(75 MHz, $CDCl_3$) δ 222.0, 140.8, 128.4, 127.8, 126.0, 88.1, 80.8, 56.7, 46.3, 34.6, 24.2, 18.6; IR (film) 2962, 1739, 1455, 1083, 1070 cm^{-1}; MS (EI) *m/z* 216.1139 (216.1140 calcd for $C_{14}H_{16}O_2$, M, 70), 131 (100), 85 (75).

The (*p*-toluenesulfonyl)hydrazone **41** (73% yield) provided X-ray-quality crystals from hexane–EtOAc: mp 168–169 °C; MS (EI) *m/z* 384.1571 (384.1507 calcd for $C_{21}H_{24}N_2O_3S$). Anal. Calcd for $C_{21}H_{24}N_{20}O_3S$: C, 65.59; H, 6.30; N, 7.29. Found: C, 65.46; H, 6.38; N, 7.24.

Preparation of (2*R,3a*S**,6a*R**)- and (2*R**,3a*R**,6a*S**)-Hexahydro-2,3a-diphenyl-4*H*-cyclopenta[*b*]furan-4-ones (42 and 43).** Following the general procedure described for the preparation of **39b**, a solution of diol **21c** (10 mg, 0.05 mmol), benzaldehyde (11 μL, 0.10 mmol), and CH_2Cl_2 (0.25 mL) was maintained at −23 °C for 1 h to provide, after aqueous workup and chromatography (3:2 hexane–EtOAc), 13 mg (90%) of a 2:1 mixture of **42** and **43**, respectively. Separation of this mixture was achieved by preparative HPLC (Supelcosil, 25 cm × 10 mm, 5-μm particle size column (9:1 hexane–THF). Data for **43**: ^1H NMR (500 MHz, $CDCl_3$) δ 7.24–7.37 (m, 10 H, Ph), 5.13 (d, *J* = 3.8 Hz, H(6a)), 4.95 (dd, *J* = 6.4, 9.6 Hz, H(2)), 3.19 (dd, *J* = 6.4, 12.6 Hz, 1 H, H(3)), 2.18–2.55 (m, 5 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 219.4, 140.6, 137.9, 128.9, 128.5, 127.8, 127.3, 126.7, 126.2, 87.0, 81.1, 65.5, 48.0, 34.4, 24.3; IR (film) 2925, 1750, 1050, 693 cm^{-1}; MS (EI) *m/z* 278.1293 (278.1307 calcd for $C_{19}H_{18}O_2$). Data for **42**: ^1H NMR (500 MHz, $CDCl_3$) δ 7.27–7.35 (m, 10 H, Ph), 5.04 (t, *J* = 8.0 Hz, H(2)), 4.98 (d, *J* = 3.8 Hz, H(6a)), 2.64–2.85 (m, 3 H), 2.42–2.55 (m, 2 H), 2.25–2.35 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 219.4, 2.85 (m, 3 H), 2.42–2.55 (m, 2 H), 2.25–2.35 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 219.4, 128.9, 128.5, 127.6, 127.6, 127.4, 126.5, 125.4, 86.0, 80.7, 66.0, 47.5, 35.3, 26.5; IR (film) 3025, 2925, 1750, 1050, 694 cm^{-1}; MS (EI) *m/z* 278.1293 (278.1307 calcd for $C_{19}H_{18}O_2$, M, 19).

Acknowledgment. The support of this research by PHS Grant NS-12389 is gratefully acknowledged. P.M. was supported by the National Engineering and Research Council of Canada. We particularly thank Dr. J. Ziller, Director, Irvine X-Ray Laboratory, for the single-crystal X-ray analyses. NMR, mass spectra, and X-ray analyses were performed with use of instrumentation supported in part by NSF Shared Instrumentation Grants.

Supplementary Material Available: Experimental procedures and characterization data for compounds **9**, **10a,b**, **12**, **16**, **17**, **19**, **21a,c**, **22a,c**, **23c**, **25b–e**, **26c–e**, **27a,b**, **28a–c**, **31a,b**, **34a–c,f**, **37a–c**, **39a,b,e–h** (20 pages). Ordering information is given on any current masthead page.

