Total Synthesis of (+)-Isolaurepinnacin. Use of Acetal-Alkene Cyclizations To Prepare Highly Functionalized Seven-Membered Cyclic Ethers

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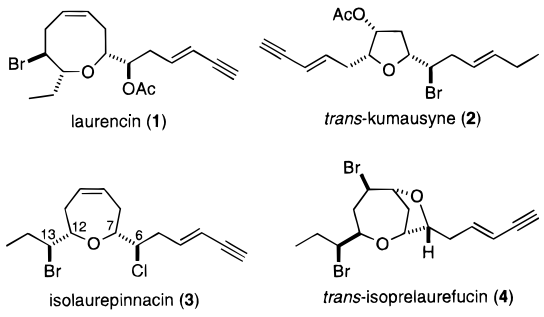
Abstract: The first synthesis of the title compound is described. The synthesis features an acetal-vinylsilane cyclization to stereoselectively form the *cis*-2,7-disubstituted oxepene ring and introduce Δ^4 unsaturation. Starting with (2*R*,3*S*)-2,3-epoxypentan-1-ol (**16**), mixed acetal **10** is formed in five steps and 72% overall yield. Treatment of **10** with excess BCl_3 in CH_2Cl_2 at −78 → 0 °C promotes cyclization to afford Δ^4-oxepene **39** in 90% yield after deprotection of the silyl ether. Elaboration of the (*E*)-enyne functionality of the six-carbon side chain completes the synthesis of (+)-isolaurepinnacin.

Red algae of the genus *Laurencia* produce a multitude of unique compounds.[2] While the majority of these secondary metabolites are terpenes, a number of structurally novel nonisoprenoid C_{15} acetogenins have also been isolated. The majority of these acetogenins are cyclic ethers adorned with distinctive enyne or allene side chains and containing at least one bromine or chlorine substituent.[2] Five- and eight-membered cyclic ethers occur particularly widely, with laurencin (**1**)[3] and *trans*-kumausyne (**2**)[4] being representative. Isolaurepinnacin (**3**)[5] and *trans*-isoprelaurefucin (**4**)[6] are examples of the rarer class of C_{15} *Laurencia* acetogenins that contain seven-membered oxacyclic (oxepane) rings. *Laurencia* metabolites have been popular targets for synthetic investigations and have spurred the development of a number of new methods for constructing cyclic ethers.[7]



Isolaurepinnacin (**3**), the second member of the oxepane class of *Laurencia* acetogenins to be discovered, was isolated in 1981 by Fukuzawa and Masamune from *L. pinnata* Yamada.[5] Through chemical correlations with degradation products of laurencin, a metabolite whose structure had been defined crystallographically,[3] these authors established that **3** had the 6*R*,7*R* stereochemistry. That the relative configuration of **3** at C(12) and C(13) differed from laurencin was suggested by isolation of a small amount of a cis Δ^{12} alkene upon reductive cleavage of octahydroisolaurepinnacin with zinc and acetic acid. The large NOE observed between the H(7) and H(12) methine hydrogens signaled a cis relationship of the two side chains and led Fukuzawa and Masamune to propound the 6*R*,7*R*,12*S*,13*S* configuration for **3**.[5] The *S* configuration at C(12) was rigorously established in 1989 by Kotsuki's synthesis of debromodechlorooctahydroisolaurepinnacin from D-mannitol.[8]

In recent years, a number of new methods have been developed for preparing seven-membered cyclic ethers.[9] Our own investigations in this area have focused on the direct construction of cyclic ethers through C−C bond-forming cyclization reactions.[10] In 1989, we reported that *cis*-2,7-disubstituted Δ^4-oxepenes could be prepared in high yield by Prins cyclizations of mixed acetals of 1-substituted-4-(trimethylsilyl)-4-penten-1-ol (Scheme 1).[11] Three subtle effects are responsible for the high-yielding formation of Δ^4-oxepene **6** from mixed acetal precursor **5**: (a) initial Prins cyclization occurs in an endocyclic sense as a result of the greater stability of a tertiary α-silyl cation than a primary *β*-silyl cation,[12] (b) cyclization of the more stable (*E*)-oxocarbenium ion[13] occurs preferentially in conformation **7** which minimizes destabilizing

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(2) (a) Moore, R. E. In *Marine Natural Products*; Scheuer, P. J., Ed.; Academic: New York, 1978; Vol. 1, pp 43−121. (b) Erickson, K. L. In *Marine Natural Products*; Scheuer, P. J., Ed.; Academic: New York, 1983; Vol. 5, pp 131−257. (c) Faulkner, D. J. *Nat. Prod. Rep.* **1996**, *13*, 75, and earlier reviews in this series.

(3) (a) Irie, T.; Suzuki, M.; Masamune, T. *Tetrahedron* **1968**, *24*, 4193. (b) Cameron, A. F.; Cheung, K. K.; Ferguson, G.; Monteath Robertson, J. *J. Chem. Soc., Chem. Commun.* **1965**, 638.

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(5) Fukuzawa, A.; Masamune, T. *Tetrahedron Lett.* **1981**, *41*, 4081.

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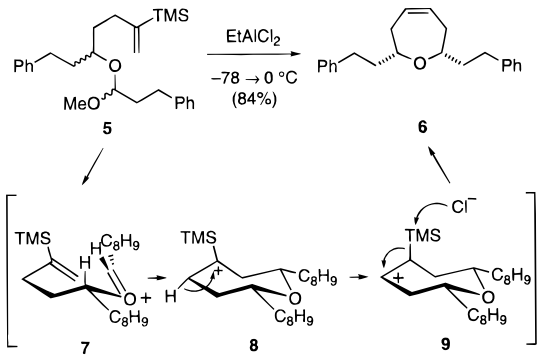
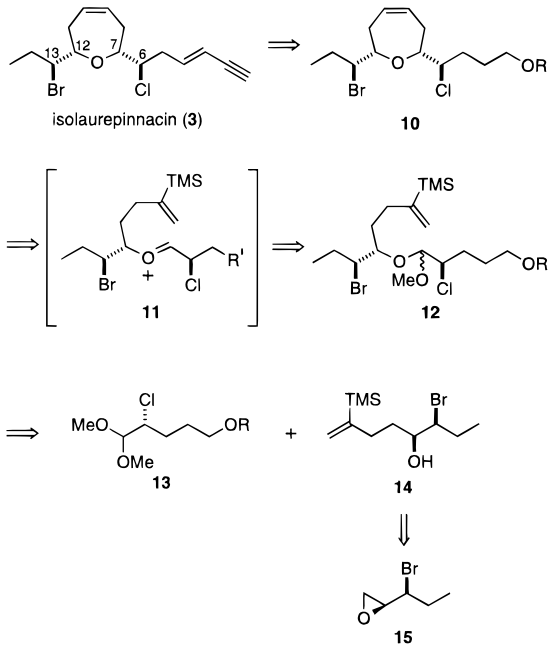
Scheme 1



Scheme 2. Synthesis Plan



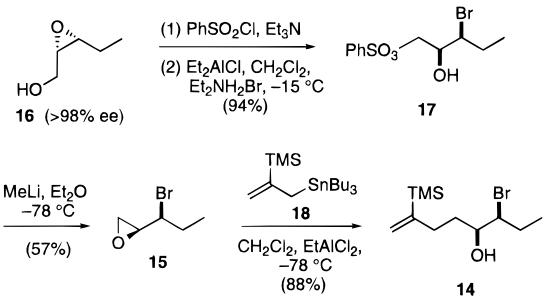
allylic interactions, and (c) electron withdrawal by the ring oxygen controls regioselectivity of the hydride migration (**8** → **9**).

