Synthesis of Medium Ring Ethers. 5. The Synthesis of (+)-Laurencin

Jonathan W. Burton, J. Stephen Clark, Sam Derrer, Thomas C. Stork, Justin G. Bendall, and Andrew B. Holmes*

Contribution from the Department of Chemistry, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW U.K.

Received March 21, 1997[⊗]

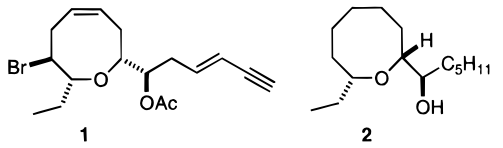
Abstract: The enantioselective synthesis of (+)-laurencin **1** has been achieved in 27 steps from (*R*)-malic acid **20**. The key steps involved methylenation of the lactone **49** followed by intramolecular hydrosilation of the enol ether **14** (Scheme 11) and one carbon homologation of the diol **13** to give the key ethyl substituted cyclic ether **59** (Scheme 13). The lactone **49** was obtained by two efficient routes, namely a Claisen ring expansion (Scheme 3) followed by α-hydroxylation (Scheme 6) and a Yamaguchi lactonization (Scheme 11). Elaboration of the (*E*)-pentenynyl side chain (Scheme 18) and introduction of bromine (Scheme 19) completed the synthesis of (+)-laurencin **1**.

Introduction

The eight-membered medium ring ether natural product (+)-laurencin **1** is the prototypical member of a growing family of marine natural product cyclic ethers isolated from red algae and those marine organisms which feed on *Laurencia* species. Laurencin was first isolated from *L. glandulifera* by Irie and Masamune and co-workers.[1,2] Its structure was assigned by chemical degradation, spectroscopic analysis, and X-ray crystallography,[3,4] and the absolute configuration was determined by the Prelog atrolactic acid method on a side-chain degradation product. Racemic laurencin was synthesized by Masamune and co-workers in an epic assault reported in the late 1970s.[5−7] In recent years we and a number of others have developed new synthetic methodology to prepare medium ring ethers by ring expansion methods. Our own approach has been based on ring expansion reactions of cyclic ketones and vinyl-substituted ketene acetals to produce, respectively, saturated[8−12] and unsaturated medium ring lactones[13−16] which have been elaborated to 2,*n*-disubstituted cyclic ethers by Tebbe methylenation and subsequent functionalization of the enol ether double bond.[8−12] Other notable approaches have been reported by Murai,[17] Overman,[18−21] Palenzuela,[22] Nicolaou[23] and others,[24−26] and these are summarized in a series of recent review articles.[27−29]

Results and Discussion

Synthesis of (+)-Octahydrodeacetyldebromolaurencin 2. Our previous experience with the hydroboration of exocyclic enol ethers derived from saturated eight-membered lactones demonstrated a preference for the *cis*-2,8-disubstitution pattern,[11,12] but we needed unambiguous chemical confirmation of the relative and absolute configuration of the products.



1 **2**

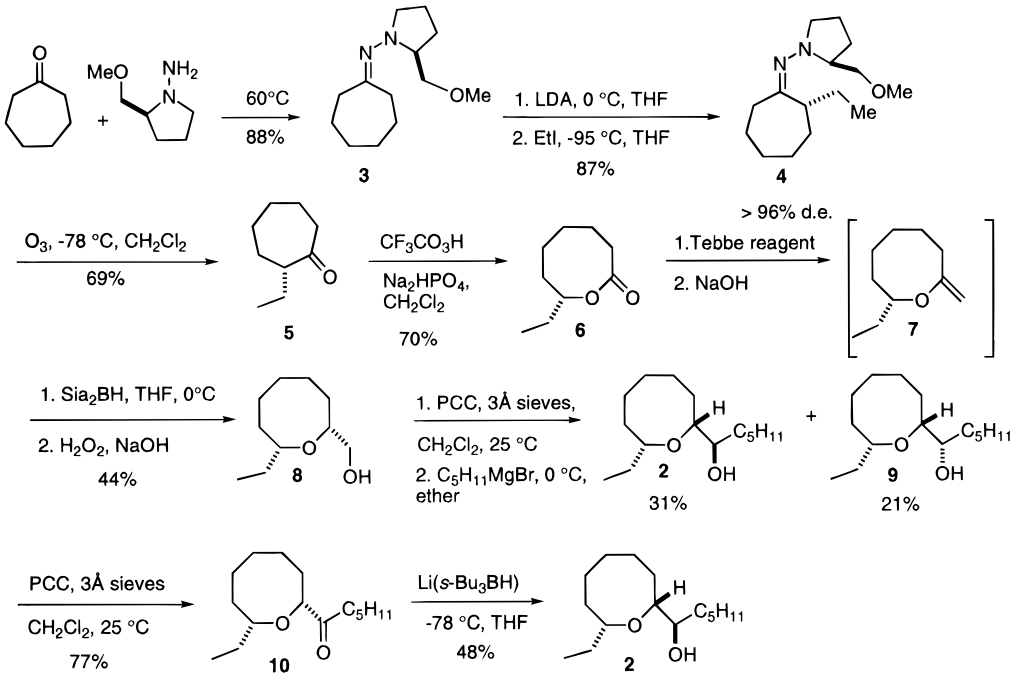
Octahydrodeacetyldebromolaurencin **2**[1,2] offered an excellent opportunity to synthesize a known degradation product of laurencin, confirm the *cis*-disubstitution pattern, and assign the absolute stereochemistry of the degradation product.[9] The Baeyer−Villiger, Tebbe methylenation, hydroboration strategy has been well documented in previous publications.[8−12] Scheme 1 summarizes the application of the route to the synthesis of **2**.

[⊗] Abstract published in *Advance ACS Abstracts,* July 15, 1997.

(1) Irie, T.; Suzuki, M.; Masamune, T. *Tetrahedron Lett.* **1965**, 1091.
(2) Irie, T.; Suzuki, M.; Masamune, T. *Tetrahedron* **1968**, *24*, 4193.
(3) Cameron, A. F.; Cheung, K. K.; Ferguson, G.; Robertson, J. M. *J. Chem. Soc., Chem. Commun.* **1965**, 638.
(4) Cameron, A. F.; Cheung, K. K.; Ferguson, G.; Robertson, J. M. *J. Chem. Soc. (B)* **1969**, 559.
(5) Murai, A.; Murase, H.; Matsue, H.; Masamune, T. *Tetrahedron Lett.* **1977**, 2507.
(6) Masamune, T.; Matsue, H.; Murase, H. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 127.
(7) Masamune, T.; Murase, H.; Matsue, H.; Murai, A. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 135.
(8) Carling, R. W.; Holmes, A. B. *J. Chem. Soc., Chem. Commun.* **1986**, 565.
(9) Clark, J. S.; Holmes, A. B. *Tetrahedron Lett.* **1988**, *29*, 4333.
(10) Carling, R. W.; Curtis, N. R.; Holmes, A. B. *Tetrahedron Lett.* **1989**, *30*, 6081.
(11) Carling, R. W.; Clark, J. S.; Holmes, A. B. *J. Chem. Soc., Perkin Trans. 1* **1992**, 83.
(12) Carling, R. W.; Clark, J. S.; Holmes, A. B.; Sartor, D. *J. Chem. Soc., Perkin Trans. 1* **1992**, 95.
(13) Carling, R. W.; Holmes, A. B. *J. Chem. Soc., Chem. Commun.* **1986**, 325.
(14) Curtis, N. R.; Holmes, A. B.; Looney, M. G. *Tetrahedron* **1991**, *47*, 7171.
(15) Congreve, M. S.; Holmes, A. B.; Hughes, A. B.; Looney, M. G. *J. Am. Chem. Soc.* **1993**, *115*, 5815.
(16) Fuhry, M. A. M.; Holmes, A. B.; Marshall, D. R. *J. Chem. Soc., Perkin Trans. 1* **1993**, 2743.
(17) Tsushima, K.; Murai, A. *Tetrahedron Lett.* **1992**, *33*, 4345.
(18) 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.
(19) Blumenkopf, T. A.; Look, G. C.; Overman, L. E. *J. Am. Chem. Soc.* **1990**, *112*, 4399.
(20) Overman, L. E.; Thompson, A. S. *J. Am. Chem. Soc.* **1988**, *110*, 2248.
(21) Bratz, M.; Bullock, W. H.; Overman, L. E.; Takemoto, T. *J. Am. Chem. Soc.* **1995**, *117*, 5958.
(22) Mujica, M. T.; Afonso, M. M.; Galindo, A.; Palenzuela, J. A. *Synlett* **1996**, 983.
(23) Nicolaou, K. C. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 589.
(24) Isobe, M.; Yenjai, C.; Tanaka, S. *Synlett* **1994**, 916.
(25) Isobe, M.; Hosokawa, S.; Kira, K. *Chem. Lett.* **1996**, 473.
(26) Grée, D. M.; Martelli, J. T.; Grée, R. L. *J. Org. Chem.* **1995**, *60*, 2316.
(27) Moody, C. J.; Davies, M. J. In *Studies in Natural Product Chemistry*; Atta-ur-Rahman, Ed.; Elsevier Science: 1992; Vol. 10, pp 201−239.
(28) Elliott, M. C. *Contemp. Org. Synth.* **1994**, *1*, 457.
(29) Rousseau, G. *Tetrahedron* **1995**, *51*, 2777.

S0002-7863(97)00913-X CCC: $14.00

Scheme 1. Synthesis of Octahydrodeacetyldebromolaurencin



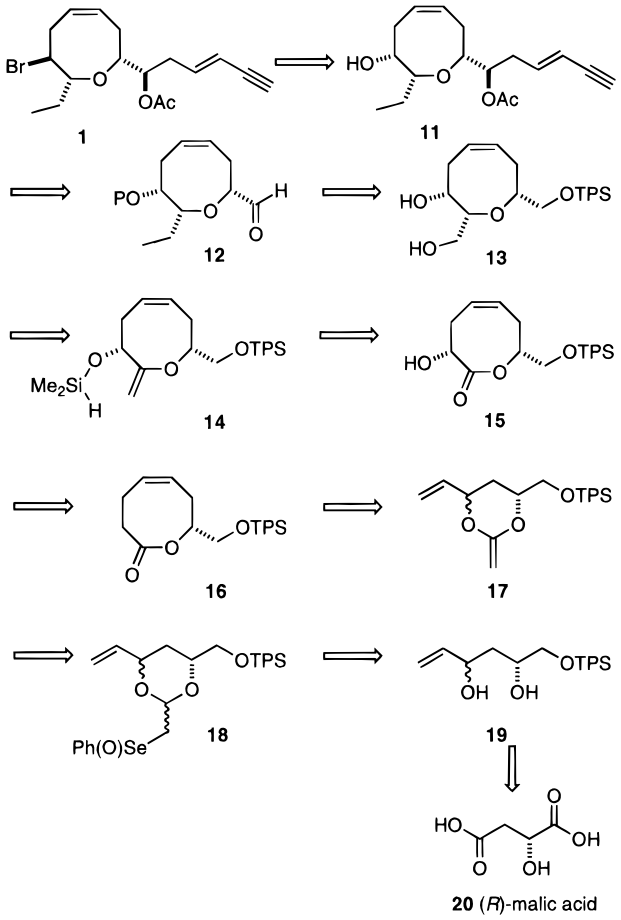
(*R*)-2-Ethylcycloheptanone **5** was prepared by Enders[30,31] alkylation of the azaenolate derived from the SAMP-hydrazone **3**. The alkylation product **4** was obtained with a de of 90% [^{1}H NMR, 90 MHz, Eu(fod)$_3$] and was converted into **5** by ozonolysis. The Baeyer−Villiger oxidation was carried out by addition of the ketone **5** to a buffered solution of trifluoroperacetic acid in order to minimize racemization. Tebbe methylenation, followed by hydroboration with the bulky diisoamylborane, afforded only one diastereoisomeric alcohol which was subsequently shown to be the *cis*-product **8**. This was oxidized with PCC, and the resulting aldehyde was treated with pentylmagnesium bromide at 0 °C to afford a 1.5:1 mixture of the alcohols **2** and **9**, favoring the required material. Attempts to improve selectivity by chelation control using magnesium bromide or mixed cuprates such as pentylcoppermagnesium iodide or bromide were unsuccessful.[32,33] Oxidation of the diastereoisomeric mixture **2** and **9** gave the ketone **10** which was reduced diastereoselectively with L-Selectride in a Felkin−Anh sense to afford exclusively the octahydrodeacetyldebromolaurencin **2**. This exhibited a specific rotation $[\alpha]_D^{21}$ +19.6 (*c* 1.52, $CHCl_3$) and was identical in all respects (TLC, ^{1}H NMR, ^{13}C NMR, IR, MS) with an authentic sample $[\alpha]_D^{18}$ +21.6 (*c* 1.86, $CHCl_3$).[1,2,34] The enantiomeric purity of **2** could not be assayed by the Mosher ester method, but based on the specific rotation it was judged to be of 91% ee. The highly diastereoselective reduction of the side-chain carbonyl group has subsequently been applied by Murai[17] and by us in the synthesis of (+)-laurencin **1** itself. The synthesis of (+)-**2** based on the well precedented Enders method for preparing (*R*)-**5** independently establishes the absolute configuration of (+)-**1**. This is an important correlation because although the absolute configuration had previously been determined by X-ray methods, the previous assignment by X-ray of the absolute configuration of a related molecule, laurenyne,[35] had to be revised after its total synthesis by Overman.[20]

Previous Syntheses of 1. The first enantioselective synthesis of (+)-laurencin was reported by Murai and co-workers and relied on a novel ring expansion reaction of a four-membered ring fused to a tetrahydropyran.[17] The resulting lactone was elaborated to the key intermediate **12** (P = TBS) (see Scheme 2) which serves as a natural focus for the ring synthesis. Overman and colleagues described the second enantioselective synthesis of laurencin using their intramolecular oxacarbenium ion cyclization procedure.[21] This was followed by Palenzuela's formal synthesis involving an intramolecular alkylation of an α-lithiosulfone.[22] It is noteworthy that the latter two syntheses demonstrated that ring closure of unconstrained acyclic precursors to eight-membered ring ethers is entirely feasible under certain circumstances.[24−26]

Retrosynthetic Analysis of 1. The purpose of this paper is to report our own synthesis of (+)-laurencin[36] and to demonstrate some interesting aspects of the functionalization of eight-membered lactones. The retrosynthetic analysis of laurencin (Scheme 2) depends on the late introduction of bromine by displacement with inversion of configuration of the corresponding alcohol **11**, a process which has precedent from all the earlier reported syntheses. The introduction of the pentenynyl side chain was planned by alkylation of the aldehyde **12**. The synthesis of the medium ring 2,8-disubstituted tetrahydro-oxocin **13** relied on elaboration of the corresponding lactone precursor **15** by methylenation and enol ether **14** functionalization. Considerable previous experience encouraged us to prepare the lactone **16** by [3,3]-sigmatropic rearrangement of the vinyl-substituted ketene acetal **17** which was to be generated *in situ* by selenoxide elimination of the precursor **18**. The synthesis therefore relied on a preparation of the triol derivative **19** from (*R*)-malic acid **20**. In the event this strategy was realized. An alternative approach to **15** by an intramolecular ring closure (lactonization) has also been developed. Furthermore, we have

(30) Enders, D.; Eichenauer, H. *Chem. Ber.* **1979**, *112*, 2933.
(31) Enders, D.; Frey, P.; Kipphardt, H. *Org. Synth.* **1987**, *65*, 173.
(32) Jefford, C. W.; Jaggi, D.; Boukouvalas, J. *Tetrahedron Lett.* **1986**, *27*, 4011.
(33) Sato, F.; Kobayashi, Y.; Takahashi, O.; Chiba, T.; Takeda, Y.; Kusakabe, M. *J. Chem. Soc., Chem. Commun.* **1985**, 1636.
(34) Authentic **2** was kindly supplied by Dr A. Fukuzawa, who degraded natural (+)-laurencin **1** to obtain the sample.
(35) Falshaw, C. P.; King, T. J.; Imre, T. J.; Islimyeli, S.; Thomson, R. H. *Tetrahedron Lett.* **1980**, *21*, 4951.
(36) Burton, J. W.; Clark, J. S.; Bendall, J.; Derrer, S.; Stork, T.; Holmes, A. B. *J. Am. Chem. Soc.* **1996**, *118*, 6806.

Scheme 2. Retrosynthesis of (+)-Laurencin **1**



found two different methods of elaborating the lactone **16** to 2,8-disubstituted oxocane derivatives.

Claisen Route to the Lactone 16. The optimum route to the lactone **16** was developed from our racemic synthesis (Scheme 3).[13] (*R*)-Malic acid **20** was esterified[37] and selectively reduced[38,39] to the diol **21** which was protected as the acetonide **22**. Reduction of the ester **22** with DIBAL-H at low temperature to minimize acetonide cleavage, followed by addition of vinylmagnesium chloride to the aldehyde **23** in the presence of thoroughly dried cerium(III) chloride,[40] afforded the allylic alcohol **24**. Vinylmagnesium bromide will also add to the aldehyde **23**, but the reagent becomes less efficient with age, and the most reproducible yields of **24** are obtained with vinylmagnesium chloride. The allylic alcohol **24** was obtained as an approximate 1:1 mixture of diastereoisomers, both of which appeared to undergo the subsequent Claisen rearrangement without difficulty, and the mixture was always carried through the synthesis without separation of the isomers. Acetonide hydrolysis followed by selective silylation of the primary alcohol afforded the TPS ether **19** which was converted with phenylselenoacetaldehyde diethyl acetal[41] into the mixture of acetals **25**. No attempt was made to separate these isomers, but the spectroscopic evidence from a number of investigations would imply that the major isomers present were **25a**, **25b**, and **25c** (Figure 1).

