General Approach to Halogenated Tetrahydrofuran Natural Products from Red Algae of the Genus *Laurencia*. Total Synthesis of (±)-Kumausallene and (±)-1-*epi*-Kumausallene

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Received December 9, 1992

An efficient, stereocontrolled entry to the dioxabicyclo[3.3.0]octane ring system of (±)-kumausallene has been developed. This synthesis builds upon our general strategy for preparing C_{15} halogenated tetrahydrofuranoid marine lipids using the ring-enlarging tetrahydrofuran annulation of cyclic, allylic diols as the central step. The key intermediate, hydrobenzofuranone 8, is available with complete stereocontrol from the Lewis acid-catalyzed condensation of 1-vinylcyclopentanediol (4) and α-(benzoyloxy)acetaldehyde (Scheme II). Elaboration of 8 into the bicyclic ring system of 13 requires only four steps and proceeds with excellent stereocontrol in 41% overall yield. The total synthesis of (±)-kumausallene from 8 is accomplished in 17 steps and 2% overall yield. As a corollary, the total synthesis of (±)-1-*epi*-kumausallene confirms the stereochemical assignment for the bromoallene moiety of the natural product.

Among the structurally diverse nonisoprenoid sesquiterpenes isolated from red algae of the genus *Laurencia* is a growing family of halogenated, tetrahydrofuran-containing, natural products.[1] The unifying structural feature of this family is an all-cis, 3-oxygenated-2,5-dialkyltetrahydrofuran unit, with one or more bromine atoms incorporated at various positions. The majority of these metabolites can be envisaged to arise from the halocyclization of various 6,7-dihydroxypentadeca-3,9,-12-trien-1-ynes (laurediols).[2] A representative selection of cyclic halo ethers of this common type is shown in Figure 1.[3-7] One of the simplest members of this family, *trans*-kumausyne (2), was recently synthesized in these laboratories.[8,9] The deacetyl derivative of 2 has been hypothesized as an intermediate in the biogenesis of a number of such metabolites by electrophile-induced cyclization of its 3-oxygen functionality onto various olefinic carbons of the alkyl side chains.[10]

We have devised a strategy for the synthesis of this family of marine acetogenins that would allow access to the various members of this family via a common synthetic intermediate, the bicyclic lactone 3 (Figure 1). Access to this intermediate is provided through oxidation of *cis*-hydrobenzofuranones 5, which are in turn available from the reaction of aldehydes and the vinylcyclopentanediol 4 (Scheme I).[11] This Prins cyclization–pinacol rearrangement approach allows construction of the oxacyclic ring of 5 with complete stereocontrol. This approach to the *Laurencia* metabolites illustrated in Figure 1 was first demonstrated in a total synthesis of *trans*-kumausyne.[8] In the present work, we detail the extension of this chemistry to the synthesis of (±)-kumausallene (1a), a member of this group having the dioxabicyclo[3.3.0]octane ring system.[4] Pivotal to the success of this total synthesis venture is the ready availability of unsaturated lactone 6 and the one-step conversion of this intermediate to the dioxabicyclic ester 7 (Scheme I). Finally, this synthetic endeavor allows unambiguous confirmation of the relative stereochemistry of the bromoallene moiety of kumausallene, which had previously been inferred on the basis of optical rotation data.[4,12]

Total Synthesis of (±)-Kumausallene. Analogous to our earlier synthesis of *trans*-kumausyne,[8] our efforts began with a *cis*-hydrobenzofuranone, in this case 8. This intermediate is available with complete stereoselectivity on a large scale by condensation of *trans*-1-vinylcyclopentane-1,2-diol (4) and α-(benzoyloxy)acetaldehyde (Scheme II).[11] The choice of benzoyl as the protecting group in this instance was predicated upon its lability to base-catalyzed cleavage at the opportune time (vide infra). Oxidation of 8 with *m*-chloroperbenzoic acid provided a 4:1 mixture of lactones 9 and 10, which could be separated on silica gel to provide the desired regioisomer 9 in 70% yield. Efforts to improve the regioselectivity of this conversion by using other common oxidants were unsuccessful.[13,14]

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(1) For reviews, see: Faulkner, D. J. *Nat. Prod. Rep.* **1984**, *1*, 251, 551. *Ibid.* **1986**, *3*, 1. *Ibid.* **1987**, *4*, 539. *Ibid.* **1988**, *5*, 613. *Ibid.* **1990**, *7*, 269. *Ibid.* **1991**, *8*, 97. *Ibid.* **1992**, *9*, 323.

(2) (a) Moore, R. E. In *Marine Natural Products*; Scheuer, P. J., Ed.; Academic: New York, 1978; Vol. 1, pp 43-121. (b) Erickson, F. L. In *Marine Natural Products*; Scheuer, P. J., Ed.; Academic: New York, 1983; Vol. 5, pp 131-257.

(3) *cis*- and *trans*-Kumausyne: Suzuki, T.; Koizumi, K.; Suzuki, M.; Kurosawa, E. *Chem. Lett.* **1983**, 1643.

(4) Kumausallene: Suzuki, T.; Koizumi, K.; Suzuki, M.; Kurosawa, E. *Chem. Lett.* **1983**, 1639.

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(13) The migratory aptitude of *sec*-alkyl in Baeyer–Villiger oxidations is typically significantly greater than primary alkyl.[14] Nevertheless, modest regioselectivity in similar systems has been reported.[8]

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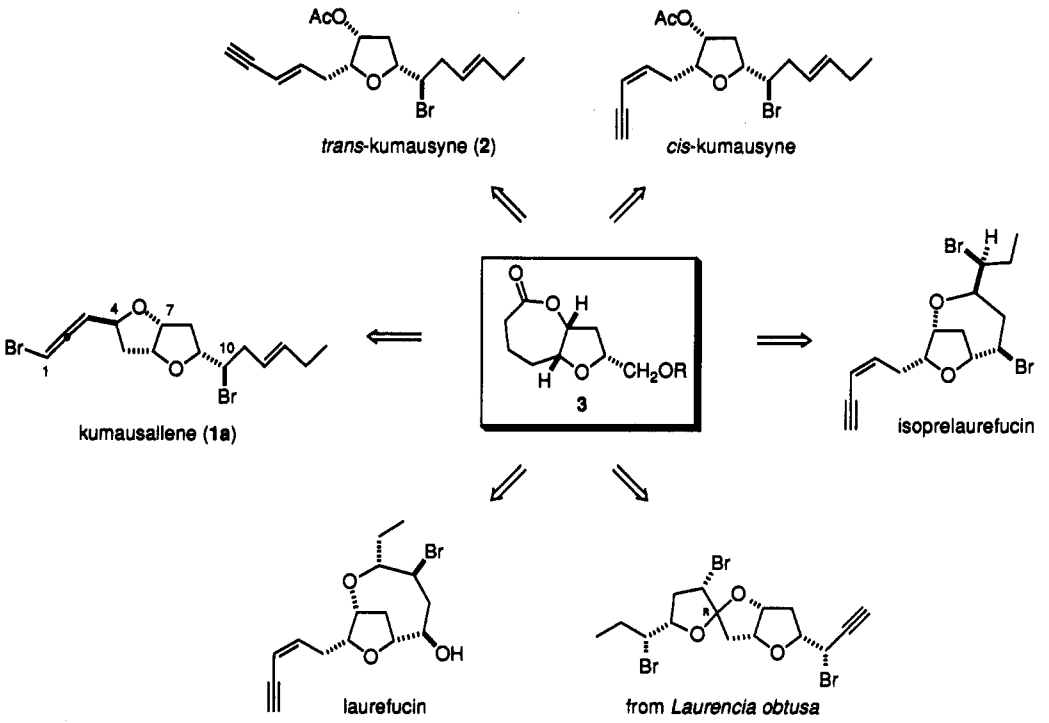
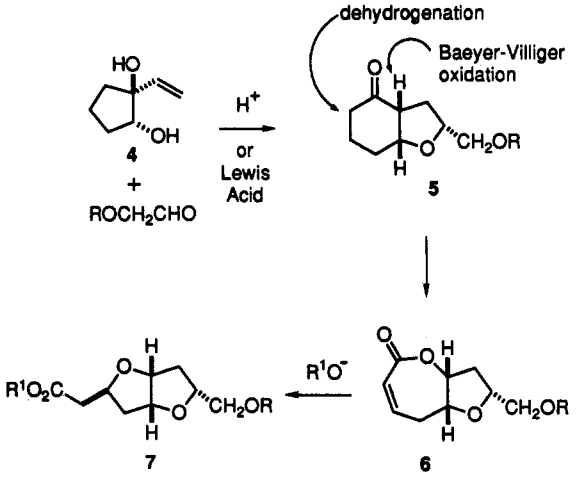
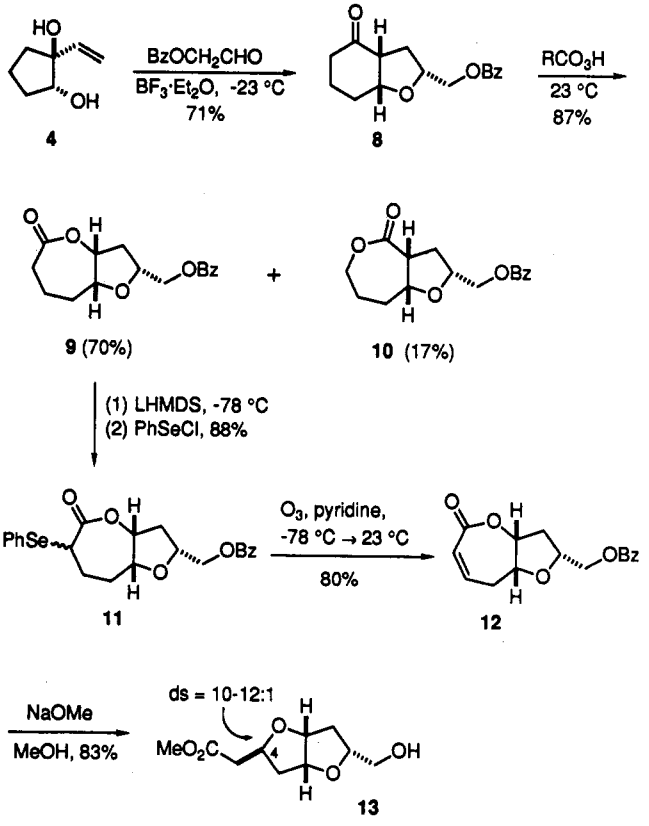


Figure 1. Representative *Laurencia* nonisoprenoid sesquiterpenes.[3-7]

Scheme I



Scheme II[a]



[a] Bz = COPh.

The dehydrogenation of lactone **9** was accomplished by a selenation/selenoxide elimination procedure (Scheme II).[15] Careful temperature control during the selenation reaction helped to minimize the formation of diselenide byproducts providing a 4:1 mixture of diastereomeric selenides **11**. Exposure of this mixture to ozone, followed by addition of pyridine, provided the unsaturated lactone **12** in 71% overall yield from **9**. This procedure proved significantly more amenable to scaleup than alternative methods that utilize hydrogen peroxide as the oxidant.

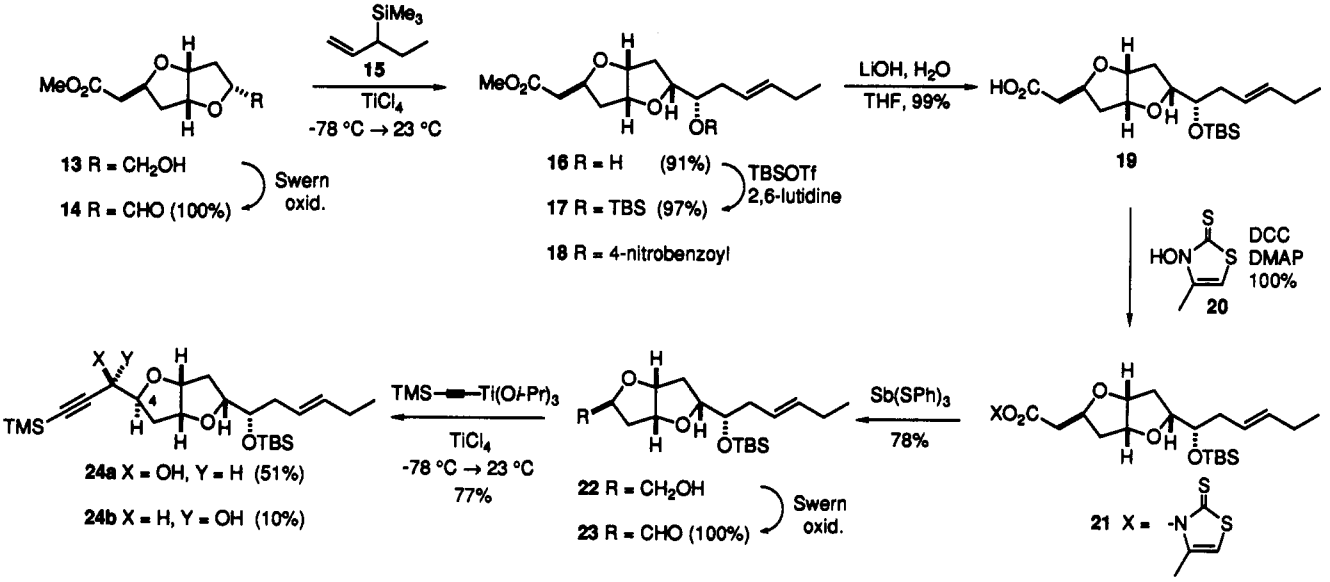
Methanolysis of lactone **12** then proceeded in tandem with cyclization of the resulting hydroxy ester to give the cis-fused dioxabicyclo[3.3.0]octane **13** with high stereoselectivity (10–12:1). The disposition of the carbomethoxymethyl side chain on the convex face of the bicyclic system was assumed, initially on the basis of thermodynamic considerations. X-ray analysis of a later intermediate (vide infra) unambiguously established this configurational issue. Since chromatographic separation was difficult, removal of the small amount of the C-4 epimer of **13** (kumausallene numbering) was delayed until later in the synthetic sequence.

