Total Synthesis of (+)-Laurencin. Use of Acetal−Vinyl Sulfide Cyclizations for Forming Highly Functionalized Eight-Membered Cyclic Ethers

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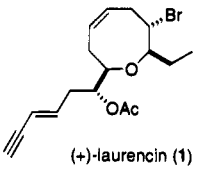
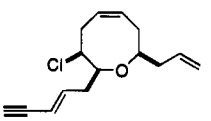
Abstract: The enantioselective total synthesis of (+)-laurencin (**1**) is accomplished in 24 steps from allyl alcohol. The synthesis features an acetal−vinyl sulfide cyclization that forms the oxocene ring and introduces, with complete control, the Δ^4 unsaturation and requisite functionality at carbons 3, 4, and 9. Starting with allyl alcohol, mixed acetal **17** is constructed in seven steps and 38% overall yield (Scheme 2). Exposure of **17** to excess $BF_3{\cdot}OEt_2$ in *t*-BuOMe at −70 → −40 °C affords Δ^4-oxocene **27** in 55−65% yield (Scheme 4). Removal of the phenylthio group, followed by elaboration of the C(9) side chain and introduction of bromine at C(4), completes the construction of (+)-laurencin (Schemes 4 and 5).

Red algae produce a breathtaking diversity of secondary metabolites.[2] Distinctive members of this marine natural products group are the C_{15} acetogenins, many of which are halogen-containing cyclic ethers of diverse ring sizes. The prototypical member of the eight-membered cyclic ether subgroup is (+)-laurencin (**1**), which was first isolated from



(+)-laurencin (**1**)



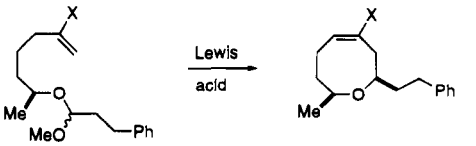
(-)-laurenyne (**2**)

methanol extracts of *Laurencia glandulifera* by Irie and Masamune in 1965.[3] On the basis of chemical degradation and spectroscopic studies, these researchers proposed that laurencin was a bromine-containing Δ^4-oxocene. Four years later this proposal was confirmed and the stereochemistry and absolute configuration of (+)-laurencin were fully defined by single-crystal X-ray analysis.[4]

The pioneering synthetic investigations in this area were carried out also in Hokkaido and culminated in the Masamune group's total synthesis of (±)-laurencin in 1977.[5] Recently, the first enantioselective total syntheses of (+)-laurencin, starting in each case from (*R*)-malic acid, were accomplished in notably concise fashion by the Murai[6] and Holmes[7] groups.

The significant challenge in forming eight-membered cyclic ethers has stimulated the development of a number of imaginative syntheses of oxocanes and oxocenes.[8] Not surprisingly, ring-expansion reactions have been a common theme in these developments, and were employed in the previous three syntheses of laurencin.[5-7] Our own investigations in this area have focused on the challenging direct construction of medium ring ethers from acyclic precursors.[9] In 1986 we first reported that Δ^4-oxocenes could be formed in preparatively useful yields by simple Prins cyclizations of 5-(trimethylsilyl)-5-hexenyl acetals.[9a] This approach was subsequently used by us to prepare (−)-laurenyne (**2**), which at the time constituted only the second total synthesis (and the first enantioselective total synthesis) of an oxocane natural product.[10]

During the latter stages of our exploratory investigations of Lewis acid-promoted cyclizations of 5-hexenyl acetals, we discovered that the yield of Δ^4-oxocene increased dramatically when the 5-substituent was changed from Me_3Si to PhS (eq 1).[9b] As a result, we wished to examine the applicability of



(1)

31% X = Me_3Si ($SnCl_4$, CH_2Cl_2, −60 → −20 °C)
78% X = PhS ($BF_3{\cdot}OEt_2$, *t*-BuOMe, −78 → −30 °C)

related acetal−vinyl sulfide cyclizations for preparing oxocene marine natural products. Laurencin was chosen as an appropriate benchmark target for these studies. Herein, we describe with

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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.* **1994**, *11*, 355 and earlier reviews in this series.

(3) (a) Irie, T.; Suzuki, M.; Masamune, T. *Tetrahedron Lett.* **1965**, 1091. (b) Irie, T.; Suzuki, M.; Masamune, T. *Tetrahedron* **1968**, *24*, 4193.

(4) (a) Cameron, A. F.; Cheung, K. K.; Ferguson, G.; Monteath Robertson, J. *J. Chem. Soc., Chem. Commun.* **1965**, 638. (b) Cameron, A. F.; Cheung, K. K.; Ferguson, G.; Monteath Robertson, J. *J. Chem. Soc. B* **1969**, 559.

(5) (a) Murai, A., Murase, H.; Matsue, H.; Masamune, T. *Tetrahedron Lett.* **1977**, 2507. (b) Masamune, T.; Matsue, H.; Murase, H. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 127. (c) Masamune, T.; Murase, H.; Matsue, H.; Murai, A. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 135.

(6) Tsushima, K.; Murai, A. *Tetrahedron Lett.* **1992**, *33*, 4345.

(7) Robinson, R. A.; Clark, J. S.; Holmes, A. B. *J. Am. Chem. Soc.* **1993**, *115*, 10400.

(8) For a recent review, see: Roxburgh, C. J. *Tetrahedron* **1993**, *49*, 10749.

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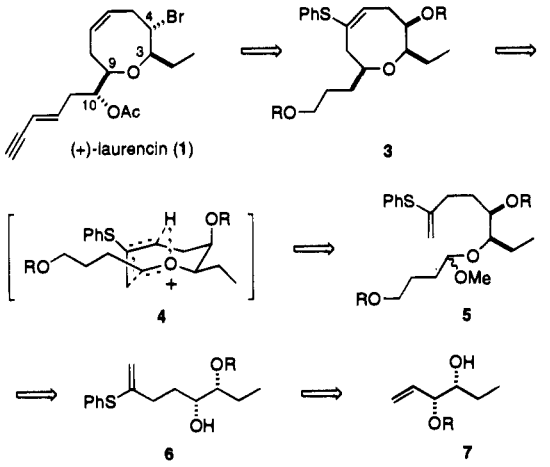
Scheme 1. Synthesis Plan



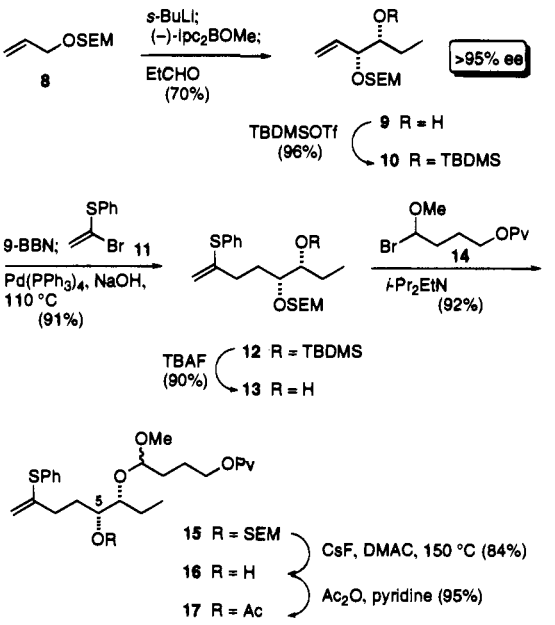
full experimental details these investigations which resulted in an expeditious total synthesis of (+)-laurencin.

Results and Discussion

Synthesis Plan. The strategy we pursued is outlined in Scheme 1. The key 4-(phenylthio)-Δ^4-oxocene intermediate **3** was envisaged to arise from Lewis acid-promoted cyclization of the mixed 5-(phenylthio)-5-hexenyl acetal **5**. As suggested by our earlier exploratory investigations,[9] intramolecular ene cyclization of an (*E*)-oxocarbenium ion intermediate in a topography represented by **4** would establish the required cis orientation of the C(3) and C(9) side chains and regioselectively introduce Δ^4 unsaturation into the eight-membered cyclic ether product. In light of the difficulties encountered in our earlier attempts to employ α-functionalized oxocarbenium ions in cyclizations of 5-(trimethylsilyl)-5-hexenyl acetals,[10] we adopted the conservative strategy of introducing the C(9) side chain with a low level of functionalization in this first generation approach to (+)-laurencin. The mixed acetal **5** could be derived from vinyl sulfide **6**, which we envisaged arising from the monoprotected (*R,R*)-*syn*-1-hexene-3,4-diol **7**.

Preparation of Mixed Acetal 17. Asymmetric allylboration of propanal with the allyldiisopinocampheylborane formed by sequential reaction of allyl ether **8** with *sec*-BuLi, (−)-*B*-methoxydiisopinocampheylborane, and $BF_3{\cdot}OEt_2$ was selected to prepare the syn-diol derivative **9** (Scheme 2). Using Brown's standard conditions,[11] allylboration of propanal at −78 °C formed **9** with high enantioselection (92% enantiomeric excess by HPLC analysis of the benzoate derivative using a Chiralcel OD column), albeit in low yield. We attributed the low yield of **9** to partial cleavage of the [2-(trimethylsilyl)ethoxy]methyl (SEM)[12] ether by $BF_3{\cdot}OEt_2$ (or $LiBF_4$)[13] during the step in which the boronate complex is converted to the allylborane reagent.[11] Omitting the $BF_3{\cdot}OEt_2$ treatment increased the yield of **9**, without compromising enantioselection. Careful optimization of this procedure allowed **9** to be obtained in 70% yield and 95% ee on a large scale. To our knowledge, this result is the

Scheme 2. Synthesis of Mixed Acetal **17**



first instance in which the boronate complex formed from the addition of an (α-alkoxyallyl)lithium to *B*-methoxydiisopinocampheylborane is employed directly (i.e., without reaction with $BF_3{\cdot}OEt_2$), with advantage, in the Brown asymmetric synthesis of *syn*-1,2-diols.

Conversion of **9** to the *tert*-butyldimethylsilyl (TBDMS) ether derivative **10** set the stage for Suzuki coupling[14] with 1-bromo-1-(phenylthio)ethene (**11**).[15] The critical conversion in the Suzuki sequence was found to be the initial hydroboration step, since **10** exhibited unexpectedly low reactivity with 9-borabicyclo-[3.3.1]nonane (9-BBN). In small scale reactions, the use of ultrasound to accelerate the reaction of **10** with 1 equiv of 9-BBN was effective.[16] However, on larger scales we found it preferable to simply employ 1.5−1.7 equiv of 9-BBN and carry out the hydroboration reaction in refluxing THF. After destroying excess 9-BBN by the addition of 3 M NaOH, cross-coupling of the intermediate organoborane with **11** proceeded in excellent yield in a sealed tube at 110 °C in the presence of 5 mol % $Pd(Ph_3P)_4$. Using this procedure, octenyl sulfide **12** was obtained in 70% (10 g scale) to 91% (1 g scale) yield.

Cleavage of the TBDMS protecting group of **12** provided the monoprotected diol **13**. Reaction of **13** with 2 equiv of the α-bromo ether **14**, which is readily available from 5-penten-1-ol as detailed in the Experimental Section, provided the mixed acetal **15** in 83% overall yield from **12**. The SEM ether of this (bis)mixed acetal could be cleaved in good yield by reaction with CsF at high temperature in *N,N*-dimethylacetamide (DMAC) to provide alcohol **16**. This notably selective conversion allowed us to modify the C(5) alcohol protecting group, an important adjustment since the nature of this functionality proved pivotal for the success of the central cyclization step (*vide infra*).

Careful attention to experimental detail was essential in effecting the sequence summarized in Scheme 2 efficiently. Paramount was preventing acid-catalyzed isomerization of the terminal vinyl sulfide unit to the more stable internal regioisomer. This isomerization was readily brought about by acid, e.g., the trace of DCl in $CDCl_3$ or acid residues in untreated glassware. Base washing of all glassware[17] and storing samples

(9) (a) Overman, L. E.; Blumenkopf, T. A.; Castañeda, A.; Thompson, A. S. *J. Am. Chem. Soc.* **1986**, *108*, 3516. (b) Blumenkopf, T. A.; Bratz, M.; Castañeda, A.; Look, G. C.; Overman, L. E.; Rodriguez, D.; Thompson, A. S. *J. Am. Chem. Soc.* **1990**, *112*, 4386. (c) Blumenkopf, T. A.; Look, G. C.; Overman, L. E. *J. Am. Chem. Soc.* **1990**, *112*, 4399. (d) Overman, L. E. *Acc. Chem. Res.* **1992**, *25*, 352.

(10) Overman, L. E.; Thompson, A. S. *J. Am. Chem. Soc.* **1988**, *110*, 2248.