To pursue the applicability of mixed acetal cyclizations for the construction of highly functionalized seven-membered cyclic ethers, we chose isolaurepinnacin (**3**) as an appropriate total synthesis target. Herein, we describe, with full experimental details, these investigations which culminated in an efficient total synthesis of (+)-(**3**).[14]

Results and Discussion

Synthesis Plan. Our approach to **3** is shown antithetically in Scheme 2. Simplification of the enyne side chain gives *cis*-2,7-disubstituted Δ^4-oxepene **10**, which was projected to arise from acetal−vinylsilane cyclization of **12**. Mixed acetal **12** would arise from coupling of dimethyl acetal **13** and vinylsilane alcohol **14**. This latter fragment, in turn, could originate from

Scheme 3. Synthesis of Vinylsilane Alcohol **14**



α-bromoepoxide **15**.[15] Key to the implementation of this approach would be our success in fashioning a mixed acetal of the complexity of **12** as well as our ability to selectively activate the methoxy group of **12** to generate a single α-alkoxycarbenium ion **11**.

Preparation of Vinylsilane Alcohol 14. The synthesis of bromoepoxide **15** began with enantioenriched epoxyalcohol **16** (Scheme 3). This intermediate was prepared as described[16] with the exception that we employed a modified workup for the Sharpless epoxidation step.[17] The enantiomeric purity of **16** was determined to be >98% ee by ^{1}H NMR analysis of Mosher ester derivatives.[18] Conversion of **16** to the phenylsulfonate derivative, followed by regioselective opening of the epoxide according to the procedure of Murai,[19] provided a single bromohydrin **17** in 94% yield. Acquisition of bromoepoxide **15** in synthetically useful amounts from **17** proved difficult due to the volatility of this epoxide. Several base−solvent pairs were screened, and it was found that the conversion of **17** → **15** was best accomplished in Et_2O by exposing **17** to an excess of MeLi at low temperature. Careful concentration of the reaction mixture and distillation of the residue provided **15** in 57% yield (91% based on consumed **17**). No improvement in the yield of **15** was realized by further increasing the amount of MeLi.

The reaction of **15** with a 2-(trimethylsilyl)allyl nucleophile should deliver **14**. Realizing this objective proved difficult and necessitated a detailed investigation of the condensation of terminal epoxides with 2-(trialkylsilyl)allyl organometallics. This study showed that allylstannane nucleophiles were optimal.[15] In the present case, treatment of **15** with a slight excess of allylstannane **18** in the presence of $EtAlCl_2$ at −78 °C provided **14** in 88% yield.[15]

Preparation of α-Chloroacetal 27. With quantities of **14** in hand, our attention turned to the synthesis of (*R*)-α-chloroacetal **27** (Scheme 4). Although many racemic α-haloacetals are found in the literature, we were unable to uncover examples of the preparation of these intermediates in high enantiomeric purity. Formation of an α-chloroacetal from an alcohol precursor was an obvious choice, and the synthesis of the requisite propargylic alcohol (*S*)-**21** is summarized in Scheme 4. Glyoxal dimethylacetal was generated *in situ* from **19** and quenched with an excess of lithium acetylide **20** to provide (±)-**21** in 88% yield.[20] Jones oxidation of this intermediate delivered propargylic ketone **22** in high yield.[21]

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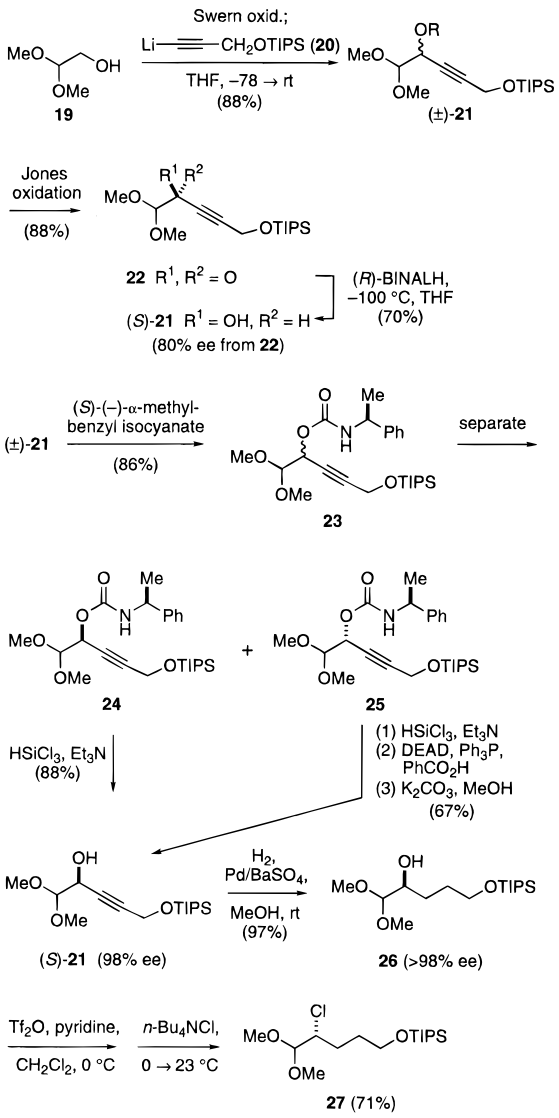
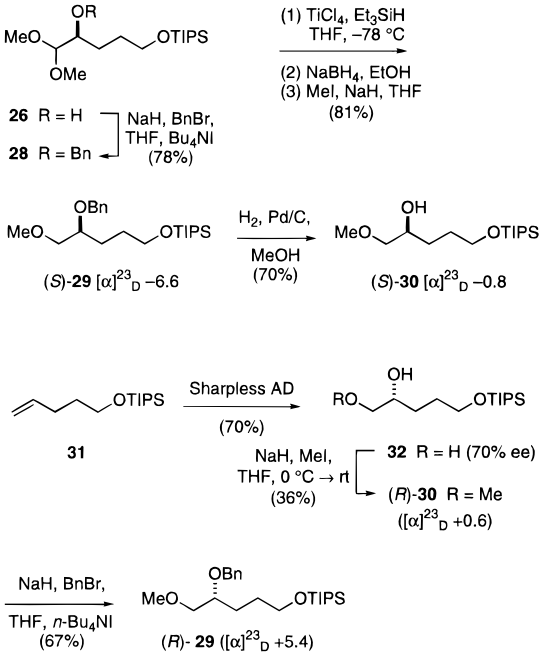
Scheme 4. Synthesis of Chloroacetal **27**



Attempted enantioselective reduction of **22** with several standard reagents ($LiAlH_4$-Darvon alcohol,[22] Alpine-Borane,[23] or oxazaborolidine catalyzed borane reductions)[24] provided (*S*)-**22** in low enantiomeric purity (<50% ee). The best reagent found was (*R*)-BINAL-H, which provided (*S*)-**21** in a somewhat disappointing 80% ee and 72% yield from **22**.[25] Although we were able to prepare gram quantities of (*S*)-**21** in this way, the cost of (*R*)-1,1′-bi-2-naphthol (which is employed in excess) and the moderate enantioselectivity of the reduction made this sequence less than ideal.