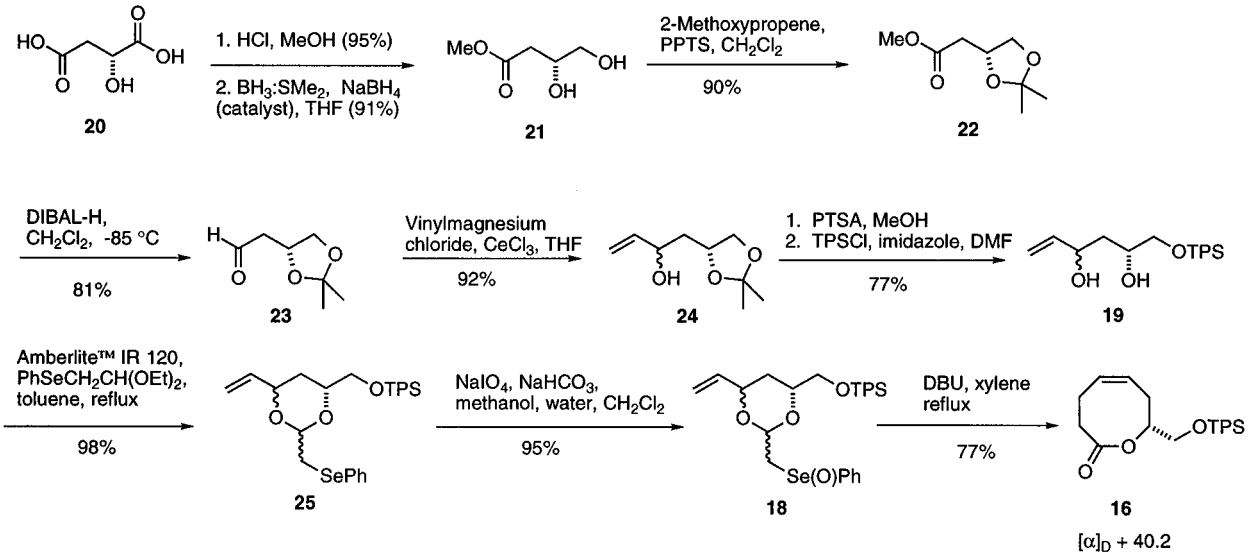
Oxidation of the selenides **25** to the selenoxides **18**, followed by selenoxide elimination in refluxing xylene in the presence of DBU is presumed to have generated the intermediate vinyl-substituted ketene acetal **17** which underwent [3,3]-sigmatropic rearrangement to the lactone **16** in good yield. The fact that high yields were consistently obtained for this rearrangement is indirect evidence that both diastereoisomeric ketene acetals rearranged almost equally well. ^{1}H NMR analysis of a later intermediate, the hydroxy lactone **15** ($J_{5,6}$ = 11.0 Hz) indicated that the lactone **16** contained a *cis*-double bond. Such Claisen ring expansions were first used by Petrzilka[41] to prepare a 10-membered lactone. We have used this procedure to obtain seven-, eight- and nine-membered lactones, and almost without exception the (*Z*)-alkene is produced in the smaller rings.[13−16] However we have seen occasional exceptions, and a recent example reported by Pearson also yielded a nine-membered lactone with mainly the (*E*)-double bonded product.[42] In the synthesis of the lactone **16** the results are consistent with the involvement of all chair-like transition states (Figure 2) for the 1,3-*anti* diol-derived precursor **TS1**, while the 1,3-*syn*-diol precursor is able to invert one of the rings to a less hindered conformation **TS2** to relieve the strain arising from the OTPS substituent.

Conversion of the Lactone 16 into a 2,8-Disubstituted Tetrahydrooxocin. Methylenation of the racemic lactone (±)-**16** with the Tebbe reagent[43,44] gave the enol ether **26** in good yield (Scheme 4). The conformational rigidity owing to the presence of the endocyclic double bond in **26** meant that it was sufficiently stable to be chromatographed on silica gel in the presence of triethylamine and a suitable solvent. All attempts at hydroborating the enol ether **26** with a variety of organoboranes were uniformly unsuccessful. Either the exocyclic double bond resisted attack, or under more forcing conditions ring-opening of the intermediate organoborane occurred together with competing hydroboration of the endocyclic double bond. It was therefore decided to attempt phenylselenoacetalization of the enol ether, according to well established precedent for simple enol ethers.[41] The enol ether **26** reacted efficiently with benzeneselenenyl chloride in methanol in the presence of triethylamine to give a 6:1 mixture of methoxy acetals **27a** and **27b**. The relative stereochemistry of these isomers was not assigned, but precedent would suggest that the major isomer was **27a**, because most examples of nucleophilic attack on eight-membered oxacarbenium ions favor the incoming reagent being *trans* to existing substituents.[8−12] In keeping with this observation, reduction of the major methoxy-acetal with alane afforded mainly the *cis*-phenylselenomethyl derivative **28a** plus a trace of the *trans*-isomer **28b**; the harsh reducing conditions resulted in cleavage of the silyl protecting group. These were each converted into the corresponding 3,5-dinitrobenzoates **29a** and **29b**, respectively. The major product formed crystals suitable for X-ray structure determination, and the structure is shown in Figure 3.[45]

This is the first crystal structure of a synthetic $\Delta^{5,6}$-2,8-disubstituted-tetrahydro-2*H*-oxocin.[26] An examination of the ring conformation of **29a** showed that it represents a global minimum characteristic of the ring conformation of the eight-

(37) Mori, K.; Takigawa, T.; Matsuo, T. *Tetrahedron* **1979**, *35*, 933.
(38) Saito, S.; Hasegawa, T.; Inaba, M.; Nishida, R.; Fujii, T.; Nomizu, S.; Moriwake, T. *Chem. Lett.* **1984**, 1389.
(39) Saito, S.; Ishikawa, T.; Kuroda, A.; Koga, K.; Moriwake, T. *Tetrahedron* **1992**, *48*, 4067.
(40) Imamoto, T.; Takiyama, N.; Nakamura, K.; Hatajima, T.; Kamiya, Y. *J. Am. Chem. Soc.* **1989**, *111*, 4392.
(41) Petrzilka, M. *Helv. Chim. Acta* **1978**, *61*, 3075.
(42) Pearson, W. H.; Hembre, E. J. *J. Org. Chem.* **1996**, *61*, 5546.
(43) Tebbe, F. N.; Parshall, G. W.; Reddy, G. S. *J. Am. Chem. Soc.* **1978**, *100*, 3611.
(44) Pine, S. H.; Zahler, R.; Evans, D. A.; Grubbs, R. H. *J. Am. Chem. Soc.* **1980**, *102*, 3270.
(45) Compound **29a**, $C_{22}H_{22}O_7Se$, MW 505.39, was obtained as yellow crystals, space group *P*1 (No. 2), a = 8.574(1) Å, b = 11.434(1) Å, c = 12.702(1) Å, α = 114.14(1)°, β = 92.33(1)°, γ = 103.39(1)°, V = 1092.6 Å^3, Z = 2, D_{calcd} = 1.54 g cm^{-3}, F(000) = 516, λ (Cu $K\alpha$) 1.5418 Å, μ (Cu $K\alpha$) 27.67 cm^{-1}.

Scheme 3. Synthesis of the Lactone **16**



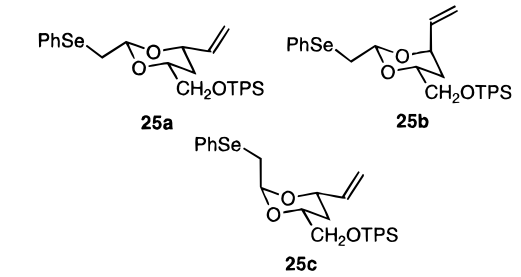


Figure 1. Diastereoisomeric acetals **25**.

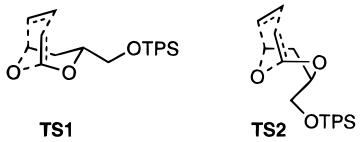
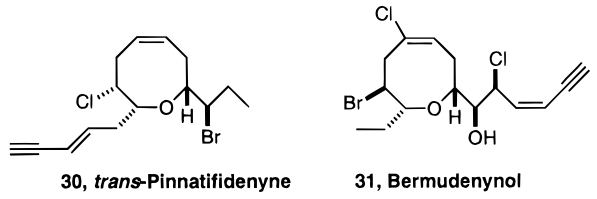


Figure 2. Claisen transition states.

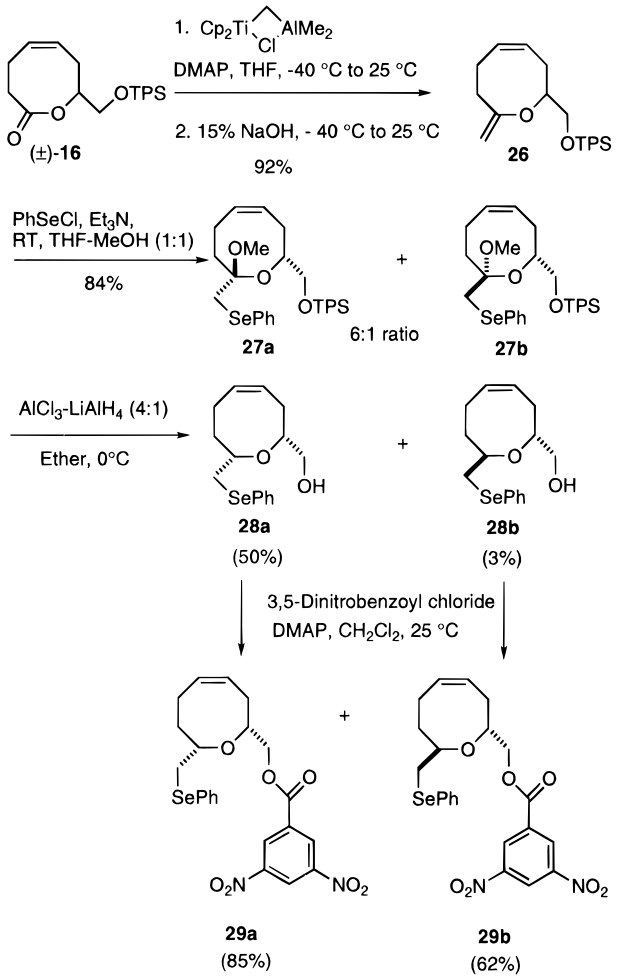
membered unsaturated *Laurencia* metabolites laurencin[3,4] **1**, *trans*-pinnatifidenyne[46] **30**, and bermudenynol[47] **31** (Figure 4).



The *cis*-phenylselenomethyl derivative **28a** was protected and then readily transformed by Pummerer rearrangement into the α-acetoxy derivative **32** and then by reduction into the hydroxymethyl derivative **33** (Scheme 5). This sequence therefore established an alternative to hydroboration for the conversion of enol ethers into functionalized eight-membered ring ethers.

α-Hydroxylation of the Lactone 16. Before applying a methylenation sequence to the laurencin precursor itself it was necessary to introduce an α-hydroxyl substituent adjacent to the lactone carbonyl group of **16** in anticipation of the need ultimately to replace this substituent by bromine at the end of the synthesis. We were attracted to the possibility of using the Davis oxaziridine reagents to oxidize the lactone enolate diastereoselectively.[48]

Scheme 4. Elaboration of the Lactone **16**



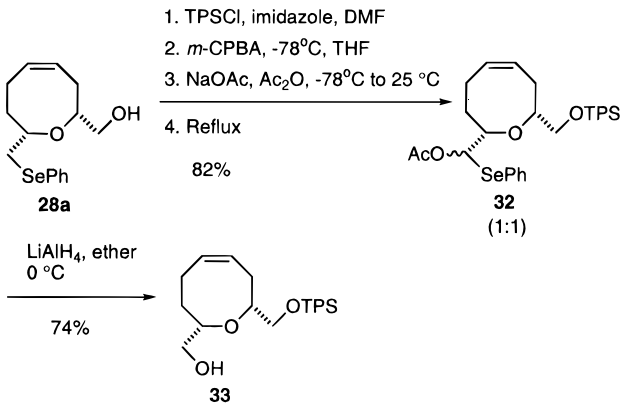
Formation of the potassium enolate derived from the lactone **16**, as a solution in THF at −78 °C followed by addition of *trans*-(±)-2-(phenylsulfonyl)-3-phenyloxaziridine **34**[49,50] gave the hydroxy lactones **15** and **35** as a 1:1 mixture of diastereoisomers in 22% yield (Scheme 6).

(46) González, A. G.; Martín, J. D.; Martín, V. S.; Norte, M.; Pérez, R.; Ruano, J. Z.; Drexler, S. A.; Clardy, J.*Tetrahedron* **1982**, *38*, 1009.

(47) Cardellina II, J.; Horsley, S. B.; Clardy, J.; Leftow, S. R.; Meinwald, J. *Can. J. Chem.* **1982**, *60*, 2675.

(48) Davis, F. A.; Chen, B. C. *Chem. Rev.* **1992**, *92*, 919.

Scheme 5. Pummerer Rearrangement of **28a**



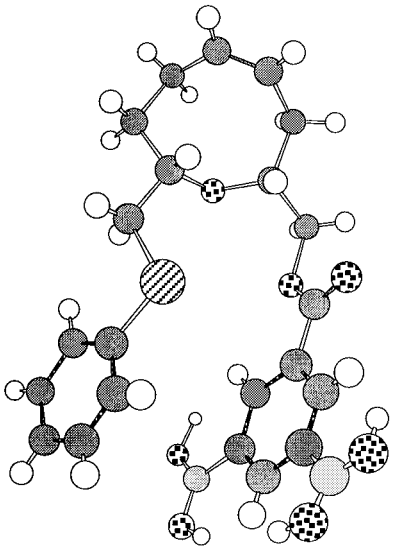
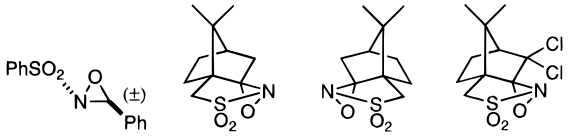


Figure 3. The X-ray crystal structure of the dinitrobenzoate **29a**.



The poor selectivity indicated that the remote CH_2OTPS substituent in the enolate derived from **16** provided insufficient conformational bias to favor the required 3(*R*)-alcohol **15** for the proposed synthesis of (+)-laurencin. It was clear that reagent control would be required to control the diastereoselectivity of attack. Davis[48] has advocated the use of the (10-camphorsulfonyl)oxaziridines **36** and **37** to perform diastereoselective enolate oxidations. The use of **36** in THF at −78 °C with the potassium enolate derived from **16** afforded only the 3(*S*)-alcohol **35** in 7% yield. The configuration of the 3(*S*)-alcohol **35** was rigorously established *via* ^{1}H NMR 1D gradient NOE measurements[51,52] (Figure 5) and Mosher ester analysis[53] (see Supporting Information). Irradiation of 8-H (δ 4.82−4.78, m, 1H) led to an enhancement of the signal due to 6-H (δ 5.82, dt, J = 11.0, 7.7, 1H) but no enhancement of 3-H (δ 4.64−4.61, m, 1H); irradiation of the signal due to 3-H did not lead to enhancement of 8-H. These experiments indicated that 3-H and 8-H were in a *trans*-relationship. Molecular modeling (Monte Carlo conformational search[54] using the MM2 force field[55] in MacroModel version 5.5[56]) provided a unique global minimum conformation for the analogous lactone **35a**. This model fitted the NOE data very well and indicated that 8-H and 6-H were in close proximity (3.31 Å apart).

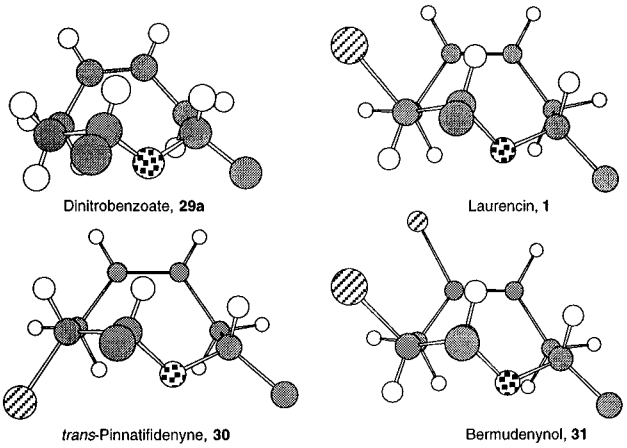
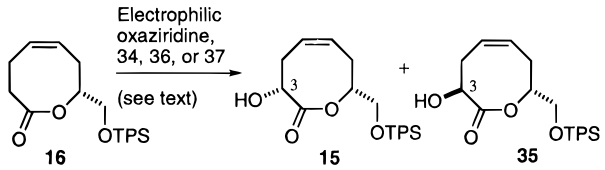


Figure 4. Chem3D representations of the crystal structures of the dinitrobenzoate **29a**, laurencin **1**, *trans*-pinnatifidenyne **30**, and bermudenynol **31** taken from the Cambridge Crystallographic Database to show the comparison of the oxocane ring conformation (viewed along the 3-C−4-C bond). For clarity, the side chains have been deleted from all the models.

Scheme 6. Enolate Hydroxylation of **16**



Reaction of a THF solution of the potassium enolate derived from the lactone **16** with 1(*R*)-(−)-(10-camphorsulfonyl)-oxaziridine **37** at −78 °C provided the hydroxy lactones **15** and **35** as a 5.3:1 mixture of diastereoisomers (11%). The structure of the 3(*R*)-alcohol **15** was established *via* 1D gradient NOE measurements[51,52] which fit well with the results obtained from molecular modeling of the analogous lactone **15a** (Figure 6). In particular strong reciprocal NOEs were observed in the ^{1}H NMR spectra between the signals due to 3-H (δ 4.40−4.36, m, 1H) and 8-H (δ 4.62, m, 1H).

Performing the above experiments using toluene as the solvent provided the hydroxy lactones in reasonable yield (see Table 1). The desired 3(*R*)-alcohol **15** could be obtained in an optimum yield of 26% (entry 9) but not as the exclusive product. We have subsequently shown that both **15** and **35** could, in principle, be employed in a synthesis of laurencin, but alternative higher yielding routes to **15** became desirable.