(11) Brown, H. C.; Jadhav, P. K.; Bhat, K. S. *J. Am. Chem. Soc.* **1988**, *110*, 1535.

(12) The standard abbreviations employed in this account are summarized in *J. Org. Chem.* **1994**, *59*, 7A.

(13) Lipshutz, B. H.; Pegram, J. J.; Morey, M. C. *Tetrahedron Lett.* **1981**, *22*, 4603.

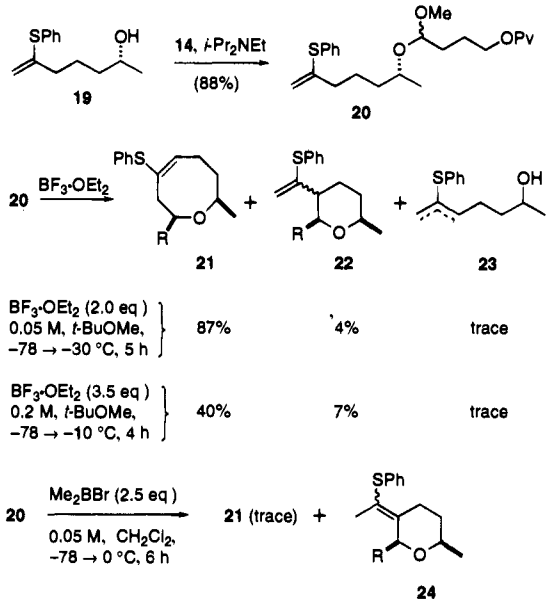
(14) (a) Ishiyama, T.; Miyaura, N; Suzuki, A. *Org. Synth.* **1992**, *71*, 89. (b) Ishiyama, T.; Miyaura, N; Suzuki, A. *Tetrahedron Lett.* **1988**, *29*, 3983.

(15) Paquette, L. A.; Carr, V. C. *Organic Syntheses;* Wiley: New York, 1990; Collect. Vol. VII, p 453.

(16) Brown, H. C.; Racherla, U. S. *Tetrahedron Lett.* **1985**, *26*, 2187.

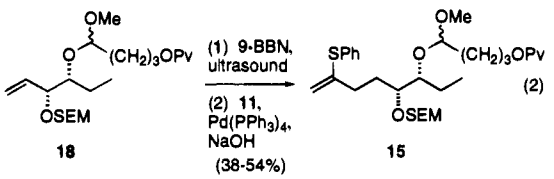
(17) Pine, S. H.; Kim, G; Lee, V. *Org. Synth.* **1990**, *69*, 72.

Scheme 3. Cyclization Model Studies (R = $(CH_2)_3OPv$)



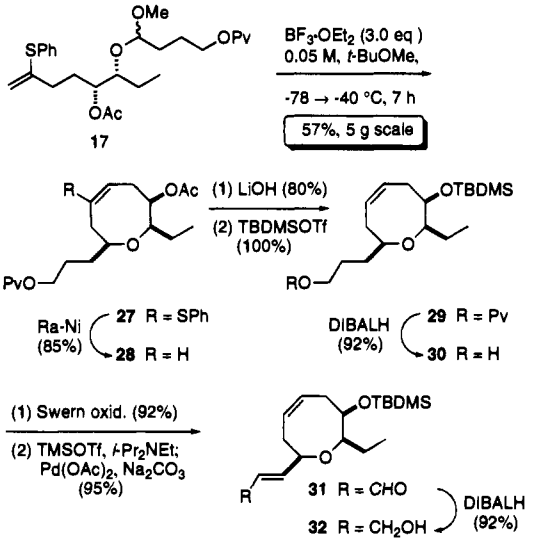
containing the 1-alkenyl-2-(phenylthio) group in frozen benzene were crucial to minimizing double bond isomerization.

Unfortunately, it did not prove possible to accomplish the Suzuki coupling step with alkene substrates that would obviate the need for the C(6) silyl protecting group. Thus, although hydroboration of homoallylic alcohol **9** could be accomplished (established by oxidation to form the corresponding primary alcohol), the Suzuki coupling step failed completely with the derived organoborane intermediate. Attempted reaction of the mixed acetal **18** (readily prepared from **9** and **14**) with 9-BBN at room temperature resulted in reduction of the acetal. Hydroboration of **18** could be executed at room temperature in the presence of $Rh(Ph_3P)_3Cl$;[18] however, the subsequent Pd-catalyzed coupling step was apparently undermined by the presence of rhodium residues. The desired hydroboration of **18** and subsequent cross-coupling with **11** could be achieved in 38−54% yield using ultrasound to accelerate the initial hydroboration step (eq 2).[16] However, we were never successful in further optimizing this more direct, though less efficient, synthesis of **15**.

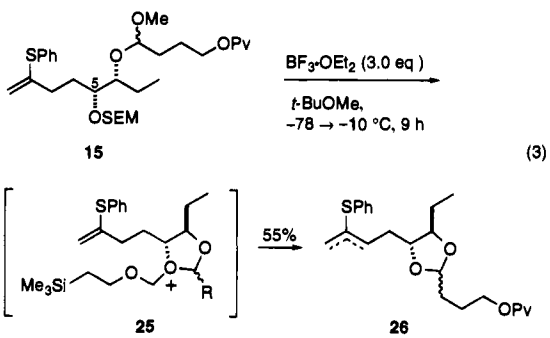


Cyclization to form Oxocene 27. Prior to examining the cyclization of the mixed acetals **15** and **17**, we studied the intramolecular Prins reaction of the mixed acetal **20** which lacks oxidation at C(5) (Scheme 3). Low-temperature cyclization of **20** in *t*-BuOMe in the presence of BF_3·OEt_2 (the solvent and Lewis acid found optimal in our earlier studies)[9b] provided oxocene **21** in an outstanding 87% yield when 2 equiv of BF_3·OEt_2 was employed. Use of a larger excess of BF_3·OEt_2 dramatically lowered the cyclization efficiency. Minor products produced in this reaction were the tetrahydropyrans **22** resulting from Prins cyclization of the internal vinyl sulfide regioisomer of **20** and the alcohol vinyl sulfides **23**. These latter products undoubtedly result from cleavage of the mixed acetal **20** in the undesired sense to form the methoxyoxocarbenium ion (*vide infra*). Since BCl_3 had proven effective in activating OMe to achieve selective oxocarbenium ion formation in a demanding acetal−vinylsilane cyclization,[19] the related Lewis acid Me_2BBr was examined also. However, Me_2BBr treatment of the vinyl sulfide mixed acetal **20** afforded a complex mixture of products from which only a trace of oxocene **21** and the tetrahydropyran vinyl sulfide **24** could be isolated.

Scheme 4. Cyclization of Oxocene **27** and Elaboration to **32**



We turned next to the cyclization of vinyl sulfide acetal **15** (eq 3). Not surprisingly, treatment of **15** with BF_3·OEt_2 under a variety of conditions led to the formation of dioxolane **26**,



which showed diagnostic signals for the C(2) methine hydrogen at δ 5.0. Dioxolane **26** would arise from capture of the oxocarbenium ion intermediate by the proximal oxygen of the SEM ether (or from direct participation of this group in acetal cleavage) to form **25**.

The nucleophilic character of the C(5) oxygen clearly had to be moderated, and employing an electron-withdrawing protecting group was an obvious solution. Therefore, we examined analogs of **15** in which the alcohol protecting group was Ts, $COCF_3$, or Ac, and the acetate group proved optimal. Cyclization of acetate **17** in *t*-BuOMe at −78 → −40 °C in the presence of 3 equiv of BF_3·OEt_2 afforded the *cis*-2,8-disubstituted oxocene **27** as the major product (Scheme 4). Yields for this conversion ranged from 55% to 65%, with a 57% yield being realized in a 5 g scale cyclization. Analysis of the crude cyclization product by ^1H and ^{13}C NMR data confirmed that **27** was formed as a single regio- and stereoisomer.

Four additional products were isolated from large scale cyclizations of **17**: tetrahydropyran **33** (7%), the internal vinyl sulfide acetals **34** (~18%) and two polar products (~14%), the

(18) (a) Burgess, K.; Ohlmeyer, M. J. *Chem. Rev.* **1991**, *91*, 1179. (b) Burgess, K.; van der Donk, W. A.; Weskott, S. A.; Marder, T. B.; Baker, R. T.; Calabrese, J. C. *J. Am. Chem. Soc.* **1992**, *114*, 9350. (c) Evans, D. A.; Fu, G. C.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1988**, *110*, 6917.

(19) Berger, D.; Overman, L. E.; Renhowe, P. A. *J. Am. Chem. Soc.* **1993**, *115*, 9305.

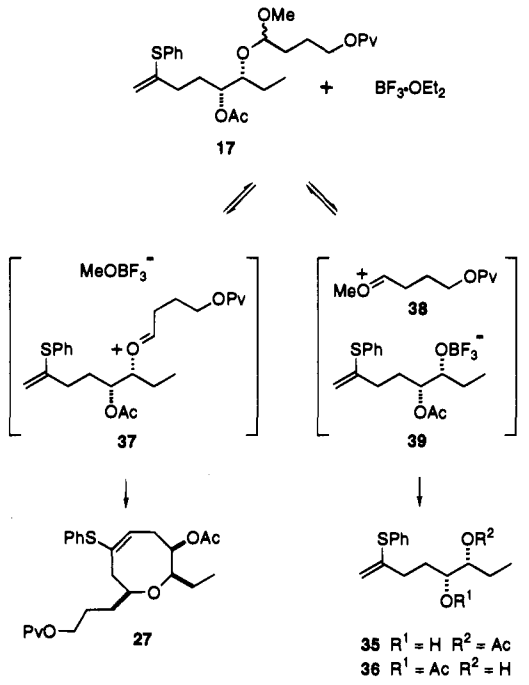
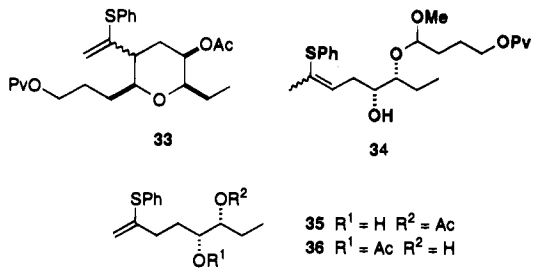


Figure 1. Alternate modes of cleavage of mixed acetal **17**.

hydroxy vinyl sulfide acetates **35** and **36**. We assume that the acetate precursor of **34** was cleaved during workup and that **36** arose by acetyl migration.



The isolation of these byproducts provides some insight into the origin of the lower yield of oxocene realized in the BF_3·OEt_2-promoted cyclization of mixed acetal **17** than in the cyclization of the simpler acetal **20**. Notably, in cyclizations of this latter mixed acetal that lacks the proximal acetate substituent, no polar byproducts corresponding to **35** and **36** were seen by TLC analysis of the crude cyclization product. Apparently, electron withdrawal by the acetate group of **17** destabilizes oxocarbenium ion **37** sufficiently that acetal cleavage in the undesired sense to form **38** and **39** (and ultimately **35** and **36**) is a competing process (Figure 1). This destabilization of **37** by the neighboring acetate group could also decrease the rate of oxocene formation and, thus, be responsible for the larger degree of double bond isomerization seen in the cyclization of **17** (leading to the isolation of **33** and **34**).

Completion of the Total Synthesis of (+)-Laurencin. Desulfurization of oxocene **27** took place cleanly with Raney nickel to deliver **28** (Scheme 4). The conversion of **28** to (+)-laurencin requires development of the six-carbon C(9) side chain and the introduction of bromine with inversion at C(4). To set the stage for the former functionalization, the hydroxy protecting group at C(4) was first changed to TBDMS and the pivaloyl group of **29** was cleaved to form the primary alcohol **30**. Oxidation of **30** to aldehyde **31** was followed by Saegusa–Ito oxidation[20] to provide the (*E*)-enal **31** (none of the *Z* stereoisomer was seen in the 500 MHz ^{1}H NMR spectrum of the crude oxidation product). Reduction of **31** with DIBAL-H then provided **32**. Although requiring seven steps, the conversion of **28** → **32** could be accomplished in a quite satisfactory overall yield of 59%.