(*S*)-Alcohol **21** could be obtained more conveniently in multigram quantities and high enantiopurity from (±)-**21** by chromatographic separation of diastereomeric carbamates **23** obtained from the reaction of (±)-**21** with (*S*)-(−)-α-methylbenzyl isocyanate.[26] Cleavage of diastereomer **24** with $HSiCl_3$[27] provided (*S*)-**21**, $[\alpha]^{23}_D$ −3.7 (>98% ee).[18] Identical formation of the *R* alcohol from **25**, inversion of this intermediate by Mitsunobu reaction with benzoic acid,[28] and hydrolysis of the derived benzoate also provided (*S*)-**21** in >98% ee. Using this resolution sequence, enantiopure (*S*)-**21** was available in 30% overall yield from the racemate. Catalytic hydrogenation of (*S*)-**21** then provided α-hydroxy acetal **26** in essentially quantitative yield.

Scheme 5. Determination of the Absolute Configuration of **26**



The absolute configuration of **26** was established by chemical correlation with (2*R*)-1-methoxy-5-(triisopropylsiloxy)-2-pentanol (Scheme 5). Benzylation of **26** provided **28** in 78% yield. Attempted reduction of this intermediate to yield methyl ether **29** with $TiCl_4$ and Et_3SiH, unexpectedly, delivered the corresponding aldehyde in high yield. Reduction of this latter intermediate with $NaBH_4$, followed by methylation of the resulting primary alcohol, yielded **29**, $[\alpha]^{23}_D$ −6.6. Hydrogenolysis of **29** provided the required sample of (2*S*)-1-methoxy-5-(triisopropylsiloxy)-2-pentanol (*S*-**30**, $[\alpha]^{23}_D$ −0.8).

Preparation of an authentic sample of (*R*)-**29** began with the Sharpless asymmetric dihydroxylation of 1-(triisopropylsiloxy)-4-pentene (**31**) with $(DHQD)_2$-PHAL[29] to give diol **32** in 70% yield (70% ee).[18] Based on ample precedent, this intermediate is assigned the *R* configuration.[29] Methylation of **32** then provided a mixture of ethers from which (*R*)-**30**, $[\alpha]^{23}_D$ +0.6, could be isolated in 36% yield. Since the rotation of this intermediate was low, (*R*)-**30** was benzylated to give (*R*)-**29**, $[\alpha]^{23}_D$ +5.4. Based on this correlation, the absolute configuration of **21** obtained from (*R*)-BINAL-H reduction of propargylic ketone **22** is *S*. Since reduction of ynones with (*R*)-BINAL-H typically yields (*R*)-alcohols,[25] the reversal in this case (originally unanticipated) is abscribed to modification of the transition state assembly by the neighboring acetal group.

Conversion of **26** (>98% ee) into the corresponding α-chloroacetal **27**, not unexpectedly, proved difficult (Scheme 4). Several standard methods for introducing the chlorine func-

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(28) For a review, see: Mitsunobu, O. *Synthesis* **1981**, 1.
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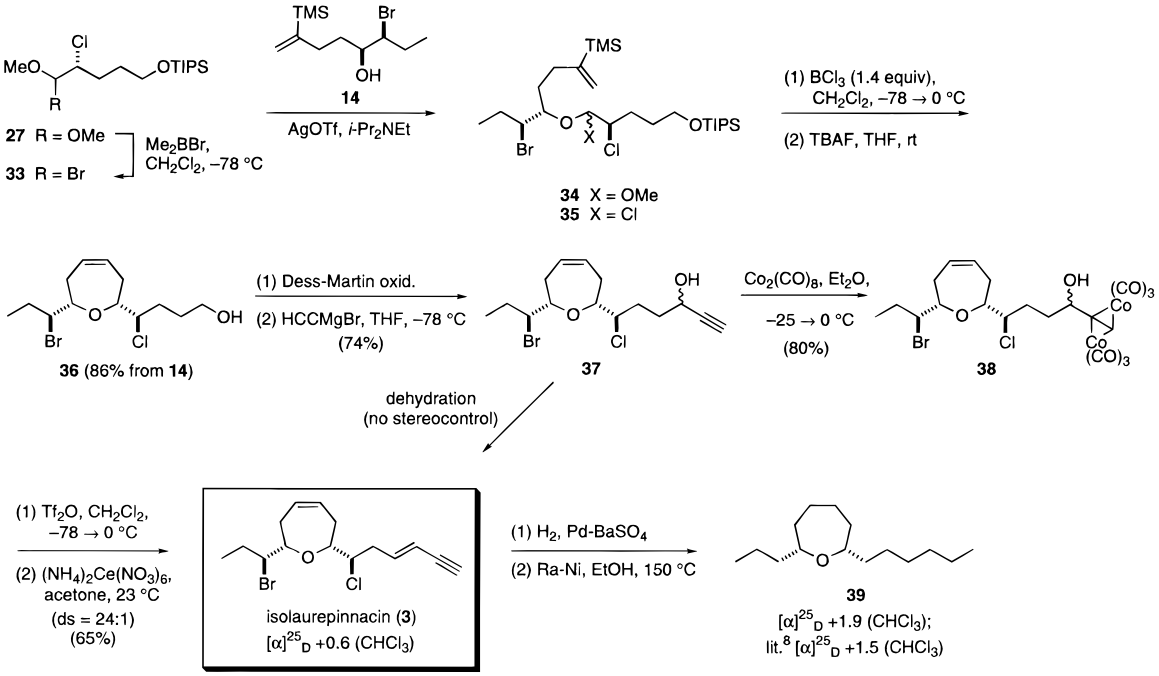
Scheme 6. Synthesis of (+)-Isolaurepinnacin (**3**)



tionality were initially screened and found to be unsatisfactory.[30] Success was finally realized by activating **26** as the triflate derivative, which subsequently was allowed to react with an excess of anhydrous *n*-Bu_4NCl in CH_2Cl_2 at room temperature to yield α-chloroacetal **27** in 71% yield. We are unaware of a precedent for neighboring group participation by a *β*-acetal group in displacement reactions, and, therefore, assume that the conversion of **26** → **27** occurred with inversion of configuration.[31] Since there was no simple way to confirm or refute this conclusion, evaluation of the correctness of this assumption was deferred until completion of the total synthesis of **3**. The enantiopurity of **27** also could not be directly assessed; however, it was later established to be high based on the exquisite diastereoselection observed in the pivotal cyclization step (*vide infra*).

Formation of Mixed Acetal 34 and Cyclization to Oxepene 36. The synthesis of mixed acetal **34** was readily accomplished by treating dimethyl acetal **27** at −78 °C with 1 equiv of Me_2BBr, followed by removal of Me_2BOMe under reduced pressure, to provide α-bromo ether **33** (Scheme 6).[32] A 2.5-fold excess of this crude intermediate was then coupled with alcohol **14** in the presence of AgOTf and diisopropylethylamine to afford mixed acetal **34** in quantitative crude yield and a purity of approximately 90%.[33]

Successful cyclization of **34** requires selective activation of only the methoxy group in a substrate containing five distinct Lewis basic functional groups. Not surprisingly, treatment of **34** with many common Lewis acids led to the formation of complex product mixtures. Boron trichloride, however, proved uniquely effective affording oxepene **36** in 86% yield, after desilylation. This key conversion was most simply accomplished by treating **34** with 1.4 equiv of BCl_3 at −78 °C and allowing the reaction to warm slowly to 0 °C. At −78 °C, BCl_3 selectively cleaves the methoxy group of **34** to afford α,*β*-dichloro ether **35**, an intermediate that can be isolated if the reaction is carefully quenched at low temperature.[34] Upon warming in the presence of BCl_3, **35** is cleanly transformed to the TIPS ether precursor of **36**. Use of the robust TIPS protecting group was also key to the success of this conversion; *tert*-butyldimethylsilyl and benzoyl protecting groups in congeners of **34** were cleaved under these cyclization conditions. To the limits of detection by 500 MHz ^1H NMR analysis, only a single stereoisomer is produced upon cyclization. That the C(6) epimer of **36** would have been detected was confirmed by cyclization of the mixed acetal formed from **14** and racemic **27** to provide ∼1:1 mixture of **36** and 6-*epi*-**36**.

