed by addition of 1.44 mL (4.84 mmol) of Ti(*i*-PrO)$_4$ at −20 °C. The suspension was stirred at −20 °C for 10 min, and 1.7 mL (ca. 8.42 mmol) of *tert*-butyl hydroperoxide (TBHP) (∼5 M in decane) was added dropwise. The mixture was stirred at −20 °C for 16 h, quenched with 2 mL of H_2O, and filtered through a short pad of Celite. The solution was concentrated under reduced pressure and purified by column chromatography on silica gel (elution with 50% EtOAc in hexanes containing 1% Et_3N) to afford 1.03 g (79%) of epoxy alcohol **33** as a white solid: mp 61−63 °C; $[\alpha]_D$ = −9.5 (*c* 0.96, $CHCl_3$); IR (neat) 3449, 2968, 2846, 1614, 1247 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.42 (d, J = 8.7 Hz, 2 H), 6.89 (d, J = 9.0 Hz, 2 H), 5.48 (s, 1 H), 4.08 (dd, J = 11.1, 2.1 Hz, 1 H), 4.01 (dd, J = 11.1, 1.5 Hz, 1 H), 3.9 (m, 1 H), 3.80 (s, 3 H), 3.71 (dd, J = 9.6, 1.8 Hz, 1 H), 3.65 (m, 1 H), 3.11 (m, 1 H), 2.84 (dd, J = 6.6, 2.4 Hz, 1 H), 1.88−1.73 (m, 3 H), 1.22 (d, J = 8.1 Hz, 3 H), 1.07 (d, J = 6.9 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 159.9, 131.3, 127.2, 113.6, 102.0, 81.7, 73.7, 61.4, 57.6, 56.4, 55.3, 36.2, 30.7, 12.8, 11.8. Anal. Calcd for $C_{17}H_{24}O_5$: C, 66.21; H, 7.84. Found: C, 66.17; H, 7.78.

***syn,syn,syn*-Tosylate 35.** To a suspension of 10 mg (0.03 mmol) of CuI in 5 mL of THF was added 0.4 mL (1.2 mmol) of EtMgBr (3 M in ether) at −78 °C. After the solution was stirred for 30 min at −78 °C, 100 mg (0.32 mmol) of epoxy alcohol **33** was added. The solution was warmed to −30 °C and stirred for 16 h. The reaction was quenched with 9:1 NH_4Cl:NH_4OH and stirred for 1.5 h. The clear layers were separated, and the aqueous layer was extracted with EtOAc. The combined organic extracts were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue, diol **34**, was dissolved in 2 mL of CH_2Cl_2, and 0.2 mL of pyridine was added followed by the addition of 68 mg (0.32 mmol) of TsCl. The mixture was stirred for 18 h at room temperature and quenched with 2 mL of saturated $NaHCO_3$. The layers were separated, and the aqueous layer was extracted with EtOAc. The combined organic extracts were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (elution with 40% EtOAc in hexanes containing 1% Et_3N) to produce 125 mg (78%, two steps) of *syn,syn,syn*-tosylate **35** as a thick amber oil: $[\alpha]_D$ = −3.03 (*c* 1.09, $CHCl_3$); IR (neat) 3541, 2966, 2936, 1613, 1509 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.8 (d, J = 8.1 Hz, 2 H), 7.42 (d, J = 8.7 Hz, 2 H), 7.36 (d, J = 7.8 Hz, 2 H), 6.88 (d, J = 8.7 Hz, 2 H), 5.47 (s, 1 H), 4.44 (dd, J = 9.9, 3.3 Hz, 1 H), 4.13−3.98 (m, 3 H), 3.86 (dd, J = 9.6, 2.1 Hz, 1 H), 3.79 (s, 3 H), 3.61 (m, 1 H), 2.45 (s, 3 H), 2.08 (d, J = 6.6 Hz, 1 H), 1.86 (m, 1 H), 1.60−1.75 (m, 2 H), 1.43−1.24 (m, 2 H), 1.15 (d, J = 6.9 Hz, 3 H), 0.95 (d, J = 6.9 Hz, 3 H), 0.83 (t, J = 7.5 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 159.7, 144.9, 132.7, 131.5, 129.9, 127.8, 127.2, 113.5, 101.8, 82.1, 77.4, 77.2, 73.8, 68.8, 55.2, 43.1, 35.6, 29.6, 21.6, 19.1, 11.5, 10.9, 8.1. Anal. Calcd for $C_{26}H_{36}O_7S$: C, 63.39; H, 7.37. Found: C, 63.35; H, 7.46.