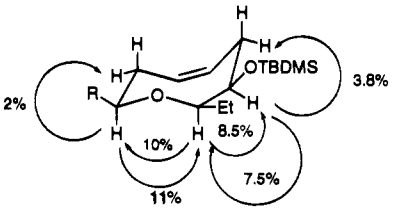
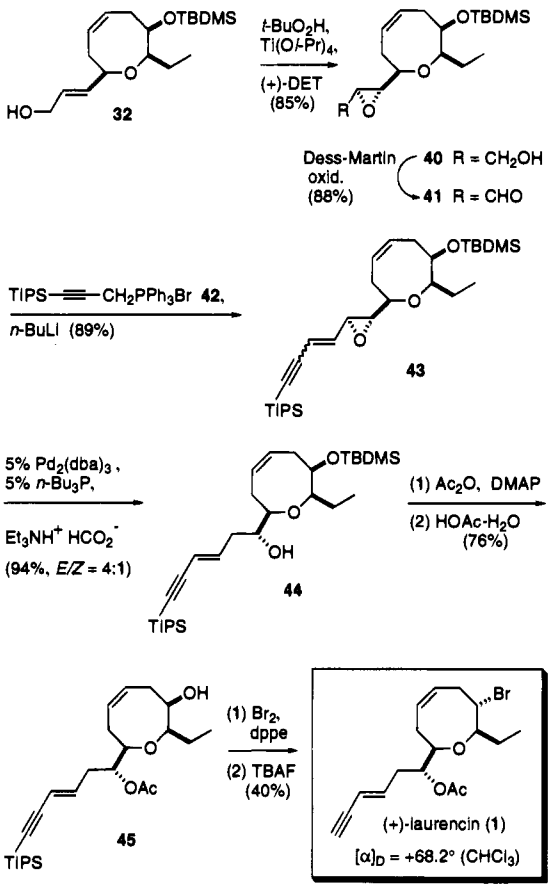


Figure 2. ^{1}H NMR NOE enhancements of oxocene **29** [R = $(CH_2)_3$-OPv].

Scheme 5. Conversion of **32** to (+)-Laurencin



At the stage of **29** the stereochemistry of the Δ^4-oxocene could be confirmed by the ^{1}H NOE enhancements summarized in Figure 2. The boat–chair (*BC*-2) conformation depicted for **29** in Figure 2 is the one found for laurencin by single-crystal X-ray analysis.[4]

Several approaches were then explored for introducing the (*E*)-enyne and (*R*)-acetate functionalities of the C(9) side chain. The ultimately successful strategy is summarized in Scheme 5. Sharpless epoxidation of **32** using the reagent derived from (+)-diethyl tartrate provided a single epoxy alcohol, **40**.[21] The high selectivity of this conversion (no stereoisomer was detectable in the 500 MHz ^{1}H NMR spectrum of the crude oxidation product) is attributable to matching of substrate, and reagent-controlled diastereoselection.[21] Oxidation of **40** to epoxy aldehyde **41** was most efficiently accomplished with the Dess–Martin periodinane.[22] Subsequent Wittig condensation of **41**

(20) Ito, Y.; Hirao, T.; Saegusa, T. *J. Org. Chem.* **1978**, *43*, 1011.

(21) Rossiter, B. E. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic: New York, 1985; Vol. 5, Chapter 7.

(22) (a) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4156. (b) Ireland, R. E.; Liu, L. *J. Org. Chem.* **1993**, *58*, 2899.

with the ylide derived from phosphonium salt **42**[23] provided enyne **43** in 89% yield as a 3:1 mixture of *E* and *Z* stereoisomers. Stereoselection in this step was of no consequence, since both double bond isomers were converted to **44** with similar stereoselectivity (*E*:*Z* = 4:1) in nearly quantitative yield upon palladium-catalyzed hydrogenolysis.[24] At this point, the (*E*)- and (*Z*)-enyne stereoisomers were separated on silica gel and the *E* isomer **44** was taken on to (+)-laurencin.[25]

Acetylation of **44** followed by cleavage of the TBDMS group at room temperature with 80% aqueous acetic acid provided **45**. Conversion of this intermediate to (+)-laurencin was achieved by treatment with the bromophosphonium salt prepared from bis(diphenylphosphino)ethane and Br_2, followed by cleavage of the triisopropylsilyl group with tetrabutylammonium fluoride (TBAF). Although trioctylphosphine−CBr_4[6] and 1,2-bis(diphenylphosphino)ethane−Br_2[7] have been reported to convert the trimethylsilyl analog of **45** to the trimethylsilyl derivative of (+)-laurencin in high yield, bromination of the triisopropylsilyl (TIPS) derivative **45** with either reagent was inefficient, resulting in a modest 40% overall yield for the conversion of **45** → (+)-**1**. Synthetic **1** showed ^{1}H NMR and ^{13}C NMR spectra indistinguishable from those of natural and synthetic (+)-laurencin. Moreover, the optical rotation of synthetic **1** was nearly identical to that reported for the natural sample: synthetic (+)-**1**, $[\alpha]^{24}_D$ +68.2° (*c* 0.35, $CHCl_3$); natural (+)-laurencin, $[\alpha]^{24}_D$ +70.2° (*c* 1.0, $CHCl_3$).

Conclusion

In summary, (+)-laurencin was prepared in 24 steps and ~2% overall yield from allyl alcohol as summarized in Schemes 2, 4, and 5. Our synthesis of this benchmark oxocene natural product is the first to employ a cyclization reaction to directly form the eight-membered cyclic ether. The efficiency of the central acetal−vinyl sulfide cyclization step (**17** → **27**) highlights the advantage of employing vinyl sulfide (vis-à-vis vinylsilane) nucleophiles in Prins cyclization reactions to form medium ring ethers.

Experimental Section

Reactions with substrates containing a vinyl sulfide unit were performed in base-washed glassware,[17] and intermediates containing a terminal vinyl sulfide unit were stored in frozen benzene. Unless noted otherwise, new compounds were nearly colorless oils. Other general experimental details were recently described.[26]

3-[[2-(Trimethylsilyl)ethoxy]methoxy]-1-propene (8). To a solution of allyl alcohol (62 g, 1.1 mol), *i*-Pr_2EtN (53 mL, 0.30 mol), and 200 mL of CH_2Cl_2 was added [2-(trimethylsilyl)ethoxy]methyl chloride (30.0 g, 0.18 mol) dropwise over 30 min while the internal temperature was maintained below 0 °C using an ice−salt bath. After the addition was complete, the reaction solution was cooled in an ice−salt bath for 1 h, maintained at room temperature (rt) for 24 h, and then concentrated. The resulting residue was diluted with 200 mL of pentane and then washed with water (100 mL), 1 M HCl (100 mL), saturated aqueous $NaHCO_3$ (100 mL), and brine (100 mL). The organic layer was dried ($MgSO_4$) and concentrated, and the residue was purified by distillation to afford the corresponding SEM ether **8** (27.0 g, 80%): bp 63−65 °C (10 mmHg); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.92 (ddd, J = 17.2, 10.4, 5.6 Hz, 1H), 5.23 (dq, J = 17.2, 1.6 Hz, 1H), 5.18 (dq, J = 10.3, 1.3 Hz, 1H), 4.69 (s, 2H), 4.07 (dt, J = 5.6, 1.3 Hz, 2H), 3.63 (m, 2H), 0.94 (m, 2H), 0.02 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 134.4, 116.9, 94.0, 68.2, 65.1, 18.1, −1.5.

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(24) (a) Oshima, M; Yamazaki, H.; Shimizu, I; Nisar, M.; Tsuji, J. *J. Am. Chem. Soc.* **1989**, *111*, 6280. (b) Shimizu, I; Hayashi, K.; Ide, N.; Oshima, M. *Tetrahedron* **1991**, *47*, 2991.

(25) Although not pursued, conversion of the *Z* stereoisomer of **44** to the (*E*)-enyne should be possible: Ishihara, J.; Kanoh, N.; Fukuzawa, A.; Murai, A. *Chem. Lett.* **1994**, 1563.

(26) Deng, W.; Overman, L. E. *J. Am. Chem. Soc.* **1994**, *116*, 11241.

(3*R*,4*R*)-4-[[2-(Trimethylsilyl)ethoxy]methoxy]-5-hexen-3-ol (9). A modification of the general procedure of Brown was employed.[11] To a cooled solution of ether **8** (10.3 g, 54.7 mmol) and 110 mL of THF was added *sec*-BuLi (49.7 mL of 1.1 M solution in cyclohexane, 54.7 mmol) over 30 min while the internal temperature was maintained below −73 °C. The resulting yellow solution was maintained for 20 min at −78 °C, and then (−)-*B*-methoxydiisopinocampheylborane (54.7 mL of a 1.0 M solution in THF) was added dropwise over 30 min while the internal temperature was maintained below −75 °C. The resulting colorless solution was stirred for 1 h at −78 °C and then cooled to −100 °C. Propanal (9.5 g, 160 mmol) was then added dropwise while the internal temperature was maintained below −97 °C. The reaction was stirred for 3 h at −97 °C and then allowed to slowly warm to rt. The resulting colorless solution was concentrated, and the residue was dissolved in 200 mL of ether. To this solution was added 30% hydrogen peroxide (40 mL) and 8 pellets of NaOH under ice-cooling. The resulting mixture was stirred overnight at rt, and the ether layer was separated. The aqueous layer was extracted with ether (2 × 100 mL), and the combined organic layers were washed with water (100 mL) and brine (100 mL), dried ($MgSO_4$), and concentrated. Isopinocampheol was removed from the crude product by fractionational distillation using a short-path distillation apparatus (64−66 °C, 0.5 mmHg), and the residue was submitted to bulb-to-bulb distillation to afford **9** (9.4 g, 70%): bp 130−140 °C (0.5 mmHg); $[\alpha]^{25}_D$ −88.2°, $[\alpha]^{25}_{577}$ −91.9° $[\alpha]^{25}_{546}$ −104°, $[\alpha]^{25}_{435}$ −173°, $[\alpha]^{25}_{405}$ −205° (*c* 3.4, benzene); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.67 (ddd, J = 17.6, 9.9, 7.9 Hz, 1H), 5.30 (d, J = 15.0 Hz, 1H), 5.27 (d, J = 11.9 Hz, 1H), 4.70 (d, J = 6.9 Hz, 1H), 4.64 (d, J = 6.9 Hz, 1H), 3.85 (t, J = 7.9 Hz, 1H), 3.73 (dt, J = 9.7, 7.6 Hz, 1H), 3.51 (dt, J = 9.7, 7.6 Hz, 1H), 3.43 (m, 1H), 2.60 (br s, 1H), 1.55 (ddd, J = 14.5, 7.4, 3.8 Hz, 1H), 1.39 (dt, J = 14.2, 7.3 Hz, 1H), 0.96 (t, J = 7.4 Hz, 3H), 0.92 (m, 2H), 0.00 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.0, 119.6, 92.3, 81.0, 74.6, 65.5, 25.5, 18.0, 9.8, −1.5; IR (film) 3482, 2925, 1406, 1192, 1135 cm^{-1}; HRMS (CI, isobutane) *m/z* 247.1704 (247.1729 calcd for $C_{12}H_{27}O_3Si$, MH). Anal. Calcd for $C_{12}H_{26}O_3Si$: C, 58.49; H, 10.63. Found: C, 58.58; H, 10.59.

The enantiomeric excess of **9** was determined by chiral HPLC analysis of the corresponding benzoate derivative. To a solution of **9** (30 mg, 0.12 mmol) and pyridine (1 mL) was added benzoyl chloride (17 mg, 0.12 mmol) under ice-cooling. The reaction was stirred under ice-cooling for 1 h and then at rt for 24 h. The reaction then was poured into ice−water and extracted with ether (3 × 5 mL). The combined organic layer was washed with 1 M HCl (10 mL), saturated aqueous $NaHCO_3$ (10 mL), and brine (10 mL), dried ($MgSO_4$), and concentrated. The residue was purified by flash column chromatography (10:1 hexane−EtOAc) to give the benzoate derivative (30 mg). HPLC analysis (Chiralcel OD, hexane, flow rate 0.5 mL/min) showed an enantiomeric purity of >95%: t_R(*R*,*R* enantiomer) = 38 min, t_R(*S*,*S* enantiomer) = 29.7 min.