Installation of the six-carbon side chain of kumausallene was then accomplished by a sequence analogous to that used in our earlier synthesis of *trans*-kumausyne (Scheme

(14) See, e.g., Krow, G. R. *Tetrahedron* **1981**, *37*, 2697 and references cited therein.

(15) For a definitive account, see: Reich, H. J.; Renga, J. M.; Reich, I. L. *J. Am. Chem. Soc.* **1975**, *97*, 5434.

Scheme III[a]



[a] TBS = *t*-BuMe$_2$Si.

III). Oxidation of **13** under Swern[16] conditions utilizing a nonaqueous workup[17] provided the sensitive aldehyde **14**, which was elaborated immediately. Sakurai reaction[18] of **14** with 3-(trimethylsilyl)-1-pentene (**15**),[8] in the presence of $TiCl_4$, then afforded alcohol **16** as a single diastereomer (still contaminated with a small amount of its C-4 epimer) in 91% overall yield. The use of BF_3·Et_2O as the Lewis acid provided **16** also with high stereoselectivity, although in somewhat lower yield. Crystallographic analysis of the 4-nitrobenzoate derivative **18** indicated that simple Cram stereoselection[19] was operative, even in the presence of the multidentate Lewis acid $TiCl_4$.[20] Presumably, the disposition of the aldehyde on the concave face of the bicyclic system precludes chelation of the tetrahydrofuran oxygen to the titanium complex for steric reasons. Silylation of **16**, under standard conditions,[21] then led to silyl ether **17** in excellent yield (97%).

With the hexenyl side chain in place, our plan for elaboration of the bromoallene functionality required excision of a methylene group from the carbomethoxymethyl subunit of **17**. Attempts to accomplish this degradation by silyl ketene acetal formation[22] followed by oxidative cleavage were undermined by rapid β-elimination of enolate derivatives of **17**.[23] We therefore investigated the oxidative decarboxylation methodology developed by Barton,[24] which involves radical decomposition of *O*-acyl thiohydroxamates. This sequence appeared ideal for our needs, since carbon radicals are not prone to elimination of β-heteroatom functionality. For our purposes, activation of the carboxylic acid with the *N*-hydroxythiazolinethione **20**[25] proved superior to the more common activation with *N*-hydroxypyridine-2-thione, since the greater stability of the derived mixed anhydrides allowed for easier handling on a small scale. Hydrolysis of ester **17**, followed by coupling[26] of the resultant acid **19** with **20** provided the *O*-acyl thiohydroxamate **21** in nearly quantitative yield. Exposure of **21** to $Sb(SPh)_3$[27] under an air atmosphere then led to the nor-alcohol **22** in 77% overall yield from **17**. It was essential to maintain the reaction with $Sb(SPh)_3$ under strictly anhydrous conditions until after addition of **21**, since hydrolytic formation of thiophenol led to competitive reaction pathways.[28]

With **22** in hand, the stage was set for introduction of the bromoallene functionality.[29] We hoped to achieve Felkin–Anh stereocontrol[30] in the addition of an acetylide subunit to aldehyde **23** with subsequent conversion of the product propargyl alcohol, via a sulfonate, to the (*R**)-bromoallene by anti-S_N2' addition of a bromocuprate reagent.[31] Towards that end, oxidation[16] of **22** provided the extremely labile aldehyde **23**, which was used immediately. Our experience with the addition of lithium acetylides to **23** parallels earlier results of Feldman in a related series in giving the desired propargylic alcohol in low yield (<45%) and poor stereoselectivity ($\simeq$1.5:1). The use of boryl[32] or stannyl[33] acetylide nucleophiles offered

(16) Mancuso, A. J.; Huang, S.-L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480.
(17) See, e.g., Paquette, L. A.; Oplinger, J. A. *J. Org. Chem.* **1988**, *53*, 2953. Williams, D. R.; Harigaya, Y.; Moore, J. L.; D'sa, A. *J. Am. Chem. Soc.* **1984**, *106*, 2641.
(18) Hosomi, A.; Sakurai, H. *Tetrahedron Lett.* **1976**, 1295.
(19) For closely related examples, see: Danishefsky, S. J.; DeNinno, M. P.; Phillips, G. B.; Zelle, R. E.; Lartey, P. A. *Tetrahedron*, **1986**, *42*, 2809. Danishefsky, S. J.; Selnick, H. G.; Zelle, R. E.; DeNinno, M. P. *J. Am. Chem. Soc.* **1988**, *110*, 4368.
(20) Danishefsky, S.; DeNinno, M. P. *Tetrahedron Lett.* **1985**, 823.
(21) Corey, E. J.; Cho, H.; Reucker, C.; Hua, D. H. *Tetrahedron Lett.* **1981**, 3455.
(22) Emde, H.; Domsch, D.; Feger, H.; Frick, U.; Gotz, A.; Hergott, H. H.; Hofmann, K.; Kober, W.; Krageloh, K.; Oesterle, T.; Steppan, W.; West, W.; Simchen, G. *Synthesis* **1982**, 1. Larson, G. L.; Cruz de Maldonado, V.; Fuentes, L. M.; Torres, L. E. *J. Org. Chem.* **1988**, *53*, 633. Babston, R. E.; Lynch, V.; Wilcox, C. S. *Tetrahedron Lett.* **1989**, 447. Wilcox, C. S.; Babston, R. E. *Tetrahedron Lett.* **1984**, 699.
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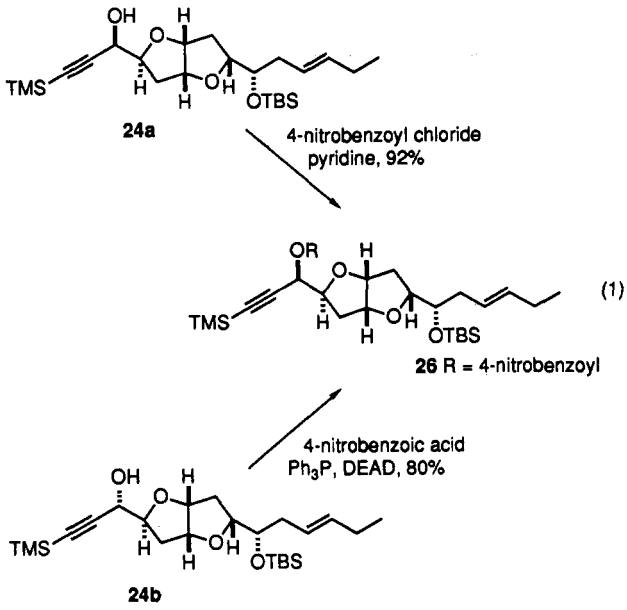
(25) Barton, D. H. R.; Crich, D.; Kretzschmar, G. *J. Chem. Soc., Perkin Trans. I* **1986**, 39.
(26) Neises, B.; Steglich, W. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 522.
(27) Barton, D. H. R.; Dadoun, H.; Gourdon, A. *Nouv. J. Chim.* **1982**, *6*, 53.
(28) Barton, D. H. R.; Ozbalik, N.; Schmitt, M. *Tetrahedron Lett.* **1989**, 3263.
(29) A related sequence was used by Feldman in the synthesis of (±)-panacene, see: Feldman, K. S.; Mechem, C. C.; Nader, L. *J. Am. Chem. Soc.* **1982**, *104*, 4011.
(30) Tabusa, F.; Yamada, T.; Suzuki, K.; Mukaiyama, T. *Chem. Lett.* **1984**, 405.
(31) Montury, M.; Goré, J. *Synthetic Commun.* **1980**, 873. Elsevier, C. J.; Vermeer, P.; Gedanken, A.; Runge, W. *J. Org. Chem.* **1985**, *50*, 364.

no improvement. Prompted by the reports of Seebach[34] and Mukaiyama[30] we turned to the reaction of 2-(trimethylsilyl)ethynyltitanium triisopropoxide with the $TiCl_4$ complex of aldehyde **23**. Under these conditions, we were gratified to observe a substantial improvement in yield (77%) as well as stereoselectivity (>3.1:1 by analytical HPLC analysis). Stereoselection in this addition showed a marked dependence on the purity of aldehyde **23**. Since **23** showed a strong tendency toward hydrate formation, strictly anhydrous conditions were maintained during its isolation. Altering the nature of the titanium reagents[30,34] provided no further improvements in selectivity or yield.

At this juncture, it was finally feasible to remove C-4 epimeric materials chromatographically. Preparative HPLC allowed isolation of the major propargyl alcohol **24a** in 51% overall yield from **22**. The minor isomer **24b** was also isolated in 10% yield, with the remaining mixed chromatography fractions containing additional **24b** as well as various C-4 epimers.

The epimeric relationship of **24a** and **24b** was established by their independent conversion to 4-nitrobenzoate **26** (eq 1).[35] The stereochemistry of the major isomer **24a** was



(1)

assigned as erythro on the basis of literature precedent[30] and ^1H NMR evidence. Several studies of α-tetrahydrofurylpropargyl alcohols and their derivatives have concluded that the relative configuration of the propargyl and tetrahydrofuryl stereocenters can be assigned on the basis of the magnitude of the associated ^1H NMR vicinal coupling constants.[29,36] In all cases studied, the erythro isomer shows smaller vicinal coupling (J = 2–4 Hz) than the corresponding threo isomer (J = 6–8 Hz). In the present system, the resonances of the propargyl hydrogens in the derived 2,4,6-triisopropylbenzenesulfonates (trisylates) **27a** and **27b** were suitable for exact analysis as depicted in Figure 2. The smaller, 3.6 Hz, coupling constant for **27a** is consistent with the assignment of **27a** as the erythro isomer.

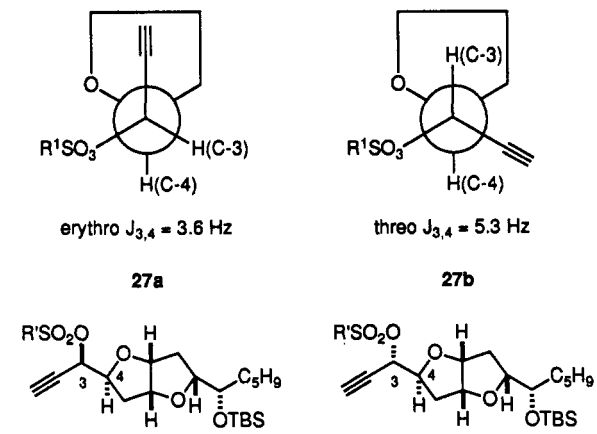


Figure 2.

Selective desilylation of **24a** was accomplished with K_2CO_3/MeOH to give the terminal alkyne **25a** in 92% yield (Scheme IV). Contrary to our expectations based on literature reports,[31] the reaction of the mesylate derivative of **25a** with $LiCuBr_2$ gave only modest yields (≃50%) of bromoallene products that were contaminated with large amounts (25–30%) of the corresponding propargyl bromides. Reasoning that a larger leaving group would allow for greater discrimination between the termini of the propargyl system, we prepared the related trisylate **27a**. Reaction of **27a** with $LiCuBr_2$ provided a 73% yield of the bromoallenes **28a** and **28b** (ratio >15:1), after removal of 10–15% of the contaminating propargyl bromides by chromatography on $AgNO_3$-impregnated silicia gel. After desilylation, the bromoallene stereoisomers could be separated by HPLC to provide alcohol **29a** in 60% overall yield from **25a**. This intermediate was surprisingly sensitive and readily showed evidence of decomposition, even upon short-term storage at −5 °C.