***syn,syn,syn*-TES Ether 37.** To a solution of 323 mg (0.66 mmol) of tosylate **35** in 5 mL of CH_2Cl_2 were added 0.3 mL (2.6 mmol) of 2,6-lutidine and 0.3 mL (1.3 mmol) of TESOTf at 0 °C. The mixture was stirred at 0 °C for 0.5 h and quenched with 2 mL of saturated $NaHCO_3$. The layers were separated, and the aqueous layer was extracted with ether. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (elution with 30% EtOAc in hexanes containing 1% Et_3N) to afford 357 mg (90%) of TES-protected tosylate **37** as a clear oil: $[\alpha]_D$ = +21.56 (*c* 1.09, $CHCl_3$); IR (neat) 2960, 2872, 1361 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.79 (d, J = 8.4 Hz, 2 H), 7.41 (d, J = 8.4 Hz, 2 H,), 7.34 (d, J = 8.1 Hz, 2 H), 6.88 (d, J = 9.0 Hz, 2 H), 5.41 (s, 1 H), 4.15 (dd, J = 9.9, 3.9 Hz, 1 H), 4.05 (dd, J = 9.6, 5.1 Hz, 1 H), 4.03 (d, J = 1.8 Hz, 2 H), 3.79 (s, 3 H), 3.73−3.67 (m, 2 H), 2.44 (s, 3 H), 1.82 (m, 1 H), 1.73−1.65 (m, 2 H), 1.47−1.21 (m, 2 H), 1.14 (d, J = 3.9 Hz, 3 H), 0.93 (t, J = 8.1 Hz, 9 H), 0.92 (d, J = 7.8 Hz, 3 H), 0.77 (t, J = 7.2 Hz, 3 H), 0.54 (q, J = 8.4 Hz, 6 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 159.7, 144.7, 132.9, 131.4, 129.7, 127.9, 127.1, 133.4, 101.8, 80.9, 73.7, 70.6, 69.5, 55.2, 43.8, 37.7, 30.3, 21.5, 20.1, 11.5, 11.1, 9.1, 7.0, 6.5, 5.7, 5.5.

***syn,syn,syn,syn*-TES Ether 38.** To a solution of 224 mg (0.369 mmol) of tosylate **37** in 15 mL of benzene was added 1.85 mL (1.85 mmol) of $LiBHEt_3$ (1.0 M in hexanes). The mixture was heated to reflux and stirred for 18 h. The reaction was quenched at 0 °C with saturated potassium sodium tartrate and stirred for 1.5 h. The layers were separated, and the aqueous layer was extracted with EtOAc. The combined organic extracts were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (elution with 20% EtOAc in hexanes containing 1% Et_3N) to afford 148 mg (92%) of TES ether **38** as a colorless oil: $[\alpha]_D$ = +24.07 (*c* 1.06, $CHCl_3$); IR (neat) 2958, 2873, 1613, 1517 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.45 (d, J = 8.7 Hz, 2 H), 6.90 (d, J = 8.7 Hz, 2 H), 5.46 (s, 1 H), 4.06 (d, J = 1.8 Hz, 2 H), 3.8 (s, 3 H), 3.74 (dd, J = 9.9, 2.1 Hz, 1 H), 3.51 (dd, J = 6.6, 0.9 Hz, 1 H), 1.90 (m, 1 H), 1.75 (m, 1 H), 1.62−1.51 (m, 2 H), 1.18 (d, J = 6.9 Hz, 3 H), 1.04 (m, 1 H), 1.02 (t, J = 7.8 Hz, 9 H), 1.0 (d, J = 5.7 Hz, 3 H), 0.93 (d, J = 6.6 Hz, 3 H), 0.90 (t, J = 7.5 Hz, 3 H), 0.64 (q, J = 8.1 Hz, 6 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 159.7, 131.7, 127.2, 113.5, 101.9, 81.9, 74.9, 73.8, 55.2, 36.7, 37.2, 30.2, 25.6, 16.0, 11.9, 11.4, 9.6, 7.2, 5.8. Anal. Calcd for $C_{25}H_{44}O_4Si$: C, 68.76; H, 10.16. Found: C, 68.93; H, 10.03.