(3*R*,4*R*)-4-(*tert*-Butyldimethylsiloxy)-3-[[2-(trimethylsilyl)ethoxy]methoxy]-1-hexene (10). To a solution of **9** (6.60 g, 26.8 mmol), 2,6-lutidine (9.3 mL, 80 mmol), and 80 mL of CH_2Cl_2 was added *tert*-butyldimethylsilyl trifluoromethanesulfonate (10.6 g, 40.1 mmol) dropwise over 5 min at 0 °C. The reaction was stirred at 0 °C for 1 h and then at rt for 2 h. The reaction then was diluted with CH_2Cl_2 (100 mL) and washed with saturated aqueous $NaHCO_3$ (100 mL) and brine (100 mL), dried ($MgSO_4$), and concentrated. The residue was purified by short-path distillation to afford **10** (9.3 g, 96%): bp 129−130 °C (1.2 mmHg); $[\alpha]^{25}_D$ −12.6°, $[\alpha]^{25}_{577}$ −13.5°, $[\alpha]^{25}_{546}$ −15.2°, $[\alpha]^{25}_{435}$ −21.0°, $[\alpha]^{25}_{405}$ −25.3 (*c* 1.5, benzene); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.78 (ddd, J = 17.4, 10.5, 6.7 Hz, 1H), 5.26 (m, 1H), 5.22 (m, 1H), 4.69 (d, J = 6.9 Hz, 1H), 4.66 (d, J = 6.9 Hz, 1H), 4.02 (t, J = 5.2 Hz, 1H), 3.70 (dt, J = 9.6, 7.3 Hz, 1H), 3.62 (dt, J = 7.6, 4.4 Hz, 1H), 3.52 (dt, J = 7.6, 4.4 Hz, 1H), 1.60 (ddd, J = 14.4, 7.4, 4.1 Hz, 1H), 1.35 (dt, J = 14.4, 7.3 Hz, 1H), 0.87−0.94 (m, 5H), 0.89 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H), 0.01 (s, 9H), ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.1, 117.7, 92.9, 79.6, 75.6, 65.1, 25.9, 25.2, 18.2, 18.1, 10.0, −1.4, −4.3, -4.7; IR (film) 2957, 2931, 2885, 2859, 1251 cm^{-1}; HRMS (CI, isobutane) *m/z* 345.2281 (345.2278 calcd for $C_{17}H_{37}O_3Si_2$, M − Me). Anal. Calcd for $C_{18}H_{40}O_3Si_2$: C, 59.94; H, 11.17. Found: C, 60.06; H, 11.20.

(5*R*,6*R*)-6-(*tert*-Butyldimethylsiloxy)-2-(phenylthio)-5-[[2-(trimethylsilyl)ethoxy]methoxy]-1-octene (12). A THF solution of 9-BBN

(0.5 M, 12.8 mL, 6.43 mmol) was added dropwise to neat **10** (1.16 g, 3.21 mmol) at 0 °C. The resulting solution was stirred at rt for 30 min and then gently heated at reflux for 3 h. The reaction was then cooled in an ice bath and excess 9-BBN was destroyed by the slow addition of 3 M NaOH (4.3 mL, 13 mmol; ***Caution!***). After stirring for 30 min at rt, the resulting mixture was transferred into a heavy wall tube, and solutions of $Pd(PPh_3)_4$ (185 mg, 5 mol %) in benzene (3 mL) and bromide **11**[15] (1.00 g, 4.80 mmol) in benzene (3 mL) were added. After deoxygenation of the solution with nitrogen, the tube was sealed and heated at 110 °C for 3 h with rapid magnetic stirring. The resulting brown mixture was cooled to rt and poured into 1:1 hexane−water (20 mL). The organic layer was separated, the aqueous layer was extracted with hexane (3 × 10 mL), and the combined organic layer was washed with water (10 mL) and brine (10 mL), dried ($MgSO_4$), and concentrated. This residue was purified by flash chromatography (20:1 hexane−EtOAc) to afford **12** (1.46 g, 91%) as a colorless oil: $[\alpha]^{25}_D$ +0.83°, $[\alpha]^{25}_{577}$ −0.36°, $[\alpha]^{25}_{546}$ −1.77°, $[\alpha]^{25}_{435}$ −5.84°, $[\alpha]^{25}_{405}$ −9.77° (*c* 1.2, benzene); ^{1}H NMR (300 MHz, C_6D_6) δ 7.44−7.47 (m, 2H), 6.94−7.03 (m, 3H), 5.22 (s, 1H), 5.03 (s, 1H), 4.67 (d, *J* = 6.9 Hz, 1H), 4.62 (d, *J* = 6.9 Hz, 1H), 3.84 (ddd, *J* = 10.5, 9.4, 6.5 Hz, 1H), 3.52−3.73 (m, 3H), 2.63 (ddd, *J* = 14.6, 9.8, 5.0 Hz, 1H), 2.49 (ddd, *J* = 14.6, 8.7, 6.8 Hz, 1H), 2.15−2.26 (m, 1H), 1.72−1.87 (m, 2H), 1.38−1.51 (m, 1H), 0.93−1.03 (m, 14H), 0.16 (s, 3H), 0.12 (s, 3H), 0.01 (s, 9H); ^{13}C NMR (75 MHz, C_6D_6) δ 146.7, 133.7, 133.6, 129.4, 127.9, 112.8, 95.9, 81.3, 75.4, 65.4, 33.7, 28.7, 26.1, 24.4, 18.4, 11.2, −1.3, −4.0, −4.4; IR (film) 2896, 2885, 1608, 1440, 1378, 1137, 919 cm^{-1}; HRMS (CI, isobutane) *m/z* 539.3378 (539.3410 calcd for $C_{29}H_{55}O_3SSi_2$, M + C_3H_7). Anal. Calcd for $C_{26}H_{48}O_3Si_2$: C, 62.84; H, 9.74. Found: C, 62.74; H, 9.71.

(3*R*,4*R*)-7-(Phenylthio)-4-[[2-(trimethylsilyl)ethoxy]methoxy]-7-octen-3-ol (13). A solution of **12** (392 mg, 0.79 mmol), TBAF (1.6 mL of 1.0 M solution in THF) and 5 mL of THF was maintained at rt for 18 h. The reaction then was poured into water (5 mL) and extracted with ethyl acetate (3 × 5 mL), and the combined organic layer was washed with water (5 mL), brine (5 mL) and dried ($MgSO_4$), and concentrated. The residue was purified by flash chromatography (10:1 hexane−EtOAc) to afford alcohol **13** (271 mg, 90%): $[\alpha]^{25}_D$ −30.0°, $[\alpha]^{25}_{577}$ −50.7°, $[\alpha]^{25}_{546}$ −49.9°, $[\alpha]^{25}_{435}$ −69.2°, $[\alpha]^{25}_{405}$ −76.6° (*c* 0.46, benzene); ^{1}H NMR (300 MHz, C_6D_6) δ 7.42−7.45 (m, 2H), 6.94−7.02 (m, 3H), 5.10 (s, 1H), 4.98 (s, 1H), 4.56 (d, *J* = 6.9 Hz, 1H), 4.50 (d, *J* = 6.9 Hz, 1H), 3.66 (dt, *J* = 9.3, 8.3 Hz, 1H), 3.49 (dt, *J* = 9.3, 8.3 Hz, 1H), 3.44 (m, 1H), 3.33 (m, 1H), 3.06 (d, *J* = 3.9 Hz, 1H), 2.40 (m, 2H), 1.31−1.98 (m, 4H), 1.05 (t, *J* = 7.3 Hz, 3H), 0.92 (m, 2H), −0.05 (s, 9H); ^{13}C NMR (75 MHz, C_6D_6) δ 146.4, 133.7, 133.5, 129.4, 128.5, 112.8, 95.9, 83.5, 74.3, 65.8, 32.7, 30.4, 26.3, 18.2, 10.2, −1.4; IR (film) 3448, 2995, 2936, 1608, 1249, 1025, 860 cm^{-1}; HRMS (CI, isobutane) *m/z* 425.2548 (425.2546 calcd for $C_{23}H_{41}O_3SSi$, M + C_3H_7). Anal. Calcd for $C_{20}H_{34}O_3SSi$: C, 62.78; H, 8.95. Found: C, 62.75; H, 8.98.

4,4-Dimethoxybutyl 2,2-Dimethylpropanoate. To a solution of 1-penten-5-ol (20 g, 0.23 mol) and 200 mL of pyridine was added trimethylacetyl chloride (30 mL, 0.24 mol) dropwise under ice-cooling over 30 min. The reaction then was allowed to warm to rt with stirring over 2 h. After 2 d, the reaction was poured into ice−water (300 mL) and extracted with ether (3 × 200 mL). The combined organic layer was washed with 1 M HCl (2 × 300 mL), water (300 mL), saturated aqueous $NaHCO_3$ (300 mL), and brine (300 mL), dried ($MgSO_4$), and concentrated. The residue was purified by distillation to afford 4-pentenyl 2,2-dimethylpropanoate (31 g, 79%): bp 78−79 °C (30 mmHg); HRMS (CI, isobutane) *m/z* 171.1397 (171.1385 calcd for $C_{10}H_{19}O_2$, MH).

A portion of this sample (12.6 g, 73.1 mmol) was dissolved in 200 mL of CH_2Cl_2 and cooled to −78 °C. Ozone was added until the solution turned blue, and then excess ozone was removed by sparging with oxygen. Triphenylphosphine (28.7 g, 109 mmol) then was added portionwise at −78 °C, and the reaction was allowed to warm to rt overnight. After concentration, 200 mL of pentane was added and the resulting solution was cooled in an ice bath to precipitate triphenylphosphine oxide. The concentrated filtrate was purified by distillation to afford 4-oxobutyl 2,2-dimethylpropanoate (10.4 g, 83%): bp 99-100 °C (45 mmHg); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.79 (t, *J* = 1.3 Hz, 1H), 4.08 (t, *J* = 6.3 Hz, 2H), 2.52 (dt, *J* = 7.2, 1.3 Hz, 2H), 1.97 (dt, *J* = 14.6, 6.5 Hz), 1.17 (s, 9H).

A solution of a portion of this aldehyde (8.7 g, 51 mmol), trimethyl orthoformate (100 mL, 0.94 mol), pyridinium *p*-toluenesulfonate (2.5 g, 10 mmol), and methanol (400 mL) was maintained for 24 h at rt and then concentrated. This residue was dissolved in 100 mL of ether and washed with saturated aqueous $NaHCO_3$ (100 mL) and brine (100 mL), dried ($MgSO_4$), and concentrated. The resulting residue was purified by distillation to afford 4,4-dimethoxybutyl 2,2-dimethylpropanoate (10.1 g, 92%): bp 105−106 °C (35 mmHg); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.37 (t, *J* = 5.2 Hz, 1H), 4.05 (m, 2H), 3.30 (s, 6H), 1.66 (m, 4H), 1.18 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.5, 104.0, 64.0, 52.7, 38.7, 28.9, 27.1, 23.8; IR (film) 2919, 2910, 2833, 1729, 1481, 1464, 1285, 1070, 666 cm^{-1}; MS (CI, isobutane) *m/z* 187.1339 (187.1334 calcd for $C_{10}H_{19}O_3$, MH − MeOH).

4-Bromo-4-methoxybutyl 2,2-Dimethylpropanoate (14). To a solution of 4,4-dimethoxybutyl 2,2-dimethylpropanoate (9.0 g, 41 mmol) and 100 mL of CH_2Cl_2 was a 2 M CH_2Cl_2 solution of bromodimethylborane (20.6 mL, 41 mmol) dropwise over 15 min at −78 °C. The reaction was maintained at −78 °C for 2 h and then allowed to warm to rt. This solution was concentrated under high vacuum (1 h at 0.5 mmHg), and crude **14** (10.8 g, 98%) was used directly without further purification: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.88 (t, *J* = 5.0 Hz, 1H), 4.06 (t, *J* = 6.3 Hz, 2H), 3.48 (s, 3H), 2.17−2.24 (m, 2H), 1.80−1.90 (m, 2H), 1.16 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.3, 98.5, 63.1, 59.1, 37.2, 26.9, 24.9, 21.2.