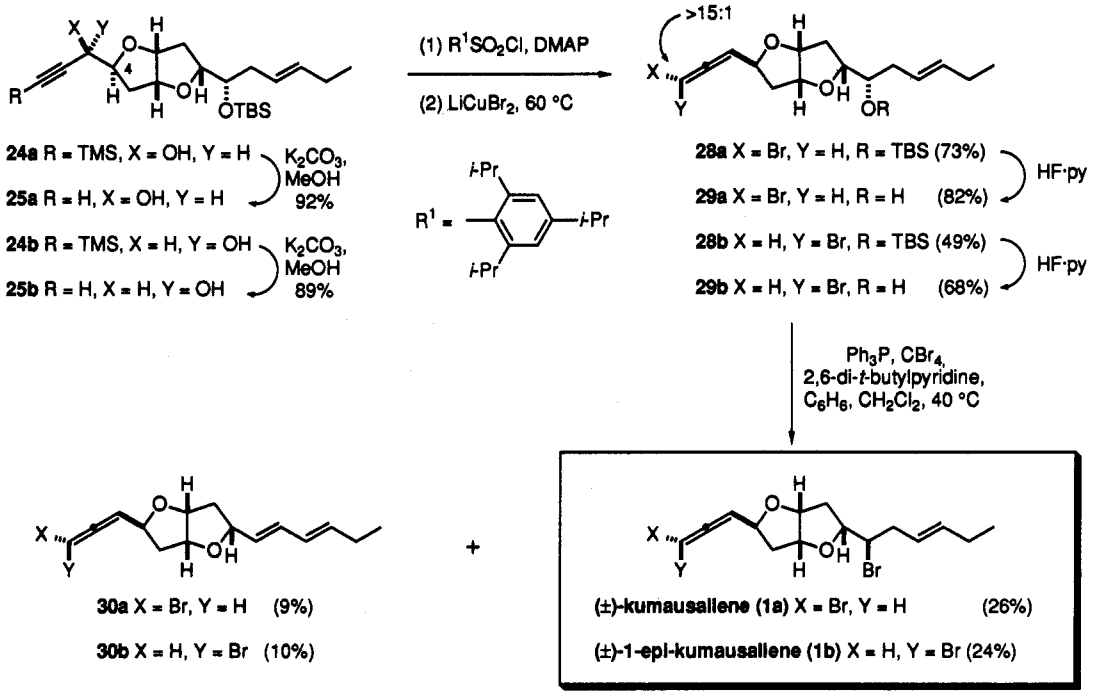
With the carbon skeleton of kumausallene in place, we turned our attention to the final bromination step. As in our *trans*-kumausyne synthesis,[8] this seemingly simple transformation proved nontrivial. After considerable experimentation with a variety of bromination protocols,[37] the triphenylphosphine–carbon tetrabromide reagent system proved to be uniquely effective. Optimum conditions involved treatment of freshly purified **29a** with 4 equiv each of Ph_3P and purified CBr_4 in the presence of 4 equiv of 2,6-di-*tert*-butylpyridine (PhH/CH_2Cl_2, 40 °C, 30 min) to provide (±)-kumausallene (**1a**) in 26% yield as well as 9% of the diene **30a**.

Synthesis of (±)-1-*epi*-Kumausallene. Since the relative configuration of the bromoallene subunit of kumausallene had not unambiguously been determined[4] and since neither an authentic sample of natural kumausallene nor copies of original spectra were available for comparison,[38] we elected to prepare (±)-1-*epi*-kumausallene in order to confirm the stereochemistry of the natural product. Elaboration of propargyl alcohol **24b** by the sequence described previously in the natural series provided the hydroxy bromoallene **29b** in 30% overall yield (Scheme IV). Bromination of **29b** then gave (±)-1-*epi*-kumausallene in 24% yield together with 10% of diene **30b**.

Spectral data for **1a** and **1b**, as well as that reported for natural kumausallene, are compiled in Table I. As can be

(32) Yamaguchi, M.; Hirao, I. *Tetrahedron Lett.* **1983**, 391.
(33) Yamamoto, Y.; Nishii, S.; Maruyama, K. *J. Chem. Soc., Chem. Commun.* **1986**, 102.
(34) Krause, N.; Seebach, D. *Chem. Ber.* **1987**, *120*, 1845.
(35) For examples of Mitsunobu inversion in similar systems, see: Jarosz, S.; Glodek, J.; Zamojski, A. *Carbohydr. Res.* **1987**, *163*, 289.
(36) Horton, D.; Hughes, J. B.; Thomson, J. K. *J. Org. Chem.* **1968**, *33*, 728. Horton, D.; Tronchet, J. M. J. *Carbohydr. Res.* **1966**, *2*, 315.
(37) Castro, B. R. *Org. React.* **1983**, *29*, 1.
(38) Our request for a sample of natural kumausallene or copies of original spectra received no reply.

Scheme IV[a]



[a] TBS = *t*-BuMe$_2$Si.

Table I. Characterized Data for Natural Kumausallene,[4] Synthetic (±)-Kumausallene (1a), and Synthetic (±)-1-*epi*-Kumausallene (1b)

	(±)-kumausallene	1a	1b
		^{1}H NMR[a,b]	
H(C-1)	6.08 [dd(6,2)]	6.08 [dd(5.7,1.5)]	6.09 [dd(5.8,1.2)]
H(C-13)	5.61 [dt(15,6)]	5.60 [dt(15.2,6.2)]	5.60 [dt(15.2,6.4)]
H(C-3)	5.46 [dd(6.6)]	5.46 [t(5.9)]	5.42 [t(6.1)]
H(C-12)	5.46 [ddd(15,7,7)]	5.46 [m(7.0)]	5.46 [dt(15.0,6.9)]
H(C-7)	4.83 [ddd(7.5,5,3.5)]	4.83 [dt(7.7,3.9)]	4.82 [dt(7.8,3.8)]
H(C-4)	4.73 [dddd(10,6,6,2)]	4.75 [dtd(9.8,5.0,1.1)]	4.75 [dtd(9.8,5.2,0.8)]
H(C-6)	4.55 [dd(5,5)]	4.55 [t,(4.8)]	4.55 [t(4.8)]
H(C-10)	4.00 [ddd(8,6,5)]	4.01 [dt(8.2,5.3)]	4.01 [dt(8.3,5.2)]
H(C-9)	3.92 [ddd(9,6,6)]	3.91 [dt(9.3,6.2)]	3.91 [dt(9.3,6.1)]
H(C-11)a	2.67 [ddd(15,7,5)]	2.64 [dt(14.8,5.6)]	2.64 [dt(14.8,5.8)]
H(C-11)b	2.53 [ddd(15,8,7)]	2.53 [dt(14.8,7.6)]	2.54 [dt(14.8,7.7)]
H(C-5)a	2.35 [dd(13.5,6)]	2.36 [dd(13.5,5.6)]	2.37 [dd(13.8,5.0)]
H(C-8)a	2.34 [ddd(14,7.5,6)]	2.34 [dt(14.1,7.1)]	2.33 [dt(13.9,7.0)]
H$_2$(C-14)	2.04 [br dq(6,7.5)]	2.04 [quintet(7.2)]	2.04 [quintet(7.1)]
H(C-8)b	1.89 [ddd(14,9,3.5)]	1.88 [ddd(13.7,9.6,3.6)]	1.87 [ddd(13.5,9.6,3.7)]
H(C-5)b	1.77 [ddd(13.5,10,5)]	1.76 [ddd(13.6,9.8,4.9)]	1.76 [ddd(13.6,9.9,4.9)]
H$_3$(C-15)	0.99 [t(7.5)]	0.99 [t(7.4)]	0.98 [t(7.4)]
		^{13}C NMR[b]	
	201.4, 135.8, 124.6, 100.7, 83.7, 83.7, 81.6, 74.2, 73.9, 57.0, 39.5, 38.3, 37.8, 25.5, 13.6	201.6, 136.0, 124.5, 100.7, 83.9, 83.7, 81.8, 74.2, 73.9, 57.1, 39.5, 38.4, 37.8, 25.6, 13.7	201.9, 136.0, 124.5, 100.4, 83.8, 83.7, 81.7, 74.7, 73.8, 57.0, 39.5, 38.4, 37.5, 25.6, 13.6
		IR[c]	
	3050, 1960, 1250, 1195, 1085, 965, 925, 850	3056, 1963, 1256, 1199, 1081, 969, 927, 858	3057, 1963, 1257, 1200, 1081, 970, 927, 857

[a] Kumausallene numbering. [b] Parts per million in $CDCl_3$. Coupling constants in hertz are in parentheses. [c] Film; cm^{-1}.

seen, the spectral distinctions between the diastereomeric bromoallenes are subtle at best. The ^{1}H NMR signal for H(C-3), which is reported as coincident with that for H(C-12) for the natural isolate,[4] is shifted by 0.04 ppm in the epi-isomer. Furthermore, the ^{13}C NMR chemical shifts for all three allene carbons in **1b** differ from the reported values (δ 201.4, 100.7, 74.2) for kumausallene by 0.3–0.5 ppm. Although these differences are minor, the close homology between the spectral characteristics of **1a** and those reported for natural kumausallene, in combination with the optical rotation evidence based on Lowe's rule,[12] support the original stereochemical assignment for kumausallene.

Conclusion

The first total synthesis of the C_{15} tetrahydrofuranoid lipid (±)-kumausallene (**1a**) has been accomplished. The key intermediate, hydrobenzofuranone **8**, is available in four steps and 31% overall yield from commercial starting materials using the "ring-enlarging tetrahydrofuran annulation" developed earlier in these laboratories.[11] This

oxabicyclic is efficiently converted in four steps and 41% yield into the dioxabicyclo[3.3.0]octane ring system of **1a** with excellent stereoselectivity. The total synthesis of (±)-kumausallene proceeded in 17 total steps and 2% overall yield from hydrobenzofuranone **8**. Preparation of the bromoallene epimer, (±)-1-*epi*-kumausallene, confirmed the allene stereochemistry of the natural product.

Recorded here is the second total synthesis of a halogenated *Laurencia* C_{15} lipid metabolite based upon the Prins cyclization–pinacol rearrangement synthesis of tetrahydrofurans. This successful endeavor verifies the generality of the strategem suggested in Figure 1 to access this class tetrahydrofuranoid marine metabolites.

Experimental Section[39]

(3a*R,8a*R**)-2(*R**)-[(Benzoyloxy)methyl]-5-oxotetrahydrofuro[3,2-*b*]oxepane (9) and (3a*R**,8a*R**)-2(*R**)-[(Benzoyloxy)methyl]-4-oxotetrahydrofuro[3,2-*c*]oxepane (10).** Solid 80% *m*-chloroperoxybenzoic acid (*m*-CPBA) (8.90 g, 51.7 mmol) was added to a solution of hydrobenzofuranone **8**[11] (3.00 g, 10.9 mmol) in CH_2Cl_2 (120 mL) at 23 °C. After 24 h additional *m*-CPBA (4.49 g, 26.1 mmol) was added and the reaction was maintained at 23 °C for 2 days. The mixture was then poured into a separatory funnel and saturated Na_2SO_3 (200 mL) solution was added carefully. The layers were separated, the organic layer was washed with saturated $NaHCO_3$ solution (200 mL), dried (Na_2SO_4), and concentrated, and the solid residue was purified by column chromatography (1:1 hexane–EtOAc) to give 2.23 g (70%) of **9** as a viscous oil, which solidified upon standing, and 0.53 g (17%) of **10** as a viscous oil, which also solidified upon standing. Both **9** and **10** were recrystallized (9:1 hexane–EtOAc) to give colorless needles.

Spectral data for **9**: mp 71–72 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.06–8.09 (m, 2 H, Ph), 7.54–7.57 (m, 1 H, Ph), 7.42–7.45 (m, 2 H, Ph), 4.94 (dt, *J* = 7.9, 4.0 Hz, H-3a), 4.51 (dd, *J* = 11.7, 3.8 Hz, 1 H, CH_2OBz), 4.37 (dd, *J* = 11.7, 6.6 Hz, 1 H, CH_2OBz), 4.23 (dq, *J* = 7.2, 3.8 Hz, H-2), 3.99 (dt, *J* = 10.2, 5.1 Hz, H-8a), 2.54–2.66 (m, 3 H), 2.11–2.24 (m, 2 H), 1.88–2.01 (m, 1 H), 1.69–1.78 (m, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.6, 166.4, 133.1, 129.8, 128.4, 80.7, 79.8, 77.2, 75.8, 65.9, 35.6, 31.6, 26.6, 16.7; IR (film) 2931, 1737, 1725, 1281 cm^{-1}; MS (CI) *m/z* 291.1229 (MH, 291, 1232 calcd. for $C_{16}H_{19}O_5$), 137, 105, 77. Anal. Calcd for $C_{16}H_{18}O_5$: C, 66.18; H 6.26. Found: C, 66.07; H, 6.29.