General Approach to Halogenated Tetrahydrofuran Natural Products from Red Algae of the Genus *Laurencia*. Total Synthesis of (±)-*trans*-Kumausyne and Demonstration of an Asymmetric Synthesis Strategy

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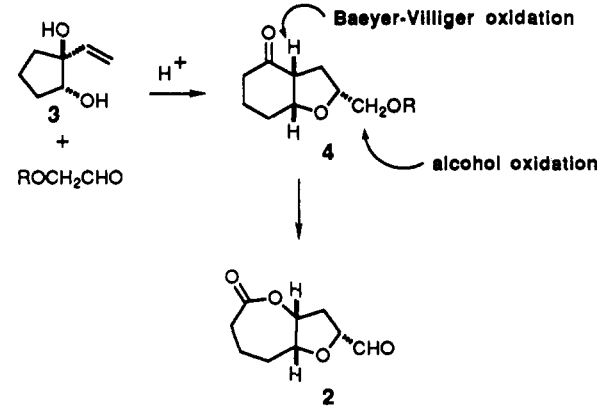
Abstract: A general strategy for the synthesis of C_{15} halogenated tetrahydrofuranoid lipids from red algae of the genus *Laurencia* has been developed. The central step is the convenient formation of hydrobenzofuranone (±)-**5** on a large scale, and with complete stereocontrol, from the acid-catalyzed condensation of 1-vinylcyclopentanediol (**3**) and α-(benzyloxy)acetaldehyde (Scheme II). Starting with the chiral, nonracemic (1*S*,2*R*)-diol **3**, hydrobenzofuranone (−)-**5** is also available in good enantiomeric purity (Scheme V). The total synthesis of (±)-*trans*-kumausyne from *rac*-**5** is accomplished in 13 steps and >5% overall yield.

A rich variety of halogenated, nonisoprenoid sesquiterpenes have been isolated from the widely distributed red algae of the genus *Laurencia*.[1] 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 large number of these *Laurencia* lipids contain at least one tetrahydrofuran ring. In many of these, the oxygen of the tetrahydrofuran ring is flanked by cis side chains which are also cis related to an oxygen substituent at C(3). A representative selection of metabolites of this common type is shown in Figure 1.[3-7] Also depicted in Figure 1 is a proposed approach for the assembly of members of this class

Scheme I



of marine natural products from a common bicyclic lactone aldehyde precursor **2**. This intermediate embodies the three stereogenic centers of the central tetrahydrofuran ring and also provides loci for the elaboration of the remaining six carbons of these halogenated lipid targets.

A central feature of this potentially widely applicable synthesis plan is the ready assembly of *cis*-hydrobenzofuranones of general structure **4** by ring enlarging tetrahydrofuran annulations of cy-

(1) For reviews, see: Faulkner, D. J. *Nat. Prod. Rep.* **1984**, *1*, 251; **1986**, *3*, 1.
(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, H.; Kurosawa, E. *Chem. Lett.* **1983**, 1643.
(4) Kumausallene: Suzuki, T.; Koizumi, K.; Suzuki, M.; Kurosawa, E. *Chem. Lett.* **1983**, 1639.
(5) Laurefucin: Furusaki, A.; Kurosawa, E.; Fukuzawa, A.; Irie, T. *Tetrahedron Lett.* **1973**, 4579.
(6) Isoprelaurefucin: Suzuki, M.; Kurata, K.; Suzuki, T.; Kurosawa, E. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 2953.
(7) Tricyclic tris(tetrahydrofuran) from *Laurencia* obtusa: González, A. G.; Martín, J. D.; Norte, M.; Rivera, P.; Ruano, J. Z. *Tetrahedron* **1984**, *40*, 3443.