The selectivities observed in the above reactions are hard to account for and do not appear to fit the recent model put forward by Bach and Davis[57] for oxidation of ketone enolates using the chlorocamphorsulfonyl oxaziridine **38**. We relied, in part, on

(49) Davis, F. A.; Stringer, O. D. *J. Org. Chem.* **1982**, *47*, 1774.
(50) Vishwakarma, L. C.; Stringer, O. D.; Davis, F. A. *Org. Synth.* **1988**, *66*, 203.
(51) Stonehouse, J.; Adell, P.; Keeler, J.; Shaka, A. J. *J. Am. Chem. Soc.* **1994**, *116*, 6037.
(52) Stott, K.; Stonehouse, J.; Keeler, J.; Hwang, T. L.; Shaka, A. J. *J. Am. Chem. Soc.* **1995**, *117*, 4199.
(53) Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092.
(54) Chang, G.; Guida, W. C.; Still, W. C. *J. Am. Chem. Soc.* **1989**, *111*, 4379.
(55) Allinger, N. L. *J. Am. Chem. Soc.* **1977**, *99*, 8127.
(56) Mohamadi, F.; Richards, N. G. J.; Guida, W. C.; Liskamp, R.; Lipton, M.; Caufield, C.; Chang, G.; Hendrickson, T.; Still, W. C. *J. Comput. Chem.* **1990**, *11*, 440.
(57) Bach, R. D.; Andrés, J. L.; Davis, F. A. *J. Org. Chem.* **1992**, *57*, 613.

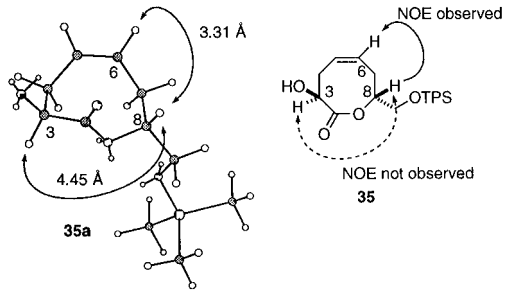


Figure 5. Chem3D representation of the global minimum conformation (Macromodel, MM2 force field, Monte Carlo conformational search) of **35a** (TPS group modeled as TMS group) analogous to the hydroxy lactone **35** and 1D gradient NOE data for **35**.

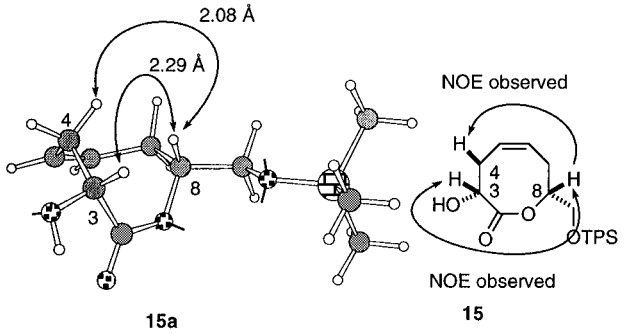


Figure 6. Chem3D representation of the global minimum conformation (MacroModel, MM2 force field, Monte Carlo conformational search) of **15a** (TPS modeled as TMS group) analogous to the hydroxy lactone **15** and 1D gradient NOE data for **15**.

Table 1. Oxidation of the Enolate Derived from **16**

entry	solvent	oxaziridine	base	yield **15** and **35**	ratio **15**:**35**
1	THF	34	KHMDS	22	1:1
2	THF	36	KHMDS	7	4.5:95.5
3	THF	37	KHMDS	11	5.3:1
4	THF	36	LiHMDS	trace	nd[a]
5	THF	36	LDA	trace	nd[a]
6	THF	36	NaHMDS	20	nd[a]
7	toluene	34	KHMDS	64	1:4
8	toluene	36	KHMDS	65	1:2
9	toluene	37	KHMDS	52	1:1

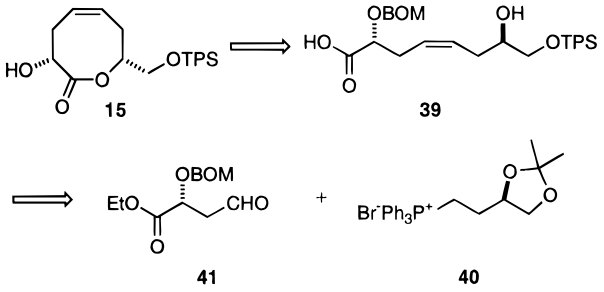
[a] Not determined is abbreviated as nd.

the previous model put forward by Davis for ketone enolates in our original incorrect assignment of the structure of **15**, although one reported example of a lactone enolate hydroxylation does seem more consistent with our own findings.[48] Therefore we conclude that the application of this model to chiral lactone enolates should be exercised with caution. Given that our original hydroxy lactone was compound **35** and not **15**, we concluded that we could not have synthesized laurencin; the original paper was therefore withdrawn, and the synthetic sequence was repeated using authentic **15**.[36] The alternative route to **15** is described below.

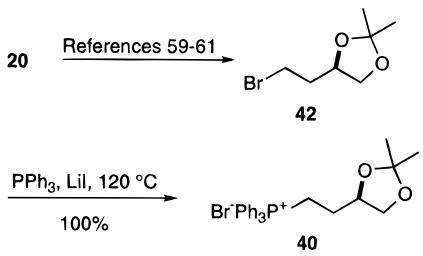
We note in passing that the major byproduct from the oxaziridine oxidations was the ring opened hydroxy acid, suggesting that the involvement of ketene intermediates may well explain the poor yields of hydroxy lactones isolated.

Yamaguchi Lactonization Route to the α-Hydroxy Lactone 15. The recent promising advances in ring closure of *seco*-acids to eight-membered lactones[58] suggested the direct lactonization of the hydroxy acid **39**. The *cis*-double bond in **39** implies a Wittig disconnection to provide the phosphonium salt **40** and the aldehyde **41**, both available from (*R*)-malic acid **20** (Scheme 7).

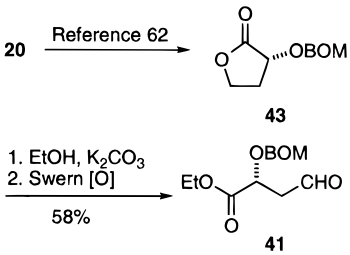
Scheme 7. Retrosynthesis of the Lactone **15**



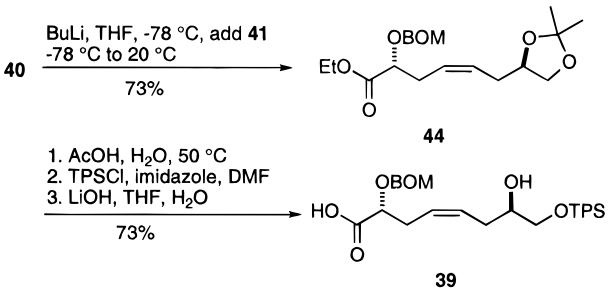
Scheme 8. Synthesis of the Phosphonium Salt **40**



Scheme 9. Synthesis of the Aldehyde **41**



Scheme 10. Synthesis of the *seco*-Acid **39**



The known bromide **42**[59−61] was treated with molten triphenylphosphine under lithium iodide catalysis to provide the phosphonium salt **40** which could be crystallized by sonication with ether (Scheme 8).

The aldehyde **41** was prepared by ethanolysis of the known BOM-protected lactone **43**[62] and Swern oxidation[63] of the resulting primary alcohol (Scheme 9).

Wittig reaction of the ylid derived from the phosphonium salt **40** (BuLi, THF, −78 °C to 0 °C) with the aldehyde **41**

(58) Buszek, K. R.; Sato, N.; Jeong, Y. *J. Am. Chem. Soc.* **1994**, *116*, 5511.

(59) Mori, K.; Watanabe, H. *Tetrahedron Lett.* **1984**, *25*, 6025.

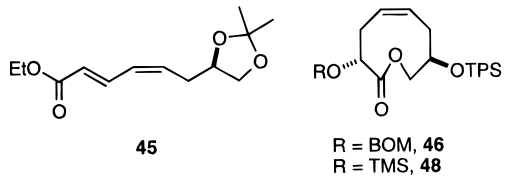
(60) Barth, M.; Bellamy, F. D.; Renaut, P.; Samreth, S.; Schuber, F. *Tetrahedron* **1990**, *46*, 6731.

(61) Meyers, A. I.; Lawson, J. P.; Walker, D. G.; Linderman, R. J. *J. Org. Chem.* **1986**, *51*, 5111.

(62) Collum, D. B.; McDonald III, J. H.; Still, W. C. *J. Am. Chem. Soc.* **1980**, *102*, 2118.

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

provided the alkene **44** (73%) (Scheme 10). The geometry of the alkene **44** was assigned as (*Z*) according to precedent and was later confirmed by the measurement of a 10.9 Hz coupling between 5-H and 6-H in the lactone **47**. A small quantity of the dienes [predominantly the 2(*E*),4(*Z*) isomer **45**, $J_{2,3} = 15.3$



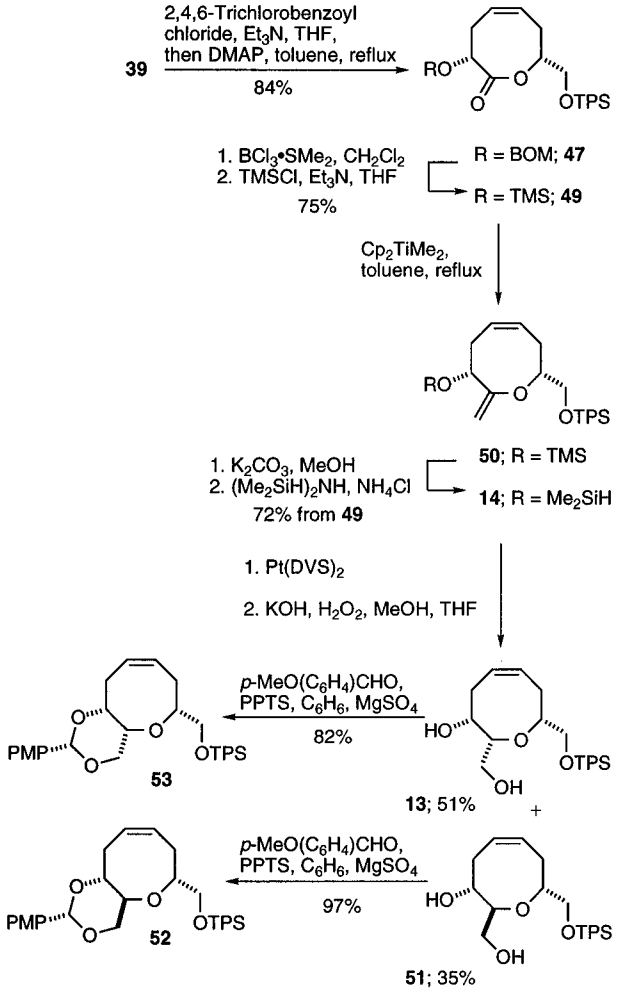
45 R = BOM, **46**; R = TMS, **48**

Hz, $J_{4,5} = 10.9$ Hz] was obtained from the Wittig reaction (the structure of the minor geometrical isomer could not be proved). Standard protecting group manipulations on the alkene **44** provided the lactonization precursor **39** in good overall yield.

Corey−Nicolaou[64−66] lactonization of the *seco*-acid **39** gave the required lactone **47** in moderate yield. However, **47** could be prepared in excellent yield using the Yamaguchi lactonization conditions (Scheme 11).[67,68] A small quantity of the nine-membered lactone **46** (ratio **47**:**46**, 10:1) was also obtained, owing to silyl group migration from primary to secondary hydroxyl groups before lactonization. The nine-membered lactone **46** was not separated at this stage but was removed by flash chromatography of a later intermediate. Deprotection of the BOM ether from the lactones **46** and **47** with $BCl_3{\cdot}SMe_2$[69] afforded the corresponding hydroxy lactones from which **15** could be separated by HPLC for analytical purposes. The hydroxy lactone **15** synthesized *via* the *seco*-acid **39** was identical to the major diastereoisomer formed by Davis oxidation of the potassium enolate of the lactone **16** with the oxaziridine **37** (Table 1, Entry 3). Trimethylsilylation of the hydroxy lactones allowed quantitative separation of the nine-membered lactone **48** by flash chromatography.

Methylenation and Intramolecular Hydrosilation Studies. Methylenation of the eight-membered lactone **49** with the Petasis reagent,[70,71] which is more convenient to prepare than Tebbe's reagent,[43] gave the enol ether **50** which was converted into the silane **14** (Scheme 11).[72] The intramolecular hydrosilation of acyclic enol ethers has been developed by Tamao[73] and has subsequently been exploited by us in an approach to the nine-membered cyclic ether obtusenyne.[74] The key intramolecular hydrosilation reaction of **14** was carried out with the catalyst bis(1,3-divinyl-1,1,3,3-tetramethyldisiloxane)platinum(0) [$Pt(DVS)_2$].[75−77] This reagent has been shown to operate *via* a

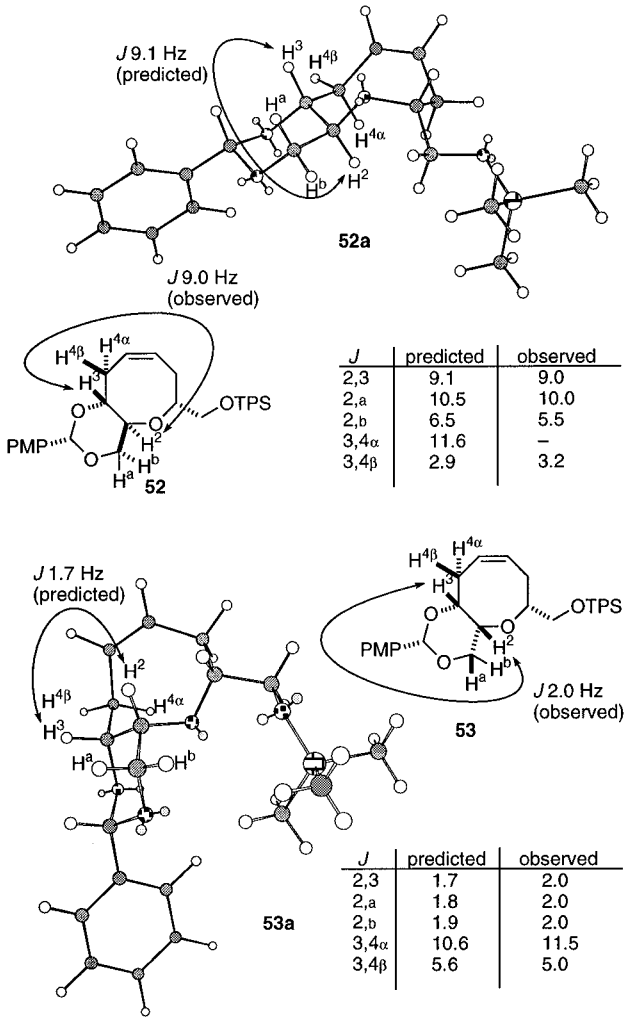
Scheme 11. Yamaguchi Lactonization and Hydrosilation Studies



mechanism that involves reduction of the ligands on platinum followed by the formation of colloids which then act as the catalyst for the reaction.[78,79] The best result obtained in the hydrosilation of **14** involved the portionwise addition of 8 mol % of the catalyst (0.1 M in toluene) to the neat silane **14** under an atmosphere of dry air, followed by oxidation with basic hydrogen peroxide.[72,77] This provided the diols **13** and **51** as a 58:42 mixture in 86% yield. However, the reaction was capricious and generally favored the *trans*-isomer **51**. Although control of the stereochemistry of the hydrosilation of **14** is a highly desirable objective, we have been able to use both **13** and **51** in the present route to (+)-laurencin (*vide infra*). Larger scale hydrosilation reactions (860 μmol, see Experimental Section) provided the diols in substantially lower yield, which may be due to the development of oxygen deficiency which results in irreversible colloid agglomeration and a consequent loss of catalytic activity.[78]

Conversion of the diols **51** and **13** into the corresponding *p*-methoxybenzylidene acetals **52** and **53** allowed assignment of the stereochemistry at 2-C and 3-C. The acetal **52**, derived from the *trans*-diol **51**, exhibited a 9.0 Hz coupling constant between 3-H and 2-H in the ^{1}H NMR spectrum, which is consistent with a *trans*-diaxial relationship between 2-H and 3-H in a six-membered ring, whereas the acetal **53**, derived from the *cis*-diol **13** exhibited a 2.0 Hz coupling constant between 3-H and 2-H. This is consistent with an axial−equatorial coupling in a six-membered ring. Other coupling constants were

(64) Corey, E. J.; Nicolaou, K. C. *J. Am. Chem. Soc.* **1974**, *96*, 5614.
(65) Corey, E. J.; Brunelle, D. J.; Stork, P. J. *Tetrahedron Lett.* **1976**, *38*, 3405.
(66) Gerlach, H.; Thalmann, A. *Helv. Chim. Acta* **1974**, *57*, 2661.
(67) Inanaga, J.; Hirata, K.; Hiroko, S.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989.
(68) Mulzer, J.; Kirstein, H. M.; Buschmann, J.; Lehmann, C.; Luger, P. *J. Am. Chem. Soc.* **1991**, *113*, 910.
(69) Congreve, M. S.; Davison, E. C.; Fuhry, M. A. M.; Holmes, A. B.; Payne, A. N.; Robinson, R. A.; Ward, S. E. *Synlett* **1993**, 663.
(70) Petasis, N. A.; Bzowej, E. I. *J. Am. Chem. Soc.* **1990**, *112*, 6392.
(71) Petasis, N. A.; Lu, S. P.; Bzowej, E. I.; Fu, D. K.; Staszewski, J. P.; Akritopoulou-Zanze, I.; Patane, M. A.; Hu, Y. H. *Pure Appl. Chem.* **1996**, *68*, 667.
(72) Tamao, K.; Nakagawa, Y.; Arai, H.; Higuchi, N.; Ito, Y. *J. Am. Chem. Soc.* **1988**, *110*, 3712.
(73) Tamao, K.; Nakagawa, Y.; Ito, Y. *Organometallics* **1993**, *12*, 2297.
(74) Curtis, N. R.; Holmes, A. B. *Tetrahedron Lett.* **1992**, *33*, 675.
(75) Karstedt, B. D. (General Electric Co.), U.S. Appl. 226,928, 16 Feb 1972. *Chem. Abstr.* **1974**, *80*, P16134j.
(76) Karstedt, B. D. (General Electric Co.), Ger. Offen., 2,307,085, 23 Aug 1973. *Chem. Abstr.* **1974**, *80*, P16134j.
(77) Tamao, K.; Ishida, N.; Tanaka, T.; Kumada, M. *Organometallics* **1983**, *2*, 1694.
(78) Lewis, L. N. *J. Am. Chem. Soc.* **1990**, *112*, 5998.