Conversion of Oxepene 36 to (+)-Isolaurepinnacin. The (*E*)-enyne side chain was developed by initial oxidation of **36** with Dess−Martin periodinane,[35] followed by reaction of the resulting crude aldehyde with ethynylmagnesium bromide to yield propargyl alcohol **37**. Dehydration of this intermediate using a variety of standard conditions was efficient, but not stereoselective, providing the corresponding (*E*)- and (*Z*)-enynes in comparable amounts.

Based on considerable precedent that formation of the dicobalthexacarbonyl complex of the alkyne would increase the stereoselectivity of the dehydration by effectively bulking up the alkyne group,[36] **37** was allowed to react with 1.1 equiv of $Co_2(CO)_8$ in Et_2O to afford hexacarbonyldicobalt complex **38** in 80% yield. Dehydration of this intermediate was best accomplished by treatment with Tf_2O at −78 °C in CH_2Cl_2. After decomplexation of the crude enyne product with ceric ammonium nitrate, (+)-isolaurepinnacin (**3**) was isolated in 65% yield as a 24:1 mixture of *E*:*Z* stereoisomers.

Synthetic **3** displayed ^1H and ^{13}C NMR and IR spectra that were indistinguishable from those of the natural isolate and

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showed the following optical properties: $[\alpha]^{23}_D$ +0.6, $[\alpha]^{23}_{546}$ +1.2, and $[\alpha]^{23}_{405}$ +3.2 (*c* 1.4, $CHCl_3$). A small negative rotation, $[\alpha]^{23}_D$ −6.2 ($CHCl_3$), was originally reported for **3** that had been isolated from *L. pinnata* Yamada.[5] This rotation, however, is believed to be erroneous and derived from contamination of the natural sample with strongly levorotatory laurepinnacin, $[\alpha]^{23}_D$ −35.3 (*c* 1.1, $CHCl_3$).[37] Co-occurring (*Z*)-isolaurepinnacin showed a rotation of $[\alpha]^{23}_D$ +2.0 (*c* 1.0, $CHCl_3$), which is more in line with the rotation we observe for our synthetic product.[37]

To further confirm that the absolute configuration of our synthetic product was the same as natural isolaurepinnacin, synthetic **3** was reduced by sequential treatment with $H_2/BaSO_4$ and Ra-Ni to give debromodechlorooctahydroisolaurepinnacin **39**.[5] The rotation observed for this product, $[\alpha]^{23}_D$ +1.9 (*c* 0.43, $CHCl_3$), corresponded closely to the rotation reported, $[\alpha]^{24}_D$ +1.5 (*c* 1.0, $CHCl_3$),[8] for this well characterized degradation product of isolaurepinnacin.

In the original report, isolaurepinnacin was claimed to exhibit insecticidal activity.[5] As a result, a sample of synthetic isolaurepinnacin was screened by the Insect Management Research Group of DowElanco. No insecticidal activity was observed in these tests, a result suggesting that an impurity in the natural isolate, perhaps laurepinnacin, is the active insecticidal component.[37,38]

Conclusion

The first total synthesis of (+)-isolaurepinnacin was achieved with high stereoselectivity in 12 steps and 15% overall yield from *cis*-2-penten-1-ol. This synthesis rigorously establishes the *S* configuration of **3** at C(13) and corrects the rotation of natural **3** to be dextrorotatory. Of particular note is the integrity of bromine and chlorine functionalities during the Lewis acid-promoted mixed acetal cyclization (**32** → **34**), a conversion that highlights the extraordinary selectivity that can be achieved in acetal-alkene cyclizations. The formation of a single stereoisomer in this key step, moreover, demonstrates that chiral α-chloro oxocarbenium do not epimerize during a favorable acetal-alkene cyclization. This observation suggests that other oxacyclic marine natural products containing common 1-haloalkyl side chains can be accessed in asymmetric fashion by Prins-type cyclizations of β-haloacetals.

Experimental Section[39]

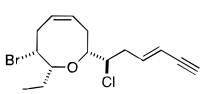
(2*S*,3*S*)-3-Bromo-1,2-pentanediol, 1-Phenylsulfonate Ester (17). To a solution of **16** (2.01 g, 19.7 mmol, 98% ee)[16a] and dry CH_2Cl_2 (25 mL) cooled to 0 °C were added successively Et_3N (3.6 mL, 26 mmol), phenylsulfonyl chloride (3.0 mL, 24 mmol), and DMAP (120 mg, 0.99 mmol). The resulting yellow solution was allowed to warm to 23 °C over 2.5 h, during which time a colorless precipitate of Et_3N·HCl formed. The mixture was quenched with aqueous 10% citric acid (20 mL), and the layers were separated. The aqueous layer was extracted twice with Et_2O (20 mL), and the combined organic layers were washed with saturated aqueous $NaHCO_3$ (20 mL) and brine (20 mL) and dried ($MgSO_4$). Filtration followed by concentration of the filtrate yielded a thick yellow liquid that was placed under vacuum (0.1 mm) to remove residual solvent. The crude sulfonate residue was taken up in 25 mL of dry CH_2Cl_2 and placed under an atmosphere of N_2.

Following the general procedure of Murai,[19] a solution of $HNEt_2$·HBr (12 g, 80 mmol) and dry CH_2Cl_2 (125 mL) was treated at 23 °C with neat Et_2AlCl (5.0 mL, 39 mmol). The resulting solution was maintained at 23 °C for 15 min and then cooled to −15 °C. The crude solution of the phenylsulfonate derivative of **16** then was added, the resulting yellow solution was maintained at −15 °C for 4 h, and the reaction then was slowly quenched with H_2O (50 mL) at −15 °C. After warming to 23 °C, the layers were separated, the aqueous layer was extracted with Et_2O (2 × 25 mL), and the combined organic layers were washed with brine (20 mL), dried (Na_2SO_4), filtered, and concentrated. The resulting orange oil was purified on silica gel (4:1 pentane−Et_2O; 2:1 pentane−Et_2O) to yield 5.98 g (94%) of **17** as a thick orange oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.93 (br d, 2H), 7.69 (br t, 1H), 7.58 (br t, 2H), 4.15−4.11 (m, 1H), 4.08−4.05 (m, 2H), 3.83−3.81 (m, 1H), 2.16 (br d, 1H), 1.92 (app d of quint, J = 7.3, 2.0 Hz, 2H), 1.04 (dt, J = 7.3, 2.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 135.3, 134.1, 129.4, 128.0, 71.4, 70.7, 60.6, 28.7, 12.4; IR (film) 3525, 2975, 2938, 2881 cm^{-1}; MS (CI, isobutane) *m/e* calcd for $C_{11}H_{16}BrO_4S$: 322.9952; found 322.9925 (MH); $[\alpha]_D^{25}$ −6.9, $[\alpha]_{577}$ −6.5, $[\alpha]_{546}$ −7.2 $[\alpha]_{435}$ −2.6, $[\alpha]_{405}$ −14.6 (*c* 1.3, $CHCl_3$). Anal. Calcd for $C_{11}H_{15}BrO_4S$: C, 40.88; H, 4.68. Found: C, 40.85; H, 4.67.