***syn,syn,syn,syn*-Alcohol 39.** To a solution of 140 mg (0.320 mmol) of TES ether **38** in 6 mL of CH_2Cl_2 was added 3.2 mL (3.2 mmol) of DIBAl-H (1.0 M in hexanes) at −78 °C. The solution was warmed to −30 °C and stirred for 20 h. The reaction was quenched with saturated potassium sodium tartrate and stirred for 1.5 h. The layers were separated, and the aqueous layer was extracted with ether. The combined organic extracts were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (elution with 20% EtOAc in hexanes containing 1% Et_3N) to produce 125 mg (89%) of alcohol **39** as a colorless oil: $[\alpha]_D$ −0.80 (*c* 1.01, $CHCl_3$); IR (neat) 3458, 2960, 2872 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.26 (d, J = 7.5 Hz, 2 H), 6.87 (d, J = 9.0 Hz, 2 H), 4.49 (s, 2 H), 3.80 (s, 3 H), 3.70−3.56 (m, 2 H), 3.49−3.44 (m, 2 H), 2.02 (m, 1 H), 1.92−1.86 (m, 2 H), 1.53−1.34 (m, 2 H), 1.13 (m, 1 H), 1.02 (d, J = 6.9 Hz, 3 H), 0.98 (t, J = 8.1 Hz, 9 H), 0.93 (d, J = 6.9 Hz, 3 H), 0.87 (t, J = 7.5 Hz, 3 H), 0.84 (d,

J = 6.6 Hz, 3 H), 0.63 (q, J = 8.1 Hz, 6 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 159.1, 130.8, 129.2, 113.7, 81.5, 77.3, 73.8, 66.4, 51.2, 39.9, 38.7, 38.0, 26.7, 14.2, 12.2, 11.5, 11.2, 7.2, 5.6. Anal. Calcd for $C_{25}H_{46}O_4Si$: C, 68.44; H, 10.57. Found: C, 68.15; H, 10.33.

***syn,syn,syn,syn*-Aldehyde 40.** To a solution of 107 mg (0.24 mmol) of alcohol **38** in 5 mL of CH_2Cl_2 was added 155 mg (0.37 mmol) of periodinane reagent.[14] The solution was stirred for 1 h at rt and quenched by the simultaneous addition of 2 mL of saturated $NaHCO_3$ and 2 mL of saturated $Na_2S_2O_3$. The mixture was stirred for 40 min or until the layers were clear. The layers were separated, and the aqueous layer was extracted with ether. The combined organic extracts were washed with brine and dried over Na_2SO_4. After filtration and removal of solvent under reduced pressure, 107 mg (99%) of aldehyde **40** was obtained as a clear oil. This material was used without further purification: $[\alpha]_D$ = +27.16 (*c* 0.81, $CHCl_3$); IR (neat) 2960, 2872, 1720, cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.83 (d, J = 0.9 Hz, 1 H), 7.21 (d, J = 8.7 Hz, 2 H), 6.86 (d, J = 8.7 Hz, 2 H), 4.43 (d, J = 10.8 Hz, 1 H), 4.37 (d, J = 10.8 Hz, 1 H), 3.84 (dd, J = 6.6, 3.9 Hz, 1 H), 3.79 (s, 3 H), 3.50 (t, J = 4.5 Hz, 1 H), 2.70 (m, 1 H), 1.86 (m, 1 H), 1.55−1.34 (m, 2 H), 1.15 (d, J = 6.9 Hz, 3 H), 1.12 (m, 1 H), 0.99 (d, J = 6.9 Hz, 3 H), 0.97 (t, J = 7.8 Hz, 9 H), 0.87 (t, J = 7.5 Hz, 3 H), 0.84 (d, J = 6.6 Hz, 3 H), 0.62 (q, J = 7.2 Hz, 6 H).