(5*R*,6*R*)-6-[1-Methoxy-4-(pivaloyloxy)butoxy]-2-(phenylthio)-5-[[2-(trimethylsilyl)ethoxy]methoxy]-1-octene (15). To a solution of alcohol **13** (6.1 g, 15.9 mmol), *i*-Pr_2EtN (14 mL, 80 mmol), and 70 mL of CH_2Cl_2 was added a solution of bromo acetal **14** (8.5 g, 32 mmol) and 20 mL of CH_2Cl_2 dropwise over 30 min with ice−salt bath cooling. The resulting solution was maintained at 0 °C for 1 h and then allowed to warm to rt over 1 h. After 2.5 h at rt, the reaction solution was washed with saturated aqueous $NaHCO_3$ (100 mL) and brine (100 mL), dried ($MgSO_4$), and concentrated. The resulting residue was purified by flash chromatography (10:1 hexane−EtOAc) to afford **15** (8.8 g, 97%) as a 1:1 mixture of the diastereomer: $[\alpha]^{25}_D$ +3.4°, $[\alpha]^{25}_{577}$ +3.0°, $[\alpha]^{25}_{546}$ +3.3°, $[\alpha]^{25}_{435}$ +3.5°, $[\alpha]^{25}_{405}$ +2.6° (*c* 4.0, benzene); ^{1}H NMR (300 MHz, C_6D_6) δ 7.44−7.47 (m, 2H), 6.94−7.03 (m, 3H), 5.22 and 5.21 (s, 1H total), 5.01 (s, 1H), 4.68 and 4.67 (d, *J* = 6.9 Hz, 1H total), 4.64 and 4.62 (d, *J* = 6.9 Hz, 1H total), 4.56 and 4.43 (m, 1H total), 4.01 (m, 2H), 3.87 and 3.77 (m, 1H total), 3.58−3.67 (m, 3H), 3.15 and 3.14 (s, 3H total), 2.44−2.65 (m, 2H), 2.06−2.30 (m, 1H), 1.68−1.88 (m, 1H), 1.61−1.64 (m, 4H), 1.47 (m, 1H), 1.16 and 1.15 (s, 9H total), 1.09 and 0.99 (t, *J* = 7.4 Hz, 3H total), 0.93−0.99 (m, 2H), 0.00 (s, 9H); ^{13}C NMR (75 MHz, C_6D_6) δ 177.6, 146.7, 146.6, 133.6, 129.4, 129.3, 112.8, 112.7, 104.5, 102.8, 95.7, 80.8, 79.6, 78.8, 78.6, 65.4, 64.2, 64.1, 52.1, 52.0, 38.7, 33.7, 33.5, 30.2, 29.2, 27.3, 24.2, 22.9, 22.4, 18.3, 11.1, 10.9, −1.8; IR (film) 2958, 2935, 2909, 2902, 1728, 1609, 1479, 1284, 1158, 1026 cm^{-1}; HRMS (CI, isobutane) *m/z* 611.3780 (611.3800 calcd for $C_{33}H_{59}O_6SSi$, M + C_3H_7). Anal. Calcd for $C_{30}H_{52}O_6SSi$: C, 63.34; H, 9.21. Found: C, 63.38; H, 9.15.

(3*R*,4*R*)-3-[1-Methoxy-4-(pivaloyloxy)butoxy]-7-octen-4-ol (16). A mixture of CsF (700 mg, 4.6 mmol), the mixed acetal **15** (264 mg, 0.46 mmol), and 8 mL of *N,N*-dimethylacetamide (DMAC) was heated at 150 °C. After 5 h, the reaction was allowed to cool to rt and then poured into saturated aqueous $NaHCO_3$ (5 mL). The resulting mixture was extracted with EtOAc (3 × 5 mL), and the combined organic layer was washed with water (5 mL) and brine (5 mL), dried ($MgSO_4$), and concentrated. The resulting residue was purified by flash chromatography (3:1 hexane−EtOAc) to afford **16** (171 mg, 84%) as a 1:1 mixture of stereoisomers: $[\alpha]^{25}_D$ −8.3°, $[\alpha]^{25}_{577}$ −11.1°, $[\alpha]^{25}_{546}$ −13.6°, $[\alpha]^{25}_{435}$ −26.2°, $[\alpha]^{25}_{405}$ −36.0° (*c* 0.99, benzene); ^{1}H NMR (300 MHz, C_6D_6) δ 7.43−7.46 (m, 2H), 6.95−7.01 (m, 3H), 5.23 and 5.20 (s, 1H total), 5.04 and 5.03 (s, 1H total), 4.40 and 4.17 (t, *J* = 4.8 Hz, 1H total), 3.96−4.02 (m, 2H), 3.52−3.64 (m, 1H), 3.32 (d, *J* = 3.0 Hz, 1H), 3.14−3.27 (m, 1H), 3.06 and 2.97 (s, 3H total), 2.57−2.78 (m, 2H), 2.50 (ddd, *J* = 11.9, 7.6, 4.2 Hz, 1H), 1.21−1.96 (m, 7H), 1.15 (s, 9H), 0.92 and 0.80 (t, *J* = 7.4 Hz, 3H total); ^{13}C NMR (75 MHz, C_6D_6) δ 177.7, 146.4, 146.3, 129.4, 129.3, 128.5, 127.8, 113.3, 104.4, 103.9, 84.3, 81.8, 71.4, 71.2, 53.1, 52.3, 38.7, 33.3, 33.0, 32.5, 30.0, 27.3, 24.2, 24.0, 23.8, 9.7, 9.4; IR (film) 3484, 2955, 2934, 1727, 1608, 1479, 1160 cm^{-1}; HRMS (CI, isobutane) *m/z* 407.2257 (407.2255 calcd for $C_{23}H_{35}O_4S$, MH − MeOH).

(5*R*,6*R*)-5-Acetoxy-6-[1-methoxy-4-(pivaloyloxy)butoxy]-2-(phenylthio)-1-octene (17). To a solution of alcohol **16** (4.9 g, 11 mmol) and 60 mL of pyridine was added acetic anhydride (10 mL, 110 mmol) dropwise at 0 °C, and the resulting solution was maintained at rt for 24 h. The reaction was then poured into cold saturated aqueous $NaHCO_3$ (200 mL) and extracted with EtOAc (3 × 150 mL). The combined organic layer was washed with saturated aqueous $NaHCO_3$ (200 mL), water (200 mL), and brine (200 mL), dried ($MgSO_4$), and concentrated. The resulting residue was purified by flash chromatography (3:1 hexane−EtOAc) to afford acetate **17** (5.1 g, 95%) as a 1:1 mixture of stereoisomers: $[\alpha]^{25}_D$ −0.84°, $[\alpha]^{25}_{577}$ −2.70°, $[\alpha]^{25}_{546}$ −2.90°, $[\alpha]^{25}_{435}$ −10.9°, $[\alpha]^{25}_{405}$ −16.4° (*c* 0.97, benzene); ^{1}H NMR (300 MHz, C_6D_6) δ 7.41 (d, *J* = 7.3 Hz, 2H), 6.93−7.04 (m, 3H), 5.27 and 5.11 (dt, *J* = 9.6, 3.7 Hz, 1H total), 5.14 and 5.13 (s, 1H total), 5.02 and 5.01 (s, 1H total), 4.55 and 4.37 (t, *J* = 4.7 Hz, 1H total), 3.98 (m, 2H), 3.59 and 3.49 (dt, *J* = 6.5, 4.9 Hz, 1H total), 3.14 and 3.12 (s, 3H total), 2.33 (ddd, *J* = 15.2, 13.0, 7.9, 2H), 1.42−2.25 (m, 8H), 1.66 and 1.64 (s, 3H total), 1.14 (s, 9H), 0.96 and 0.84 (t, *J* = 7.3 Hz, 3H total); ^{13}C NMR (75 MHz, C_6D_6) δ 177.6, 169.8, 145.7, 145.5, 133.5, 131.5, 129.4, 129.3, 113.7, 113.5, 103.7, 103.6, 78.5, 78.1, 73.5, 73.2, 64.1, 64.0, 52.5, 38.7, 33.1, 33.0, 30.2, 30.1, 28.7, 28.3, 27.2, 24.1, 24.0, 23.5, 22.8, 20.5, 10.3, 10.2; IR (film) 2988, 2938, 1739, 1731, 1479, 1238, 1150, 1035 cm^{-1}; HRMS (CI, isobutane) *m/z* 449.2408 (449.2361 calcd for $C_{25}H_{37}O_5S$, MH − MeOH).

***cis*-8-Methyl-4-(phenylthio)-2-[3-(pivaloyloxy)propyl]-3,6,7,8-tetrahydro-2*H*-oxocin (21).** To a solution of **20** (262 mg, 0.64 mmol) and *t*-BuOMe (13 mL) was added BF_3·OEt_2 (0.16 mL, 1.3 mmol) dropwise at −78 °C. After 2 h at −78 °C, the reaction was slowly warmed to −50 °C and was maintained between −30 and −50 °C for an additional 5 h. The reaction was then quenched by adding 1 M NaOH (5 mL) and allowed to warm to rt. The resulting mixture was extracted with EtOAc (3 × 10 mL), and the organic layer was washed with brine (20 mL), dried ($MgSO_4$), and concentrated. The residue was purified by flash chromatography (10:1 hexane−EtOAc) to give oxocene **21** (209 mg, 87% yield): ^{1}H NMR (300 MHz, C_6D_6) δ 7.34 (d, *J* = 6.4 Hz, 2H), 6.96−7.05 (m, 3H), 5.97 (dd, *J* = 10.3, 6.9, Hz, 1H), 3.95 (t, *J* = 6.5 Hz, 2H), 3.29 (m, 2H), 2.54 (d, *J* = 14.0 Hz, 1H), 2.51 (m, 1H), 2.04 (d, *J* = 14.0 Hz, 1H), 1.78 (m, 1H), 1.00−1.73 (m, 6H), 1.14 (s, 9H), 0.96 (d, *J* = 6.2 Hz, 3H); ^{13}C NMR (75 MHz, C_6D_6) δ 177.6, 135.7, 134.2, 133.8, 131.0, 129.3, 126.9, 80.3, 74.9, 64.3, 41.2, 38.7, 38.3, 33.4, 27.3, 25.9, 25.7, 22.0; IR (film) 2973, 2933, 2849, 1728, 1583, 1383, 1041 cm^{-1}; HRMS (CI, isobutane) *m/z* 377.2144 (377.2148 calcd for $C_{22}H_{33}O_3S$, MH).

In a similar reaction on a smaller scale (21 mg), the crude product (18 mg) was found by ^{1}H NMR analysis to be a 21:1 mixture of **21** and tetrahyropyran **22**. Separation on silica gel (10:1 hexane−EtOAc) provided a pure specimen of tetrahydropyran **22**: ^{1}H NMR (300 MHz, C_6D_6) δ 7.45 (m, 2H), 6.98 (m, 3H), 4.93 (s, 1H), 4.65 (s, 1H), 4.16 (dt, *J* = 6.4, 1.8, Hz, 2H), 3.47 (m, 1H), 3.20 (m, 1H), 2.15 (m, 1H), 1.23−2.06 (m, 8H), 1.19 (s, 9H); IR (film) 2921, 2914, 1728, 1663, 1536, 1450, 1324 cm^{-1}; HRMS (CI, isobutane) *m/z* 377.2167 (377.2148 calcd for $C_{22}H_{33}O_3S$, MH).

Tetrahydropyran **24** was also isolated as a mixture of stereoisomers from cyclizations of **20** carried out with Me_2BBr: ^{1}H NMR (300 MHz, C_6D_6) δ 7.44 (m, 2H), 6.99 (m, 3H), 3.93−4.02 (m, 3H), 3.47−3.60 (m, 1H), 2.18−2.42 (m, 1H, 2H), 1.20−1.84 (m, 6H), 1.42 and 1.50 (s, 3H total), 1.15 and 1.17 (s, 9H total), 1.05 and 1.03 (d, *J* = 6.1 Hz, 3H total); IR (film) 2977, 2932, 1729, 1663, 1480, 1380, 1269 cm^{-1}; HRMS (CI, isobutane) *m/z* 377.2153 (377.2148 calcd for $C_{22}H_{33}O_3S$, MH).

BF_3·OEt_2-Promoted Cyclization of Mixed Acetal 17. Formation of (2*R*,3*R*,8*R*)-3-Acetoxy-2-ethyl-6-(phenylthio)-8-[3-(pivaloyloxy)-propyl]-3,4,7,8-tetrahydro-2*H*-oxocin (27). To a solution of **17** (5.1 g, 10.6 mmol) and 210 mL of *t*-BuOMe was added BF_3·OEt_2 (3.9 mL, 32 mmol) dropwise over 10 min at −78 °C. After 0.5 h at −78 °C, the resulting solution was warmed to 0 °C by changing the cooling bath to an ice bath and then poured into saturated aqueous $NaHCO_3$ (200 mL) and carefully shaken. The organic layer was separated and washed with brine (200 mL), dried ($MgSO_4$), and concentrated. The residue was purified by flash chromatography (5:1 hexane−EtOAc, two times) to give 2.75 g (57%) of pure oxocene **27**: $[\alpha]^{24}_D$ −152°, $[\alpha]^{24}_{577}$ −140°, $[\alpha]^{24}_{546}$ −153°, $[\alpha]^{24}_{435}$ −309°, $[\alpha]^{24}_{405}$ −408° (*c* 0.4, $CHCl_3$); ^{1}H NMR (300 MHz, C_6D_6) δ 7.31 (d, *J* = 7.0 Hz, 2H), 6.99 (m, 3H), 5.80 (dd, *J* = 10.5, 7.0 Hz, 1H), 4.93 (ddd, *J* = 11.0, 5.0, 2.1 Hz, 1H), 3.88 (t, *J* = 6.3 Hz, 2H), 3.29 (m, 2H), 2.79 (q, *J* = 11.0 Hz, 1H), 2.58 (dd, *J* = 14.4, 9.8 Hz, 1H), 2.33 (dt, *J* = 11.7, 6.2 Hz, 1H), 2.01 (d, *J* = 14.4 Hz, 1H), 1.67 (s, 3H), 1.15−1.64 (m, 6H), 1.13 (s, 9H), 0.76 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, C_6D_6) δ 177.6, 169.8, 137.0, 134.4, 132.1, 129.4, 128.5, 128.2, 81.9, 81.6, 76.4, 64.2, 41.0, 38.7, 33.6, 31.2, 27.3, 25.6, 20.6, 10.7; IR (film) 2966, 2936, 1735, 1729, 1479, 1373, 1264, 1159, 1023 cm^{-1}; HRMS (EI) *m/z* 448.2370 (448.2283 calcd for $C_{25}H_{36}O_5S$, M), 279.1968 (86%, 279.1959 calcd for M − $C_8H_9SO_2$). Anal. Calcd for $C_{25}H_{36}O_5S$: C, 66.93; H, 8.09. Found: C, 66.67; H, 8.03.