(2*S*,3*S*)-3-Bromo-1,2-epoxypentane (15). To a solution of **17** (21.5 g, 66.4 mmol) and dry Et_2O (50 mL) cooled to −78 °C was added slowly over 25 min MeLi (2.2 M in Et_2O, 30 mL, 66 mmol). A white precipitate formed immediately, and TLC analysis (2:1 pentane−Et_2O) after 3 h showed that some starting material was still present. Over the next 12 h, a total of 74 mL of MeLi (2.2 M in Et_2O, 160 mmol) was added in portions to the −78 °C mixture. The reaction was then quenched with H_2O (50 mL) at −78 °C and slowly allowed to warm to 23 °C. The layers were separated, and the aqueous layer was extracted with Et_2O (3 × 25 mL). The combined organic layers were washed with brine (2 × 20 mL), dried (Na_2SO_4), filtered, and concentrated. The resulting yellow oil was purified on silica gel (9:1 pentane−Et_2O; 2:1 pentane−Et_2O) to give 7.91 g of recovered **17** and a pentane−Et_2O solution of **15**. This solution was concentrated by careful distillation using a 54 cm concentric tube column to yield 6.29 g of pure **15** as a light yellow liquid (57%, 91% based on consumed **17**): ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.60 (dt, J = 8.0, 5.5 Hz, 1H), 3.21 (ddd, J = 6.5, 3.5, 3.0 Hz, 1H), 2.97 (dd, J = 4.5, 4.5 Hz, 1H), 2.74 (dd, J = 5.0, 2.5 Hz, 1H), 2.02−1.97 (m, 1H), 1.95−1.86 (m, 1H), 1.08 (t, J = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 57.8, 55.5, 48.9, 28.4, 12.2; IR (film) 2975, 2938, 2881 cm^{-1}; MS (CI, isobutane) *m/e* calcd for $C_5H_{10}BrO$: 164.9916; found 164.9931 (MH); $[\alpha]_D^{25}$ +24.1, $[\alpha]_{577}$ +26.5, $[\alpha]_{546}$ +30.1, $[\alpha]_{435}$ +52.1, $[\alpha]_{405}$ +63.2 (*c* 1.1, $CHCl_3$).

(5*S*,6*S*)-6-Bromo-5-hydroxy-2-trimethylsilyl-1-octene (14). To a solution of **15** (310 mg, 1.9 mmol), **18** (1.13 g, 2.80 mmol),[15] and dry CH_2Cl_2 (5 mL) cooled to −78 °C was added neat $EtAlCl_2$ (0.22 mL, 2.1 mmol). The resulting solution was maintained at −78 °C for 19 h. The reaction then was quenched at −78 °C with saturated aqueous NH_4Cl (5.0 mL) and allowed to warm to 23 °C over 1 h. The layers were separated, the aqueous layer was extracted with Et_2O (2 × 10 mL), and the combined organic layers were washed with brine (10 mL), dried ($MgSO_4$), and concentrated. Purification of the residue on silica gel (9:1 pentane−Et_2O) provided 460 mg (88%) of **14**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.58 (s, 1H), 5.35 (s, 1H), 4.03−3.99 (m, 1H), 3.54−3.48 (m, 1H), 2.34−2.27 (m, 1H), 2.23−2.17 (m, 1H), 1.95 (app quint, J = 7.0 Hz, 2H), 1.86 (d, J = 8.5 Hz, 1H), 1.75−1.62 (m, 2H), 1.05 (t, J = 7.0 Hz, 3H), 0.09 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.5, 124.4, 73.2, 67.2, 35.0, 31.8, 29.1, 12.6, −1.44; IR (film) 3413 (br), 2956, 2879 cm^{-1}; MS (EI) *m/e* calcd for $C_{11}H_{24}BrOSi$: 278.0701; found 278.0696 (M); $[\alpha]_D^{25}$ −12.4, $[\alpha]_{577}$ −11.3, $[\alpha]_{546}$ −12.3, $[\alpha]_{435}$ −21.5, $[\alpha]_{405}$ −5.2 (*c* 1.1, $CHCl_3$). Anal. Calcd for $C_{11}H_{23}BrOSi$: C, 47.31; H, 8.30. Found: C, 47.36; H, 8.31.

(37) Fukuzawa, A., personal communication to L.E.O. on June 10, 1993.



(−)-laurepinnacin

(38) Gipson, R. W.; Pechacek, J. T. DowElanco Insect Management Research Group, personal communication to L.E.O., January 25, 1994.

(39) Unless noted otherwise, new compounds were nearly colorless oils. Temperatures refer to external bath temperatures unless noted otherwise. General experimental details have been described: Deng, W.; Overman, L. E. *J. Am. Chem. Soc.* **1994**, *116*, 11241.

(40) The C(6) epimer of **3**, which is available by the sequence outlined in Scheme 6 starting with *rac*-**27**, shows the following diagnostic signals for C(6) and C(13) in the ^{13}C NMR spectrum: δ 63.3 (natural), 63.1 (*epi*), 61.7 (*epi*), 61.4 (natural).

(±)-1,1-Dimethoxy-5-(triisopropylsiloxy)pent-3-yn-2-ol (21). Glyoxal dimethylacetal was first generated *in situ* as described.[20] To a solution of oxalyl chloride (2.5 mL, 29 mmol) and dry THF (100 mL) at −60 °C was added a solution of DMSO (2.3 mL, 32 mmol) and dry THF (16 mL) over a period of 5 min. The resulting mixture was warmed to −30 °C for 3 min and then cooled to −60 °C, at which time a solution of 2,2-dimethoxyethanol (**19**, 2.75 g, 25.9 mmol) and dry THF (24 mL) was added dropwise over 5 min. The resulting mixture was stirred for 1 h at −60 °C and then was treated with Et_3N (18.0 mL, 129 mmol). After warming to 23 °C, the mixture was stirred for 1 h and then recooled to −78 °C.

3-(Triisopropylsiloxy)propynyllithium (**20**), prepared by dropwise addition of *n*-BuLi (2.3 M in hexane, 56.3 mL, 130 mmol) to a solution of the corresponding alkyne (27.5 g, 129 mmol) and dry THF (100 mL) at −78 °C to 23 °C, was added *via* cannula to the solution of the crude aldehyde at −78 °C. The resulting mixture was allowed to warm to 23 °C with stirring for over 3 h. After quenching with H_2O (100 mL), the layers were separated, the aqueous layer was extracted with Et_2O (3 × 50 mL), and the combined organic layers were washed with brine (75 mL), dried (Na_2SO_4), and concentrated. Purification of the residue on silica gel (19:1 pentane−Et_2O; 2:1 pentane−Et_2O) provided 7.19 g (88%) of (±)-**21**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.43 (d, J = 1.5 Hz, 2H), 4.40−4.39 (m, 1H), 4.33 (d, J = 5.4 Hz, 1H), 3.50 (s, 3H), 3.49 (s, 3H), 1.08 (s, 21H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 105.4, 84.7, 81.5, 63.5, 56.0, 55.6, 52.0, 17.9, 11.9; IR (film) 3431 (br), 2950, 2869, 1463, 1369, 1263, 1194, 1125, 1088 cm^{-1}; MS (CI, isobutane) *m*/*e* calcd for $C_{16}H_{33}O_4Si$: 317.2148; found 317.2223 (MH).