J	predicted	observed
2,3	9.1	9.0
2,a	10.5	10.0
2,b	6.5	5.5
3,4α	11.6	–
3,4β	2.9	3.2

J	predicted	observed
2,3	1.7	2.0
2,a	1.8	2.0
2,b	1.9	2.0
3,4α	10.6	11.5
3,4β	5.6	5.0

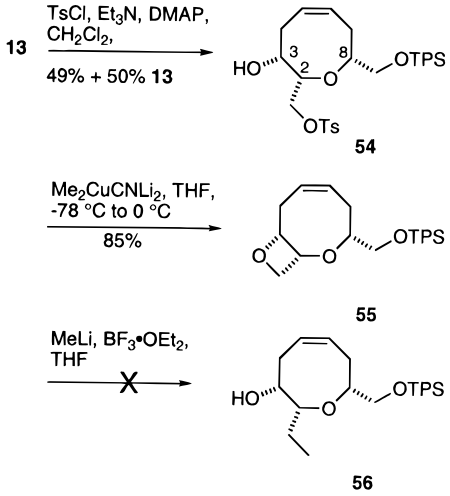
Figure 7. Chem3D representations of the ground state conformations (MacroModel, MM2 force field, Monte Carlo conformational search) of **53a** and **52a** (TPS group modeled as TMS group) analogous to **53** and **52** with predicted coupling constants from Macromodel and coupling constants measured by 500 MHz ^{1}H NMR for **53** and **52**.

also in good agreement with those predicted *via* computer modeling (Figure 7).

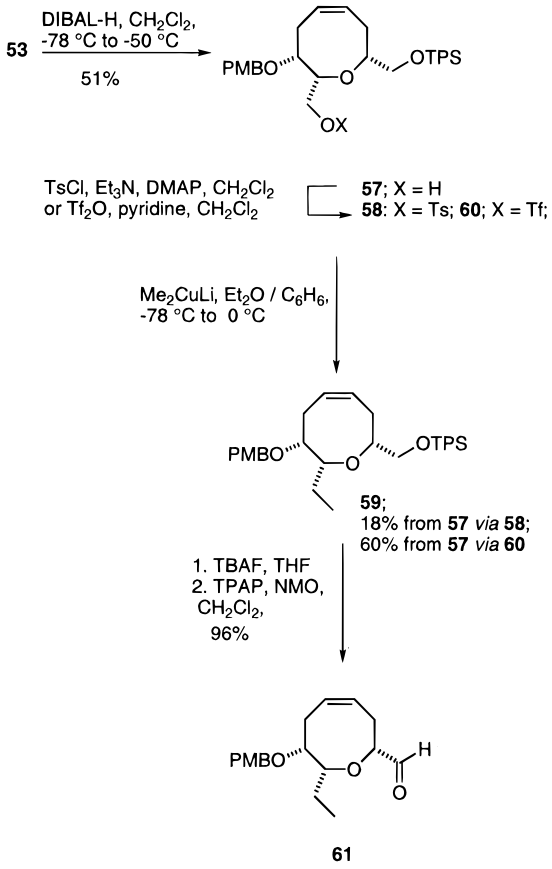
Introduction of the Ethyl Side Chain. For the synthesis of (+)-laurencin it was necessary to convert the hydroxymethyl group of **13** into an ethyl substituent. This could be achieved by displacement of a sulfonate ester with an organocuprate. The monotosylate **54** (Scheme 12), formed from the diol **13**, showed a large cross-peak between 2-H and 8-H in the ^{1}H NMR NOESY spectrum, lending strength to the structural assignment for the *cis*-diol **13** given above. However, treatment of **54** with $Me_2CuCNLi_2$ afforded the oxetane **55** (85%) and not the required ethyl-substituted oxocane **56** (Scheme 12). Formation of **55** further demonstrates the *cis*-relationship of 2-H and 3-H. The oxetane **55** failed to react with methyllithium in the presence of $BF_3{\cdot}OEt_2$ to afford **56**[80] and therefore it was necessary to protect the 3-hydroxyl group to prevent intramolecular cyclization.

Cleavage of the previously formed acetal **53** with DIBAL-H[81] afforded the primary alcohol **57** which was converted into the corresponding tosylate **58** (Scheme 13). Reaction of **58** with

Scheme 12. Organocuprate Studies



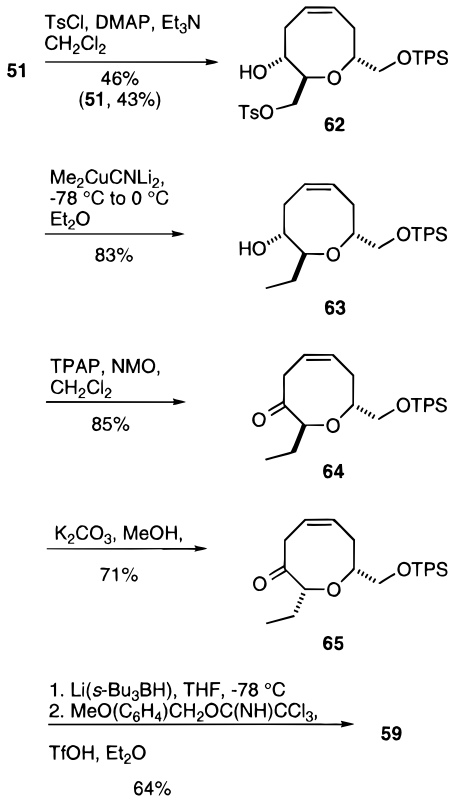
Scheme 13. Organocuprate Studies



Me_2CuLi in an ether/benzene solvent system[82] provided the required ethyl-substituted oxocane **59** in 19% yield. Reaction of the corresponding triflate **60** under the same conditions provided **59** in an improved 60% yield. If benzene was omitted from these reactions, then no product was observed. This observation can probably be attributed to solvation of the PMB group of **58** and **60** by benzene, which allows reaction to occur. Use of the more reactive $Me_2CuCNLi_2$ in the above reactions provided substantial amounts of the alcohol **57** arising *via* attack of the organocuprate at sulfur. Removal of the silyl protecting group followed by tetrapropylammonium per-ruthenate(VII)

(79) Lewis, L. N.; Lewis, N. *J. Am. Chem. Soc.* **1986**, *108*, 7228.
(80) Elis, M. J.; Wrobel, J. E.; Ganem, B. *J. Am. Chem. Soc.* **1984**, *106*, 3693.
(81) Schreiber, S. L.; Wang, Z.; Schulte, G. *Tetrahedron Lett.* **1988**, *29*, 4085.
(82) Pougny, J. R. *Tetrahedron Lett.* **1984**, *25*, 2363.
(83) Ley, S. V.; Norman, J.; Griffith, W. P.; Marsden, S. P. *Synthesis* **1994**, 639.

Scheme 14. Epimerization Studies

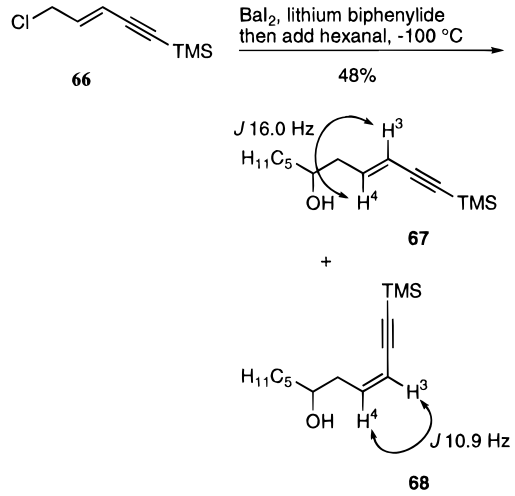


(TPAP) oxidation[83,84] gave the aldehyde **61** in good yield in readiness for introduction of the pentenynyl side chain.

In order to make use of the *trans*-diol **51** in the synthesis of (+)-laurencin it was necessary to epimerize the 2-C stereocenter (Scheme 14). Treatment of the *trans*-diol **51** under standard tosylation conditions provided the monotosylate **62** (46%) along with starting material (43%). Reaction of the tosylate **62** with $Me_2CuCNLi_2$ in ether gave the ethyl-substituted product **63**. TPAP oxidation[83,84] of **63** afforded the ketone **64** in good yield (85%). Epimerization at 2-C was then accomplished by treatment with potassium carbonate in methanol providing the desired 2-C epimer **65** (71%). This epimerization is precedented from the work of Murai[17] and Palenzuela.[22] Reduction of the ketone **65** with L-Selectride in THF[17] followed by PMB protection afforded the oxocane **59**, identical to that previously synthesized, indicating that the reduction had occurred in the expected sense.[17,22]

Introduction of the Pentenynyl Side Chain. All that remained for the synthesis of (+)-laurencin was the introduction of the unsaturated side chain and replacement of the 3-C oxygen with bromine. The proposed route for introduction of the unsaturated side-chain involved the addition of a pentenynyl anion to the corresponding aldehyde **61**. A large number of model studies were conducted in order to realize this plan. For example, reaction of the pentenynyl chloride **66**[85] with barium metal, formed by the reduction of barium(II) iodide, followed by addition of hexanal yielded the (*E*)-**67** and (*Z*)-alkenes **68** as a 1:1.5 mixture in 48% overall yield (Scheme 15).[86,87]

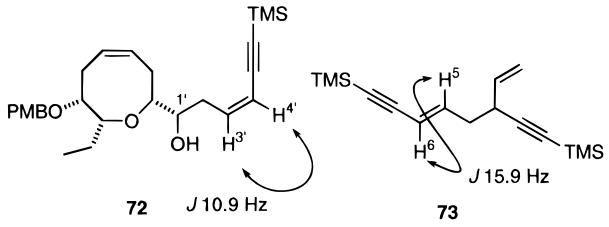
Scheme 15. Model Side Chain Studies



This result is in contrast to the work of Yamamoto who demonstrated complete retention of alkene geometry for allylations involving a large number of allylbarium reagents; the reason for the loss of stereochemistry is not clear. The ultimately successful strategy for side-chain introduction involved a samarium(II) iodide Barbier-type reductive coupling reaction.[17,88] The reaction was first tested on some model oxocanes. Treatment of the racemic aldehydes **74**[9] or **75**[11] with the bromide **69**[89] in the presence of samarium(II) iodide provided the corresponding alcohols **76** and **77** and **78** and **79** as 1:1 mixtures of diastereoisomers in 68% and 71% yield, respectively (Schemes 16 and 17).

The structural assignment of all these products is discussed below. Similarly, reaction of **61** with **69** in the presence of samarium(II) iodide provided the alcohols **70** and **71** as a 1:1 mixture of diastereoisomers in 63% yield (Scheme 18).

The geometry of the side-chain alkene was confirmed by coupling constant analysis (for **70** $J_{3',4'} = 15.9$ Hz, for **71** $J_{3',4'} = 16.0$ Hz). However, a small amount of the (*Z*)-enyne side chain was also observed in all the unpurified reaction mixtures (for **72** $J_{3',4'} = 10.9$ Hz), along with the side-chain dimer **73** arising from cross-coupling of the side-chain bromide **69**. In all reactions no control of the newly formed stereocenter could be realized, as expected from the synthesis of octahydrodeacetyldebromolaurencin **2**.



Octahydrodeacetyldebromolaurencin **2** and the 1′-epimer **9** exhibited two major distinguishing features in the ^{1}H NMR spectrum; in the 1′(*R*)-alcohol **2** the three hydrogens next to oxygen appeared as a single multiplet [δ 3.42−3.27 (m, 3H, 2 × CHOR, C*H*$^{1'}$OH)] and the OH resonance was broad [δ 2.71 (br, 1H, OH)]. For the 1′(*S*)-alcohol **9** the hydrogens next to

(84) Griffith, W. P.; Ley, S. V.; Whitcombe, G. P.; White, A. D. *J. Chem. Soc., Chem. Commun.* **1987**, 1625.

(85) This reagent was prepared from (*E*)-pent-2-en-4-yn-1-ol; (a) BuLi, TMSCl, THF then HCl (93%); (b) Me_2S, *N*-chlorosuccinimide, CH_2Cl_2 (80%).

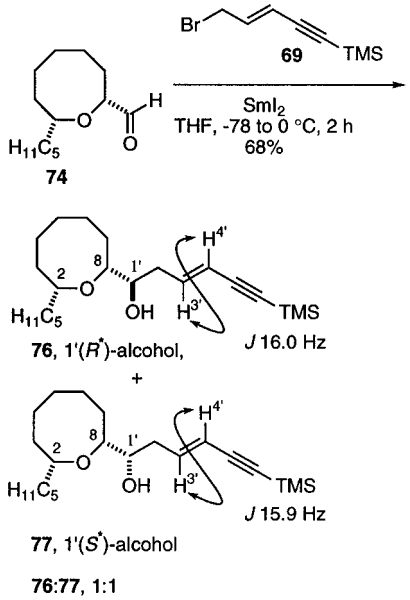
(86) Yanagisawa, A.; Habaue, S.; Yamamoto, H. *J. Am. Chem. Soc.* **1991**, *113*, 8955.

(87) Yanagisawa, A.; Habaue, S.; Yasue, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1994**, *116*, 6130.

(88) Souppe, J.; Namy, J. L.; Kagan, H. B. *Tetrahedron Lett.* **1982**, *23*, 3497.

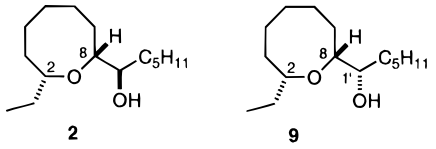
(89) This reagent was prepared from (*E*)-5-trimethylsilylpent-2-en-4-yn-1-ol,[85] $(CH_3)_2NC(Br)=C(CH_3)_2$, CH_2Cl_2 (58%); Bendall, J. G.; Payne, A. N.; Screen, T. E. O.; Holmes, A. B. *J. Chem. Soc., Chem. Commun.* **1997**, 1067.

Scheme 16. Barbier-Type Coupling



Compound	δ_H OH	δ_H 2-H, 8-H, 1'-H
1'(*R**)-**76**	2.63	3.50-3.35
1'(*S**)-**77**	1.99	3.62-3.58, 3.46-3.45, 3.42

oxygen appeared as two separate multiplets [δ 3.60−3.56 (m, 1H, CHOR) and 3.41−3.35 (m, 2H, CHOR, C*H*$^{1'}$OH)], and the OH resonance was also broad [δ 2.04−2.03 (br, 1H, OH)].

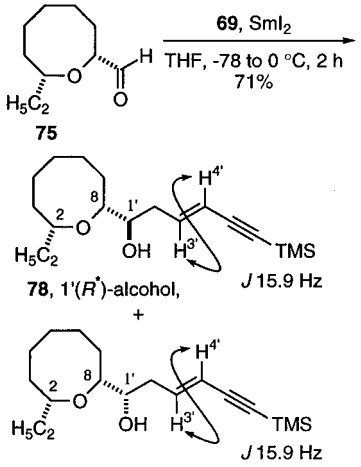


Compound	δ_H OH	δ_H 2-H, 8-H, 1'-H
1'(*R*)-**2**	2.71	3.42-3.27
1'(*S*)-**9**	2.03-2.04	3.61-3.53, 3.42-3.32

Each diastereomer of the three pairs synthesized by the samarium(II) iodide mediated reductive coupling fitted the pattern of spectral data observed for octahydrodeacetyldebromolaurencin **2** and its 1′-epimer **9**. For one of the pair, the two protons α to the oxocane oxygen and the C*H*$^{1'}$OH appeared as an overlapping multiplet (approximately δ 3.55−3.30), and the OH appeared in the range δ 2.80−2.60. For the other, the two protons α to the oxocane oxygen and the C*H*$^{1'}$OH appeared as distinct multiplets, and the OH appeared at higher field (approximately δ 2.20−2.00) (see tables). The OH signal was well defined in these cases, suggesting that it may be involved in an intramolecular hydrogen bond with the oxocane oxygen, which fixes the ring conformation and produces chemical shifts indicative of the side-chain alcohol configuration. The structural assignment of all these alcohols was therefore made on the basis of the ^{1}H NMR chemical shift of the OH proton and, to a lesser extent, on the shift of the protons α to oxygen. It was also

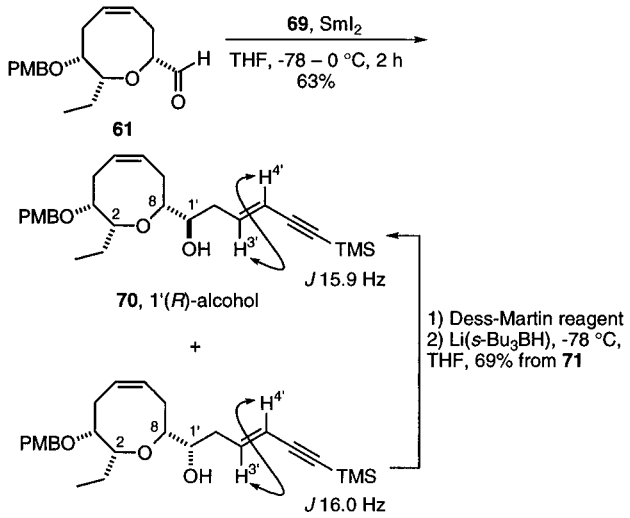
(90) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155.
(91) Ireland, R. E.; Liu, L. *J. Org. Chem.* **1993**, *58*, 2899.
(92) Meyer, S. D.; Schreiber, S. L. *J. Org. Chem.* **1994**, *59*, 7549.