Spectral data for **10**: mp 88–89 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.08–8.05 (m, 2 H, Ph), 7.53–7.58 (m, 1 H, Ph), 7.40–7.46 (m, 2 H, Ph), 4.58 (dd, *J* = 11.8, 3.9 Hz, 1 H, CH_2OBz), 4.09–4.36 (m, 5 H), 3.51 (dd, *J* = 17.1, 9.2 Hz, 1 H), 2.42–2.51 (m, 1 H), 2.03–2.28 (m, 3 H), 1.51–1.75 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.1, 166.4, 133.0, 129.9, 129.7, 128.3, 76.6, 76.5, 65.8, 64.9, 46.5, 30.8, 27.2, 22.6; IR (film) 2956, 2888, 1743, 1706, 1456, 1281 cm^{-1}; MS (CI) *m/z* 291.1225 (MH, 291.1232 calcd for $C_{16}H_{19}O_5$), 169, 123, 105. Anal. Calcd for $C_{16}H_{18}O_5$: C, 66.18; H, 6.26. Found: C, 66.18; H, 6.27.

(3a*R,8a*R**)-2(*R**)-[(Benzoyloxy)methyl]-5-oxo-3a,5,8,8a-(tetrahydro)tetrahydrofuro[3,2-*b*]oxepin (12).** A solution of lithium bis(trimethylsilyl)amide (10.6 mL of a 1.09 M solution in THF, 11.6 mmol) was diluted with THF (35 mL) and cooled to −78 °C. A solution of **9** (2.80 g, 9.64 mmol) in THF (5 mL) was then added dropwise, maintaining the internal temperature below −72 °C, and the resulting mixture was maintained at −75 °C for 1 h. A solution of PhSeCl (2.22 g, 11.6 mmol) in THF (10 mL) was then added, as rapidly as possible, via syringe. After 20 min the mixture was poured into saturated NH_4Cl solution (75 mL) and extracted with EtOAc (4 × 75 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated, and the residue was purified on silica gel (4:1 hexane–EtOAc) to give 3.78 g (88%) of a mixture of compounds, of which the desired selenides **11** were the major component, as a yellow foam. Integration of ^{1}H NMR signals at 5.43 and 4.99 ppm indicated a 4.1:1 mixture of epimers: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.05–8.10 (m), 7.30–7.65 (m), 5.42–5.44 (m), 4.96–5.02 (m), 4.13–4.52 (m), 3.91–4.07 (m), 2.41–2.61 (m), 2.04–2.26 (m), 1.56–1.87 (m); IR (film) 2944, 1725, 1456, 1281, 1106 cm^{-1}; MS (CI) *m/z* 447 (MH).

Ozone was bubbled through a solution of the mixture of selenides **11** (3.78 g, 8.5 mmol) in CH_2Cl_2 (75 mL) at −78 °C, at a rate of 2.0 mL/min, until a faint blue color persisted. Nitrogen was then bubbled through to remove excess ozone, pyridine (1.61 g, 1.65 mL, 20.4 mmol) was added, and the reaction was allowed to warm to room temperature. The mixture was then diluted with CH_2Cl_2 (100 mL) and washed with 5% HCl (75 mL) followed by saturated $NaHCO_3$ solution (75 mL). Each aqueous layer was extracted with CH_2Cl_2 (25 mL), the combined organic extracts were dried ($MgSO_4$) and concentrated, and the residue was purified on silica gel (2:1–1:1 hexanes–EtOAc) to give 1.97 g (80%, 71% overall from **9**) of **12** as a light yellow oil, which crystallized upon trituration with ether. Recrystallization (9:1 hexane–EtOAc) gave fine colorless crystals: mp 79–82 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.10–8.11 (m, 2 H, Ph), 7.55–7.58 (m, 1 H, Ph), 7.43–7.46 (m, 2 H, Ph), 6.64 (ddd, *J* = 10.9, 8.5, 5.5 Hz, H-7), 6.05 (ddd, *J* = 11.0, 2.4, 1.0 Hz, H-6), 4.78 (ddd, *J* = 7.0, 4.2, 2.1 Hz, H-3a), 4.52 (dd, *J* = 11.6, 3.9 Hz, 1 H, CH_2OBz), 4.44 (dd, *J* = 11.6, 6.4 Hz, 1 H, CH_2OBz), 4.38 (tdd, *J* = 8.2, 6.4, 3.9 Hz, H-2), 4.26 (ddd, *J* = 10.7, 6.5, 4.2 Hz, 1 H), 2.74–2.80 (m, 1 H), 2.52–2.63 (m, 2 H), 2.25 (ddd, *J* = 14.6, 6.5, 1.9 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.8, 166.3, 140.8, 133.0, 129.8, 129.7, 128.3, 125.8, 83.0, 80.4, 77.7, 66.2, 34.5, 29.1; IR (film) 3063, 2969, 1725, 1250 cm^{-1}; MS (EI) *m/z* 135 (43%), 105 (92%), 81 (100%), 77 (76%); MS (CI) *m/z* 288.1005 (MH, 288.09975 calcd for $C_{16}H_{16}O_5$), 167, 123. Anal. Calcd for $C_{16}H_{16}O_5$: C, 66.65; H, 5.60. Found: C, 66.49; H, 5.62.

(3a*R,8a*R**)-2(*R**)-(Hydroxymethyl)-5(*S**)-(carbomethoxymethyl)tetrahydrofuro[3,2-*b*]tetrahydrofuran (13).** NaOMe (1.2 mL of a 1% solution in MeOH) was added to a solution of lactone **12** (1.2 g, 4.2 mmol) and anhydrous MeOH (40 mL). The mixture was maintained at room temperature for 12 h and then neutralized with 5% HCl and concentrated in vacuo. The resulting oil was dissolved in EtOAc (50 mL) and washed with brine (10 mL) and the aqueous layer extracted with EtOAc (3 × 10 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated, and the residue was purified on silica gel (1:2 hexanes–EtOAc) to give 748 mg (83%) of **13** as a colorless oil, 92% pure based upon integration of ^{1}H NMR signals at 2.62 and 2.77 ppm (minor component believed to be epimeric at C-5): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.78 (dt, *J* = 7.5, 3.7 Hz, H-3a), 4.53 (t, *J* = 4.7 Hz, H-6a), 4.45–4.50 (m, H-5), 3.97–4.02 (m, H-2), 3.76 (ddd, *J* = 11.6, 6.5, 3.0 Hz, 1 H, C*H*$_2$OH), 3.70 (s, 3 H, CH_3), 3.63 (dt, *J* = 11.6, 5.8 Hz, 1 H, C*H*$_2$OH), 2.62 (dd, *J* = 15.3, 6.9 Hz, 1 H, CH_2CO_2), 2.54 (dd, *J* = 15.2, 5.8 Hz, 1 H, CH_2CO_2), 2.29 (dd, *J* = 13.4, 5.0 Hz, 1 H, H-6), 2.23 (dt, *J* = 13.9, 7.0 Hz, 1 H, H-3), 1.96 (t, *J* = 6.1 Hz, OH), 1.79 (ddd, *J* = 13.5, 8.6, 3.3 Hz, 1 H, H-3), 1.64 (ddd, *J* = 13.6, 10.2, 4.9 Hz, 1 H, H-6); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.3, 84.2, 83.8, 80.3, 74.0, 64.6, 51.8, 39.5, 39.1, 35.3; IR (film) 3450, 2937, 1744, 1444 cm^{-1}; MS (CI) *m/z* 217.1078 (217.1076 calcd for $C_{10}H_{16}O_5$), 185, 167, 151, 141, 125, 111. Anal. Calcd for $C_{10}H_{16}O_5$: C, 55.54; H, 7.47. Found: C, 55.37; H, 7.46.

(3a*R,8a*R**)-2(*R**)-[1(*S**)-Hydroxy-3(*E*)-hexenyl]-5(*S**)-(carbomethoxymethyl)tetrahydrofuro[3,2-*b*]tetrahydrofuran (16).** Following the general procedure of Swern,[16] DMSO (414 mg, 376 μL, 5.3 mmol) was added to a solution of oxalyl chloride (628 mg, 432 μL, 5.0 mmol) in CH_2Cl_2 (15 mL) at −78 °C. After 20 min at −78 °C, a solution of the alcohol **13** (714 mg, 3.3 mmol) and CH_2Cl_2 (3 mL) was added dropwise, maintaining the internal temperature below −70 °C, and the resulting solution was stirred at −78 °C for 1 h. Triethylamine (1.0 g, 1.4 mL, 9.9 mmol) was added and the reaction was allowed to warm to 23 °C, diluted with ether (200 mL), filtered through Celite, and concentrated to give 733 mg of **14** as a yellow oil, which was used without further purification: ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.65 (d, *J* = 1.4 Hz, CHO), 4.70 (m, H-6a), 4.65 (m, H-3a), 4.53 (dq, *J* = 8.9, 6.3 Hz, H-5), 4.29 (ddd, *J* = 8.5, 5.1, 1.2 Hz, H-2), 3.67 (s, 3 H, OCH_3), 2.30–2.55 (m, 5 H), 1.82 (ddd, *J* = 13.9, 9.0, 4.7 Hz, 1 H, H-3).

(39) General experimental details were recently described: Fisher, M. J.; Overman, L. E. *J. Org. Chem.* **1988**, *53*, 2630. The standard abbreviations employed can be found in *J. Org. Chem.* **1992**, *57*, 14A. The *R**(*S**) nomenclature is employed to specify relative configuration of racemic intermediates.

$TiCl_4$ (6.6 mL of a 1.0 M solution in CH_2Cl_2, 6.6 mmol) was added to a solution of the crude aldehyde **14** and CH_2Cl_2 (35 mL) at −78 °C, maintaining the internal temperature below −70 °C. A solution of allyl silane **15**[8] (705 mg, 4.95 mmol) and CH_2Cl_2 (7 mL) was added dropwise and after 30 min at −78 °C, the mixture was allowed to warm to 23 °C and poured into brine (70 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 × 40 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated to an oil, and the residue was purified by column chromatography (3:1 hexane–EtOAc) to give 850 mg (91% from **13**) of **16** as a pale yellow oil (a 11.6:1 mixture of C-5 epimers by ^1H NMR analysis): ^1H NMR (300 MHz, $CDCl_3$) δ 5.54–5.63 (m, 1 H, C=CH), 5.35–5.44 (m, 1 H, C=CH), 4.73–4.79 (m, 1 H), 4.38–4.50 (m, 2 H), 3.73–3.84 (m, 2 H), 3.69 (s, 3 H, OCH_3), 2.62 (dd, J = 15.2, 6.0 Hz, 1 H, CH_2CO_2), 2.52 (dd, J = 15.2, 6.8 Hz, 1 H, CH_2CO_2), 1.92–2.31 (m, 8 H), 1.60–1.67 (m, 1 H), 0.97 (t, J = 7.4 Hz, 3 H, CH_2CH_3); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 171.3, 135.8, 124.2, 83.7, 83.6, 82.1, 73.8, 71.3, 51.8, 39.6, 39.2, 36.5, 33.4, 25.6, 13.7; IR (film) 3463, 2963, 1731, 1444, 1075, 1056 cm^{-1}; MS (CI) m/z 285.1690 (MH, 285.1702 calcd for $C_{15}H_{24}O_5$), 267, 249, 215, 186, 185, 141, 103, 81.