1,1-Dimethoxy-5-(triisopropylsiloxy)pent-3-yn-2-one (22). A solution of (±)-**21** (1.82 g, 5.75 mmol) and acetone (35 mL) was treated dropwise at 0 °C with Jones reagent.[21] After the disappearance of (±)-**21** had been confirmed by TLC analysis (2:1 pentane−Et_2O), the reaction was quenched with *i*-PrOH (5 mL) and solid $NaHCO_3$ (100 mg). The resulting mixture was filtered through silica gel to remove chromium salts, and the plug was washed with ∼250 mL of Et_2O. The resulting solution was concentrated, and the oily residue was purified on silica gel (2:1 pentane−Et_2O) to yield 1.58 g (88%) of **22** as a light yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.65 (s, 1H), 4.58 (s, 2H), 3.44 (s, 6H), 1.09 (s, 21H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 181.9, 102.8, 94.8, 82.0, 54.3, 52.0, 17.8, 11.9; IR (film) 2944, 2869, 2213, 1694, 1463, 1369, 1250, 1194, 1175, 1119, 1075, 994 cm^{-1}; MS (CI, isobutane) *m*/*e* calcd for $C_{16}H_{31}O_4Si$: 315.1991; found 315.2007 (MH).

(2*S*)-1,1-Dimethoxy-5-(triisopropylsiloxy)pent-3-yn-2-ol (*S*-21) from Reduction of 22 with (*R*)-BINAL-H. Following the general procedure of Noyori,[25] (*R*)-(−)-BINAL-H was prepared in dry THF (51 mL) from (*R*)-(−)-1,1′-bi-2-naphthol (3.00 g, 10.5 mmol), $LiAlH_4$ (1 M in THF, 10.4 mL, 10.4 mmol), and EtOH (0.61 mL, 11 mmol). This reagent was cooled to −100 °C in a liquid nitrogen−isooctane bath and a solution of **22** (1.36 g, 4.33 mmol), and dry THF (7 mL) was added dropwise (down the side of the cooled flask) over 2 h using a syringe pump. The resulting mixture was stirred at −100 °C for an additional 3 h and then at −85 °C for 12 h. The reaction was then quenched with MeOH (4 mL) and poured into a 1 M solution of NaOH (4 mL). The layers were separated, and the organic layer was washed with 1 M NaOH until TLC analysis of the organic layer indicated that all of the binaphthol had been removed. The aqueous layer was extracted with Et_2O (2 × 50 mL), and the combined organic layers were washed with brine (75 mL), dried (Na_2SO_4) and concentrated. Purification of the residue on silica gel (2:1 pentane−Et_2O) provided 0.96 g (70%) of (*S*)-**21** (80% ee by Mosher ester analysis):[18] $[\alpha]^{23}_D$ −3.7, $[\alpha]_{405}$ −7.7, $[\alpha]_{435}$ −7.4, $[\alpha]_{546}$ −5.5, $[\alpha]_{577}$ −5.2 (*c* 1.1, $CHCl_3$).

Preparation of (2*S*)-1,1-Dimethoxy-5-(triisopropylsiloxy)pent-3-yn-2-ol (*S*-21) by Chromatographic Resolution of (±)-21. Following the general procedure of Pirkle,[26] a solution of alcohol (±)-**21** (16.8 g, 53.0 mmol), *N*,*N*-dimethylethanolamine (200 mg, 2.2 mmol), and dry toluene (11 mL) was treated dropwise with (*S*)-(−)-α-methylbenzyl isocyanate (11.4 mL, 79.5 mmol), and the resulting solution was heated at 110 °C for 6 h. The crude product was concentrated, and the residue was purified on silica gel (1 kg; 2:1 pentane−Et_2O) to afford 4.15 g of **24**, 5.45 g of **25**, and 11.5 g of mixed fractions (combined yield of 86%). **24**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35−7.29 (m, 5H), 5.48 (br d, J = 4.7 Hz, 1H), 5.09 (br d, J = 7.0 Hz, 1H), 4.85−4.83 (m, 1H), 4.43 (br d, J = 4.9 Hz, 1H), 4.40 (s, 2H), 3.47 (s, 3H), 3.43 (s, 3H), 1.49 (d, 3H, J = 6.8 Hz), 1.06 (br s, 21H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.0, 143.0, 128.6, 127.4, 125.9, 103.4, 85.2, 79.0, 64.0, 55.5, 54.6, 52.0, 50.9, 22.4, 17.9, 11.9; IR (film) 3331, 2944, 2869, 1719, 1506, 1456, 1375, 1244, 1150, 1088 cm^{-1}; MS (CI, isobutane) *m*/*e* calcd for $C_{25}H_{42}NO_5Si$: 464.2832; found 464.2840 (MH); $[\alpha]^{23}_D$ −14.0, $[\alpha]_{405}$ −46.7, $[\alpha]_{435}$ −35.6, $[\alpha]_{546}$ −20.7, $[\alpha]_{577}$ −17.9 (*c* 0.64, $CHCl_3$).

Following the general procedure of Pirkle,[27] a solution of carbamate **24** (1.21 g, 2.62 mmol), Cl_3SiH (0.30 mL, 2.88 mmol), Et_3N (0.40 mL, 2.88 mmol), and dry toluene (7 mL) was stirred at 23 °C for 12 h. The resulting mixture was quenched with saturated aqueous NH_4Cl (20 mL), the layers were separated, and the aqueous layer was extracted with Et_2O (3 × 20 mL). The combined organic layers were washed with brine (2 × 10 mL), dried (Na_2SO_4), and concentrated. Purification of the residue on silica gel (2:1 pentane−Et_2O) yielded 0.73 g (88%) of (*S*)-**21** as a light yellow oil (>98% ee by Mosher ester analysis):[18] $[\alpha]^{23}_D$ −3.7.

Carbamate diastereoisomer **25** (4.34 g, 9.38 mmol) was cleaved with Cl_3SiH and Et_3N, exactly as described for epimer **24**, to give the corresponding (*R*)-alcohol (2.62 g, 8.28 mmol, >98% ee).[18] A solution of this sample, Ph_3P (3.46 g, 13.2 mmol) and dry THF (100 mL) was treated dropwise with a solution of DEAD (2.1 mL, 13.2 mmol) and dry THF (10 mL) over 10 min at −20 °C. After 1 h, a solution of benzoic acid (0.96 g, 7.9 mmol) and dry THF (10 mL) was added dropwise over 5 min, and the resulting solution was allowed to warm to 23 °C. After 3 h, the reaction was concentrated, and the resulting residue was purified on silica gel to provide 3.3 g of the (2*S*)-benzoate.

To a solution of this sample of the (2*S*)-benzoate and dry MeOH (160 mL) at 23 °C was added K_2CO_3 (5.43 g, 39.3 mmol) in portions over 5 min. After 4 h, the reaction was concentrated, and the resulting residue was dissolved in Et_2O (50 mL). The organic layer was washed with H_2O (2 × 10 mL) and brine (2 × 10 mL), dried ($MgSO_4$), filtered, and concentrated. Purification of the residue on silica gel yielded 1.67 g (64%) of (*S*)-**21** (>98% ee by Mosher ester analysis)[18] as a light yellow oil.