Scheme 17. Barbier-Type Coupling



Compound	δ_H OH	δ_H 2-H, 8-H, 1'-H
1'(*R**)-**78**	2.63	3.49-3.31
1'(*S**)-**79**	2.00	3.63-3.59, 3.46-3.39

Scheme 18. Side-Chain Introduction

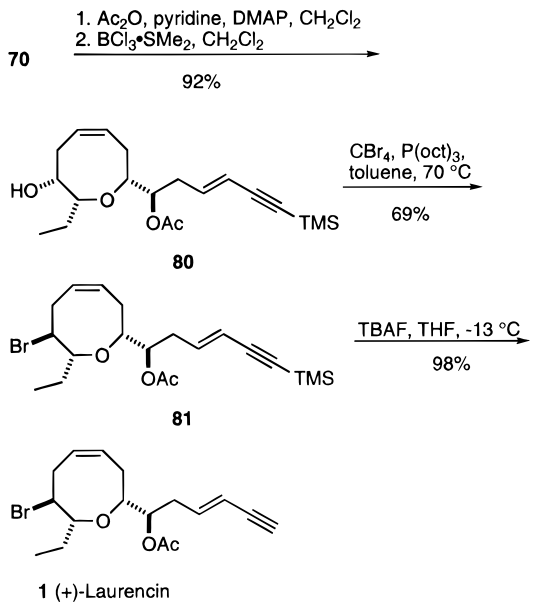


Compound	δ_H OH	δ_H 2-H, 8-H, 1'-H
1'(*R*)-**70**	2.80	3.53-3.42, 3.12
1'(*S*)-**71**	2.20-2.15	3.71-3.68, 3.49-3.46, 3.18

found that the 1′(*R*)-alcohols were all less polar than the corresponding 1′(*S*)-alcohols.

Following the precedent observed for octahydrodeacetyldebromolaurencin **2**, recycling of the 1′(*S*)-alcohol **71** was achieved by oxidation with the Dess−Martin reagent[90−92] to give the corresponding ketone in good yield; this was reduced with L-Selectride to yield the 1′(*R*)-alcohol **70** as the sole product (as judged by 250 MHz ^{1}H NMR) in accordance with previous experience.[9,17] The best procedure required separation of the alcohols **70** and **71** by HPLC, followed by the oxidation/

Scheme 19. Completion of the Synthesis



reduction sequence to convert the 1′(*S*)-alcohol **71** into the 1′-(*R*)-alcohol **70**.

Introduction of Bromine and Completion of the Synthesis. The free hydroxyl group of **70** was acetylated under standard conditions, and the PMB group was removed on exposure to BCl_3·SMe_2 according to the method of Congreve[69] to yield the alcohol **80** (Scheme 19).

The bromine atom was successfully introduced by treatment of the alcohol **80** with freshly purified carbon tetrabromide and freshly distilled trioctylphosphine in hot toluene.[17] This resulted in a very clean reaction to form trimethylsilyl-laurencin **81** in 69% yield. The spectra of **81** were essentially identical to those of the corresponding triisopropylsilyl analog reported by Overman.[21]

Treatment of TMS-laurencin **81** with a cold solution of TBAF in THF afforded (+)-laurencin **1** {$[\alpha]_D^{20}$ +70 (*c* 0.05 in $CHCl_3$), lit.[1] $[\alpha]_D^{27}$ +70.2 (*c* 1.00 in $CHCl_3$)} in 98% yield. The synthetic sample was isolated as a white gum, and therefore a melting point could not be obtained. However, in all other respects (^{1}H NMR, ^{13}C NMR, IR, $[\alpha]_D$, MS) the synthetic sample had characteristics in accordance with the data supplied by Professor Murai for a natural and a synthetic sample.

Conclusion

In summary, this work has demonstrated that medium-ring ether natural products can be obtained from the corresponding lactone precursors by methylenation and subsequent enol−ether functionalization. The Claisen ring expansion route is a convenient method for the preparation of medium-ring lactones, but efficient lactonization of *seco*-acid precursors is equally effective.

Experimental Section

For general experimental techniques see Supporting Information.

(*Z*),2(*R*)-Ethyl-2-[[(benzyloxy)methyl]oxy]-6-[(*R*)-2,2-dimethyl-1,3-dioxolan-4-yl]-hex-4-enoate 44. The phosphonium salt **40** (4.51 g, 9.57 mmol) was freshly prepared from the bromide **42**[59−61] and was dried *in vacuo* (<0.5 mmHg) for 48 h. The vacuum was quenched with argon and THF (140 cm^3) was added. The resulting suspension was freeze-thaw degassed (three cycles) and cooled to −78 °C. Butyllithium (10.3 cm^3 of a 1.6 M solution in hexanes, 16.5 mmol) was added dropwise over a period of 5 min causing the reaction mixture to change from colorless to dark red. The reaction mixture was stirred at this temperature for 5 min after which the cooling bath was removed, and the reaction mixture was allowed to warm to room temperature and was stirred for 1 h whereupon nearly all the salt had dissolved. The reaction mixture was recooled to −78 °C, and a concentrated solution of the aldehyde **41** (2.21 g, 8.30 mmol) in THF (9 cm^3, 3 cm^3 rinse) (obtained by Swern oxidation of the alcohol resulting from ethanolysis of **43**[62]) was slowly added. During the addition of the aldehyde most of the color was discharged. The reaction mixture was stirred for 1 min and then allowed to warm to room temperature. Stirring was continued for 5 min, and then the reaction was quenched by the addition of half-saturated ammonium chloride solution (100 cm^3). EtOAc (150 cm^3) was added and the organic phase separated. The aqueous phase was further extracted with EtOAc (2 × 150 cm^3), and the organic phases were combined, washed with brine (200 cm^3), and dried ($MgSO_4$). The solvent was removed *in vacuo*, and purification by flash chromatography (light petroleum:EtOAc, 5:1) yielded the diene **45** (52 mg) and the alkene **44** (2.28 g, 6.03 mmol, 72% based on aldehyde) as clear and colorless oils; $[\alpha]_D^{26}$ +17.3 (*c* 0.44, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33−7.26 (m, 5H), 5.61−5.53 (m, 2H), 4.83 (d, *J* = 7.2 Hz, 1H), 4.81 (d, *J* = 7.2 Hz, 1H), 4.64 (d, *J* = 12.3 Hz, 1H), 4.62 (d, *J* = 12.3 Hz, 1H), 4.23 (dd, *J* = 6.8, 5.8 Hz, 1H), 4.16 (q, *J* = 7.1 Hz, 2H), 4.12 (dq, *J* = 6.5, 6.0 Hz, 1H), 4.02 (dd, *J* = 8.0, 6.0 Hz, 1H), 3.57−3.54 (dd, *J* = 8.0, 6.5 Hz, 1H), 2.58−2.52 (m, 2H), 2.41 (dt, *J* = 14.1, 6.5 Hz, 1H), 2.31 (dt, *J* = 14.2, 6.5 Hz, 1H), 1.42, 1.35 (2 × s, 2 × 3H), 1.25 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 172.0, 137.6, 128.4, 127.8, 127.6, 126.5, 109.0, 94.2, 75.4, 75.3, 70.0, 69.0, 60.9, 31.6, 31.0, 26.8, 25.6, 14.2; IR ($CDCl_3$) 1741 (CO) cm^{-1}; MS (CI, NH_3) *m/z* (rel intensity) 396 [100, $(M + NH_4)^+$], 379 [12, $(M + H)^+$]; HRMS (CI, NH_3) *m/z* 379.2121 (379.2121 calcd for $C_{21}H_{31}O_6$, MH). Anal. Calcd for $C_{21}H_{30}O_6$: C, 66.7; H, 8.0. Found: C, 66.9; H, 7.9.

2(*E*),4(*Z*),(*R*)-Ethyl-6-(2,2-dimethyl-1,3-dioxolan-4-yl)-hex-2,4-dienoate 45. The diene **45** was isolated in various quantities from the Wittig reactions attempted, the major isomer being 2(*E*),4(*Z*); $[\alpha]_D^{26}$ −25.2 (*c* 0.575, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.55 (ddd, *J* = 15.3, 11.6, 1.0 Hz, 1H), 6.24 (dddt, *J* = 11.6, 10.9, 1.6, 0.7 Hz, 1H), 5.90 (d, *J* = 15.3 Hz, 1H, 2-H), 5.84 (dddt, *J* = 10.9, 7.8, 1.0, 1.0 Hz, 1H), 4.21 (q, 2H), 4.17 (m, 1H), 4.04 (dd, *J* = 8.1, 6.1 Hz, 1H), 3.58 (dd, *J* = 8.1, 6.9 Hz, 1H), 2.59 (m, 2H), 1.43, 1.35 (2 × s, 2 × 3H), 1.29 (t, *J* = 7.1 Hz, 3H); δ_C (100 MHz, $CDCl_3$) 167.0, 138.7, 135.1, 128.8, 122.4, 109.2, 75.0, 68.8, 60.4, 32.4 (C-6), 26.8, 25.5, 14.3; IR ($CDCl_3$) 1706 (CO), 1638 (C═C), 1607 (C═C) cm^{-1}. Satisfactory mass spectral data could not be obtained on this compound probably due to its instability.

(*Z*),2(*R*),7(*R*)-Ethyl-2-[[(benzyloxy)methyl]oxy]-7,8-dihydroxy-oct-4-enoate and (*Z*),2(*R*),7(*R*)-Ethyl-2-[[(benzyloxy)methyl]oxy]-8-[(*tert*-butyldiphenylsilyl)oxy]-7-hydroxy-oct-4-enoate. The alkene **44** (2.35 g, 6.2 mmol) was dissolved in 80% aqueous acetic acid (75 cm^3), and the resulting solution was heated to 55 °C for 20 min with stirring. The solvent was removed *in vacuo*, and the residual solvent was removed by coevaporation with toluene (3 × 50 cm^3) to yield the deprotected material (*Z*),2(*R*),7(*R*)-ethyl-2-[[(benzyloxy)methyl]oxy]-7,8-dihydroxy-oct-4-enoate as a clear and colorless oil which was directly used for the next reaction without purification. For characterization purposes purification by flash chromatography gave homogeneous material; $[\alpha]_D^{26}$ +40.4 (*c* 0.47, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36−7.27 (m, 5H), 5.62−5.54 (m, 2H), 4.84 (d, *J* = 7.1 Hz, 1H), 4.81 (d, *J* = 7.1 Hz, 1H), 4.64 (s, 2H), 4.27 (dd, *J* = 12.1, 6.0 Hz, 1H), 4.18 (q, *J* = 7.1 Hz, 2H), 3.78−3.72 (brm, 1H), 3.65 (brd, *J* = 11.0 Hz, 1H), 3.50 (dd, *J* = 11.0, 6.5 Hz, 1H), 2.62−2.54 (m, 2H), 2.54−2.46 (br, 1H), 2.34−2.22 (m, 2H), 2.22−2.12 (br, 1H), 1.26 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.0, 137.4, 128.4, 127.8, 126.7, 94.1, 74.9, 71.4, 70.1, 66.1, 61.1, 31.4, 30.7, 14.2; IR ($CDCl_3$) 3593 (OH), 1742 (CO) cm^{-1}; MS (CI, NH_3) *m/z* (rel intensity) 356 [40, $(M + NH_4)^+$], 339 [20, $(M + H)^+$]; HRMS (CI, NH_3) *m/z* 356.2070 (356.2073 calcd for $C_{18}H_{30}O_6N$, MNH_4). Anal. Calcd for $C_{18}H_{26}O_6$: C, 63.9; H, 7.7. Found: C, 63.6; H, 7.8.

(93) *Organocopper Reagents A Practical Approach*; Taylor, R. J. K., Ed.; Oxford University Press: Oxford, 1994; pp 105−110.
(94) Girard, P.; Namy, J. L.; Kagan, H. B. *J. Am. Chem. Soc.* **1980**, *102*, 2693.

The residue was dissolved in DMF (20 cm^3), imidazole (2.28 g, 17.4 mmol) and *tert*-butylchlorodiphenylsilane (2.22 g, 8.1 mmol) were added, and the reaction was stirred at ambient temperature overnight. The reaction mixture was poured into water (100 cm^3). The aqueous phase was extracted with EtOAc (3 × 50 cm^3), and the combined organic phases washed with brine (50 cm^3). The organic phase was dried ($MgSO_4$), and purification by flash chromatography (light petroleum:EtOAc, 2:1) yielded (*Z*),2(*R*),7(*R*)-ethyl-2-[[(benzyloxy)-methyl]oxy]-8-[(*tert*-butyldiphenylsilyl)oxy]-7-hydroxy-oct-4-enoate (2.9 g, 5 mmol, 81% from the acetonide **44**) as a clear and colorless oil; $[\alpha]_D^{26}$ +26.0 (*c* 0.75, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.67−7.65 (m, 4H), 7.43−7.27 (m, 11H), 5.59−5.51 (m, 2H), 4.79 (d, *J* = 7.1 Hz, 1H), 4.77 (d, *J* = 7.1 Hz, 1H), 4.60 (s, 2H), 4.21 (t, *J* = 6.2 Hz, 1H), 4.14 (q, *J* = 7.2 Hz, 2H), 3.75−3.74 (brm, 1H), 3.65 (dd, *J* = 10.1, 4.1 Hz, 1H), 3.56 (dd, *J* = 10.1, 6.9 Hz, 1H), 2.56−2.51 (m, 3H), 2.31−2.21 (m, 2H), 1.22 (t, *J* = 7.2 Hz, 3H), 1.07 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.0, 137.6, 135.5, 133.2, 129.8, 128.4, 127.8, 127.7, 126.2, 94.1, 75.1, 71.5, 70.0, 67.5, 61.0, 31.1, 30.8, 26.8, 19.2, 14.2; IR ($CHCl_3$) 3566 (OH), 1731 (CO) cm^{-1}; MS (CI, NH_3) *m/z* (rel intensity) 594 [65, $(M + NH_4)^+$]; HRMS (CI, NH_3) *m/z* 594.3250 (594.3251 calcd for $C_{34}H_{48}O_6SiN$, MNH_4). Anal. Calcd for $C_{34}H_{44}O_6Si$: C, 70.8; H, 7.7. Found: C, 70.8; H, 7.6.

(*Z*),2(*R*),7(*R*)-2-[[(Benzyloxy)methyl]oxy]-8-[(*tert*-butyldiphenylsilyl)oxy]-7-hydroxy-oct-4-enoic Acid 39. Lithium hydroxide monohydrate (924 mg, 22 mmol) was added to a stirring suspension of (*Z*),2(*R*),7(*R*)-ethyl-2-[[(benzyloxy)methyl]oxy]-8-[(*tert*-butyldiphenylsilyl)oxy]-7-hydroxy-oct-4-enoate (2.54 g, 4.4 mmol) in THF and water (1:1, 160 cm^3). The milky reaction mixture was stirred for 4.5 h whereupon it became clear. The reaction mixture was acidified to pH 2 (pH paper) with 2 M hydrochloric acid (20 cm^3), and the THF was removed *in vacuo*. Water (100 cm^3) was added, and the aqueous phase extracted with EtOAc (3 × 100 cm^3). The combined organic phases were washed with brine (100 cm^3) and dried ($MgSO_4$), and the solvent was removed *in vacuo*. Purification by flash chromatography (EtOAc: light petroleum:acetic acid, 200:200:1) followed by coevaporation with toluene (3 × 30 cm^3) yielded the acid **39** (2.18 g, 3.97 mmol, 90%) as a clear and colorless oil; $[\alpha]_D^{20}$ +2.89 (*c* 0.87, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67−7.65 (m, 4H), 7.44−7.33 (m, 6H), 7.33−7.28 (m, 4H), 5.62−5.51 (m, 2H), 4.81 (d, *J* = 7.1 Hz, 1H), 4.77 (d, *J* = 7.1 Hz, 1H), 4.61 (s, 2H), 4.27 (t, *J* = 6.0 Hz, 1H), 3.77−3.74 (m, 1H), 3.65 (dd, *J* = 10.1, 4.1 Hz, 1H), 3.56 (dd, *J* = 10.1, 6.9, 1H), 2.57−2.54 (m, 2H), 2.29−2.24 (m, 2H), 1.07 (s, 9H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 175.9, 137.3, 135.5, 133.1, 129.8, 128.8, 128.4, 127.8, 126.0, 94.2, 75.0, 71.6, 70.2, 67.4, 31.0, 30.5, 26.8, 19.2; IR ($CDCl_3$) 3600−2500 (broad OH), 1764 (CO), 1722 (CO) cm^{-1}; MS (CI, NH_3) *m/z* (rel intensity) 548 [10, $(M + NH_4 - H_2O)^+$]. Anal. Calcd for $C_{32}H_{40}O_6Si$: C, 70.0; H, 7.4. Found: C, 69.9; H, 7.4.

8(*R*),3(*R*)-3-[[(Benzyloxy)methyl]oxy]-8-[[(*tert*-butyldiphenylsilyl)-oxy]methyl]-2-oxo-3,4,7,8-tetrahydro-(2*H*)-oxocin 47. The lactone **47** was prepared using the Yamaguchi lactonization procedure described by Mulzer.[67,68] To a stirred solution of the acid **39** (1.0 g, 1.82 mmol) in THF (40 cm^3) was added triethylamine (0.381 cm^3, 276 mg, 2.74 mmol). After 10 min 2,4,6-trichlorobenzoyl chloride (0.328 cm^3, 512 mg, 2.09 mmol) was added, and the solution was stirred for 2 h. The resulting cloudy reaction mixture was transferred *via* cannula into toluene (500 cm^3, 50 cm^3 rinse) in a pressure equalizing dropping funnel. This solution was added dropwise, down a Vigreux column, heated by refluxing toluene, into refluxing toluene (550 cm^3) containing DMAP (3.12 g, 25.5 mmol) over a period of 4 h. The reaction was heated under reflux for a further 0.5 h and then allowed to cool. The solvent was removed *in vacuo*, and purification by flash chromatography (CH_2Cl_2:light petroleum, 4:1) gave the title compound **47** (806 mg, 1.52 mmol, 84%); $[\alpha]_D^{23}$ +28.8 (*c* 0.6, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.67−7.63 (m, 4H), 7.45−7.26 (m, 11H), 5.86 (dt, *J* = 10.9, 8.0 Hz, 1H), 5.70−5.64 (m, 1H), 4.81 (d, *J* = 7.0 Hz, 1H), 4.78 (d, *J* = 7.0 Hz, 1H), 4.75−4.72 (m, 1H), 4.66 (d, *J* = 12.0 Hz, 1H), 4.54 (d, *J* = 12.0 Hz, 1H), 4.13 (dd, *J* = 9.8, 5.3 Hz, 1H), 3.85 (dd, *J* = 10.5, 5.9 Hz, 1H), 3.76 (dd, *J* = 10.5, 6.2 Hz, 1H), 2.82−2.75 (m, 1H), 2.54−2.50 (m, 1H), 2.48−2.43 (m, 1H), 2.33−2.29 (m, 1H), 1.06 (s, 9H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 174.8, 137.4, 135.6, 133.2, 130.5, 129.8, 128.3, 127.7, 94.3, 80.4, 78.3, 69.9, 65.1, 31.7, 30.6, 26.7, 19.3; IR ($CDCl_3$) 1744 (CO) cm^{-1}; MS (CI, NH_3) *m/z* (rel intensity) 548 [10, $(M + NH_4)^+$]; HRMS (CI, NH_3) *m/z* 548.2830 (548.2832 calcd for $C_{32}H_{42}O_5SiN$, MNH_4). Anal. Calcd for $C_{32}H_{38}O_5Si$: C, 72.4; H, 7.2. Found: C, 72.4; H, 7.1.