(3a*R,8a*R**)-2(*R**)-[1(*S**)-[[Dimethyl(1,1-dimethylethyl)-silyl]oxy]-3(*E*)-hexenyl]-5(*S**)-(carbomethoxymethyl)tetrahydrofuro[3,2-*b*]tetrahydrofuran (17).** A solution of alcohol **16** (689 mg, 2.42 mmol, a 11.6:1 mixture of isomers) and 2,6-lutidine (1.04 g, 1.09 mL, 9.68 mmol) in CH_2Cl_2 (30 mL) was cooled to 0 °C and treated with TBSOTf (1.28 g, 1.11 mL, 4.84 mmol) dropwise. After 1 h, the mixture was diluted with hexanes (100 mL), washed with 5% HCl (2 × 40 mL) and saturated $NaHCO_3$ solution (40 mL), dried ($MgSO_4$), and concentrated. The residue was purified on silica gel (15:1 hexanes–EtOAc) to give 939 mg (97%) of **17** as a colorless oil, which was 92% pure based upon integration of ^1H NMR signals at 2.61 and 2.74 ppm (a minor component believed to be epimeric at C-5): ^1H NMR (500 MHz, $CDCl_3$) δ 5.48 (dt, J = 13.7, 6.9 Hz, 1 H, C=CH), 5.38 (dt, J = 14.5, 7.3 Hz, 1 H, C=CH), 4.74–4.77 (m, 1 H, H-3a), 4.40–4.43 (m, 2 H), 3.81–3.85 (m, 1 H), 3.69 (s, 3 H, OCH_3), 3.63–3.67 (m, 1 H), 2.61 (dd, J = 15.1, 7.0 Hz, 1 H, CH_2CO_2), 2.51 (dd, J = 15.1, 6.0 Hz, 1 H, CH_2CO_2), 2.11–2.22 (m, 4 H), 2.00 (quintet, J = 7.1 Hz, 2 H), 1.84–1.90 (m, 1 H), 1.50–1.54 (m, 1 H), 0.96 (t, J = 7.5 Hz, 3 H, CH_2CH_3), 0.90 (s, 9 H, $C(CH_3)_3$), 0.07 (s, 3 H, $SiCH_3$), 0.06 (s, 3 H, $SiCH_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.3, 134.7, 124.7, 83.7, 83.2, 81.9, 73.3, 72.5, 51.7, 39.5, 38.2, 34.2, 25.9, 25.9, 25.6, 18.1, 13.6, −4.3; IR (film) 2958, 1745, 1473, 1463, 1437, 1254, 1160, 1077, 837 cm^{-1}; MS (EI) m/z 341 (14%), 239 (11%), 213 (17%), 185 (12%). 153 (36%), 141 (45%), 81 (43%), 75 (71%), 73 (100%); MS (CI) m/z 399.2549 (MH, 399.2566 calcd for $C_{21}H_{38}O_5Si$), 341, 329, 267, 185, 141. Anal. Calcd for $C_{21}H_{38}O_5Si$: C, 63.26; H, 9.63. Found: C, 63.36; H, 9.60.

(3a*R,8a*R**)-2(*R**)-[1(*S**)-[(4-Nitrobenzoyl)oxy]-3(*E*)-hexenyl]-5(*S**)-(carbomethoxymethyl)tetrahydrofuro[3,2-*b*]-tetrahydrofuran (18).** 4-Nitrobenzoyl chloride (15.8 mg, 0.086 mmol) was added to a solution of the alcohol **16** (10.0 mg, 0.034 mmol) in pyridine (0.5 mL). The reaction was maintained at 23 °C for 30 min then concentrated to a solid. Purification by column chromatography (1:1 hexane–EtOAc) gave 9.0 mg (58%) of **18** as an oil, which solidified under vacuum. This solid was recrystallized from 1:1 hexane–EtOAc to give X-ray-quality crystals: mp 58–59 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 8.30 (d, J = 8.9 Hz, 2 H, ArH), 8.24 (d, J = 8.9 Hz, 2 H, ArH), 5.51–5.59 (m, 1 H), 5.34–5.43 (m, 2 H), 4.75–4.81 (m, 1 H), 4.47 (t, J = 4.6 Hz, 1 H), 4.26–4.34 (m, 1 H), 3.98–4.09 (m, 1 H), 3.68 (s, 3 H, OCH_3), 1.90–2.60 (m, 9 H), 1.50–1.61 (m, 1 H), 0.87 (t, J = 7.4 Hz, 3 H, CH_2CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.1, 164.1, 136.3, 135.7, 130.8, 123.6, 123.5, 122.9, 83.9, 83.3, 80.0, 74.6, 73.7, 51.7, 39.3, 38.9, 34.8, 34.2, 25.5, 13.6; IR (film) 2950, 1725, 1537, 1281 cm^{-1}; MS (CI) m/z 434 (MH), 404, 267, 185, 138, 81.

The authors have deposited atomic coordinates for the X-ray structure of **18** with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

(3a*R,8a*R**)-2(*R**)-[1(*S**)-[[Dimethyl(1,1-dimethylethyl)-silyl]oxy]-3(*E*)-hexenyl]tetrahydrofuro[3,2-*b*]tetrahydrofuran-5(*S**)-acetic acid (19).** LiOH (13.9 mL of a 1 N aqueous solution, 13.9 mmol) was added to a solution of ester **17** (1.85 g, 4.63 mmol, a 11.9:1 mixture of isomers) in THF (46 mL) and the mixture stirred at room temperature for 5 h. After dilution with Et_2O (200 mL) and H_2O (60 mL), the mixture was brought carefully to pH 5 with 1 M $NaHSO_4$ with vigorous stirring. The layers were separated and the aqueous layer was washed with Et_2O (3 × 200 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated to give 1.75 g (99%) of **19** as a viscous oil, which solidified upon standing. ^1H NMR analysis indicated the presence of one additional compound (<10%, minor component believed to be epimeric at C-5): ^1H NMR (300 MHz, $CDCl_3$) δ 5.47 (dt, J = 15.4, 5.8 Hz, 1 H, C=CH), 5.35 (dt, J = 15.4, 7.0 Hz, 1 H, C=CH), 4.78 (dt, J = 8.0, 4.6 Hz, H-3a), 4.43 (t, J = 4.9 Hz, H-6a), 4.39 (m, H-5), 3.81 (td, J = 5.7, 4.3 Hz, H-2), 3.65 (m, 1 H, CHOTBS), 2.60 (m, 2 H, CH_2CO_2H), 1.80–2.25 (m, 7 H), 1.53 (ddd, J = 13.3, 10.6, 5.1 Hz, 1 H, H-6), 0.94 (t, J = 7.5 Hz, 3 H, CH_2CH_3), 0.87 (s, 9 H, $C(CH_3)_3$), 0.04 (s, 6 H, $Si(CH_3)_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.5, 134.6, 124.6, 83.7, 83.1, 81.9, 73.1, 72.4, 39.3, 39.1, 38.2, 34.0, 25.8, 25.6, 18.1, 13.6, −4.3, −4.5; IR (film) 3000–3200, 2960, 1735, 1716, 1434, 1256, 1072, 837 cm^{-1}; MS (EI) m/z 327 (13%), 315 (15%), 213 (25%), 139 (49%), 127 (32%), 75 (72%), 73 (100%); MS (CI) m/z 385.2425 (MH, 385.2411 calcd for $C_{20}H_{36}O_5Si$), 253, 171, 133. Anal. Calcd for $C_{20}H_{36}O_5Si$: C, 62.45; H, 9.45. Found: C, 62.47; H, 9.37.

(3a*R,8a*R**)-2(*R**)-[1(*S**)-[[Dimethyl(1,1-dimethylethyl)-silyl]oxy]-3(*E*)-hexenyl]-5(*S**)-(hydroxymethyl)tetrahydrofuro[3,2-*b*]tetrahydrofuran (22).** *N*-Hydroxy-4-methylthiazolinethione (**20**)[25] (368 mg, 2.5 mmol), DMAP (25 mg, 0.2 mmol), and DCC (515 mg, 2.5 mmol) were added sequentially to a solution of carboxylic acid **19** (800 mg, 2.08 mmol, a >11:1 mixture of isomers) in CH_2Cl_2 (30 mL) in a foil-wrapped flask at room temperature. After 2 h, the mixture was filtered through Celite (Et_2O) and concentrated, and the residue was purified on silica gel (3:1 hexanes–EtOAc) to give 1.07 g (100%) of **21** as a colorless solid, which was used without further purification: ^1H NMR (300 MHz, $CDCl_3$) δ 6.20 (broad s, 1 H, C=CHS), 5.46 (dt, J = 15.4, 5.9 Hz, 1 H, C=CH), 5.40 (dt, J = 15.4, 6.9 Hz, 1 H, C=CH), 4.76 (m, H-3a), 4.43–4.53 (m, 2 H, H-5, H-6a), 3.80 (m, H-2), 3.65 (ddd, J = 9.8, 5.9, 4.6 Hz, 1 H, CHOTBS), 2.80–3.10 (m, 2 H, CH_2CO_2), 1.55–2.20 (m, 8 H), 2.15 (d, J = 0.8 Hz, 3 H, CH_3C=C), 0.94 (t, J = 7.5 Hz, 3 H, CH_2CH_3), 0.84 (s, 9 H, $C(CH_3)_3$), 0.04 (s, 6 H, $Si(CH_3)_2$).

A tared flask was charged with $Sb(SPh)_3$[27] (3.0 g) under N_2 and the yellow crystals were washed with anhydrous methanol (3 × 10 mL) and dried in vacuo. The $Sb(SPh)_3$ was reweighed (2.74 g, 6.1 mmol) and suspended in Et_2O (80 mL) and a solution of mixed anhydride **21** (1.07 g, 2.08 mmol) in dry Et_2O (60 mL) was added. After 5 min, the flask was opened and the resulting yellow suspension was stirred in an open flask for 24 h. A white precipitate was removed by filtration through a pad of Celite (Et_2O) and the resulting yellow liquid was washed with 10% K_2CO_3 solution. The aqueous layer was washed with Et_2O (50 mL), the combined organic extracts were dried ($MgSO_4$) and concentrated, and the residue was purified on silica gel (1:1 hexanes–Et_2O). The chromatography fractions were combined, washed with additional 10% K_2CO_3 (50 mL) solution, dried ($MgSO_4$), and concentrated to give 581 mg (78% overall from **19**) of **22** as a clear colorless oil, that was homogeneous by TLC analysis: ^1H NMR (300 MHz, $CDCl_3$) δ 5.47 (dt, J = 15.4, 5.8 Hz, 1 H, C=CH), 5.36 (dt, J = 15.4, 7.0 Hz, 1 H, C=CH), 4.72 (dt, J = 7.7, 4.3 Hz, H-3a), 4.43 (t, J = 5.0 Hz, H-6a), 4.19 (m, H-5), 3.80 (m, 2 H), 3.66 (ddd, J = 9.5, 6.1, 4.5 Hz, 1 H, CHOTBS), 3.50 (dd, J = 11.7, 4.3 Hz, 1 H, CH_2OH), 1.70–2.22 (m, 9 H), 0.94 (t, J = 7.4 Hz, 3 H, CH_2CH_3), 0.87 (s, 9 H, $C(CH_3)_3$), 0.04 (s, 6 H, $Si(CH_3)_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 134.6, 124.7, 83.9, 83.7, 82.0, 78.0, 72.7, 63.5, 38.1, 34.6, 34.4, 25.8, 25.6, 18.1, 13.6, −4.3, −4.4; IR (film) 3448, 2958, 1473, 1463, 1439, 1254, 1072, 836 cm^{-1}; MS (EI) m/z 299 (20%), 251 (35%), 213 (24%), 111 (28%), 73 (100%); MS (CI) m/z 357.2450 (MH, 357.2462 calcd for $C_{19}H_{36}O_4Si$) 225, 143, 132. Anal. Calcd for $C_{19}H_{36}O_4Si$: C, 63.98; H, 10.20. Found: C, 63.89; H, 10.13.

(3a*R,8a*R**)-2(*R**)-[1(*S**)-[[Dimethyl(1,1-dimethylethyl)-silyl]oxy]-3(*E*)-hexenyl]-5(*S**)-[1(*R**)-hydroxy-3-(trimethylsilyl)-2-propynyl]tetrahydrofuro[3,2-*b*]tetrahydrofuran (24a) and (3a*R**,8a*R**)-2(*R**)-[1(*S**)-[[Dimethyl(1,1-dimethylethyl)silyl]oxy]-3(*E*)-hexenyl]-5(*S**)-[1(*S**)-hydroxy-3-(trimethylsilyl)-2-propynyl]tetrahydrofuro[3,2-**

b]tetrahydrofuran (24b). DMSO (110 mg, 100 μL, 1.4 mmol) was added dropwise to a solution of oxalyl chloride (142 mg, 98 μL, 1.12 mmol) in CH_2Cl_2 (10 mL) at −78 °C. After 30 min, a solution of alcohol **22** (200 mg, 0.56 mmol) in CH_2Cl_2 (2.5 mL) was added dropwise and the mixture was maintained at −78 °C for 1 h. Triethylamine (228 mg, 314 μL, 2.25 mmol) was then added and the reaction allowed to warm to room temperature and then was diluted with dry Et_2O (125 mL). The resulting suspension was filtered through Celite under N_2, rinsing with additional Et_2O (30 mL), and concentrated in vacuo to give 231 mg of crude aldehyde **23** as a light yellow oil, which was used without further purification: ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.64 (d, *J* = 2.0 Hz, CHO), 5.30–5.50 (m, 2 H, CH=CH), 4.80 (m, H-3a), 4.44 (m, 2 H, H-5, H-6a), 3.70–3.80 (m, 2 H, H-2, CHOTBS), 2.31 (dd, *J* = 13.6, 6.4 Hz, 1 H), 1.80–2.21 (m, 7 H), 0.94 (t, *J* = 7.5 Hz, 3 H, CH_2CH_3), 0.87 (s, 9 H, $C(CH_3)_3$), 0.05 (s, 6 H, $Si(CH_3)_2$).