***syn,syn,syn,syn*-Unsaturated Ester 41.** To a solution of 184 mg (0.42) mmol of aldehyde **40** in 20 mL of CH_2Cl_2 was added 380 mg (1.05 mmol) of $Ph_3PC(Me)CO_2Et$. The solution was heated to reflux and stirred for 12 h. The solvent was removed under reduced pressure, and the residue was purified by column chromatography on silica gel (elution with 10% EtOAc in hexanes) to afford 202 mg (93%) of ester **41** as a thick oil: $[\alpha]_D$ = +14.3 (*c* 0.86, $CHCl_3$); IR (neat) 2957, 2874, 1710, 1613 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.27 (d, J = 8.7 Hz, 2 H), 6.88 (d, J = 8.1 Hz, 2 H), 6.60 (d, J = 10.8 Hz, 1 H), 4.52 (d, J = 10.5 Hz, 1 H), 4.45 (d, J = 14.4 Hz, 1 H), 4.26−4.12, (m, 2 H), 3.90 (s, 3 H), 3.57 (dd, J = 8.4, 1.8 Hz, 1 H), 3.27 (dd, J = 8.1, 2.7 Hz, 1 H), 2.82 (m, 1 H), 1.85 (s, 3 H), 1.70 (m, 1 H), 1.57 (m, 1 H), 1.36−1.13 (m, 2 H), 1.29 (t, J = 7.2 Hz, 3 H), 1.1 (d, J = 6.6 Hz, 3 H), 0.96 (t, J = 8.4 Hz, 3 H), 0.95 (d, J = 7.8 Hz, 3 H), 0.90 (t, J = 7.2 Hz, 9 H), 0.79 (d, J = 6.6 Hz, 3 H), 0.61 (q, J = 8.1 Hz, 6 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 168.1, 159.2, 144.3, 130.8, 129.2, 127.0, 113.7, 83.6, 77.5, 77.3, 74.8, 60.4, 55.2, 40.2, 38.0, 37.7, 27.6, 16.5, 14.2, 12.5, 12.4, 11.1, 7.2, 5.6. Anal. Calcd for $C_{30}H_{52}O_5Si$: C, 69.18; H, 10.06. Found: C, 68.95; H, 10.04.

***syn,syn,syn,syn*-Alcohol 42.** To a solution of 45 mg (0.086 mmol) of TES ether **41** in 2 mL of THF was added 0.11 mL (0.11 mmol) of TBAF (1.0 M in THF) dropwise. The solution was stirred at rt for 1 h and quenched with saturated NH_4Cl. The layers were separated, and the aqueous layer was extracted with ether. The combined organic layers were washed with brine and dried over Na_2SO_4. After filtration and removal of solvent under reduced pressure, the filtrate was purified by column chromatography on silica gel (elution with 20% EtOAc in hexanes) to afford 27 mg (77%) of alcohol **42** as a clear oil: $[\alpha]_D$ = +19.66 (*c* 0.89, $CHCl_3$); IR (neat) 3519, 2960, 1710 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.28 (d, J = 8.4 Hz, 2 H), 6.87 (d, J = 8.7 Hz, 2 H), 6.64 (dd, J = 10.5, 1.5 Hz, 1 H), 4.58 (d, J = 10.5 Hz, 1 H), 4.52 (d, J = 10.5 Hz, 1 H), 4.25−4.13 (m, 2 H), 3.79 (s, 3 H), 3.46−3.39 (m, 2 H), 2.88 (m, 1 H), 2.15 (d, J = 3.6 Hz, 1 H), 1.87 (d, J = 1.2 Hz, 3 H), 1.79 (m, 1 H), 1.55 (m, 1 H), 1.32 (m, 1 H), 1.29 (t, J = 6.9 Hz, 3 H), 1.13 (d, J = 6.9 Hz, 3 H), 1.11 (m, 1 H), 0.94 (d, J = 6.9 Hz, 3 H), 0.92 (d, J = 6.6 Hz, 3 H), 0.87 (t, J = 7.5 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 168.1, 159.2, 144.2, 130.2, 129.4, 127.2, 113.8, 86.5, 77.9, 77.2, 74.7, 60.5, 55.2, 37.9, 37.3, 37.1, 25.9, 16.3, 14.2, 12.5, 11.2, 8.0. Anal. Calcd for $C_{24}H_{38}O_5$: C, 70.90; H, 9.42. Found: C, 70.98; H, 9.43.