8(*R*),3(*R*)-8-[[(*tert*-Butyldiphenylsilyl)oxy]methyl]-3-hydroxy-2-oxo-3,4,7,8-tetrahydro-(2*H*)-oxocin 15. To a stirred solution of the lactone **47** (2.33 g, 4.40 mmol) in CH_2Cl_2 (150 cm^3) was added boron trichloride−methyl sulfide complex (4.39 cm^3 of a 2.0 M solution in CH_2Cl_2, 8.80 mmol). Stirring was continued for 1 min, and the reaction was rapidly quenched by pouring onto a vigorously stirred solution of saturated sodium bicarbonate (130 cm^3). THF (50 cm^3) was immediately added, and vigorous stirring was continued for 0.5 h. The organic layer was separated, and the aqueous phase was extracted with CH_2Cl_2 (2 × 100 cm^3). The organic phases were combined and dried ($MgSO_4$), and purification by flash chromatography (CH_2Cl_2) yielded the title compound **15** (1.67 g 93%) as a clear and colorless oil which was identical to the material prepared by the oxidation of **16** with **37** (see Supporting Information); $[\alpha]_D^{23}$ −13.3 (*c* 0.59, $CHCl_3$); δ_H(500 MHz, $CDCl_3$) 7.67−7.66 (m, 4H), 7.46−7.39 (m, 6H), 5.79 (dt, *J* = 11.0, 8.1 Hz, 1H), 5.70 (dt, *J* = 11.0, 7.1 Hz, 1H), 4.66−4.62 (m, 1H), 4.40−4.36 (m, 1H), 3.91 (dd, *J* = 10.8, 5.8 Hz, 1H), 3.78 (dd, *J* = 10.8, 5.7 Hz, 1H), 2.87 (d, *J* = 7.2 Hz, 1H), 2.67−2.62 (m, 1H), 2.49−2.43 (m, 2H), 2.34 (dt, *J* = 15.3, 8.2 Hz, 1H), 1.07 (9H, s); ^{13}C NMR (50 MHz, $CDCl_3$) δ 176.3, 135.6, 129.9, 128.9, 127.8, 77.5, 73.2, 65.2, 34.0, 30.1, 26.8, 19.2; IR ($CDCl_3$) 3551 (OH), 1743 (CO) cm^{-1}; MS (CI, NH_3) *m/z* (rel intensity) 428 [80, $(M + NH_4)^+$], 411 [18, $(M + H)^+$]; HRMS (CI, NH_3) *m/z* 411.1992 (411.1992 calcd for $C_{24}H_{31}O_4Si$, MH).

3(*R*),8(*R*)-8-[[(*tert*-Butyldiphenylsilyl)oxy]methyl]-3-[(trimethylsilyl)oxy]-2-oxo-3,4,7,8-tetrahydro-(2*H*)-oxocin 49 and 3(*R*),8(*R*)-8-[(*tert*-Butyldiphenylsilyl)oxy]-3-[(trimethylsilyl)oxy]-2-oxo-3,4,7,8,9-pentahydro-(2*H*)-oxonin 48. To a stirred solution of the alcohols prepared by deprotection of a 10:1 mixture of **47** and **46** (1.35 g, 3.29 mmol) in THF (50 cm^3) was added triethylamine (0.5 cm^3). Chlorotrimethylsilane (2.5 cm^3) and triethylamine (2.5 cm^3) were mixed in a sealed centrifuge tube and centrifuged for 3 min. A portion of the supernatant liquid (5 cm^3) was added to the reaction mixture, and a white precipitate was formed immediately. After 1 h the reaction was quenched by the addition of pH 7 buffer (50 cm^3) and ether (50 cm^3). The organic layer was separated, and the aqueous phase was extracted with ether (2 × 50 cm^3). The organic phases were combined, washed with brine (50 cm^3), and dried ($MgSO_4$). Purification by flash chromatography (light petroleum:ether, 10:1) gave the nine-ring lactone **48** (142 mg, 0.29 mmol, 9%) as a clear and colorless oil; $[\alpha]_D^{20}$ −17.6 (*c* 1.4, CH_2Cl_2); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.72−7.62 (m, 4H), 7.44−7.33 (m, 6H), 5.69−5.48 (m, 1H), 5.43−5.24 (brm, 1H), 4.67 (dd, *J* = 11.2, 5.8 Hz, 1H), 4.46 (brt, *J* = 4.0, Hz, 1H), 4.12−4.00 (m, 1H), 3.80 (dd, *J* = 11.2, 5.8 Hz, 1H), 2.85−2.73 (brm, 1H), 2.58−2.47 (brm, 1H), 2.27−2.13 (brm, 1H), 2.07−1.97 (brm, 1H), 1.09 (s, 9H), 0.14 (s, 9H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 173.3, 135.8, 135.7, 133.7, 133.5, 129.9, 129.9, 127.8, 127.7, 125.5, 112.6, 70.9, 70.5, 68.5, 34.0, 33.3, 27.0, 19.1, −0.2; IR ($CDCl_3$) 1757 (CO) cm^{-1}; MS (CI, NH_3) *m/z* (rel intensity) 483 [20, $(M + H)^+$]; HRMS (CI, NH_3) *m/z* 483.2375 (483.2387 calcd for $C_{27}H_{39}O_4Si_2$, MH).

Further elution of the column gave the eight-ring lactone **49** (1.28 g, 2.66 mmol, 81%) as a clear and colorless oil; $[\alpha]_D^{18}$ +27.8 (*c* 0.27, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69−7.63 (m, 4H), 7.45−7.38 (m, 6H), 5.84 (dt, *J* = 10.7, 8.1 Hz, 1H), 5.66 (dt, *J* = 10.7, 7.5 Hz, 1H), 4.70−4.68 (m, 1H), 4.19 (dd, *J* = 9.8, 5.3 Hz, 1H), 3.93 (dd, *J* = 10.5, 5.4 Hz, 1H), 3.80 (dd, *J* = 10.5, 5.9 Hz, 1H), 2.75 (q, *J* = 10.5 Hz, 1H), 2.53−2.47 (m, 1H), 2.36 (ddd, *J* = 12.2, 6.9, 5.4 Hz, 1H), 2.27 (ddd, *J* = 13.8, 8.3, 1.7 Hz, 1H), 1.08 (s, 9H), 0.17 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.6, 135.6, 135.6, 133.3, 133.2, 130.3, 129.7, 128.1, 127.7, 78.7, 75.7, 65.2, 34.7, 30.7, 26.7, 19.2, −0.3; IR ($CDCl_3$) 1745 (CO) cm^{-1}; MS (CI, NH_3) *m/z* (rel intensity) 500 [18, $(M + NH_4)^+$], 483 [10, $(M + H)^+$]; HRMS (CI, NH_3) *m/z* 483.2387 (483.2387 calcd for $C_{27}H_{39}O_4Si_2$, MH). Anal. Calcd for $C_{27}H_{38}O_4Si_2$: C, 67.2 H, 7.9. Found: C, 67.6; H, 7.9.

3(*R*),8(*R*)-8-[[(*tert*-Butyldiphenylsilyl)oxy]methyl]-2-methylene-3-[(trimethylsilyl)oxy]-3,4,7,8-tetrahydro-(2*H*)-oxocin 50 and 3(*R*),8(*R*)-8-[[(*tert*-Butyldiphenylsilyl)oxy]methyl]-3-hydroxy-2-methylene-3,4,7,8-tetrahydro-(2*H*)-oxocin. To a stirred solution of the silylether **49** (1.41 g, 2,93 mmol) in toluene (100 cm^3) was added dimethylti-

tanocene (14.6 cm^3 of a 50 mg/cm^3 solution in toluene, 3.5 mmol), and the resultant orange solution was heated under reflux, in the dark, for 35 min. The reaction mixture was allowed to cool, and the solvent was removed *in vacuo*. The resulting orange oil was taken up in EtOAc, and the crude reaction mixture was preadsorbed onto UG1 alumina (previously deactivated by the addition of 6% w/w water). Purification by gravity chromatography on deactivated UG1 alumina (light petroleum:ether, 20:1) yielded the impure enol ether **50**. For analytical purposes the enol ether could be purified further by chromatography in the same solvent system. Data for **50**; R_f 0.8 (light petroleum:ether, 1:1); $[\alpha]_D^{26}$ +9.2 (*c* 0.13, EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70−7.67 (m, 4H), 7.43−7.37 (m, 6H), 5.85−5.73 (m, 1H), 5.64−5.59 (m, 1H), 4.49 (s, 1H), 4.46 (s, 1H), 4.18, (dd, J = 10.7, 4.9 Hz, 1H), 3.92 (dd, J = 10.2, 6.0 Hz, 1H), 3.81−3.76 (m, 1H), 3.65 (dd, J = 10.2, 6.5 Hz, 1H), 2.74 (q, J = 11.0 Hz, 1H), 2.40−2.34 (m, 1H), 2.23 (ddd, J = 13.8, 8.3, 0.9 Hz, 1H), 2.12 (ddd, J = 11.9, 6.6, 5.0 Hz, 1H), 1.09 (s, 9H), 0.13 (s, 9H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 165.4, 135.6, 135.6, 133.6, 129.6, 129.6, 129.2, 127.6, 100.3, 85.9, 76.2, 66.4, 33.2, 30.8, 26.8, 19.2, −0.2; IR ($CDCl_3$) 1646 (enol ether) cm^{-1}; HRMS (+FAB) *m/z* 480.2479 (480.2516 calcd for $C_{28}H_{40}O_3Si_2$, M).

The impure enol ether **50** was dissolved in methanol (20 cm^3) and cooled to 0 °C, and solid potassium carbonate was added (150 mg). The reaction mixture was stirred vigorously, allowed to warm to ambient temperature over a 0.5 h period, and filtered. Purification by gravity chromatography on deactivated UG1 alumina (light petroleum: ether, 2:1) yielded the hydroxy-enol ether 3(*R*),8(*R*)-8-[[(*tert*-butyldiphenylsilyl)oxy]methyl]-3-hydroxy-2-methylene-3,4,7,8-tetrahydro-(2*H*)-oxocin (863 mg, 2.1 mmol, 72% from **49**); $[\alpha]_D^{20}$ +3.3 (*c* 0.22, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69−7.68 (m, 4H), 7.44−7.39 (m, 6H), 5.75−5.64 (m, 2H), 4.58 (d, J = 1.5 Hz, 1H), 4.55 (d, J = 1.5 Hz, 1H), 4.19 (m, 1H), 3.91 (ddt, J = 12.2, 6.1, 4.1 Hz, 1H), 3.85 (dd, 10.3, 6.1 Hz, 1H), 3.66 (dd, J = 10.3, 6.1 Hz, 1H), 2.61 (dt, J = 12.7, 9.0 Hz, 1H), 2.34−2.32 (m, 2H), 2.27 (ddd, J = 12.7, 6.3, 3.9 Hz, 1H), 1.97 (d, J = 8.2 Hz, 1H), 1.08 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.0, 135.6, 135.6, 133.5, 133.4, 129.7, 129.2, 129.0, 127.7, 99.3, 84.1, 75.4, 65.7, 33.0, 29.5, 26.6, 19.2; IR (CH_2Cl_2) 3593 (OH), 1649 (enol ether) cm^{-1}; MS (CI, NH_3) *m/z* (rel intensity) 426 [17, $(M + NH_4)^+$], 409 [7, $(M + H)^+$]; HRMS (CI, NH_3) *m/z* 409.2199 (409.2199 calcd for $C_{25}H_{33}O_3Si$, MH).

3(*R*),8(*R*)-8-[[(*tert*-Butyldiphenylsilyl)oxy]methyl]-3-[(Dimethylsilyl)oxy]-2-methylene-3,4,7,8-tetrahydro-(2*H*)-oxocin 14. To a stirred solution of the enol ether 3(*R*),8(*R*)-8-[[(*tert*-butyldiphenylsilyl)oxy]-methyl]-3-hydroxy-2-methylene-3,4,7,8-tetrahydro-(2*H*)-oxocin (160 mg, 0.39 mmol) in 1,1,3,3-tetramethyldisilazane (0.8 cm^3) was added solid ammonium chloride (4 mg), and the reaction mixture was heated to 60 °C and stirred at that temperature overnight. The reaction mixture was allowed to cool, dry hexane was added, and filtration through a cotton wool plug followed by removal of the solvent *in vacuo* gave the required silane **14** (182 mg, 0.39 mmol, 99%) as a very unstable oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71−7.67 (m, 4H), 7.41−7.37 (m, 6H), 5.78 (dt, J = 10.3, 7.8 Hz, 1H), 5.63 (dt, J = 10.3, 6.9 Hz, 1H), 4.67 (sp, J = 2.8 Hz, 1H), 4.53 (d, J = 0.8 Hz, 1H), 4.51 (d, J = 0.8 Hz, 1H), 4.18 (dd, J = 10.7, 4.9 Hz, 1H), 3.93 (dd, J = 10.1, 6.0, 1H), 3.83−3.78 (m, 1H), 3.66 (dd, J = 10.1, 6.4 Hz, 1H), 2.77 (q, J = 10.8 Hz, 1H); 2.42−2.34 (m, 1H), 2.27−2.17 (m, 2H), 1.08 (s, 9H), 0.23 (d, J = 2.8 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.7, 135.6, 135.6, 133.6, 133.5, 129.6, 129.1, 127.6, 100.7, 85.9, 77.8, 66.4, 32.7, 30.8, 26.8, 19.2, −1.0, −1.0; IR ($CDCl_3$) 2960, 2932, 2859, 2120 (SiH), 1647 (enol ether) cm^{-1}. Due to the instability of this compound satisfactory mass spectral data was not obtained.

2(*R*),3(*R*),8(*R*)-8-[[(*tert*-Butyldiphenylsilyl)oxy]methyl]-3-hydroxy-2-(hydroxymethyl)-3,4,7,8-tetrahydro-(2*H*)-oxocin 13 and 2(*S*),3(*R*),8(*R*)-8-[[(*tert*-Butyldiphenylsilyl)oxy]methyl]-3-hydroxy-2-(hydroxymethyl)-3,4,7,8-tetrahydro-(2*H*)-oxocin 51. *Note: This reaction must be carried out under dry air*. The silane **14** (487 mg, 1.03 mmol) was dried *in vacuo* for 48 h. The vacuum was purged with air, a stirrer flea was added, and the reaction flask was fitted with a drying tube ($CaCl_2$). The platinum catalyst $Pt(DVS)_2$ (0.52 cm^3 of a 0.1 M solution in toluene, 5.2 μmol) was added *via* syringe. The reaction mixture immediately became yellow and gradually turned dark red as gas was evolved. After stirring for 2 h, further catalyst was added (0.2 cm^3, 200 μmol), and stirring was continued for 2 h. Dry hexane (15 cm^3) and ethylenediaminetetraacetic acid, disodium salt dihydrate (615 mg, 1.65 mmol) were added, and the resulting suspension was stirred for 1 h. The reaction mixture was filtered through a pad of Celite, and the filter cake was washed with dry hexane. The solvent was removed *in vacuo* to furnish a brown oil. This residue was taken up in THF/MeOH (1:1, 16 cm^3) to which a 15% solution of potassium hydroxide (0.43 cm^3) and 30% H_2O_2 (0.64 cm^3, 6.0 mmol) were added. The reaction mixture was stirred for 1.25 h whereupon further potassium hydroxide solution (0.05 cm^3) and H_2O_2 (0.06 cm^3) were added. After 0.5 h the reaction was quenched by the addition of powdered sodium thiosulfate (1.89 g, 12 mmol), and stirring was continued overnight. The suspension was diluted with EtOAc (25 cm^3), dried ($MgSO_4$), and filtered through a pad of Celite. The solvent was removed *in vacuo*, and purification by flash chromatography (CH_2Cl_2:MeOH, 97:3) yielded the enol ether 3(*R*),8(*R*)-8-[[(*tert*-butyldiphenylsilyl)oxy]methyl]-3-hydroxy-2-methylene-3,4,7,8-tetrahydro-(2*H*)-oxocin (121 mg, 0.3 mmol, 29%). Further elution of the column furnished **13** (70 mg) as a clear and colorless oil; R_f 0.4 (CH_2Cl_2:MeOH, 95:5); $[\alpha]_D^{20}$ −18.2 (*c* 0.22, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.72−7.67 (m, 4H), 7.46−7.38 (m, 6H), 5.80−5.70 (m, 2H), 3.90−3.86 (brm, 1H), 3.85−3.78 (brm, 1H), 3.72 (ddd, J = 9.0, 3.5, 2.0 Hz, 1H), 3.69−3.65 (m, 2H), 3.63−3.58 (m, 1H), 3.51−3.45 (m, 1H), 2.97 (d, J = 9.5 Hz, 1H), 2.56 (dt, J = 12.5, 9.5 Hz, 1H), 2.36−2.30 (m, 1H), 2.27−2.20 (m, 1H), 2.02−1.97 (ddd, J = 14.5, 8.4, 1.5 Hz, 1H), 1.66 (d, J = 9.0 Hz, 1H), 1.07 (s, 9H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 135.6, 135.6, 132.9, 129.9, 129.4, 128.7, 127.8, 83.4, 82.1, 73.1, 67.7, 64.1, 33.6, 30.4, 26.7, 19.0; IR ($CHCl_3$) 3478 (OH) cm^{-1}; MS (CI, NH_3) *m/z* (rel intensity) 444 [60, $(M + NH_4)^+$], 427 [8, $(M + H)^+$]; HRMS (CI, NH_3) *m/z* 444.2570 (444.2570 calcd for $C_{25}H_{38}O_4SiN$, MNH_4).