0002-7863/91/1513-5378$02.50/0

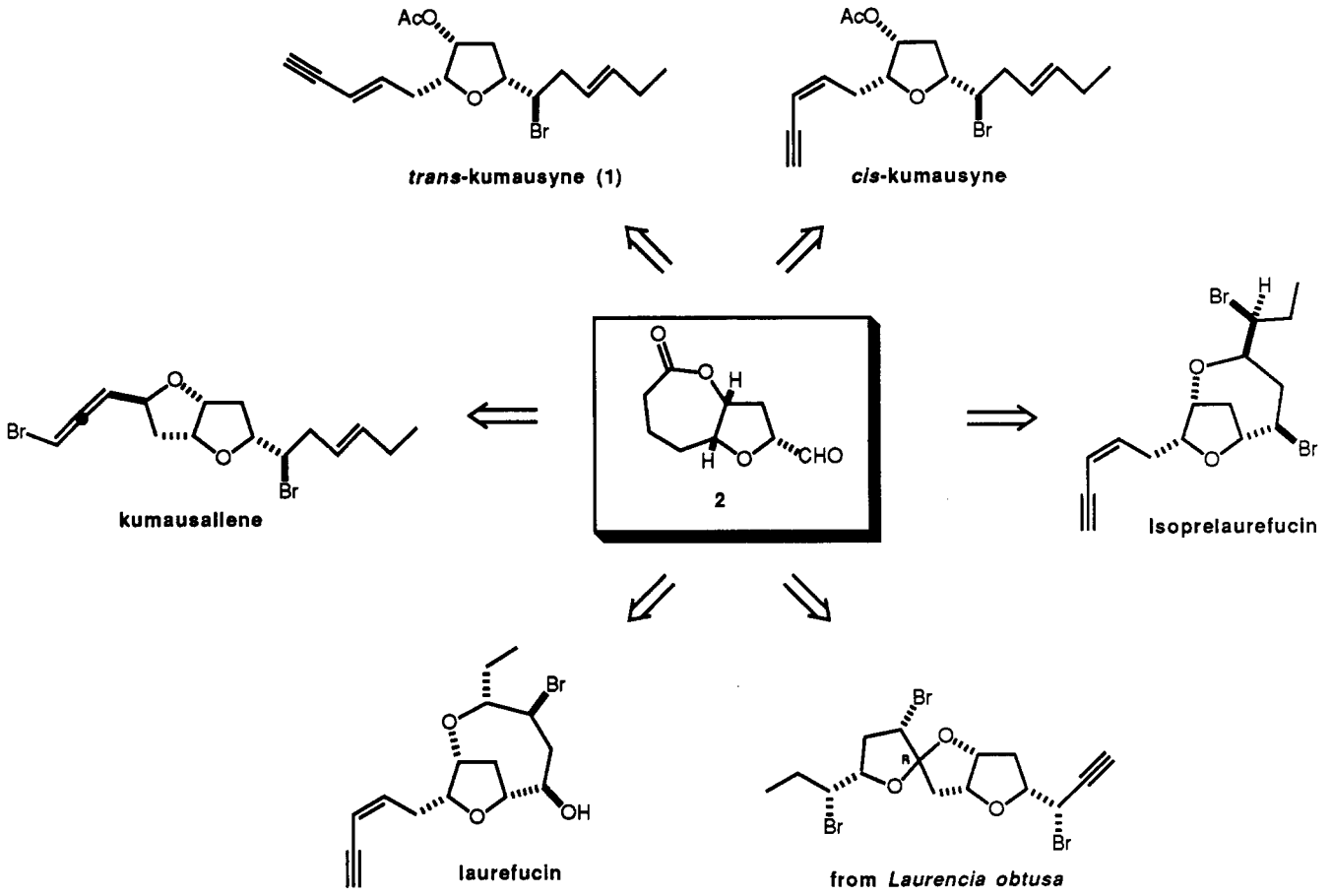


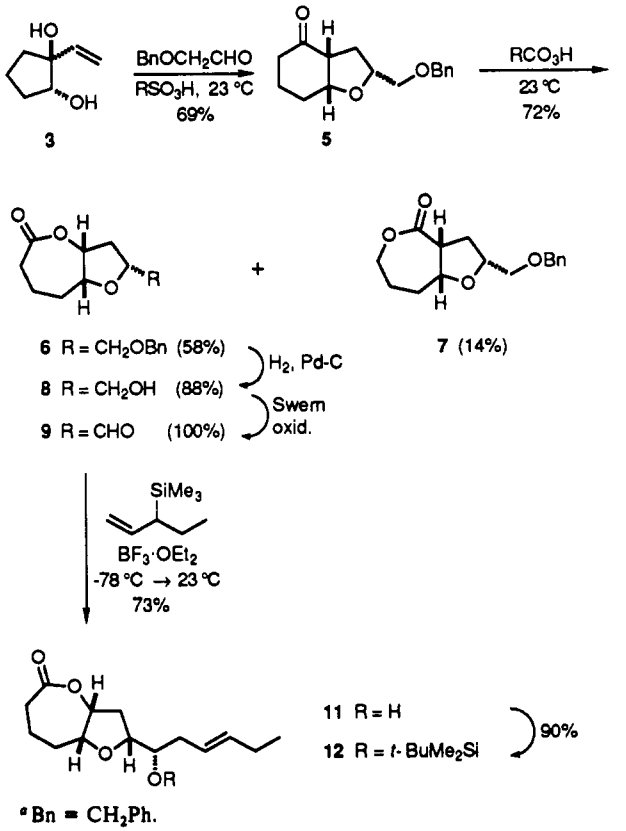
Figure 1. Representative *Laurencia* nonisoprenoid sesquiterpenes.[3-7]

clopentanediol precursor **3** (Scheme I).[8] As depicted in Scheme I, two ostensibly straightforward oxidations would be required to transform **4** to the pivotal bicyclic lactone aldehyde intermediate **2**.

The preceding papers in this series[8,9] reported the development of a new stereocontrolled synthesis of tetrahydrofurans from allylic diol and carbonyl components, of which the conversion depicted in Scheme I is one example. In this paper we illustrate the use of this new method of oxacyclic ring construction as the centerpiece of the first total synthesis of a member of the marine natural products group depicted in Figure 1. Specifically, we report a concise, highly stereocontrolled synthesis of *trans*-kumausyne, the simplest member of this group.[10,11] This halogenated *Laurencia* lipid was first isolated and characterized by Kurosawa and coworkers in 1983.[3] *trans*-Kumausyne, together with its deacetyl derivative, are the most abundant terpenoids found in methanolic extracts of *Laurencia nipponica* Yamada, a red algae indigenous to waters off the coast of Hokkaido, Japan.

Total Synthesis of (±)-*trans*-Kumausyne. Our efforts began with the *cis*-hydrobenzofuranone **5**, which is available with complete stereoselectivity on a large scale from the reaction of (1*R**,2*S**)-1-vinylcyclopentane-1,2-diol (**3**) and α-(benzyloxy)-acetaldehyde (Scheme II).[8] Oxidation of **5** with *m*-chloroperoxybenzoic acid provided a 4:1 mixture of regioisomeric lactones **6** and **7**, which were readily separated on silica gel to provide

Scheme II[a]



[a] Bn = CH_2Ph.

lactone **6** (58%) and its crystalline isomer **7** (14%). The regioselectivity of this transformation was no better with other