Also isolated from other chromatography fractions were the mixed acetal **34** (18% yield, a mixture of stereoisomers) and a 1.3:1 mixture of hydroxy acetates **35** and **36** (14% yield). Data for acetals **34**: ^{1}H NMR (500 MHz, C_6D_6) (major isomer) δ 7.28−7.32 (m, 2H), 6.90−7.02 (m, 3H), 6.02 (t, *J* = 7.1 Hz, 1H), 4.90 (m, 1H), 4.02 (m, 2H), 3.05 and 3.04 (S, 3H total) 1.69 (d, *J* = 4.1 Hz, 3H), 1.17 (s, 9H), 0.91 (t, *J* = 7.4 Hz, 3H); (minor isomer) δ 7.28−7.32 (m, 2H), 6.90−7.02 (m, 3H), 5.92 (dt, *J* = 15.6, 7.1 Hz, 1H), 5.06 (m, 1H), 4.02 (m, 2H), 3.03 and 3.02 (s, 3H total), 1.76 (d, *J* = 2.2 Hz, 3H), 1.18 (s, 9H), 0.82 (t, *J* = 7.4 Hz, 3H); IR (film) 3490, 2964, 2926, 2874, 1725, 1474, 1239, 1163 cm^{-1}. Data for **35/36**: ^{1}H NMR (500 MHz, C_6D_6) (major isomer) δ 7.15−7.43 (m, 2H), 6.89−6.98 (m, 3H), 5.09 (s, 1H), 5.01 (s, 1H), 4.78 (m, 1H), 3.43 (m, 1H), 1.62 (s, 3H), 0.86 (t, *J* = 7.4 Hz, 3H); minor isomer: ^{1}H NMR (500 MHz, C_6D_6) δ 7.15−7.43 (m, 2H), 6.89−6.98 (m, 3H), 5.13 (s, 1H), 5.10 (s, 1H), 4.90 (m, 1H), 3.23 (m, 1H), 1.67 (s, 3H), 0.78 (t, *J* = 7.4 Hz, 3H); IR (film) 3461, 2968, 2874, 1735, 1608, 1371, 1238 cm^{-1}; GC−MS (EI) showed similar fragmentation patterns for both isomers, *m/z* 294 (M), 276 (M − H_2O), 234.

In a similar 1 g scale cyclization, ^{1}H NMR analysis of the crude product showed that oxocene **27** and tetrahydropyran **33** were formed in a ratio of 8.2:1. Purification on silica gel (5:1 hexane−EtOAc) provided a pure sample of **33**: $[\alpha]^{24}_D$ −44.3°, $[\alpha]^{24}_{577}$ −49.8°, $[\alpha]^{24}_{546}$ −57.6°, $[\alpha]^{24}_{435}$ −109°, $[\alpha]^{24}_{405}$ −135.0° (*c* 0.57, $CHCl_3$); ^{1}H NMR (500 MHz, C_6D_6) δ 7.41 (d, *J* = 7.4 Hz, 2H), 7.00 (m, 3H), 4.91 (s, 1H), 4.88 (m, 1H), 4.69 (s, 1H), 4.10 (m, 2H), 3.36 (t, *J* = 9.5 Hz, 1H), 2.90 (dd, *J* = 7.8, 5.5 Hz, 1H), 2.61 (m, 1H), 2.17 (dt, *J* = 14.3 3.2 Hz), 1.64 (s, 3H), 1.16 (s, 9H), 0.89 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 177.7, 169.8, 148.3, 135.0, 132.3, 129.5, 128.7, 128.3, 110.7, 80.0, 79.6, 68.5, 64.3, 44.6, 38.7, 36.1, 29.8, 27.4, 25.3, 25.0, 20.6, 10.3, IR (film) 2967, 2866, 1730, 1603, 1478, 1239, 1156 cm^{-1}; HRMS (CI, isobutane) *m/z* 449.2346 (449.2361 calcd for $C_{25}H_{37}O_5S$, MH).

(2*R*,3*R*,8*R*)-3-Acetoxy-2-ethyl-8-[3-(pivaloyloxy)propyl]-3,4,7,8-tetrahydro-2*H*-oxocin (28). A suspension of Raney Ni (ca. 15 g) was activated by washing with water (3 × 100 mL), EtOH (3 × 100 mL), and acetone (3 × 100 mL), and then was overlayed with 130 mL of acetone. A solution of **27** (710 mg, 1.58 mmol) and 20 mL of acetone was added dropwise, and the resulting mixture was stirred at reflux for 6 h. After cooling to rt, Raney Ni was removed by filtration, the filtrate was concentrated, and the residue was purified by flash chromatography (20:1 benzene−EtOAc) to afford oxocene **28** (461 mg, 85%): $[\alpha]^{24}_D$ −27.2°, $[\alpha]^{24}_{577}$ −30.2°, $[\alpha]^{24}_{546}$ −35.4°, $[\alpha]^{24}_{435}$ −66.7°, $[\alpha]^{24}_{405}$ −78.9° (*c* 0.35, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.80 (dt, *J* = 10.3, 8.0 Hz, 1H), 5.67 (m, 1H), 4.87 (ddd, *J* = 11.2, 5.0, 2.6 Hz, 1H), 4.01 (m, 2H), 3.51 (ddd, *J* = 8.0, 5.7, 2.6 Hz, 1H), 3.23 (m, 1H), 2.65 (q, *J* = 11.3 Hz, 1H), 2.36 (dt, *J* = 14.0, 8.8 Hz, 1H), 2.21 (dt, *J* = 11.7, 6.1 Hz, 1H), 1.98−2.06 (m, 4H), 1.30−1.80 (m, 6H), 1.14 (s, 9H), 0.80 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.4, 170.7, 130.6, 128.0, 82.1, 81.3, 76.1, 38.6, 34.9, 33.4, 29.1, 27.0, 25.6, 25.1, 21.0, 10.3; IR (film) 2985, 2935, 2875, 1735, 1729, 1480, 1458, 1373, 1284, 1240, 1159, 1022 cm^{-1}; HRMS (CI, isobutane) *m/z* 341.2337 (341.2329 calcd for $C_{19}H_{33}O_5$, MH). Anal. Calcd for $C_{19}H_{32}O_5$: C, 67.03; H, 9.47. Found: C, 67.10; H, 9.37.

(2*R*,3*R*,,8*R*)-(3-*tert*-Butyldimethylsiloxy)-2-ethyl-8-[3-(pivaloyloxy)propyl]-3,4,7,8-tetrahydro-2*H*-oxocin (29). A mixture of acetate **28** (20.6 mg, 0.061 mmol), 0.5 mL of MeOH, and 2 M aqueous LiOH (30 μL, 0.06 mmol) was stirred at rt for 3.5 h. After concentration, the residue was extracted with EtOAc (3 × 5 mL) and the combined organic layer was washed with brine (10 mL), dried ($MgSO_4$), and concentrated. The resulting residue was purified by flash chromatography (3:1 hexane−EtOAc) to afford the corresponding C(3) alcohol

(14.5 mg, 80%): $[\alpha]^{20}_D$ −42.3°, $[\alpha]^{20}_{577}$ −46.4°, $[\alpha]^{20}_{546}$ −50.8°, $[\alpha]^{20}_{435}$ −89°, $[\alpha]^{20}_{405}$ −106° (*c* 0.48, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 5.75 (m, 2H), 4.03 (m, 2H), 3.64 (dd, *J* = 9.3, 3.9 Hz, 1H), 3.40 (m, 2H), 2.52 (dt, *J* = 12.5, 9.3 Hz, 1H), 2.27 (m, 1H), 2.20 (t, *J* = 5.6 Hz, 2H), 2.00 (broad s, 1H), 1.41−1.84 (m, 6H), 1.16 (s, 9H), 0.88 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.5, 129.3, 129.0, 81.9, 79.9, 73.7, 64.2, 38.6, 33.7, 33.3, 32.5, 27.1, 25.8, 25.6, 10.5; IR (film) 3442, 2961, 2936, 1728, 1480, 1458, 1285, 1160, 1129, 1070 cm^{-1}; HRMS (CI, isobutane) *m/z* 299.2231 (299.2221 calcd for $C_{17}H_{31}O_4$, MH). Anal. Calcd for $C_{17}H_{30}O_4$: C, 68.42; H, 10.13. Found: C, 68.35; H, 10.12.

A solution of this alcohol (272 mg, 0.91 mmol), 2,6-lutidine (285 mg, 2.74 mmol), (TBDMS)OTf (356 mg, 1.37 mmol), and CH_2Cl_2 (5 mL) was maintained at 0 °C for 1.5 h and then diluted with CH_2Cl_2 (10 mL), washed with saturated aqueous $NaHCO_3$ (10 mL), dried ($MgSO_4$), and concentrated. The resulting residue was purified by flash chromatography (10:1 hexane−EtOAc) to afford **29** (378 mg, 100%): $[\alpha]^{22}_D$ −17.3°, $[\alpha]^{22}_{577}$ −19.1°, $[\alpha]^{22}_{546}$ −25.2°, $[\alpha]^{22}_{435}$ −36.4°, $[\alpha]^{22}_{405}$ −42.8° (*c* 0.38, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 5.61−5.80 (m, 2H), 4.04 (m, 2H), 3.69 (ddd, *J* = 13.4, 4.8, 2.6 Hz, 1H), 3.35 (ddd, *J* = 8.4, 4.8, 2.6 Hz, 1H), 3.19 (dt, *J* = 9.9, 5.7 Hz, 1H), 2.71 (q, *J* = 11.8 Hz, 1H), 2.38 (m, 1H), 2.09 (dt, *J* = 11.8, 5.7 Hz, 1H), 2.00 (dd, *J* = 13.4, 8.4 Hz, 1H), 1.34−1.82 (m, 6H), 1.18 (s, 9H), 0.89 (s, 9H), 0.87 (t, *J* = 7.3 Hz, 3H), 0.06 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.6, 129.8, 129.1, 83.5, 81.5, 75.7, 64.4, 38.7, 35.0, 33.6, 33.4, 27.2, 26.1, 25.8, 25.7, 18.3, 10.9, −3.9, −4.7; IR (film) 2959, 2931, 2857, 1731, 1463, 1284, 1157, 1077, 836 cm^{-1}; HRMS (CI, isobutane) *m/z* 413.3103 (413.3086 calcd for $C_{23}H_{45}O_4Si$, MH). Anal. Calcd for $C_{23}H_{44}O_4Si$: C, 66.94; H, 10.75. Found: C, 67.22; H, 10.69.

(2*R*,3*R*,8*R*)-3-(*tert*-Butyldimethylsiloxy)-2-ethyl-8-(3-hydroxypropyl)-3,4,7,8-tetrahydro-2*H*-oxocin (30). To a solution of **29** (65 mg, 0.157 mmol) and CH_2Cl_2 (2 mL) was added DIBAL-H (61 μL, 0.35 mmol) dropwise at −78 °C, and the resulting solution was maintained at −78 °C for 1 h. The reaction was then quenched by adding water (0.2 mL), the resulting mixture was allowed to warm to rt, and the precipitate was removed by filtration through Celite. Concentration of the filtrate gave essentially pure alcohol **30** (47.6 mg, 92%): $[\alpha]^{22}_D$ −17.9°, $[\alpha]^{22}_{577}$ −20.5°, $[\alpha]^{22}_{546}$ −23.3°, $[\alpha]^{22}_{435}$ −39.5°, $[\alpha]^{22}_{405}$ −46.3° (*c* 0.59, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 5.79 (dt, *J* = 11.0, 7.7 Hz, 1H), 5.67 (dddd, *J* = 11.0, 9.4, 6.2, 1.5 Hz, 1H), 3.67 (m, 3H), 3.42 (ddd, *J* = 8.6, 4.6, 2.2 Hz, 1H), 3.33 (dt, *J* = 9.8, 4.9 Hz, 1H), 3.07 (t, *J* = 5.7 Hz, 1H), 2.67 (q, *J* = 11.0 Hz, 1H), 2.52 (m, 1H), 2.13 (dt, *J* = 11.0, 5.9 Hz, 1H), 1.97 (dd, *J* = 13.1, 8.1 Hz, 1H), 1.32−1.73 (m, 6H), 0.90 (m, 12H), 0.07 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 130.0, 129.0, 83.5, 81.3, 75.2, 63.0, 34.3, 34.2, 33.5, 28.7, 25.9, 25.8, 18.1, 10.9, −4.0, −4.9; IR (film) 3421, 2958, 2931, 2857, 1472, 1463, 1255, 1074, 1057, 836 cm^{-1}; HRMS (CI, isobutane) *m/z* 329.2494 (329.2511 calcd for $C_{18}H_{37}O_3Si$, MH). Anal. Calcd for $C_{18}H_{36}O_3Si$: C, 65.80; H, 11.04. Found: C, 65.71; H, 10.94.