Further elution of the column gave mixed fractions which were repurified by flash chromatography (CH_2Cl_2:MeOH, 97:3) to yield **13** (140 mg total, 0.33 mmol, 32%) and **51** (120 mg, 0.28 mmol, 27%); R_f 0.3 (CH_2Cl_2:MeOH, 95:5); $[\alpha]_D^{20}$ −15.9 (*c* 0.23, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70−7.68 (m, 4H), 7.50−7.38 (m, 6H), 5.83 (dt, J = 10.3, 7.9 Hz, 1H), 5.68−5.63 (m, 1H), 3.96 (dd, J = 11.8, 9.3 Hz, 1H), 3.98−3.94 (br, 1H), 3.73−3.65 (m, 4H), 3.60−3.59 (brm, 1H), 3.48 (dd, J = 11.8, 3.3 Hz, 1H), 2.44−2.32 (m, 2H), 2.17−2.07 (m, 1H), 1.90 (ddd, J = 14.2, 7.2, 3.4 Hz, 1H), 1.57 (br, 1H), 1.07 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.6, 135.6, 132.7, 130.0, 129.9, 128.2, 127.9, 76.9, 76.2, 72.2, 65.0, 64.3, 35.4, 28.2, 26.7, 19.1; IR ($CHCl_3$) 3452 (OH) cm^{-1}; MS (CI, NH_3) *m/z* (rel intensity) 444 [20, $(M + NH_4)^+$], 427 [40, $(M + H)^+$]; HRMS (CI, NH_3) *m/z* 444.2570 (444.2570 calcd for $C_{25}H_{38}O_4SiN$, MNH_4).

2(*R*),3(*R*),8(*R*)-8-[[(*tert*-Butyldiphenylsilyl)oxy]methyl]-3-hydroxy-2-(hydroxymethyl)-3,4,7,8-tetrahydro-(2*H*)-oxocin *p*-Methoxybenzylidene Acetal 53. To a stirred solution of the diol **13** (190 mg, 0.45 mmol) in benzene (10 cm^3) was added freshly distilled anisaldehyde (81 μL, 91 mg, 0.67 mmol), PPTS (5 mg), and $MgSO_4$ (50 mg). The reaction mixture was heated to reflux for 5.5 h and then allowed to cool. The solvent was then removed *in vacuo*, and purification by preparative layer chromatography (CH_2Cl_2:MeOH, 99:1) yielded the title compound **53** (200 mg, 82%) as a clear and colorless oil; $[\alpha]_D^{20}$ −27.5 (*c* 0.375, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.72−7.70 (m, 4H), 7.45−7.35 (m, 8H), 6.86 (d, J = 9.0 Hz, 2H), 5.94−5.89 (m, 1H), 5.70 (ddt, J = 10.3, 6.6, 1.8 Hz, 1H), 5.45 (s, 1H), 4.23 (dd, J = 12.0, 2.0 Hz, 1H, C*H*HOCHAr), 3.98 (ddd, J = 11.5, 5.0, 2.0 Hz, 1H, 3-H), 3.95 (dd, J = 12.0, 2.0 Hz, 1H, CH*H*OCHAr), 3.83 (dd, J = 10.0, 5.5, Hz, 1H), 3.79 (s, 3H), 3.60 (dd, J = 10.0, 6.5, 1H), 3.49−3.39 (m, 1H), 3.35 (q, J = 2.0 Hz, 1H, 2-H), 2.86 (q, J = 11.5 Hz, 1H, 4-H), 2.44−2.37 (m, 1H), 2.35−2.27 (m, 2H, 4-H, 7-H), 1.07 (s, 9H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 159.9, 135.7, 133.7, 133.6, 131.0, 129.6, 129.6, 127.7, 127.6, 127.3, 113.5, 100.9, 83.6, 79.9, 73.3, 72.2, 67.3, 55.3, 31.5, 30.1, 26.8, 19.2; IR ($CDCl_3$) 2932, 2858, 1615, 1589, 1517 cm^{-1}; MS (CI, NH_3) *m/z* (rel intensity) 562 [35, $(M + NH_4)^+$], 545 [100, $(M + H)^+$]; HRMS (CI, NH_3) *m/z* 545.2720 (545.2723 calcd for $C_{33}H_{41}O_5Si$, MH).

2(*S*),3(*R*),8(*R*)-[[(*tert*-Butyldiphenylsilyl)oxy]methyl]-3-hydroxy-2-(hydroxymethyl)-3,4,7,8-tetrahydro-(2*H*)-oxocin *p*-Methoxybenzylidene Acetal 52. Compound **52** was prepared in an analogous fashion to compound **53** (97% yield); $[\alpha]_D^{19}$ −2.0 (*c* 0.61, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69−7.65 (m, 4H), 7.46−7.38 (m,

8H), 6.88 (d, J = 9.0 Hz, 2H), 5.97−5.87 (m, 1H), 5.76−5.71 (m, 1H), 5.40 (s, 1H), 4.18 (dd, J = 11.0, 5.5 Hz, 1H, C*H*HOCHAr), 3.88 (ddd, J = 10.0, 9.0, 5.5 Hz, 1H, 2-H), 3.82 (dd, J = 11.0, 6.4 Hz, 1H), 3.79 (s, 3H), 3.70 (dd, J = 11.0, 4.7 Hz, 1H), 3.65−3.59 (m, 1H), 3.59 (dd, J = 11.0, 10.0 Hz, 1H, C*H*HOCHAr), 3.52 (ddd, J = 10.9, 9.0, 3.2 Hz, 1H, 3-H), 2.52−2.45 (m, 2H, 7-H, 4-H), 2.40 (ddd, J = 13.5, 8.4, 3.2 Hz, 1H, 4-H), 2.05 (ddd, J = 13.9, 7.1, 3.0 Hz, 1H), 1.09 (9H, s); δ_C(100 MHz, $CDCl_3$) 160.0, 135.6, 133.1, 130.4, 129.5, 128.8, 127.8, 127.4, 113.7, 100.7, 80.4, 76.0, 70.3, 67.7, 65.4, 55.3, 32.9, 28.2, 26.8, 19.2; IR (CH_2Cl_2) 2933, 2859, 1615, 1518 cm^{-1}; HRMS (+FAB) *m/z* 545.2692 (545.2723 calcd for $C_{33}H_{41}O_5Si$, MH).

2(*R*),3(*R*),8(*R*)-8-[[(*tert*-Butyldiphenylsilyl)oxy]methyl]-2-(hydroxymethyl)-3-[(*p*-methoxybenzyl)oxy]-3,4,7,8-tetrahydro-(2*H*)-oxocin 57. To a stirred solution of **53** (190 mg, 0.35 mmol) in CH_2Cl_2 (20 cm^3) at −78 °C was added DIBAL-H (1.57 cm^3 of 1.0 M solution in CH_2Cl_2, 1.57 mmol). The resulting solution was stirred for 10 min at −78 °C and then for 1 h at −50 °C before being quenched with MeOH (3 cm^3). The reaction mixture was allowed to warm to ambient temperature, and a saturated solution of ammonium chloride (2.5 cm^3) and 1 M sodium potassium tartrate (2.5 cm^3) were added. The resulting gel was stirred until dissolution occurred. The organic phase was separated, and the aqueous phase was extracted with CH_2Cl_2 (2 × 5 cm^3). The organic phases were combined and dried ($MgSO_4$), and the solvent was removed *in vacuo*. Purification by flash chromatography (light petroleum:ether, 2:1) gave the title compound **57** (98 mg, 0.18 mmol, 51%) as a clear and colorless oil; R_f 0.2 (light petroleum:ether, 2:1); $[\alpha]_D^{17}$ −1.3 (*c* 0.32, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.73−7.66 (m, 4H), 7.43−7.37 (m, 6H), 7.25 (d, J = 8.6 Hz, 2H), 6.88 (d, J = 8.6 Hz, 2H), 5.81−5.76 (m, 1H), 5.70−5.65 (m, 1H), 4.60 (d, J = 11.8 Hz, 1H), 4.36 (d, J = 11.8 Hz, 1H), 3.99 (t, J = 10.1 Hz, 1H), 3.81 (s, 3H), 3.76−3.71 (m, 2H), 3.60−3.55 (m, 2H), 3.49−3.41 (m, 2H), 3.36 (d, J = 11.7 Hz, 1H), 2.69 (q, J = 11.0 Hz, 1H), 2.42−2.37 (m, 1H), 2.30−2.24 (m, 1H), 1.85 (dd, J = 14.0, 8.4 Hz, 1H), 1.05 (s, 9H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 159.2, 135.7, 135.6, 132.8, 132.7, 130.3, 129.8, 129.6, 129.5, 128.6, 127.8, 113.7, 84.8, 83.3, 79.1, 70.2, 68.2, 64.5, 55.3, 30.7, 29.1, 26.7, 18.9; IR ($CDCl_3$) 3478 (OH) cm^{-1}; MS (CI, NH_3) *m/z* (rel intensity) 564 [10, $(M + NH_4)^+$], 547 [1, $(M + H)^+$]; HRMS (CI, NH_3) *m/z* 564.3140 (564.3145 calcd for $C_{33}H_{46}O_5SiN$, MNH_4).

2(*R*),3(*R*),8(*R*)-8-[[(*tert*-Butyldiphenylsilyl)oxy]methyl]-3-[(*p*-methoxybenzyl)oxy]-2-[[(trifluoromethanesulfonyl)oxy]methyl]-3,4,7,8-tetrahydro-(2*H*)-oxocin 60 and 2(*R*),3(*R*),8(*R*)-[[(*tert*-butyldiphenylsilyl)oxy]methyl]-2-ethyl-3-[(*p*-methoxybenzyl)oxy]-3,4,7,8-tetrahydro-(2*H*)-oxocin 59. Trifluoromethanesulfonic anhydride (20 μL, 33 mg, 118 μmol) was added to a stirred solution of the alcohol **57** (18.4 mg, 33.6 μmol) in CH_2Cl_2 (1 cm^3) containing pyridine (0.15 cm^3) at −15 °C. The solution was stirred for 10 min and then quenched by the addition of a saturated solution of sodium bicarbonate (2 cm^3). The liquid phases were extracted with CH_2Cl_2 (3 × 5 cm^3). The organic phases were combined, washed with 1 M hydrochloric acid (10 cm^3) and a saturated solution of sodium bicarbonate (10 cm^3), and dried ($MgSO_4$). The solvent was removed *in vacuo* to yield the unstable triflate **60**; ^{1}H NMR (500 MHz, THF-d_8) δ 7.68−7.66 (m, 4H), 7.39−7.33 (m, 6H), 7.19 (d, J = 8.6 Hz, 2H), 6.83 (d, J = 8.6, 2H), 5.91−5.86 (m, 1H), 5.73−5.68 (m, 1H), 4.54 (d, J = 11.2 Hz, 1H), 4.51−4.47 (m, 2H), 4.27 (d, J = 11.2 Hz, 1H), 4.00 (dt, J = 7.6, 3.6 Hz, 1H), 3.80 (dd, J = 9.1, 4.0 Hz, 1H), 3.72 (s, 3H), 3.65 (ddd, J = 11.2, 5.0, 3.1 Hz, 1H), 3.52−3.45 (m, 2H), 2.64 (q, J = 11.0 Hz, 1H), 2.48−2.39 (m, 3H), 1.02 (s, 9H).

The cuprate displacement was performed according to the procedure of Pougny.[82] The triflate **60** was coevaporated with toluene (2 × 2 cm^3) and put under an argon atmosphere. Recrystallized copper(I) iodide[93] (67 mg, 0.35 mmol) was placed in a round-bottomed flask which was then purged with argon. Ether (1 cm^3) was added, and the grey suspension was cooled to −78 °C. Methyllithium (530 μL of a 1.3 M solution in ether, 0.70 mmol) was added quickly, while the suspension was stirred vigorously. The cooling bath was removed, and the reaction mixture was allowed to warm to 0 °C and was stirred at that temperature for 1 min to yield a grey, almost homogeneous, solution. The reaction mixture was recooled to −78 °C, and the triflate, prepared above, was added as a solution in benzene (1 cm^3, 2 × 0.5 cm^3 rinse). The cooling bath was removed, and the heterogeneous mixture was allowed to warm to 0 °C, whereupon the reaction mixture became homogeneous. The reaction mixture was stirred at this temperature for 3 h and was then quenched by the addition of a saturated solution of ammonium chloride and stirred until all the solid had dissolved. The organic phase was separated, and the aqueous phase was extracted with ether (2 × 5 cm^3). The organic phases were combined and dried ($MgSO_4$). Purification by flash chromatography (light petroleum:ether, 3:2) gave the ethyl-substituted oxocane **59** (10.9 mg, 20.0 μmol, 60%) as a clear and colorless oil; $[\alpha]_D^{20}$ +8.6 (*c* 0.09, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.65 (d, J = 7.6 Hz, 4H), 7.41−7.34 (m, 6H), 7.23 (d, J = 8.5 Hz, 2H), 6.84 (d, J = 8.5 Hz, 2H), 5.87−5.81 (m, 1H), 5.71−5.65 (m, 1H), 4.60 (d, J = 11.8 Hz, 1H), 4.38 (d, J = 11.8 Hz, 1H), 3.81 (dd, J = 10.0, 5.0 Hz, 1H), 3.79 (s, 3H), 3.51 (dd, J = 10.0, 8.0 Hz, 1H), 3.43−3.34 (m, 3H), 2.66 (q, J = 11.0 Hz, 1H), 2.44−2.39 (m, 1H), 2.35−2.27 (m, 2H), 1.68−1.61 (m, 1H), 1.33−1.23 (m, 1H), 1.05 (s, 9H), 0.78 (t, J = 7.4 Hz, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 159.0, 135.6, 133.8, 133.7, 130.9, 130.1, 129.6, 129.5, 129.2, 127.6, 113.6, 83.2, 82.4, 80.7, 70.7, 66.8, 55.2, 31.6, 29.1, 26.9, 25.7, 19.2, 10.8; IR ($CDCl_3$) 2932, 1612 cm^{-1}; MS (CI, NH_3) *m/z* (rel intensity) 562 [20, $(M + NH_4)^+$]; HRMS (CI, NH_3) *m/z* 562.3353 (562.3352 calcd for $C_{34}H_{48}O_4SiN$, MNH_4). Further elution of the column yielded the starting alcohol **57** (7.3 mg, 13.3 μmol, 40%).

2(*R*),3(*R*),8(*R*)-2-Ethyl-8-(hydroxymethyl)-3-[(*p*-methoxybenzyl)oxy]-3,4,7,8-tetrahydro-(2*H*)-oxocin. To a stirred solution of the oxocane **59** (43 mg, 79 μmol) in THF (6 cm^3) at 0 °C was added TBAF (0.4 cm^3 of a 1.0 M solution in THF, 0.40 mmol). The resulting solution was stirred at 0 °C for 5 min and then stirred at ambient temperature for 1.5 h. The solvent was removed *in vacuo* and purification by preparative layer chromatography (EtOAc:light petroleum, 2:1) yielded the title compound (23 mg, 75 μmol, 96%) as a clear and colorless oil; $[\alpha]_D^{19}$ −25.8 (*c* 0.26, CH_2Cl_2); ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.27 (d, J = 8.6 Hz, 2H), 6.86 (d, J = 8.6 Hz, 2H), 5.87−5.61 (m, 2H), 4.65 (d, J = 11.7 Hz, 1H), 4.41 (d, J = 11.7 Hz, 1H), 3.80 (s, 3H), 3.57−3.37 (m, 5H), 2.65 (q, J = 10.5 Hz, 1H), 2.44−2.35 (m, 2H), 2.31−2.22 (m, 1H), 1.96 (ddd, J = 14.0, 8.2, 1.1 Hz, 1H), 1.81−1.63 (m, 1H), 1.50−1.39 (m, 1H), 0.87 (t, J = 7.4 Hz, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 159.2, 130.5, 129.7, 129.4, 129.2, 113.7, 82.9, 82.5, 80.1, 71.1, 66.1, 55.3, 30.9, 29.0, 25.7, 10.7; IR ($CDCl_3$) 3685 (OH) cm^{-1}; MS (CI, NH_3) *m/z* (rel intensity) 324 [21, $(M + NH_4)^+$], 307 [5, $(M + H)^+$]; HRMS (CI, NH_3) *m/z* 307.1915 (307.1909 calcd for $C_{18}H_{27}O_4$, MH).

2(*R*),3(*R*),8(*R*)-8-Carboxaldehyde-2-ethyl-3-[(*p*-methoxybenzyl)oxy]-3,4,7,8-tetrahydro-(2*H*)-oxocin 61, **2(*R*),3(*R*),8(*R*)-2-Ethyl-8-[(*E*),(*R*)-1-hydroxy-6-(trimethylsilyl)-3-hexen-5-ynyl]-3-[(*p*-methoxybenzyl)oxy]-3,4,7,8-tetrahydro-(2*H*)-oxocin 70**, **2(*R*),3(*R*),8(*R*)-2-Ethyl-8-[(*E*),(*S*)-1-hydroxy-6-(trimethylsilyl)-3-hexen-5-ynyl]-3-[(*p*-methoxybenzyl)oxy]-3,4,7,8-tetrahydro-(2*H*)-oxocin 71 and (*E*)-2-Ethenyl-1,8-bis(trimethylsilyl)-oct-5-en-1,7-diyne 73.**[17] To a stirred solution of the alcohol 2(*R*),3(*R*),8(*R*)-2-ethyl-8-(hydroxymethyl)-3-[(*p*-methoxybenzyl)oxy]-3,4,7,8-tetrahydro-(2*H*)-oxocin (20 mg, 65 μmol) in CH_2Cl_2 (1.5 cm^3) was added 4-methylmorpholine *N*-oxide (23 mg, 0.20 mmol) and powdered 4Å molecular sieves, and the mixture was stirred for 5 min. TPAP (1.1 mg, 3.3 μmol) was added, and the suspension was stirred for 20 min. The reaction mixture was diluted with EtOAc and filtered through a plug of silica gel with EtOAc washing. The solvent was removed *in vacuo* to yield the aldehyde **61** (20 mg, 65 μmol, 100%) as a clear and colorless oil which was not characterized and was used in the following reaction.