A solution of (trimethylsilyl)acetylene (217 mg, 312 μL, 2.21 mmol) in THF (5 mL) was cooled to 0 °C and treated with *n*-BuLi (686 μL of a 2.42 M solution in hexanes, 1.66 mmol). After 10 min, the reaction was cooled to −78 °C and treated with $ClTi(Oi\text{-}Pr)_3$ (1.66 mL of a 1.0 M solution of hexanes, 1.66 mmol) and the resulting solution maintained at that temperature for 30 min.

The crude aldehyde prepared above (228 mg, 0.55 mmol) was dissolved in THF (10 mL), cooled to −78 °C, and treated with $TiCl_4$ (420 mg, 243 μL, 2.21 mmol) to give a bright yellow slurry. The solution of the titanium acetylide was then added slowly via cannula and the mixture stirred at −78 °C for 2.5 h and then allowed to warm gradually to −23 °C overnight. The reaction was then warmed to room temperature and poured into a mixture of Et_2O (25 mL) and saturated $NaHCO_3$ solution (50 mL). The layers were separated, the aqueous slurry was extracted with Et_2O (3 × 25 mL), and the combined organic layers were dried ($MgSO_4$) and concentrated. Purification of the residue on silica gel (5:1 hexane–Et_2O) gave 198 mg (77%) of a mixture of four diastereomers. HPLC analysis indicated that the two most abundant isomers were present in a ration of >3.1:1. Preparative HPLC (HR silica, 60 μM, 10:1 hexane–EtOAc) gave 128 mg (51%) of **24a** as a colorless oil, which solidified upon standing, 24.4 mg (10%) of **24b** as a colorless oil, and 39.6 mg (16%) of mixed isomers (**24b** plus C-5 epimers).

Data for **24a**: mp 40–42 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.47 (dt, *J* = 15.4, 6.2 Hz, 1 H, C=CH), 5.37 (dt, *J* = 15.4, 6.9 Hz, 1 H, C=CH), 4.76 (dt, *J* = 7.6, 3.9 Hz, H-3a), 4.51 (dd, *J* = 4.4, 3.4 Hz, C≡CHOH), 4.44 (t, *J* = 4.8 Hz, H-6a), 4.27 (ddd, *J* = 9.8, 5.6, 3.4 Hz, H-5), 3.81 (td, *J* = 5.6, 4.6 Hz, H-2), 3.71 (ddd, *J* = 9.1, 6.4, 4.5 Hz, CHOTBS), 2.18 (d, *J* = 4.7 Hz, OH), 1.91–2.17 (m, 8 H), 0.95 (t, *J* = 7.5 Hz, 3 H, CH_2CH_3), 0.88 (s, 9 H, $C(CH_3)_3$), 0.14 (s, 9 H, $Si(CH_3)_3$), 0.06 (s, 3 H, $SiCH_3$), 0.05 (s, 3 H, $SiCH_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 134.7, 124.7, 102.7, 90.9, 84.8, 83.5, 82.1, 80.3, 72.6, 63.4, 38.1, 34.3, 33.0, 25.9, 25.6, 18.1, 13.6, −0.2, −4.3, −4.4; IR (film) 3419, 2958, 2175, 1473, 1463, 1251, 1073, 1030, 842 cm^{-1}; MS (EI) *m*/*z* 323 (2%), 311 (5%), 275 (4%), 213 (13%), 81 (35%), 75 (67%), 73 (100%); MS (CI) *m*/*z* 453.2834 (MH, 453.2857 calcd for $C_{24}H_{44}O_4Si_2$), 395, 383, 321, 303, 239, 191, 175. Anal. Calcd for $C_{24}H_{44}O_4Si_2$: C, 63.65; H, 9.81. Found: C, 63.79; H, 9.80.

Data for **24b**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.47 (dt, *J* = 15.3, 6.2 Hz, 1 H, C=CH), 5.37 (dt, *J* = 15.3, 7.1 Hz, 1 H, C=CH), 4.72 (dt, *J* = 7.6, 3.9 Hz, H-3a), 4.42 (t, *J* = 4.9 Hz, H-6a), 4.21 (m, 2 H, C≡CHOH and H-5), 3.80 (td, *J* = 5.6, 4.8 Hz, H-2), 3.67 (ddd, *J* = 9.0, 6.4, 4.5 Hz, CHOTBS), 2.31 (d, *J* = 4.1 Hz, OH), 1.94–2.17 (m, 7 H), 1.76 (ddd, *J* = 13.5, 9.0, 5.1 Hz, 1 H), 0.94 (t, *J* = 7.5 Hz, 3 H, CH_2CH_3), 0.88 (s, 9 H, $C(CH_3)_3$), 0.14 (s, 9 H, $Si(CH_3)_3$), 0.06 (s, 3 H, $SiCH_3$), 0.04 (s, 3 H, $SiCH_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 134.6, 124.7, 103.4, 90.4, 84.6, 83.5, 82.2, 80.8, 72.5, 65.0, 38.1, 35.7, 34.2, 25.9, 25.6, 18.1, 13.6, −0.3, −4.2, −4.4; IR (film) 3427, 2958, 2175, 1473, 1463, 1436, 1251, 1074, 842 cm^{-1}; MS (EI) *m*/*z* 323 (9%), 311 (15%), 275 (20%), 213 (23%), 119 (27%), 81 (39%), 75 (74%), 73 (100%); MS (CI) *m*/*z* 453.2822 (MH, 453.2857 calcd for $C_{24}H_{44}O_4Si_2$), 395, 383, 321, 303, 239, 191, 175. Anal. Calcd for $C_{24}H_{44}O_4Si_2$: C, 63.65; H, 9.81. Found: C, 63.52; H, 9.79.

Preparation of (3a*R,8a*R**)-2(*R**)-[1(*S**)-[[Dimethyl(1,1-dimethylethyl)silyl]oxy]-3(*E*)-hexenyl]-5(*S**)-[1(*R**)-[(4-nitobenzoyl)oxy]-3-(trimethylsilyl)-2-propynyl]tetrahydrofuro[3,2-*b*]tetrahydrofuran (26) from 24a.** A solution of alcohol **24a** (15.5 mg, 34 μmol) in pyridine (0.5 mL) was treated with 4-nitrobenzoyl chloride (15.8 mg, 86 μmol) at room temperature. After 30 min, the solution was concentrated in vacuo and the residue washed with ether and filtered through Celite. After concentration, the resultant white solid was purified by preparative TLC (4:1 hexanes–EtOAc) to give 19.7 mg (96%) of **26** as a white solid: H NMR (500 MHz, $CDCl_3$) 8.29 (d, *J* = 8.8 Hz, 2 H, ArH), 8.23 (d, *J* = 8.8 Hz, 2 H, ArH), 5.84 (d, *J* = 2.8 Hz, CHOPNBz), 5.48 (dt, *J* = 15.3, 6.3 Hz, 1 H, C=CH), 5.37 (dt, *J* = 15.3, 7.1 Hz, 1 H, C=CH), 4.76 (dt, *J* = 7.4, 3.8 Hz, H-3a), 4.48 (m, 2 H, H-6a and H-5), 3.83 (td, *J* = 5.7, 4.3 Hz, H-2), 3.75 (m, CHOTBS), 2.30 (dd, *J* = 13.4, 5.5 Hz, 1 H), 1.97–2.17 (m, 7 H), 0.96 (t, *J* = 7.4 Hz, 3 H, CH_2CH_3), 0.87 (s, 9 H, $C(CH_3)_3$), 0.17 (s, 9 H, $Si(CH_3)_3$), 0.07 (s, 3 H, $SiCH_3$), 0.05 (s, 3 H, $SiCH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.4, 150.7, 135.2, 134.7, 131.0, 124.6, 123.5, 98.5, 92.8, 85.2, 83.1, 82.3, 78.8, 72.4, 66.4, 38.1, 34.4, 34.1, 25.8, 25.6, 18.1, 13.6, −0.3, −4.3, −4.4; IR (film) 2959, 1812, 1736, 1533, 1473, 1463, 1347, 1269, 1100, 842 cm^{-1}; MS (CI) *m*/*z* 602.2935 (MH, 602.2970 calcd for $C_{31}H_{47}NO_7Si_2$), 138, 133.

Preparation of 26 from 24b. A solution of alcohol **24b** (6.8 mg, 18 μmol) in THF (0.5 mL) was treated sequentially with Ph_3P (47 mg, 180 μmol), 4-nitrobenzoic acid (30 mg, 180 μmol), and DEAD (31 mg, 28 μL, 180 μmol) at room temperature. After 3 h, the mixture was diluted with hexanes (5 mL), filtered through Celite, and concentrated. The remnant was purified by preparative TLC (20:1 hexanes–EtOAc) to give 7.6 mg (80%) of **26** as a viscous oil, whose spectral characteristics were identical to **26** prepared from **24a**.

(3a*R,8a*R**)-2(*R**)-[1(*S**)-[[Dimethyl(1,1-dimethylethyl)silyl]oxy]-3(*E*)-hexenyl]-5(*S**)-[1(*R**)-hydroxy-2-propynyl]tetrahydrofuro[3,2-*b*]tetrahydrofuran (25a).** A solution of alcohol **24a** (228 mg, 0.50 mmol) in methanol (7.5 mL) cooled to 0 °C was stirred over K_2CO_3 (350 mg) for 2 h. The mixture was then warmed to room temperature, diluted with Et_2O (150 mL), filtered through Celite, and concentrated. Purification of the residue on silica gel (4:1 hexanes–EtOAc) gave 175 mg (92%) of **25a** as a clear, colorless oil that was homogeneous by TLC analysis: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.47 (dt, *J* = 15.4, 5.8 Hz, 1 H, C=CH), 5.36 (dt, *J* = 15.4, 6.9 Hz, 1 H, C=CH), 4.77 (dt, *J* = 7.6, 3.9 Hz, H-3a), 4.49 (m, C≡C*H*OH), 4.44 (t, *J* = 4.9 Hz, H-6a), 4.28 (ddd, *J* = 9.8, 5.6, 3.6 Hz, H-5), 3.79 (td, *J* = 5.6, 4.8 Hz, H-2), 3.71 (m, CHOTBS), 2.42 (d, *J* = 2.2 Hz, C≡CH), 2.24 (d, *J* = 5.1 Hz, OH), 1.88–2.20 (m, 8 H), 0.94 (t, *J* = 7.5 Hz, 3 H, CH_2CH_3), 0.87 (s, 9 H, $C(CH_3)_3$), 0.05 (s, 3 H, $SiCH_3$), 0.04 (s, 3 H, $SiCH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 134.6, 124.6, 84.8, 83.5, 82.1, 81.3, 80.3, 74.0, 72.6, 63.0, 38.0, 34.5, 33.3, 25.8, 25.6, 18.1, 13.6, −4.4; IR (film) 3419, 2958, 1473, 1463, 1255, 1074, 836 cm^{-1}; MS (EI) *m*/*z* 323 (13%), 311 (28%), 275 (20%), 213 (29%), 119 (26%), 81 (39%), 75 (71%), 73 (100%); MS (CI) *m*/*z* 381.2441 (MH, 381.2462 calcd for $C_{21}H_{36}O_4Si$), 323, 311, 249, 167. Anal. Calcd for $C_{21}H_{36}O_4Si$: C, 66.26; H, 9.55. Found: C, 66.09; H, 9.59.