(2*S*)-1,1-Dimethoxy-5-(triisopropylsiloxy)pentan-2-ol (26). A mixture of (*S*)-**21** (2.99 g, 9.46 mmol, >98% ee), 5% Pd/$BaSO_4$ (200 mg) and dry MeOH (32 mL) was stirred under 1 atm of H_2 for 3 h. The reaction was then filtered through a plug of silica gel, and the plug was washed with ∼500 mL of Et_2O. Concentration, followed by purification of the residue on silica gel (2:1 pentane−Et_2O) provided 2.93 g (97%) of **26** as a clear oil (>98% ee by Mosher ester analysis):[18] ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.14 (d, J = 5.9 Hz, 1H), 3.72 (t, J = 6.0 Hz, 2H), 3.62 (ddd, J = 9.1, 6.0, 2.6 Hz, 1H), 3.44 (s, 3H), 3.41 (s, 3H), 1.77−1.64 (m, 3H), 1.50−1.42 (m, 1H), 1.05 (s, 21H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 107.0, 71.2, 63.5, 55.0, 54.8, 29.0, 28.6, 18.0, 12.0; IR (film) 3463 (br), 2944, 2869, 1463, 1381, 1244, 1194, 1100, 981, 881 cm^{-1}; MS (CI, isobutane) *m*/*e* calcd for $C_{16}H_{37}O_4Si$: 321.2461; found 321.2436 (MH); $[\alpha]^{23}_D$ −11.7, $[\alpha]_{405}$ −26.4, $[\alpha]_{435}$ −22.8, $[\alpha]_{546}$ −13.2, $[\alpha]_{577}$ −10.5 (*c* 1.2, $CHCl_3$).

(2*R*)-2-Chloro-1,1-dimethoxy-5-(triisopropylsiloxy)pentane (27). A solution of **26** (593 mg, 1.85 mmol) and dry CH_2Cl_2 (12 mL) was cooled to 0 °C, and dry pyridine (0.25 mL, 3.2 mmol) and Tf_2O (0.47 mL, 2.8 mmol) were sequentially added dropwise. This mixture was stirred for 1 h at 0 °C, (*n*-Bu)$_4$NCl (1 M in CH_2Cl_2, 18.5 mL, 18.5 mmol) was added, and the reaction was stirred at 23 °C for 12 h and then concentrated. The residue was purified on silica gel (19:1 pentane−Et_2O) to afford 445 mg (71%) of **27** as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.33 (d, J = 6.0 Hz), 3.94 (ddd, J = 9.3, 6.3, 3.2 Hz, 1H), 3.73−3.70 (m, 2H), 3.44 (s, 3H), 3.43 (s, 3H), 2.07−2.02 (m, 1H), 1.85−1.73 (m, 1H), 1.73−1.62 (m, 2H), 1.05 (s, 21H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 106.2, 62.7, 61.6, 55.3, 54.7, 29.4, 29.2, 18.0, 11.9; IR (film) 2944, 2869, 1463 cm^{-1}; MS (CI, isobutane) *m*/*e* calcd for $C_{16}H_{36}ClO_3Si$: 339.2122; found 339.2089 (MH); $[\alpha]^{25}_D$ +13.4, $[\alpha]_{577}$ +10.6, $[\alpha]_{546}$ +11.9, $[\alpha]_{435}$ +17.6, $[\alpha]_{405}$ +19.4 (*c* 1.07, $CHCl_3$). Anal. Calcd for $C_{16}H_{36}ClO_3Si$: C, 56.69; H, 10.41. Found: C, 56.76; H, 10.41.

(3*S*,4*S*)-3-Bromo-4-[(2*R*)-2-chloro-1-methoxy-5-(triisopropylsiloxy)-pentoxy]-7-(trimethylsilyl)-7-octene (34). To a solution of **27** (286 mg, 0.844 mmol) and dry CH_2Cl_2 (4.5 mL) at −78 °C was added Me_2BBr (1.02 M in CH_2Cl_2, 0.83 mL, 0.84 mmol) over a period of 5 min. The reaction was maintained at −78 °C for 1 h, at 23 °C for an

additional h, and the solvent and Me_2BOMe were then removed under reduced pressure to yield crude α-bromoether **31**: diagnostic doublet in the ^{1}H NMR at δ 4.25 (J = 5.8 Hz, 1H, OCHBr).

A solution of this sample, dry CH_2Cl_2 (2.3 mL) and *i*-Pr_2NEt (0.96 mL, 5.5 mmol) was cooled to 0 °C. A solution of **14** (94 mg, 0.34 mmol) and dry CH_2Cl_2 (1 mL) was then added, followed by AgOTf (220 mg, 0.84 mmol). The resulting brown mixture was stirred for 3 h and then allowed to warm to 23 °C. The crude reaction was flushed through a plug of silica gel to remove the silver salts, and the plug was washed with ∼150 mL of Et_2O. Concentration of the eluent, followed by purification of the residue on silica gel (50:1 pentane−Et_2O, 25:1 pentane−Et_2O) provided 203 mg (103%) of mixed acetal **34**, which was contaminated with ∼10% of an inseparable impurity (^{1}H NMR analysis): ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.61−5.60 (m, 1H), 5.36−5.34 (m, 1H), 4.55−4.53 (m, 1H), 4.16−4.01 (m, 1H), 3.97−3.92 (m, 1H), 3.85−3.77 (m, 1H), 3.76−3.67 (m, 2H), 3.46 and 3.44 (s, 3H), 2.47−2.40 (m, 1H), 2.39−2.26 (m, 1H), 2.24−1.93 (m, 4H), 1.91−1.77 (m, 1H), 1.76−1.58 (m, 3H), 1.10−1.02 (s, 24H), 0.10 (s, 9H); IR (film) 2956, 2869, 1463, 1381, 1250, 1200, 1106, 1069, 925 cm^{-1}; MS (CI, isobutane) *m*/*e* calcd for $C_{25}H_{51}{}^{79}BrClO_2Si_2$: 553.2299; found 553.2311 (MH−MeOH).

(2*S*,7*R*)-2-[(1*S*)-1-Bromopropyl]-7-[(1*R*)-chloro-4-hydroxybutyl]-2,3,6,7-tetrahydrooxepin (36). To a solution of mixed acetal **34** (64 mg) and dry CH_2Cl_2 (2.5 mL) at −78 °C was added BCl_3 (1 M in CH_2Cl_2, 40 μL, 0.04 mmol) over a period of 10 min. The resulting solution was allowed to warm to 23 °C over 20 min and then was concentrated. This residue was dissolved in dry CH_2Cl_2 (2.5 mL) and cooled to 0 °C, and BCl_3 (1 M in CH_2Cl_2, 0.11 mL, 0.11 mmol) was then added dropwise. The resulting solution was maintained at 0 °C for 15 min, and the reaction was then quenched with 1 M NaOH (2.2 mL). The layers were separated, the aqueous layer was extracted with Et_2O (2 × 10 mL), and the combined organic layers were washed with brine (20 mL), dried (Na_2SO_4), and concentrated.