An oven dried magnetic stirrer bar was placed in a 50 cm^3 oven dried Schlenk tube which was sealed with a new septum. The system was placed under vacuum and heated with a heat-gun for approximately 2 min. The vacuum was quenched with oxygen-free argon, and the system was allowed to cool. The drying procedure was then repeated. A dry gas-tight syringe was flushed with freshly prepared samarium diiodide[94] and then used to transfer samarium diiodide (1.68 cm^3 of a 0.1 M solution in THF, 0.17 mmol) to the Schlenk tube. The Schlenk tube was then sealed completely, and the solution of samarium diiodide was allowed to stir for 10 min at ambient temperature to ensure that the system was oxygen free. The Schlenk tube was cooled to −70 °C (2-propanol/dry ice bath). A solution of the aldehyde **61** (17 mg, 56 μmol) and the enyne **69** (16 mg, 73 μmol) in THF (1 cm^3) was added

to the cooled solution of samarium diiodide *via* cannula with rinsing (0.5 cm^3). The dry ice was removed from the cold bath, and the system was allowed to warm to 0 °C over a 2 h period. The reaction mixture was quenched by the addition of 0.1 M hydrochloric acid (4 cm^3) and ether. The mixture was extracted with ether (3 × 10 cm^3). The organic phases were combined, washed with 1 M sodium thiosulfate solution (15 cm^3) and a saturated solution of sodium bicarbonate (15 cm^3), and dried ($MgSO_4$). Purification by flash chromatography (ether:light petroleum, 1:1) yielded the impure side-chain dimer **73** (4.5 mg, 16 μmol) as a clear and colorless oil; ^{1}H NMR (250 MHz, $CDCl_3$) δ 6.20 (dt, J = 15.9, 7.3 Hz, 1H), 5.74 (ddd, J = 16.9, 10.0, 5.7 Hz, 1H), 5.57 (dt, J = 15.9, 1.3 Hz, 1H), 5.32 (dt, J = 16.9, 1.3 Hz, 1H), 5.12 (dt, J = 10.0, 1.3, 1H), 3.19−3.11 (m, 1H), 2.35 (dt, J = 7.2, 1.3 Hz, 1H), 0.17, 0.18 (2 × s, 2 × 9H); HRMS (electrospray) *m/z* 275.1656 (275.1651 calcd for $C_{16}H_{27}Si_2$, MH). Further elution of the column yielded a 1:1 mixture of the epimeric alcohols **70** and **71** (15.5 mg, 35 μmol, 63%) which could be separated by HPLC (CH_2Cl_2:MeOH, 200:1).

Data for the less polar compound **70**; R_f 0.3 (ether:light petroleum, 1:1); $[\alpha]_D^{25}$ −41.0 (*c* 0.105, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27 (d, J = 8.5 Hz, 2H), 6.87 (d, J = 8.5 Hz, 2H), 6.28 (dt, J = 15.9, 7.2 Hz, 1H), 5.83−5.78 (m, 1H), 5.72−5.67 (m, 1H), 5.58 (d, J = 15.9 Hz, 1H), 4.64 (d, J = 11.6 Hz, 1H), 4.40 (d, J = 11.6 Hz, 1H), 3.81 (s, 3H), 3.53−3.42 (m, 3H, 2-H, 3-H, C*H*OH), 3.12 (dd, J = 9.1, 6.7 Hz, 1H, 8-H), 2.80 (brd, J = 2.8 Hz, 1H, OH), 2.65 (q, J = 11.0 Hz, 1H), 2.49−2.37 (m, 3H), 2.29−2.23 (m, 1H), 2.06 (dd, J = 13.6, 8.4 Hz, 1H), 1.66−1.62 (m, 1H), 1.60−1.55 (m, 1H), 0.83 (t, J = 7.4 Hz, 3H), 0.18 (s, 9H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 159.3, 141.8, 130.4, 129.6, 129.4, 129.3, 113.7, 111.9, 103.8, 93.2, 84.2, 83.3, 79.6, 73.1, 71.1, 55.3, 37.1, 30.9, 28.9, 25.3, 10.5, −0.1; IR ($CDCl_3$) 3566 (OH) cm^{-1}; MS (CI, NH_3) *m/z* (rel intensity) 460 [15, $(M + NH_4)^+$], 443 [3, $(M + H)^+$]; HRMS (CI, NH_3) *m/z* 460.2883 (460.2883 calcd for $C_{26}H_{42}O_4SiN$, MNH_4).

The more polar alcohol **71** contained signals at δ 6.16 (dt, J = 10.8, 7.4 Hz, SiC≡CCH═C*H*) assigned to **72** as a slight impurity. Data for the more polar compound **71**; R_f 0.3 (ether:light petroleum, 1:1); $[\alpha]_D^{22}$ −47.0 (*c* 0.1, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27 (d, J = 8.5 Hz, 2H), 6.87 (d, J = 8.5 Hz, 2H), 6.23 (dt, J = 16.0, 7.3 Hz, 1H), 5.82 (dt, J = 10.1, 7.9 Hz, 1H), 5.71−5.65 (m, 1H), 5.60 (d, J = 16.0 Hz, 1H), 4.63 (d, J = 11.7 Hz, 1H), 4.39 (d, J = 11.7 Hz, 1H), 3.80 (s, 3H), 3.71−3.68 (m, 1H, C*H*OH), 3.49−3.46 (m, 1H, 2-H), 3.44−3.41 (m, 1H, 3-H), 3.18 (dd, J = 9.1, 5.1 Hz, 1H, 8-H), 2.65 (q, J = 10.8 Hz, 1H), 2.50−2.43 (m, 2H), 2.40−2.36 (m, 1H), 2.30−2.22 (m, 1H), 2.20−2.15 (m, 2H, 7-H, OH), 1.68−1.63 (m, 1H), 1.52−1.48 (m, 1H), 0.82 (t, J = 7.4 Hz, 3H), 0.17 (s, 9H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 159.2, 142.1, 130.6, 129.8, 129.6, 129.2, 113.7, 112.4, 103.7, 93.4, 84.2, 83.3, 80.0, 73.3, 71.0, 55.3, 36.8, 29.4, 28.9, 25.5, 10.7, −0.1; IR ($CDCl_3$) 3586 (OH) cm^{-1}; MS (CI, NH_3) *m/z* (rel intensity) 460 [5, $(M + NH_4)^+$], 443 [1, $(M + H)^+$]; HRMS (CI, NH_3) *m/z* 460.2883 (460.2883 calcd for $C_{26}H_{42}O_4SiN$, MNH_4).

2(*R*),3(*R*),8(*R*)-8-[(*E*),(*R*)-1-Acetoxy-6-(trimethylsilyl)-3-hexen-5-ynyl]-2-ethyl-3-[(*p*-methoxybenzyl)oxy]-3,4,7,8-tetrahydro-(2*H*)-oxocin. To a stirred solution of the alcohol **70** (7 mg, 15.8 μmol) in CH_2Cl_2 (2 cm^3) containing pyridine (5 drops) at 0 °C was added DMAP (5 mg) and acetic anhydride (3 drops). The solution was stirred for 5 h and then quenched by the addition of 1 M hydrochloric acid (5 cm^3). The mixture was extracted with EtOAc (2 × 5 cm^3). The organic phases were combined, washed with a saturated solution of sodium bicarbonate (5 cm^3), and dried ($MgSO_4$). The solvent was removed *in vacuo*, and purification by flash chromatography (light petroleum:ether, 5:1) gave the title compound (7 mg, 14.4 μmol, 95%) as a clear and colorless oil; $[\alpha]_D^{25}$ −15.2 (*c* 0.105, CH_2Cl_2); ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.27 (d, J = 8.4 Hz, 2H), 6.86 (d, J = 8.5 Hz, 2H), 6.10 (dt, J = 15.9, 7.6 Hz, 1H), 5.83−5.61 (m, 2H), 5.56 (d, J = 15.9 Hz, 1H), 4.96 (dt, J = 8.7, 4.0 Hz, 1H), 4.62 (d, J = 11.7 Hz, 1H), 4.39 (d, J = 11.7 Hz, 1H), 3.80 (s, 3H), 3.49−3.30 (m, 3H), 2.72−2.47 (m, 2H), 2.44−2.22 (m, 5H), 2.17−1.97 (m, 1H), 2.06 (s, 3H), 1.68−1.46 (m, 2H), 0.84 (t, J = 7.4 Hz, 3H), 0.18 (s, 9H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 170.5, 159.2, 140.8, 130.7, 129.6, 129.4, 129.3, 113.7, 112.5, 103.6, 93.5, 84.2, 81.4, 79.9, 74.8, 70.8, 55.3, 33.5, 29.9, 28.8, 25.3, 21.1, 10.6, −0.1; IR ($CDCl_3$) 1734 (CO) cm^{-1}; MS (CI, NH_3) *m/z* (rel intensity) 502 [17, $(M + NH_4)^+$], 485 [1, $(M + H)^+$]; HRMS (CI, NH_3) *m/z* 502.2990 (502.2989 calcd for $C_{28}H_{44}O_5SiN$, MNH_4).

2(*R*),3(*R*),8(*R*)-8-[(*E*),(*R*)-1-Acetoxy-6-(trimethylsilyl)-3-hexen-5-ynyl]-2-ethyl-3-hydroxy-3,4,7,8-tetrahydro-(2*H*)-oxocin 80. To a stirred solution of the acetate 2(*R*),3(*R*),8(*R*)-8-[(*E*),(*R*)-1-acetoxy-6-(trimethylsilyl)-3-hexen-5-ynyl]-2-ethyl-3-[(*p*-methoxybenzyl)oxy]-3,4,7,8-tetrahydro-(2*H*)-oxocin (7 mg, 14.9 μmol) in CH_2Cl_2 (1 cm^3) was added boron trichloride−methyl sulfide complex (37.4 μL, 74.7 μmol).[69] The solution was stirred for 5 min and then quenched by the addition of a saturated solution of sodium bicarbonate (1 cm^3). The reaction mixture was diluted with water, and the mixture was extracted with CH_2Cl_2 (3 × 5 cm^3). The organic phases were combined and dried ($MgSO_4$). The solvent was removed *in vacuo*, and purification by flash chromatography (light petroleum:ether, 3:2) gave the title compound **80** (5 mg, 13.7 μmol, 92%) as a clear and colorless oil; $[\alpha]_D^{24}$ −25.0 (*c* 0.04, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.11 (dt, J = 16.0, 7.2 Hz, 1H), 5.77−5.74 (m, 2H), 5.58 (d, J = 16.0 Hz, 1H), 4.96 (dt, J = 8.0, 4.6 Hz, 1H), 3.73−3.65 (m, 1H), 3.47−3.45 (m, 1H), 3.41−3.39 (m, 1H), 2.54−2.49 (m, 2H), 2.44−2.38 (m, 1H), 2.37−2.31 (m, 1H), 2.17−2.12 (m, 1H), 2.08 (s, 3H), 1.66−1.58 (m, 2H), 0.93 (t, J = 7.4 Hz, 3H), 0.18 (s, 9H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 170.5, 140.3, 129.5, 128.8, 112.7, 103.4, 93.8, 83.1, 80.5, 74.4, 73.6, 34.1, 33.5, 29.8, 25.5, 21.1, 10.4, −0.1; IR ($CDCl_3$) 1734 (CO) cm^{-1}; MS (CI, NH_3) *m/z* (rel intensity) 382 [17, $(M + NH_4)^+$], 365 [12, $(M + H)^+$]; HRMS (CI, NH_3) *m/z* 365.2148 (365.2148 calcd for $C_{20}H_{33}O_4Si$, MH).

2(*R*),3(*S*),8(*R*)-8-[(*E*),(*R*)-1-Acetoxy-6-(trimethylsilyl)-3-hexen-5-ynyl]-3-bromo-2-ethyl-3,4,7,8-tetrahydro-(2*H*)-oxocin, TMS-Laurencin 81.[17] To a stirred solution of the alcohol **80** (4.0 mg, 10.9 μmol) in toluene (1 cm^3) was added carbon tetrabromide (18.2 mg, 55 μmol) that had been purified by sublimation followed by dissolution in CH_2Cl_2 and passage down a column of UG1 alumina and dried over potassium hydroxide pellets *in vacuo*. Trioctylphosphine (24.5 μL, 55 μmol), that had been purified by distillation at reduced pressure (Kugelrohr, 0.1 mmHg, 175 °C), was added *via* syringe, and the resulting solution was heated to 70 °C for 2 h. The reaction mixture was allowed to cool, and the solvent was removed *in vacuo*. Purification by flash chromatography (hexane:EtOAc, 40:1 increasing the polarity to 35:1) yielded the title compound **81** as a clear and colorless oil (3.2 mg, 7.5 μmol, 69%); $[\alpha]_D^{18}$ +37.1 (*c* 0.035, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.10 (dt, J = 15.9, 7.5 Hz, 1H), 5.95−5.86 (m, 2H), 5.57 (d, J = 15.9 Hz, 1H), 4.98 (dt, J = 8.6, 4.3 Hz, 1H), 4.07 (dt, J = 9.9, 3.5 Hz, 1H), 3.43 (ddd, J = 9.9, 7.2, 2.5 Hz, 1H), 3.39 (dd, J = 10.5, 4.4 Hz, 1H), 3.15 (ddd, J = 13.7, 8.6, 3.5 Hz, 1H), 2.52−2.44 (m, 2H), 2.41−2.31 (m, 2H), 2.11−2.05 (m, 1H), 2.08 (s, 3H), 1.95 (ddq, J = 14.5, 7.5, 2.5 Hz, 1H), 1.57 (dqu, J = 14.5, 7.5 Hz, 1H), 0.98 (t, J = 7.5 Hz, 3H), 0.18 (s, 9H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 170.4, 140.2, 129.3, 128.9, 112.7, 103.3, 93.8, 84.5, 81.3, 74.2, 55.9, 33.7, 32.3, 29.7, 25.8, 21.1, 9.2, −0.1; IR ($CHCl_3$) 1734 (CO) cm^{-1}; HRMS (electrospray) *m/z* 427.1279 (427.1305 calcd for $C_{20}H_{32}O_3Si^{79}Br$, MH).

2(*R*),3(*S*),8(*R*)-8-[(*E*),(*R*)-1-Acetoxy-3-hexen-5-ynyl]-3-bromo-2-ethyl-3,4,7,8-tetrahydro-(2*H*)-oxocin, (+)-Laurencin 1. To a stirred solution of TMS-laurencin **81** (3.2 mg, 7.5 μmol) in THF (2 cm^3) at −13 °C was added TBAF (34 μL of a 1.1 M solution in THF, 37 μmol), and the reaction mixture was stirred for 2.5 min. The reaction was quenched by the addition of brine (2 cm^3) and ether (2 cm^3). The mixture was extracted with ether (10 cm^3) and dried ($MgSO_4$). Purification by flash chromatography (hexane:EtOAc, 15:1) yielded (+)-laurencin **1** (2.6 mg, 7.3 μmol, 98%) as a white gum; $[\alpha]_D^{20}$ +70 (*c* 0.05, $CHCl_3$), {lit.[1] $[\alpha]_D^{27}$ +70.2 (*c* 1.00, $CHCl_3$)}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.16 (dt, J = 16.0, 7.2 Hz, 1H, C≡CCH═C*H*), 5.96−5.86 (m, 2H, 5-H, 6-H), 5.53 (dd, J = 16.0, 1.5 Hz, 1H, C≡CC*H*═CH), 5.00 (dt, J = 8.7, 4.4 Hz, 1H, AcOC*H*), 4.07 (dt, J = 9.9, 3.4 Hz, 1H, 3-H), 3.43 (ddd, J = 9.9, 7.4, 2.6 Hz, 1H, 2-H), 3.39 (dd, J = 10.5, 4.4 Hz, 1H, 8-H), 3.16 (ddd, J = 14.0, 8.5, 3.4 Hz, 1H, 4-H), 2.82 (d, J = 1.5 Hz, 1H, C≡CH), 2.53−2.33 (m, 4H, 4-H, 7-H, C≡CCH═CHC*H*$_2$), 2.10−2.06 (m, 1H, 7-H), 2.08 (s, 3H, CH_3COO), 1.95 (ddq, J = 14.4, 7.4, 2.6 Hz, 1H, C*H*HCH$_3$), 1.57 (dqu, J = 14.4, 7.4, 1H, CH*H*CH$_3$), 0.98 (t, J = 7.4 Hz, 3H, CH_2CH_3); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 170.3, 141.1, 129.2, 129.0, 111.6, 84.6, 81.8, 81.4, 76.7, 74.1, 56.0, 33.8, 32.3, 29.7, 25.8, 21.0, 9.3; IR ($CHCl_3$) 3304 (C≡CH), 2927,

2855, 1734 (CO) cm^{-1}; HRMS (electrospray) *m/z* 355.0909 (355.0909 calcd for $C_{17}H_{24}O_3{}^{79}Br$, MH).

Acknowledgment. We thank the Engineering and Physical Sciences Research Council (EPSRC) UK for a research grant, Pfizer Central Research, and Corpus Christi College Cambridge for the award of a studentship and a Junior Research Fellow ship (J.W.B.), the Cambridge European Overseas Trust, Ciba (Novartis) and the Swiss Foundation for Gifted Students (scholarship to S.D.), and the Commission of the European Communities (TMR award to T.C.S.) for generous financial support. We thank Dr. G. M. Williams for assistance in the preparation of **40** and **41**, Dr. S. Bunkhall for the X-ray analysis of compound **29a**, Prof. L. E. Overman for spectra of TIPS-laurencin, Prof. A. Murai for spectra of natural and synthetic laurencin, and Dr. J. M. Goodman for advice on molecular modeling. We thank Prof. R. Hoffmann (Marburg) for a preprint of the accompanying paper and Prof. J. Palenzuela for spectra of the benzyl analog of **59**. Further acknowledgments appear in the Supporting Information.

Supporting Information Available: Experimental procedures for the synthesis of **2**−**10**, **16**−**19**, **21**−**29**, **32**−**35**, **40**−**43**, **54**−**56**, **58**, **62**−**69**, and **76**−**79** and the procedure for the conversion of **71** into **70**; details of the X-ray crystal structure determination; tables of atomic coordinates, isotropic displacement parameters, anisotropic displacement parameters, bond lengths, and bond angles for **29a** (this data has been deposited with the Cambridge Crystallographic Database); ^1H and ^{13}C NMR spectra of synthetic (+)-laurencin **1** (58 pages). See any current masthead page for ordering information and Internet access instructions.

JA9709132