(3a*R,8a*R**)-2(*R**)-[1(*S**)-[[Dimethyl(1,1-dimethylethyl)silyl]oxy]-3(*E*)-hexenyl]-5(*S**)-[(*R**)-3-bromo-1,2-propadienyl]tetrahydrofuro[3,2-*b*]tetrahydrofuran (28a).** A solution of alcohol **25a** (100 mg, 0.26 mmol), DMAP (112 mg, 0.92 mmol), and 2,4,6-triisopropylbenzenesulfonyl chloride (199 mg, 0.66 mmol) in CH_2Cl_2 (4 mL) was stirred at 40 °C for 1 h. After cooling to room temperature, the mixture was diluted with Et_2O (40 mL), filtered through Celite, and concentrated in vacuo. The resulting viscous oil was purified rapidly on silica gel (25:1 hexanes–EtOAc) to give 163 mg (96%) of trisylate **27a**, which was used immediately: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.15 (s, 2 H, ArH), 5.48 (dt, *J* = 15.3, 6.2 Hz, 1 H, C=CH), 5.37 (dt, *J* = 15.3, 7.2 Hz, 1 H, C=CH), 5.26 (dd, *J* = 3.6, 2.4 Hz, $CHOSO_2$), 4.70 (dt, *J* = 7.4, 3.7 Hz, H-3a), 4.41 (t, *J* = 4.8 Hz, H-6a), 4.37 (ddd, *J* = 9.4, 5.5, 3.9 Hz, H-5), 4.14 (septet, *J* = 6.7 Hz, 2 H, $CH(CH_3)_2$), 3.78 (td, *J* = 5.5, 4.9 Hz, H-2), 3.71 (m, CHOTBS), 2.90 (septet, *J* = 6.9 Hz, 1 H, $CH(CH_3)_2$), 2.30 (d, *J* = 2.1 Hz, C≡CH), 2.23 (dd, *J* = 13.6, 5.9 Hz, 1 H), 1.92–2.17 (m, 7 H), 1.26 (m, 18 H, $CH(CH_3)_2$), 0.96 (t, *J* = 7.4 Hz, 3 H, CH_2CH_3), 0.87 (s, 9 H, $C(CH_3)_3$), 0.05 (s, 6 H, $Si(CH_3)_2$).

The trisylate prepared above (163 mg, 0.25 mmol) was dissolved in THF (2 mL) and treated with $LiCuBr_2$[31] (2.0 mL of a 0.25 M solution in THF, 0.5 mmol). The reaction was heated to 60 °C

and after 4.5 h at that temperature an additional portion of $LiCuBr_2$ (500 μL, 0.125 mmol) was added. After 2 h, the reaction was cooled to room temperature, quenched with saturated NH_4Cl solution (10 mL), and extracted with Et_2O (3 × 10 mL). The combined organic extracts were dried ($MgSO_4$), concentrated, and purified on $AgNO_3$-impregnated silica gel (40:1 hexanes–Et_2O) to provide 85.2 mg (77%, 73% overall from **25a**) of **28a** as a colorless oil (>95% pure by GLC analysis). Analysis by ^1H NMR indicated the presence of a trace amount of the isomeric bromoallene (ratio >15:1): ^1H NMR (500 MHz, $CDCl_3$) δ 6.04 (dd, J = 5.7, 1.5 Hz, 1 H, C=C=CHBr), 5.47 (dt, J = 15.4, 6.2 Hz, 1 H, C=CH), 5.42 (t, J = 5.9 Hz, 1 H, C=C=CH), 5.36 (dt, J = 15.3, 6.9 Hz, 1 H, C=CH), 4.76 (dt, J = 7.8, 4.5 Hz, H-3a), 4.65 (m, H-5), 4.43 (t, J = 5.1 Hz, H-6a), 3.81 (td, J = 5.7, 4.4 Hz, H-2), 3.67 (ddd, J = 10.0, 5.9, 4.2 Hz, CHOTBS), 2.20 (dd, J = 13.5, 5.0 Hz, 1 H), 2.10–2.18 (m, 3 H), 1.98 (quintet, J = 6.8 Hz, 2 H, CH_2CH_3), 1.89 (ddd, J = 13.5, 9.7, 3.9 Hz, 1 H), 1.69 (ddd, J = 13.3, 9.8, 5.2 Hz, 1 H), 0.94 (t, J = 7.5 Hz, 3 H, CH_2CH_3), 0.88 (s, 9 H, $C(CH_3)_3$), 0.04 (s, 6 H, $Si(CH_3)_2$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.7, 134.7, 124.6, 100.7, 84.0, 83.1, 82.1, 73.8, 73.7, 72.5, 39.6, 38.2, 34.1, 25.9, 25.6, 18.1, 13.6, −4.3, −4.4; IR (film) 3063, 2958, 1962, 1473, 1463, 1252, 1083, 836 cm^{-1}; MS (EI) m/z 213 (10%), 199 (12%), 197 (11%), 129 (13%), 75 (86%), 73 (100%); MS (CI) m/z 387.0787 ((M − C_4H_9), 387.0815 calcd for $C_{17}H_{26}{}^{81}BrO_3Si$), 385.0821 ((M − C_4H_9), 385.0835 calcd for $C_{17}H_{26}{}^{79}BrO_3Si$).

(3a*R,8a*R**)-2(*R**)-[1(*S**)-Hydroxy-3(*E*)-hexenyl]-5(*S**)-[(*R**)-3-bromo-1,2-propadienyl]tetrahydrofuro[3,2-*b*]tetrahydrofuran (29a).** A solution of bromoallene **28a** (57.7 mg, 0.13 mmol) in CH_3CN (6 mL) was treated with HF–pyridine complex (2 mL) dropwise. After 1.5 h, the mixture was diluted with Et_2O (30 mL) and quenched carefully with saturated $NaHCO_3$ solution (30 mL). The layers were separated, the aqueous layer was washed with Et_2O (20 mL), and the combined organic layers were washed with 10% HCl (30 mL). The acidic aqueous layer was also washed with Et_2O (20 mL) and the combined organic layers were then washed with saturated $NaHCO_3$ solution (30 mL). The aqueous layer was again extracted with Et_2O (20 mL), and combined organic extracts were dried ($MgSO_4$) and concentrated, and the residue was purified on silica gel (5:1 hexanes–EtOAc) to give 41.6 mg (97%) of **29a** contaminated with a small amount (^1H NMR ratio >15:1) of the isomeric bromoallene **29b**. Preparative HPLC (4:1 hexane–EtOAc) gave 35.2 mg (82%) of **29a** as a colorless oil (pure by GLC analysis), and 2.1 mg (5%) of **29b**.

Data for **29a**: ^1H NMR (500 MHz, $CDCl_3$) δ 6.05 (dd, J = 5.7, 1.3 Hz, 1 H, C=C=CHBr), 5.57 (dt, J = 15.3, 6.2 Hz, 1 H, C=CH), 5.43 (t, J = 5.8 Hz, 1 H, C=C=CH), 5.38 (dt, J = 15.3, 7.0 Hz, 1 H, C=CH), 4.76 (dt, J = 7.4, 3.8 Hz, H-3a), 4.69 (m, H-5), 4.49 (t, J = 4.7 Hz, H-6a), 3.80 (m, 2 H, H-2 and CHOH), 2.28 (dd, J = 13.5, 5.4 Hz, 1 H), 1.96–2.19 (m, 7 H), 1.78 (ddd, J = 13.5, 9.3, 4.7 Hz, 1 H), 0.95 (t, J = 7.5 Hz, 3 H, CH_2CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.5, 134.9, 124.1, 100.8, 84.0, 83.7, 82.4, 74.2, 74.0, 71.3, 39.4, 36.6, 33.3, 25.6, 13.7; IR (film) 3448, 3073, 2959, 1963, 1457, 1438, 1083, 1054, 969 cm^{-1}; MS (CI) m/z 331.0743 (MH, 331.0732 calcd for $C_{15}H_{21}{}^{81}BrO_3$), 329.0719 (MH, 329.0752 calcd for $C_{15}H_{21}{}^{79}BrO_3$), 313, 311, 185, 149, 119, 85.

(±)-Kumausallene (1a). A solution of freshly sublimed CBr_4 (730 mg, 2.20 mmol) in CH_2Cl_2 (3 mL) was degassed under N_2 for 30 min and then filtered through a short column of basic alumina, rinsing the flask and column with CH_2Cl_2 (2 × 2 mL). The resulting solution (final volume: 6 mL, 0.31 M in CBr_4) was stirred over anhydrous K_2CO_3 until use.

A solution of alcohol **29a** (19.6 mg, 59.5 μmol), 2,6-di-*tert*-butylpyridine (45.5 mg, 53.4 μL, 238 μmol), and Ph_3P (62.4 mg, 238 μmol) in benzene (2.8 mL) was treated with CBr_4 (758 μL of the solution prepared above, 238 μmol). After 10 min, the mixture was heated to 40 °C for 30 min; then cooled to room temperature, and applied directly to a silica gel column and eluted with 20:1 hexanes–EtOAc. The eluant was concentrated and purified by preparative TLC (40:20:1 hexane–CH_2Cl_2–EtOAc) to give 6.0 mg (26%) of **1a** as a clear, colorless oil, and 1.7 mg (9%) of **30a** as the only isolable products.

Data for **1a**: ^1H NMR (500 MHz, $CDCl_3$) δ 6.08 (dd, J = 5.7, 1.5 Hz, 1 H, C=C=CHBr), 5.60 (dt, J = 15.2, 6.2 Hz, 1 H, C=CH), 5.46 (t, J = 5.9 Hz, 1 H, C=C=CH), 5.46 (m, 1 H, C=CH), 4.83 (dt, J = 7.7, 3.9 Hz, H-7), 4.75 (dtd, J = 9.8, 5.0, 1.1 Hz, H-4), 4.55 (t, J = 4.8 Hz, H-6), 4.01 (dt, J = 8.2, 5.3 Hz, CHBr), 3.91 (dt, J = 9.3, 6.2 Hz, H-9), 2.64 (dt, J = 14.8, 5.6 Hz, 1 H, $CHBrCH_2$), 2.53 (dt, J = 14.8, 7.6 Hz, 1 H, $CHBrCH_2$), 2.36 (dd, J = 13.5, 5.6 Hz, H-5a), 2.34 (dt, J = 14.1, 7.1 Hz, H-8a), 2.04 (quintet, J = 7.1 Hz, 2 H, CH_2CH_3), 1.88 (ddd, J = 13.7, 9.6, 3.6 Hz, H-8b), 1.76 (ddd, J = 13.6, 9.8, 4.9 Hz, H-5b), 0.99 (t, J = 7.4 Hz, 3 H, CH_2CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.6, 136.0, 124.5, 100.7, 83.9, 83.7, 81.8, 74.2, 73.9, 57.1, 39.5, 38.4, 37.8, 25.6, 13.7; IR (film) 3056, 2959, 1963, 1458, 1436, 1256, 1199, 1081, 969, 927, 838 cm^{-1}; MS (EI) m/z 313 (1%), 311 (1%), 275 (2%), 273 (2%), 231 (6%), 229 (6%), 149 (21%), 107 (40%), 81 (74%), 55 (100%); MS (CI) m/z 394.9896 (MH, 394.9868 calcd for $C_{15}H_{20}{}^{81}Br_2O_2$), 392.9905 (MH, 392.9888 calcd for $C_{15}H_{20}{}^{81}Br^{79}BrO_2$), 390.9914 (MH, 390.9908 calcd for $C_{15}H_{20}{}^{79}Br_2O_2$), 313, 311.

Data for **30a**: ^1H NMR (500 MHz, $CDCl_3$) δ 6.21 (dd, J = 15.2, 10.3 Hz, 1 H, C=CH), 6.07 (dd, J = 5.8, 1.6 Hz, 1 H, C=C=CHBr), 6.02 (dd, J = 15.2, 10.6 Hz, 1 H, C=CH), 5.76 (dt, J = 15.1, 6.7 Hz, 1 H, C=CHCH$_2$), 5.62 (dd, J = 15.1, 7.5 Hz, 1 H, C=CHCHO), 5.46 (t, J = 5.9 Hz, 1 H, C=C=CH), 4.80 (dt, J = 7.4, 4.1 Hz, H-3a), 4.70 (m, H-5), 4.51 (t, J = 4.8 Hz, H-6a), 4.24 (dt, J = 8.8, 7.0 Hz, H-2), 2.39 (dt, J = 13.8, 6.9 Hz, 1 H), 2.29 (dd, J = 13.3, 5.2 Hz, 1 H), 2.10 (m, 2 H, CH_2CH_3), 1.75 (m, 2 H), 1.00 (t, J = 7.5 Hz, 3 H, CH_2CH_3).