The resulting residue was dissolved in dry THF (1 mL), and TBAF (1 M in THF, 260 μL, 0.26 mmol) was added at 0 °C. The reaction was then allowed to warm to 23 °C over 4 h. Concentration, followed by purification of the residue on silica gel (1:1 pentane−Et_2O) provided 30 mg (86% from **14**) of **36** as a light yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.80−5.77 (m, 2H), 3.93−3.87 (m, 2H), 3.67 (t, J = 6.1 Hz, 2H), 3.57−3.50 (m, 2H), 2.53−2.47 (m, 2H), 2.33−2.29 (m, 2H), 2.01−1.95 (m, 2H), 1.86−1.74 (m, 3H), 1.67−1.63 (m, 1H), 1.03 (t, J = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 129.0, 128.9, 82.0, 81.8, 64.9, 62.1, 61.6, 33.9, 32.4, 30.2, 29.8, 28.0, 12.6; IR (film) 3363 (br), 3025, 2938, 2875, 1700, 1656, 1456, 1381, 1325, 1219, 1113, 1063 cm^{-1}; MS (CI, isobutane) *m*/*e* calcd for $C_{13}H_{23}{}^{79}BrClO_2$: 325.0570; found 325.0558 (MH); $[\alpha]^{23}_D$ +10.2, $[\alpha]_{405}$ +25.8, $[\alpha]_{435}$ +21.4, $[\alpha]_{546}$ +12.0, $[\alpha]_{577}$ +10.1 (*c* 1.0, $CHCl_3$).

At shorter reaction times, the intermediate α-chloroether **35** could be observed by ^{1}H NMR analysis: diagnostic doublet at δ 4.45 (J = 5.9 Hz, 1H, OCHCl).

The cyclization of **34** prepared from **14** and (±)-**27** provided **36** and a diastereomer in a 1:1 ratio (GLC analysis): ^{13}C NMR (125 MHz, $CDCl_3$) diagnostic signals at δ 82.7 (*epi*), 82.0, 81.8, 81.2 (*epi*), 65.0 (*epi*), 64.9, 62.2 (*epi*), 62.1, 61.6, 61.4 (*epi*).

(2*S*,7*R*)-2-[(1*S*)-1-Bromopropyl]-7-[(1*R*)-chloro-(4*RS*)-hydroxy-5-hexynyl]-2,3,6,7-tetrahydrooxepin (37). Dess−Martin periodinane[35] (101 mg, 0.12 mmol) was added to a solution of alcohol **36** (39 mg, 0.12 mmol) and dry CH_2Cl_2 (1 mL), and the resulting mixture was stirred at 23 °C for 25 min. The reaction was then quenched with 1 M NaOH (1 mL), and the resulting mixture was stirred until the aqueous layer was homogeneous. The layers were separated, the aqueous layer was extracted with Et_2O (2 × 5 mL), and the combined organic layers were washed with brine (5 mL), dried (Na_2SO_4), and concentrated to give the corresponding aldehyde: ^{1}H NMR (300 MHz, $CDCl_3$) diagnostic singlet at δ 9.82 (1H).

A solution of this crude aldehyde and dry THF (1 mL) at −78 °C was immediately treated dropwise with ethynylmagnesium bromide (0.5 M in THF, 1.1 mL, 0.5 mmol), and the resulting solution was allowed to warm to 23 °C over 1 h. The reaction was then quenched with saturated aqueous NH_4Cl (1 mL), the layers were separated, and the aqueous layer was extracted with Et_2O (2 × 5 mL). The combined organic layers were washed with brine (10 mL), dried (Na_2SO_4), and concentrated. Purification of the residue on silica gel (2:1 pentane−Et_2O) afforded 31 mg (74%) of the propargylic alcohol **37** as a yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.80−5.78 (m, 2H), 4.43−4.40 (m, 1H), 3.95−3.89 (m, 2H), 3.60−3.49 (m, 2H), 2.54−2.48 (m, 3H), 2.32−2.29 (m, 2H), 2.11−2.05 (m, 1H), 2.02−1.80 (m, 6H), 1.03 (t, J = 7.2 Hz, 3H); IR (film) 3381 (br), 3300, 3019, 2969, 2938, 2900, 2119, 1656, 1456, 1431, 1381, 1325, 1306, 1219, 1113, 1069, 1031 cm^{-1}; MS (CI, NH_3) *m*/*e* calcd for $C_{15}H_{26}{}^{79}BrClNO_2$: 366.0835; found 366.0835 (M + NH_4).

(+)-Isolaurepinnacin (3). Following the general procedure of Nicholas and Pettit,[36a] a solution of $Co_2(CO)_8$ (47 mg, 0.14 mmol) and dry Et_2O (1 mL) was added dropwise to a solution of **37** (48 mg, 0.14 mmol) and dry Et_2O (1 mL) at −23 °C. The resulting orange-red solution was warmed to 0 °C and after 2 h was concentrated. This residue was dissolved in dry CH_2Cl_2 (2 mL) and cooled to −78 °C, and freshly distilled Tf_2O (69 μL, 0.41 mmol) was added dropwise. The resulting solution was then allowed to warm to −5 °C, and after 2 h, the reaction was quenched with saturated aqueous $NaHCO_3$ (2 mL), and the layers were separated. The H_2O layer was extracted with Et_2O (3 × 5 mL), and the combined organic layers were dried ($MgSO_4$) and concentrated. The resulting residue was dissolved in acetone (2 mL) and $(NH_4)_2Ce(NO_3)_6$ (0.75 g, 1.4 mmol) was added. After gas evolution had ceased, the solution was concentrated, and the residue was purified on silica gel (19:1 pentane−Et_2O) to provide 29 mg (65%) of **3** as a colorless oil, whose NMR data matched those of the natural isolate: $[\alpha]^{23}_D$ +0.6, $[\alpha]_{405}$ +3.2, $[\alpha]_{435}$ +2.0, $[\alpha]_{546}$ +1.2, $[\alpha]_{577}$ +0.7 (*c* 1.4, $CHCl_3$).[40]

Preparation of (2*S*,7*R*)-2-Hexyl-7-propyl-2,3,4,5,6,7-hexahydrooxepin (39) from Synthetic Isolaurepinnacin. The procedure employed in the original degradation of natural isolaurepinnacin was employed.[5] A mixture of synthetic (+)-**3** (15 mg, 0.05 mmol), Pd/$BaSO_4$ (10 mg), and dry MeOH (1 mL) was stirred under 1 atm of H_2 at 23 °C. After 1.5 h, the reaction was filtered through Florisil, the plug was washed with ∼20 mL of Et_2O, and the eluent was concentrated to yield octahydroisolaurepinnacin, which was used without further purification.

A mixture of this sample, Raney Ni (200 mg), and dry EtOH (2 mL) was heated at 150 °C for 24 h in a sealed tube. The reaction was then cooled to 23 °C, filtered, and concentrated. The resulting residue was purified on silica gel (9:1 pentane−Et_2O) to yield 8 mg (77%) of **37** as a colorless oil. The ^{1}H NMR and ^{13}C NMR spectra of this sample were identical to that reported for this compound.[5,8] The optical rotation of **37** was $[\alpha]^{23}_D$ +1.9 (*c* 0.43, $CHCl_3$); lit.[8] $[\alpha]^{24}_D$ +1.6 (*c* 1.2, $CHCl_3$).

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Supporting Information Available: Experimental procedures and characterization data for the preparation of **16**, 1-(triisopropyl)-2-propyne, and compounds reported in Scheme 5 and copies of ^{1}H NMR (500 MHz) and ^{13}C NMR (125 MHz) spectra of synthetic (+)-**3** (7 pages). See any current masthead page for ordering and Internet access instructions.

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