(2*R*,3*R*,8*R*)-3-(*tert*-Butyldimethylsiloxy)-2-ethyl-8-(3-oxo-1(*E*)-propenyl)-3,4,7,8-tetrahydro-2*H*-oxocin (31). Following the general procedure of Swern,[27] DMSO (49 μL, 0.68 mmol) was added dropwise to a solution of $(COCl)_2$ (45 μL, 0.52 mmol) and 2 mL of CH_2Cl_2 at −78 °C. After 10 min, a solution of alcohol **30** (170.8 mg, 0.52 mmol) and 1 mL of CH_2Cl_2 was added at −78 °C. The reaction was stirred at −78 °C for 30 min, and Et_3N (0.23 mL, 1.70 mmol) was added. After 30 min, the cooling bath was removed and the reaction was warmed to rt. The reaction then was diluted with EtOAc (10 mL), washed with saturated aqueous $NaHCO_3$ (5 mL), dried ($MgSO_4$), and concentrated, and the resulting residue was purified by flash chromatography (6:1 hexane−EtOAc) to afford the corresponding aldehyde (156 mg, 92%): $[\alpha]^{24}_D$ −35.2°, $[\alpha]^{24}_{577}$ −38.0°, $[\alpha]^{24}_{546}$ −40.1°, $[\alpha]^{24}_{435}$ −72.3°, $[\alpha]^{24}_{405}$ −79.1° (*c* 0.96, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 5.76 (dt, *J* = 11.0, 7.7 Hz, 1H), 5.66 (m, 1H), 3.69 (ddd, *J* = 11.0, 4.9, 2.4 Hz, 1H), 3.34 (ddd, *J* = 11.0, 5.5, 2.4 Hz, 1H), 3.25 (dt, *J* = 9.0, 4.2 Hz, 1H), 2.68 (q, *J* = 11.0 Hz, 1H), 2.59 (dq, *J* = 7.4, 1.4 Hz, 2H), 2.41 (m, 1H), 2.10 (dt, *J* = 11.9, 5.8 Hz, 1H), 2.00 (dd, *J* = 13.9, 8.2 Hz, 1H), 1.35−1.89 (m, 4H), 0.89 (s, 9H), 0.84 (t, *J* = 7.5 Hz, 3H), 0.07 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.8, 129.5, 129.3, 83.3, 80.3, 75.3, 40.8, 35.2, 33.4, 29.6, 26.0, 25.6, 18.3, 10.9, −3.9, −4.8; IR (film) 3020, 2959, 2931, 2909, 2857, 1727, 1472, 1463, 1254, 1074, 836 cm^{-1}; HRMS (CI, isobutane) *m/z* 327.2352 (327.2355 calcd for $C_{18}H_{35}O_3Si$, MH).

To a solution of this aldehyde (236 mg, 0.72 mmol), *i*-Pr_2EtN (0.5 mL, 2.90 mmol) and CH_2Cl_2 (8 mL) was added TMSOTf (0.5 M solution in CH_2Cl_2, 2.9 mL) dropwise at −10 °C (ice−salt bath). The reaction was stirred at −10 °C for 1 h and at rt for 3 h and then diluted with hexane (20 mL), washed with cold saturated aqueous $NaHCO_3$ (30 mL), dried (K_2CO_3), and concentrated. Following the general procedure of Saegusa,[20] this mixture of enoxysilanes (*E*:*Z* ≈1:1) was oxidized at rt in CH_3CN (10 mL) by adding Na_2CO_3 (150 mg, 1.4 mmol) and $Pd(OAc)_2$ (160 mg, 0.72 mmol). After 4 h, the resulting black precipitate was removed by filtration through Celite. The filtrate was then diluted with EtOAc (10 mL), washed with saturated aqueous $NaHCO_3$ and brine, dried ($MgSO_4$), and concentrated to give essentially pure enal **31** (229 mg, 98%): $[\alpha]^{24}_D$ +19.3°, $[\alpha]^{24}_{577}$ +18.5°, $[\alpha]^{24}_{546}$ +21.0°, $[\alpha]^{24}_{435}$ +44.0°, $[\alpha]^{24}_{405}$ +54.4° (*c* 1.24, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 9.56 (d, *J* = 8.0 Hz, 1H), 7.28 (d, *J* = 16.0 Hz, 1H), 6.81 (dd, *J* = 15.6, 4.4 Hz, 1H), 6.36 (ddd, *J* = 15.6, 8.0, 1.6 Hz, 1H), 5.77 (m, 2H), 3.99 (dd, *J* = 10.4, 4.4 Hz, 1H), 3.72 (ddd, *J* = 10.8, 4.9, 2.5 Hz, 1H), 3.43 (dt, *J* = 9.7, 2.5 Hz, 1H), 2.68 (q, *J* = 10.8 Hz, 1H), 2.50 (m, 1H), 2.17 (m, 2H), 1.64 (m, 1H), 1.29 (dddd, *J* = 14.7, 14.1, 7.2, 3,3 Hz, 1H), 0.89 (s, 9H), 0.85 (t, *J* = 7.4 Hz, 3H), 0.07 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 193.7, 157.7, 131.0, 130.4, 128.3, 84.5, 80.7, 75.8, 34.2, 33.6, 25.9, 25.8, 18.2, 10.7, −4.1, −4.8; IR (film) 3017, 2970, 2966, 1687, 1251, 1226, 1208, 1056 cm^{-1}; HRMS (CI, isobutane) *m/z* 325.2189 (325.2198 calcd for $C_{18}H_{33}O_3Si$, MH).

(2*R*,3*R*,8*R*)-3-(*tert*-Butyldimethylsiloxy)-2-ethyl-8-(3-hydroxy-1(*E*)-propenyl)-3,4,7,8-tetrahydro-2*H*-oxocin (32). To a solution of enal **31** (18.8 mg, 0.058 mmol) and CH_2Cl_2 (2 mL) was added DIBAL-H (0.25 M in CH_2Cl_2, 0.25 mL) dropwise at −78 °C. The reaction was maintained at −78 °C for 1.5 h and then quenched by adding water (0.2 mL). The resulting mixture was warmed to rt, and the precipitate was removed by filtration through Celite. The filtrate was then dried ($MgSO_4$) and concentrated to give essentially pure **32** (16.3 mg, 86%): $[\alpha]^{24}_D$ −6.3°, $[\alpha]^{24}_{577}$ −7.1°, $[\alpha]^{24}_{546}$ −8.7°, $[\alpha]^{24}_{435}$ −12.7°, $[\alpha]^{24}_{405}$ −15.2° (*c* 0.85, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 5.68−5.90 (m, 4H), 4.15 (d, *J* = 4.0 Hz, 2H), 3.67−3.76 (m, 2H), 3.41 (dt, *J* = 9.8, 3.0 Hz, 1H), 2.73 (q, *J* = 10.6 Hz, 1H), 2.48 (m, 1H), 2.05−2.15 (m, 2H), 1.57−1.70 (m, 2H), 1.28 (dddd, *J* = 14.8, 10.2, 7.4, 3.2 Hz, 1H), 0.87−1.24 (t and s, 12H), 0.06 (s, 3H), 0.05 (s,2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 133.4, 129.5, 129.4, 128.9, 84.0, 81.9, 76.0, 63.3, 35.0, 33.6, 26.0, 18.3, 11.0, −4.1, −4.7; IR (film) 3462, 3019, 2964, 2932, 1522, 1424, 1226, 1220, 1055 cm^{-1}; HRMS (CI, isobutane) *m/z* 327.2362 (327.2355 calcd for $C_{18}H_{35}O_3Si$, MH). Anal. Calcd for $C_{18}H_{34}O_3Si$: C, 66.20; H, 10.49. Found: C, 65.98; H, 10.48.

(2*R*,3*R*,8*R*)-3-(*tert*-Butyldimethylsiloxy)-2-ethyl-8-(3-hydroxy-1,2-epoxypropyl)-3,4,7,8-tetrahydro-2*H*-oxocin (40). A solution of allyl alcohol **32** (98 mg, 0.30 mmol), (+)-diethyl tartrate (2.0 M CH_2Cl_2 solution, 0.22 mL), and 2.0 mL of CH_2Cl_2 was cooled to −25 °C, Ti(O^{i}Pr)$_4$ (2.0 M CH_2Cl_2 solution, 0.22 mL) was added, and the resulting solution was maintained at −25 °C for 30 min.[21] *tert*-Butylhydroperoxide (4.3 M toluene solution, 0.14 mL) was added, and the resulting solution was maintained at −25 °C for 7.5 h and quenched by adding triethanolamine (1.0 M CH_2Cl_2 solution, 0.78 mL). The resulting mixture was warmed to 0 °C, stirred for 1 h, and then concentrated. This residue was purified by flash chromatography (3:1 hexane−EtOAc) to give epoxide **40** (88 mg, 86%) as a single stereoisomer: $[\alpha]^{24}_D$ −14.5°, $[\alpha]^{24}_{577}$ −20.2°, $[\alpha]^{24}_{546}$ −23.6°, $[\alpha]^{24}_{435}$ −35.3°, $[\alpha]^{24}_{405}$ −38.2° (*c* 1.02, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 5.73 (m, 2H), 3.92 (d, *J* = 12.1 Hz, 1H), 3.70 (ddd, *J* = 11.0, 5.0, 2.5 Hz, 1H), 3.66 (d, *J* = 12.1 Hz, 1H), 3.35 (dt, *J* = 9.6, 3.1 Hz, 1H), 3.15−3.22 (m, 2H), 3.11 (m, 1H), 2.71 (q, *J* = 11.6 Hz, 1H), 2.50 (m, 1H), 2.14 (dt, *J* = 11.6, 5.9 Hz, 1H), 2.02 (dd, *J* = 13.7, 7.6 Hz, 1H), 1.81 (broad s, 1H), 1.61−1.69 (m, 1H), 1.29 (dddd, *J* = 14.8, 11.7, 6.7, 3.4 Hz, 1H), 0.96 (t, *J* = 7.3 Hz, 3H), 0.90 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 129.7, 128.5, 84.6, 82.2, 76.1, 61.4, 58.1, 55.8, 33.6, 30.9, 26.0, 18.3, 10.8, −4.1, −4.7; IR (film) 3462, 3023, 3018, 2976, 2931, 1521, 1424, 1226, 1207, 1048, 929 cm^{-1}; HRMS (CI, isobutane) *m/z* 343.2253 (343.2304 calcd for $C_{18}H_{35}O_4Si$, MH).

(27) Mancuso, A. J.; Huang, S.-L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480.

(2*R*,3*R*,8*R*)-3-(*tert*-Butyldimethylsiloxy)-2-ethyl-8-(3-oxo-1,2-epoxypropyl)-3,4,7,8-tetrahydro-2*H*-oxocin (41). The Dess–Martin periodinane[22] (48 mg, 0.11 mmol) was added to a stirring solution of epoxy alcohol **40** (19 mg, 0.057 mmol) and 3 mL of CH_2Cl_2 at 0 °C. After 1 h, the reaction was diluted with CH_2Cl_2 (5 mL), washed with 50% aqueous $NaHSO_3$ (5 mL) and saturated aqueous $NaHCO_3$ (5 mL), and dried ($MgSO_4$). Concentration provided essentially pure aldehyde **41** (17 mg, 88%): $[\alpha]^{24}_D$ +15.3°, $[\alpha]^{24}_{577}$ +12.4°, $[\alpha]^{24}_{546}$ +16.2°, $[\alpha]^{24}_{435}$ +44.4°, $[\alpha]^{24}_{405}$ +66.3° (*c* 0.65, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.02 (d, J = 6.3 Hz, 1H), 5.70–5.75 (m, 2H), 3.70 (ddd, J = 10.9, 5.0, 2.5 Hz, 1H), 3.46 (dd, J = 5.3, 2.0 Hz, 1H), 3.31–3.37 (m, 2H), 3.23 (dd, J = 10.4, 5.3 Hz, 1H), 2.46–2.73 (m, 2H), 2.00–2.17 (m, 2H), 1.61–1.71 (m, 1H), 1.26–1.34 (m, 1H), 0.94 (t, J = 7.3 Hz, 3H), 0.89 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.8, 130.1, 127.9, 84.9, 81.0, 75.8, 58.7, 56.6, 33.5, 30.8, 26.0, 25.9, 18.2, 10.8, −4.1, −4.8; IR (film) 2956, 2930, 2857, 1729, 1463, 1255, 1081 cm^{-1}; HRMS (CI, NH_3) *m/z* 358.2418 (358.2413 calcd for $C_{18}H_{36}NO_4Si$, M + NH_4), 341.2152 (341.2142 calcd for $C_{18}H_{33}O_4Si$, MH). Anal. Calcd for $C_{18}H_{32}O_4Si$: C, 63.48; H, 9.47. Found: C, 62.91; H, 9.55.