***syn,syn,syn,syn*-TBS Ether 43.** To a solution of 51 mg (0.125 mmol) of alcohol **42** in 3 mL of CH_2Cl_2 were added 0.06 mL (0.5 mmol) of 2,6-lutidine and 0.06 mL (0.25 mmol) of TBSOTf at 0 °C. The mixture was stirred at 0 °C for 2 h and quenched with saturated $NaHCO_3$. The layers were separated, and the aqueous layer was extracted with ether. The organic extracts were washed with brine and dried over Na_2SO_4. The solution was filtered, and solvent was removed under reduced pressure. The crude material was purified by column chromatography on silica gel (elution with 5% EtOAc in hexanes) to afford 62 mg (95%) of ester **43** as a colorless oil: $[\alpha]_D$ = +5.16 (*c* 0.6, $CHCl_3$); IR (neat) 2960, 2933, 1710 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.28 (d, J = 10.2 Hz, 2 H), 6.89 (d, J = 9.0 Hz, 2 H), 6.63 (d, J = 10.5 Hz, 1 H) 4.53, (d, J = 10.5 Hz, 1 H), 4.47 (d, J = 10.5 Hz, 1 H), 4.48−4.11 (m, 2 H), 3.81 (s, 3 H), 3.50 (dd, J = 7.5, 2.4 Hz, 1 H), 3.26 (dd, J = 7.5, 3.3 Hz, 1 H), 2.82 (m, 1 H), 1.86 (s, 3 H), 1.73 (m, 1 H), 1.53 (m, 1 H), 1.37−1.13 (m, 2 H), 1.29 (t, J = 6.9 Hz, 3 H), 1.09 (d, J = 6.9 Hz, 3 H), 0.94 (d, J = 7.2 Hz, 3 H), 0.90 (s, 9 H), 0.88 (t, J = 7.2 Hz, 3 H), 0.80 (d, J = 6.9 Hz, 3 H), 0.03 (d, J = 5.4 Hz, 6 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 168.15, 159.14, 144.53, 130.83, 129.23, 126.82, 113.75, 83.77, 76.52, 74.86, 60.44, 55.23, 40.14, 39.89, 37.46, 27.39, 26.26, 18.54, 16.16, 14.24, 12.97, 12.56, 11.39, −3.38, −3.60. Anal. Calcd for $C_{30}H_{52}O_5Si$: C, 69.18; H, 10.06. Found: C, 69.37; H, 10.09.

Ester 44. To a solution of 55 mg (0.11 mmol) of ester **43** in 1 mL of CH_2Cl_2/H_2O (18:1) were added 48 mg (0.21 mmol) of DDQ and 17 mg (0.21 mmol) of $NaHCO_3$ at rt. After the solution was stirred for 2.5 h, the solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel (elution with 10% EtOAc in hexanes) to afford 30 mg (71%) of ester **44** as a clear oil: $[\alpha]_D$ = +22.17 (*c* 1.15, $CHCl_3$), lit. +20.1 (*c* 1.13 $CHCl_3$);[15] IR (neat) 3519, 2959, 2854, 1710 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.50 (dd, J = 10.5, 1.2 Hz, 1 H), 4.24−4.13 (m, 2 H), 3.66 (t, J = 3.6 Hz, 1 H), 3.48 (d, J = 7.2 Hz, 1 H), 2.62 (m, 1 H), 2.10 (d, J = 4.2 Hz, 1 H), 1.86 (d, J = 1.8 Hz, 3 H), 1.68−1.52 (m, 4 H), 1.29 (t, J = 6.9 Hz, 3 H), 1.08 (d, J = 6.6 Hz, 3 H), 0.91 (s, 9 H), 0.87 (t, J = 7.2 Hz, 3 H), 0.84 (d, J = 7.2 Hz, 3 H), 0.82 (d, J = 6.6 Hz, 3 H), 0.08 (d, J = 4.8 Hz, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 168.1, 143.7, 127.3, 79.9, 78.7, 60.5, 40.0, 38.0, 37.6, 26.1, 25.7, 18.3, 16.6, 14.7, 14.2, 12.5, 8.2, −3.4, −4.3. Anal. Calcd for $C_{22}H_{44}O_4Si$: C, 65.95; H, 11.07. Found: C, 65.81; H, 11.04.

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Supporting Information Available: Experimental procedures for **3**−**5**, **9**−**11**, and **18**−**27** and ^{1}H NMR spectra for key intermediates. This material is available free of charge via the Internet at http://pubs.acs.org.

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