(3a*R,8a*R**)-2(*R**)-[1(*S**)-[[Dimethyl(1,1-dimethylethyl)-silyl]oxy]-3(*E*)-hexenyl]-5(*S**)-[1(*S**)-hydroxy-2-propynyl]-tetrahydrofuro[3,2-*b*]tetrahydrofuran (25b).** Following the procedure described for the preparation of **25a**, alcohol **24b** (55.4 mg, 0.12 mmol) was desilylated with K_2CO_3 (120 mg) in methanol (2 mL) to give, after purification on silica gel (5:1 hexanes–EtOAc), 41.2 mg (89%) of **25b** as a clear, colorless oil that was homogeneous by TLC analysis: ^1H NMR (300 MHz, $CDCl_3$) δ 5.49 (dt, J = 15.5, 6.2 Hz, 1 H, C=CH), 5.39 (dt, J = 15.4, 6.8 Hz, 1 H, C=CH), 4.76 (dt, J = 7.4, 4.1 Hz, H-3a), 4.45 (t, J = 4.9 Hz, H-6a), 4.26 (m, 2 H, H-5 and C≡CHOH), 3.82 (td, J = 5.6, 4.8 Hz, H-2), 3.72 (ddd, J = 9.2, 6.2, 4.4 Hz, CHOTBS), 2.47 (d, J = 1.7 Hz, C≡CH), 2.31 (broad s, OH), 1.96–2.19 (m, 7 H), 1.84 (ddd, J = 13.6, 9.0, 5.0 Hz, 1 H), 0.96 (t, J = 7.4 Hz, 3 H, CH_2CH_3), 0.90 (s, 9 H, $C(CH_3)_3$), 0.08 (s, 3 H, $SiCH_3$), 0.07 (s, 3 H, $SiCH_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 134.7, 124.6, 84.6, 83.5, 82.2, 82.0, 80.6, 73.6, 72.6, 64.0, 38.1, 35.1, 34.4, 25.9, 25.6, 18.1, 13.6, −4.4, −4.4; IR (film) 3428, 3311, 2935, 2119, 1473, 1463, 1254, 1075, 837 cm^{-1}; MS (EI) m/z 323 (15%), 311 (26%), 275 (29%), 213 (29%), 119 (26%), 81 (36%), 75 (79%), 73 (100%); MS (CI) m/z 381.2437 (MH, 381.2462 calcd for $C_{21}H_{36}O_4Si$), 323, 311, 249, 167.

(3a*R,8a*R**)-2(*R**)-[1(*S**)-[[Dimethyl(1,1-dimethylethyl)-silyl]oxy]-3(*E*)-hexenyl]-5(*S**)-[(*S**)-3-bromo-1,2-propadienyl]tetrahydrofuro[3,2-*b*]tetrahydrofuran (28b).** Following the procedure described for the preparation of **27a**, alcohol **25b** (36.2 mg, 95 μmol) was sulfonylated with DMAP (41 mg, 333 μmol) and 2,4,6-triisopropylbenzenesulfonyl chloride (72 mg, 238 μmol) to give, after purification on silica gel (25:1 hexanes–EtOAc), 54.1 mg (88%) of trisylate **27b**, which was used immediately: ^1H NMR (300 MHz, $CDCl_3$) δ 7.16 (s, 2 H, ArH), 5.48 (dt, J = 15.4, 5.8 Hz, 1 H, C=CH), 5.38 (dt, J = 15.4, 6.7 Hz, 1 H, C=CH), 5.17 (dd, J = 5.3, 2.5 Hz, $CHOSO_2$), 4.73 (dt, J = 7.4, 3.7 Hz, H-3a), 4.44 (t, J = 4.8 Hz, H-6a), 4.38 (dt, J = 9.0, 5.6 Hz, H-5), 4.13 (septet, J = 6.7 Hz, 2 H, $CH(CH_3)_2$), 3.77 (m, 2 H, H-2 and CHOTBS), 2.90 (septet, J = 6.9 Hz, 1 H, $CH(CH_3)_2$), 2.29 (d, J = 2.2 Hz, C≡CH), 1.92–2.27 (m, 8 H), 1.26 (m, 18 H, $CH(CH_3)_2$), 0.96 (t, J = 7.5 Hz, 3 H, CH_2CH_3), 0.88 (s, 9 H, $C(CH_3)_3$), 0.05 (s, 6 H, $Si(CH_3)_2$).

Following the procedure described for the preparation of **28a**, the trisylate prepared above (54.1 mg, 84 μmol) was displaced with $LiCuBr_2$[31] (1.34 mL of a 0.25 M solution in THF, 334 μmol) to give, after purification on $AgNO_3$-impregnated silica gel (40:1 hexanes–Et_2O), 20.6 mg (56%, 49% overall) of bromoallene **28b** as a colorless oil (>89% pure by GLC analysis). Analysis by ^1H NMR indicated the presence of a trace amount of the isomeric bromoallene (ratio >15:1): ^1H NMR (500 MHz, $CDCl_3$) δ 6.07 (dd, J = 5.5, 1.1 Hz, 1 H, C=C=CHBr), 5.48 (dt, J = 15.2, 6.2 Hz, 1 H, C=CH), 5.40 (t, J = 6.8 Hz, 1 H, C=C=CH), 5.37 (m, 1 H, C=CH), 4.78 (dt, J = 7.8, 4.6 Hz, H-3a), 4.66 (m, H-5), 4.46 (t, J = 5.1 Hz, H-6a), 3.83 (td, J = 5.6, 4.5 Hz, H-2), 3.69 (ddd, J = 10.2, 5.8, 4.3 Hz, CHOTBS), 2.23 (dd, J = 13.3, 4.9 Hz, 1 H), 2.12–2.19 (m, 3 H), 2.00 (quintet, J = 7.1 Hz, 2 H, CH_2CH_3), 1.89

(ddd, J = 13.5, 9.8, 3.9 Hz, 1 H), 1.70 (ddd, J = 13.3, 9.9, 5.1 Hz, 1 H), 0.96 (t, J = 7.4 Hz, 3 H, CH_2CH_3), 0.89 (s, 9 H, $C(CH_3)_3$), 0.06 (s, 6 H, $Si(CH_3)_2$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.1, 134.7, 124.6, 100.3, 84.0, 83.1, 82.1, 74.2, 73.5, 72.6, 39.6, 38.2, 34.1, 25.9, 25.6, 18.1, 13.6, -4.4; IR (film) 3052, 2958, 1963, 1473, 1463, 1253, 1084, 910, 836 cm^{-1}; MS (CI) m/z 445.1594 (MH, 445.1598 calcd for $C_{21}H_{35}{}^{81}BrO_3Si$), 443.1607 (MH, 443.1618 calcd for $C_{21}H_{35}{}^{79}BrO_3Si$), 313, 311, 267.

(3a*R,8a*R**)-2(*R**)-[1(*S**)-Hydroxy-3(*E*)-hexenyl]-5(*S**)-[(*S**)-3-bromo-1,2-propadienyl]tetrahydrofuro[3,2-*b*]tetrahydrofuran (29b).** Following the procedure described for the preparation of **29a**, bromoallene **28b** (19.5 mg, 44 μmol) was desilylated with HF–pyridine complex (700 μL) to give, after purification on silica gel (5:1 hexanes–EtOAc), 11.1 mg (77%) of **29b** contaminated with a small amount (^1H NMR ratio >15:1) of isomeric bromoallene **29a**. Preparative HPLC (4:1 hexane:EtOAc) gave 9.9 mg (68%) of **29b** as a colorless oil and 0.5 mg (3%) of **29a**.

Data for **29b**: ^1H NMR (500 MHz, $CDCl_3$) δ 6.08 (d, J = 5.9, 1 H, C=C=CHBr), 5.58 (dt, J = 15.1, 5.9 Hz, 1 H, C=CH), 5.41 (t, J = 5.7 Hz, 1 H, C=C=CH), 5.40 (m, J = 7.1 Hz, 1 H, C=CH), 4.78 (dt, J = 7.6, 3.4 Hz, H-3a), 4.70 (dt, J = 9.7, 5.6 Hz, H-5), 4.52 (t, J = 5.0 Hz, H-6a), 3.81 (m, 2 H, H-2 and C*H*OH), 2.32 (dd, J = 13.5, 5.4 Hz, 1 H), 1.97–2.22 (m, 7 H), 1.80 (ddd, J = 13.5, 9.4, 4.5 Hz, 1 H), 0.98 (t, J = 7.7 Hz, 3 H, CH_2CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.9, 136.0, 124.1, 100.5, 84.0, 83.7, 82.4, 74.6, 73.8, 71.2, 39.4, 36.6, 33.3, 25.6, 13.7; IR (film) 3449, 3039, 2941, 1458, 1079, 1049, 960 cm^{-1}; MS (CI) m/z 331.0737 (MH, 331.0732 calcd for $C_{15}H_{21}{}^{81}BrO_3$), 329.0754 (MH, 329.0752 calcd for $C_{15}H_{21}{}^{79}BrO_3$), 313, 311.

(±)-1-*epi*-Kumausallene (1b). Following the procedure described for the preparation of **1a**, alcohol **29b** (11.2 mg, 34 μmol) was brominated with 2,6-di-*tert*-butylpyridine (26 mg, 31 μL, 136 μmol), triphenylphosphine (35.7 mg, 136 μmol), and carbon tetrabromide (227 μL of a 0.6 M solution in CH_2Cl_2, 136 μmol) to give, after purification by preparative TLC (40:20:1 hexane–CH_2Cl_2–EtOAc), 3.2 mg (24%) of **1b** as a colorless oil and 1.1 mg (10%) of **30b** as the only isolable products.

Data for **1b**: ^1H NMR (500 MHz, $CDCl_3$) δ 6.09 (dd, J = 5.8, 1.2 Hz, 1 H, C=C=CHBr), 5.60 (dt, J = 15.2, 6.4 Hz, 1 H, C=CH), 5.46 (dt, J = 15.0, 6.9 Hz, 1 H, C=CH), 5.42 (t, J = 6.1 Hz, 1 H, C=C=CH), 4.82 (dt, J = 7.8, 3.8 Hz, H-7), 4.75 (dtd, J = 9.8, 5.2, 0.8 Hz, H-4), 4.55 (t, J = 4.8 Hz, H-6), 4.01 (dt, J = 8.3, 5.2 Hz, CHBr), 3.91 (dt, J = 9.3, 6.1 Hz, H-9), 2.64 (dt, J = 14.8, 5.8 Hz, 1 H, CHBrC*H*$_2$), 2.54 (dt, J = 14.8, 7.7 Hz, 1 H, CHBrC*H*$_2$), 2.37 (dd, J = 13.8, 5.0 Hz, H-5α), 2.33 (dt, J = 13.9, 7.0 Hz, H-8α), 2.04 (quintet, J = 7.1 Hz, 2 H, C*H*$_2$CH$_3$), 1.87 (ddd, J = 13.5, 9.6, 3.7 Hz, H-8β), 1.76 (ddd, J = 13.6, 9.9, 4.9 Hz, H-5β), 0.98 (t, J = 7.4 Hz, 3 H, CH_2CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.9, 136.0, 124.5, 100.4, 83.8, 83.7, 81.7, 74.7, 73.8, 57.0, 39.5, 38.4, 37.5, 25.6, 13.6; IR (film) 3057, 2959, 1963, 1458, 1437, 1257, 1200, 1081, 970, 927, 857 cm^{-1}; MS (CI) m/z 394.9873 (MH, 394.9868 calcd for $C_{15}H_{20}{}^{81}Br_2O_2$), 392.9892 (MH, 392.9888 calcd for $C_{15}H_{20}{}^{81}Br^{79}BrO_2$), 390.9914 (MH, 390.9908 calcd for $C_{15}H_{20}{}^{79}Br_2O_2$), 313, 311.

Data for **30b**: ^1H NMR (500 MHz, $CDCl_3$) δ 6.21 (dd, J = 15.2, 10.5 Hz, 1 H, C=CH), 6.09 (dd, J = 5.6, 1.2 Hz, 1 H, C=C=CHBr), 6.02 (dd, J = 15.2, 10.6 Hz, 1 H, C=CH), 5.76 (dt, J = 15.2, 6.5 Hz, 1 H, C=C*H*CH$_2$), 5.62 (dd, J = 15.2, 7.4 Hz, 1 H, C=C*H*CHO), 5.43 (t, J = 6.1 Hz, 1 H, C=C=CH), 4.80 (dt, J = 7.5, 4.0 Hz, H-3a), 4.71 (dt, J = 10.3, 5.5 Hz, H-5), 4.52 (t, J = 4.8 Hz, H-6a), 4.24 (dt, J = 8.7, 7.2 Hz, H-2), 2.39 (dt, J = 13.7, 6.9 Hz, 1 H), 2.31 (dd, J = 13.4, 5.0 Hz, 1 H), 2.10 (m, 2 H, C*H*$_2$CH$_3$), 1.75 (m, 2 H), 1.00 (t, J = 7.4 Hz, 3 H, CH_2CH_3).

Acknowledgment. Our investigations in this area were supported by NIH Grant NS-12389 and by an NIH NRSA Postdoctoral Fellowship (CA-08881) to T. Grese. We wish to thank Dr. Joseph Ziller, Director of the UCI Crystallography Laboratory, for the X-ray analysis of **18** and Theodore Johnson of our laboratories for important suggestions. NMR and mass spectra were determined at the University of California at Irvine with spectrometers purchased with the assistance of NSF Shared Instrumentation Grants.

Supplementary Material Available: ^1H NMR spectra of **25b**, **26**, **28a**, **28b**, **29a**, **29b**, (±)-kumausallene (**1a**), and **1b** and ^{13}C NMR spectra of kumausallene (**1a**) and **1b** (11 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.