(2*R*,3*R*,8*R*)-3-(*tert*-Butyldimethylsiloxy)-8-[1,2-epoxy-6-(triisopropylsilyl)-3-hexen-5-ynyl]-2-ethyl-3,4,7,8-tetrahydro-2*H*-oxocin (43). To a stirring suspension of phosphonium salt **42**[23] (225 mg, 0.42 mmol) and 4 mL of THF was added *n*-BuLi (1.96 M, 0.19 mL) dropwise at −50 °C. The resulting pale yellow mixture was maintained at −50 °C for 30 min and then cooled to −78 °C. A solution of **41** (95 mg, 0.28 mmol) in 1 mL of THF was then added dropwise. The resulting solution was maintained at 0 °C for 2 h and then diluted with hexane (10 mL), washed with brine (10 mL), dried ($MgSO_4$), and concentrated. The residue was purified by flash chromatography (40:1 hexane–EtOAc) to afford **43** (129 mg, 89%) as a 3:1 mixture of (*E*)- and (*Z*)-enyne stereoisomers: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.85–5.93 (m, 2H), 5.69–5.77 (m, 2H), 3.68–3.72 (m, 1H), 3.10–3.16 (m, 2H), 2.70 (q, J = 11.0 Hz, 2H), 2.47–2.51 (m, 2H), 2.12 (dt, J = 11.7, 5.6 Hz, 1H), 2.01 (dd, J = 13.6, 7.7 Hz, 1H), 1.64–1.67 (m, 1H), 1.06 (m, 21H), 0.95 (t, J = 7.3 Hz, 3H), 0.90 (s, 9H), 0.07 (s, 3H), 0.05 (s, 3H); IR ($CHCl_3$) 3014, 2960, 2865, 1463, 1228 and 1077 cm^{-1}; HRMS (CI, NH_3) *m/z* 519.3694 (519.3611 calcd for $C_{30}H_{55}O_3Si_2$, MH).

(2*R*,3*R*,8*R*)-3-(*tert*-Butyldimethylsiloxy)-2-ethyl-8-[1(*R*)-hydroxy-6-(triisopropylsilyl)-3-hexen-5-ynyl]-3,4,7,8-tetrahydro-2*H*-oxocin (44). Following the general procedure of Tsuji,[24a] a solution of $Et_3NH^+HCO_2^-$ (0.5 M in dioxane, 1.2 mL, 0.62 mmol) was added dropwise to a solution of $Pd_2(dba)_3$·$CHCl_3$ (7.2 mg, 0.0063 mmol), *n*-Bu_3P (0.05 M in dioxane, 0.12 mL, 0.0063 mmol), and dioxane (3 mL). After 5 min, a solution of **43** (*E*:*Z* = 3:1; 65 mg, 0.12 mmol) and 2 mL of dioxane was added at rt. The resulting solution was maintained at rt for 4 h and concentrated, and the residue was purified by flash chromatography (30:1 hexane–EtOEt) to afford **44** (61 mg, 94%; *E*:*Z* = 4.8:1.0). Subsequent flash chromatography (CH_2Cl_2) provided 36.4 mg (56%) of the pure (*E*)-enyne **44**, along with a mixture of (*E*)- and (*Z*)-enynes (22 mg, 34%): Data for (*E*)-**44**: $[\alpha]^{24}_D$ −21.9°, $[\alpha]^{24}_{577}$ −38.4°, $[\alpha]^{24}_{546}$ −31.6°, $[\alpha]^{24}_{435}$ −49.7°, $[\alpha]^{24}_{405}$ −62.1° (*c* 0.25, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.28 (dt, J = 15.9, 7.2 Hz, 1H), 5.67–5.82 (m, 2H), 5.61 (d, J = 15.9 Hz, 1H), 3.73 (ddd, J = 10.8, 5.0, 2.2 Hz, 1H), 3.54 (m, 1H), 3.43 (m, 1H), 3.12 (dd, J = 9.7, 6.3 Hz, 1H), 2.66 (q, J = 10.7 Hz, 1H), 2.37–2.52 (m, 2H), 2.29 (ddd, J = 14.7, 7.5, 1.2 Hz, 1H), 2.14 (dt, J = 11.8, 5.8 Hz, 1H), 2.03 (dd, J = 13.4, 7.8 Hz, 1H), 1.53 (m, 2H), 1.06 (m, 21H), 0.86–0.91 (t and s, 12H), 0.08 (s, 3H), 0.06 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.5, 129.4, 129.1, 112.2, 105.6, 89.4, 83.6, 83.4, 74.9, 73.3, 37.4, 33.4, 31.2, 25.9, 25.6, 18.6, 18.2, 11.3, 10.7, −3.8, −4.8; IR (film) 3550, 2942, 2863, 1462, 1255, 1077 cm^{-1}; HRMS (CI, isobutane) *m/z* 521.3836 (521.3845 calcd for $C_{30}H_{57}O_3Si_2$, MH).

(2*R*,3*R*,8*R*)-8-[1(*R*)-Acetoxy-6-(triisopropylsilyl)-3-hexen-5-ynyl]-2-ethyl-3-hydroxy-3,4,7,8-tetrahydro-2*H*-oxocin (45). A solution of the (*E*)-enyne **44** (63 mg, 0.12 mmol, pure *E* stereoisomer), pyridine (0.2 mL, 2.4 mmol), Ac_2O (0.11 mL, 1.2 mmol), DMAP (1.5 mg), and CH_2Cl_2 (5 mL) was maintained at 0 °C for 1.5 h and then at rt for 5 h. The reaction then was diluted with CH_2Cl_2 (5 mL) and washed with dilute HCl, saturated aqueous $NaHCO_3$ (5 mL), and brine (5 mL) and dried ($MgSO_4$). Concentration provided the corresponding acetate (65 mg): $[\alpha]^{24}_D$ −21.1°, $[\alpha]^{24}_{577}$ −16.5°, $[\alpha]^{24}_{546}$ −25.1°, $[\alpha]^{24}_{435}$ −43.0°, $[\alpha]^{24}_{405}$ −55.6° (*c* 0.32, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.12 (dt, J = 16.0, 7.0 Hz, 1H), 5.66–5.75 (m, 2H), 5.60 (d, J = 16.0 Hz, 1H), 4.99 (dt, J = 8.9, 3.5 Hz, 1H), 3.71 (m, 1H), 3.32 (m, 2H), 2.57–2.68 (m, 2H), 2.35–2.43 (m, 2H), 1.97–2.13 (m, 2H), 2.06 (s, 3H), 1.55 (m, 1H), 1.39 (m, 1H), 1.07 (m, 21H), 0.89–0.93 (t and s, 12H), 0.07 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.4, 140.6, 129.6, 129.0, 112.6, 105.5, 89.6, 84.5, 80.8, 75.4, 74.6, 33.4, 33.3, 29.5, 25.9, 25.6, 21.0, 18.6, 18.2, 11.3, 10.8, −3.9, −4.6; IR ($CHCl_3$) 2945, 2865, 1734 cm^{-1}; HRMS (FAB) *m/z* 563.3942 (563.3950 calcd for $C_{32}H_{59}O_4Si_2$, MH).

A solution of this material (65 mg, 0.12 mmol) and 7 mL of 80% aqueous HOAc was maintained for 18 h at rt and then concentrated under high vacuum. The residue was extracted with CH_2Cl_2 (3 × 5 mL), and the extracts were washed with saturated aqueous $NaHCO_3$ (5 mL), water (5 mL), and brine (5 mL). After drying ($MgSO_4$) and concentration, the residue was purified by flash chromatography (2:1 hexane–EtOAc) to afford **45** (41 mg, 76% from **44**): $[\alpha]^{24}_D$ −27.1°, $[\alpha]^{24}_{577}$ −29.6°, $[\alpha]^{24}_{546}$ −33.5°, $[\alpha]^{24}_{435}$ −61.8°, $[\alpha]^{24}_{405}$ −78.7° (*c* 0.75, $CHCl_3$); ^{1}H NMR (300 MHz) δ 6.08 (dt, J = 16.0, 7.5 Hz, 1H), 5.75 (m, 2H), 5.59 (d, J = 16.0 Hz, 1H), 4.96 (dt, J = 8.0, 4.6 Hz, 1H), 3.67 (m, 1H), 3.37–3.46 (m, 2H), 2.31–2.54 (m, 5H), 2.09–2.17 (m, 1H), 2.07 (s, 3H), 1.75 (br s, 1H), 1.57 (m, 2H), 1.06 (m, 21H), 0.92 (t, J = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.5, 139.8, 129.5, 128.9, 113.0, 105.2, 90.1, 83.1, 80.5, 74.4, 73.6, 34.2, 33.5, 29.8, 25.5, 21.0, 18.6, 11.3, 10.4; IR ($CHCl_3$) 3529, 2944, 2866, 1735 cm^{-1}; HRMS (CI, isobutane) *m/z* 449.3110 (449.3086 calcd for $C_{26}H_{45}O_4Si_2$, MH).

(+)-Laurencin (1). Following the general procedure described by Holmes,[7] bromine (11 μL, 0.23 mmol) was added dropwise to a solution of 1,2-bis(diphenylphosphino)ethane (48 mg, 0.12 mmol) and 6 mL of CH_2Cl_2 at −10 °C (ice–salt bath). The resulting colorless solution was maintained at −10 °C for 5 min, and a solution of **45** (36 mg, 0.080 mmol) and 3 mL of toluene was added. The reaction was then heated at 70 °C for 2 h. After cooling to rt, the reaction was concentrated, ether (5 mL) was added, and the resulting precipitate was removed by filtration. The filtrate was washed with water (5 mL) and brine (5 mL), dried ($MgSO_4$), and concentrated. The resulting residue was purified by flash chromatography (40:1 hexane–EtOAc) to give the triisopropylsilyl derivative of (+)-laurencin (16 mg, 39%): $[\alpha]^{24}_D$ +40.3°, $[\alpha]^{24}_{577}$ +23.7°, $[\alpha]^{24}_{546}$ +33.2°, $[\alpha]^{24}_{435}$ +63.1°, $[\alpha]^{24}_{405}$ +75.3° (*c* 0.15, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.08 (dt, J = 16.0, 7.0 Hz, 1H), 5.93 (m, 2H), 5.58 (d, J = 16.0 Hz, 1H), 4.98 (dt, J = 8.5, 4.4 Hz, 1H), 4.06 (dt, J = 10.0, 3.2 Hz, 1H), 3.42 (m, 2H), 3.15 (ddd, J = 14.1, 8.5, 3.6 Hz, 1H), 2.32–2.50 (m, 4H), 2.07 (s, 3H), 1.93 (m, 2H), 1.06 (m, 21H), 0.98 (t, J = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.3, 139.7, 129.3, 128.9, 113.0, 105.2, 84.6, 81.4, 74.2, 56.0, 33.8, 32.3, 29.6, 25.7, 21.0, 18.6, 11.3, 9.3; IR ($CHCl_3$) 3000, 2866, 1735, 1522 cm^{-1}; HRMS (CI, isobutane) *m/z* 511.2229 (511.2243 calcd for $C_{26}H_{44}BrO_3Si$, MH).

A solution of this material (16 mg, 0.03 mmol), TBAF (1 M in THF, 63 μL), and THF (1 mL) was maintained at −10 °C (ice–salt bath) for 30 min and then diluted with ether (5 mL). The resulting solution was washed with brine (5 mL), dried ($MgSO_4$), concentrated, and purified by flash chromatography (15:1 hexane–EtOAc) to afford (+)-laurencin (7.0 mg, 63%): $[\alpha]^{24}_D$ = +68.2° (*c* 0.35, $CHCl_3$).

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