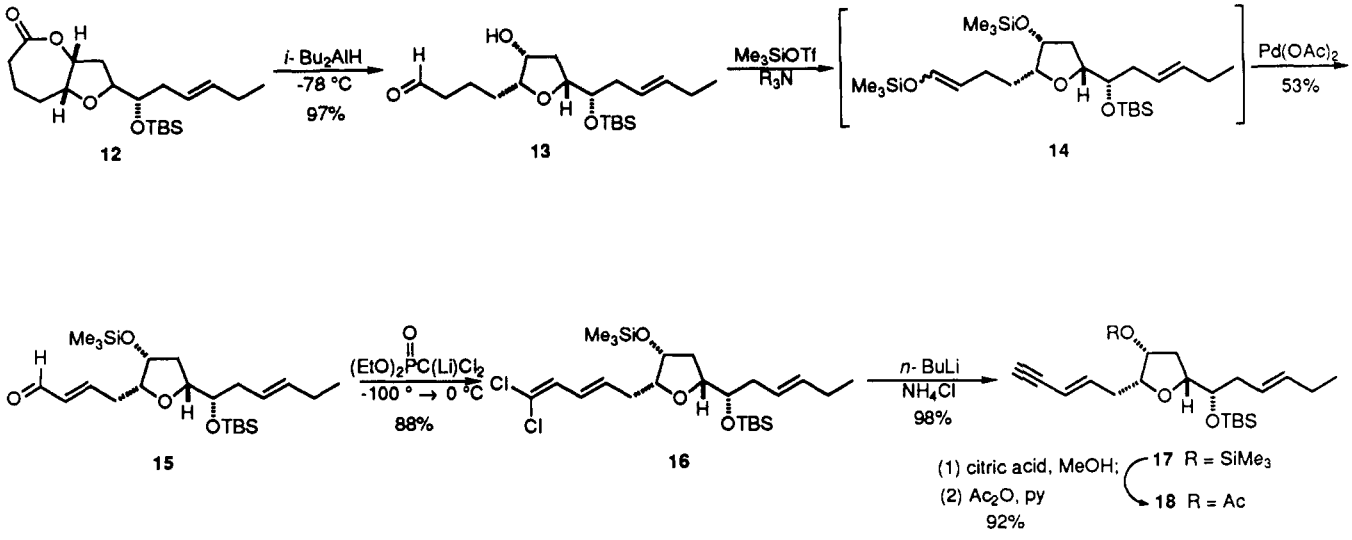
(8) Brown, M. J.; Harrison, T.; Herrinton, P. M.; Hopkins, M. H.; Hutchinson, K. D.; Overman, L. E.; Mishra, P. *J. Am. Chem. Soc.*, preceding paper in this issue.

(9) Hopkins, M. H.; Overman, L. E.; Rishton, G. M. *J. Am. Chem. Soc.*, first of the series of three in this issue.

(10) An early version of this total synthesis has been described in preliminry form, see: Overman, L. E. In *Selectivities in Lewis Acid-Promoted Reactions*; NATO ASI Series; Schenzer, D., Ed.; Kluwer Academic: Dordrecht, The Netherlands, 1989; Vol. 289, p 1.

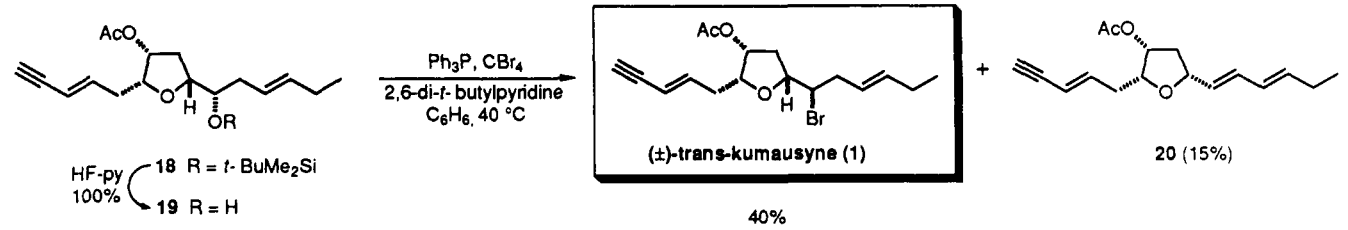
(11) For synthetic approaches to this natural products family, see: Tonn, C. E.; Palazón, J. M.; Ruiz-Pérez, C.; Rodriguez, M. L.; Martín, V. S. *Tetrahedron Lett.* **1988**, *29*, 3149.

Scheme III[a]



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

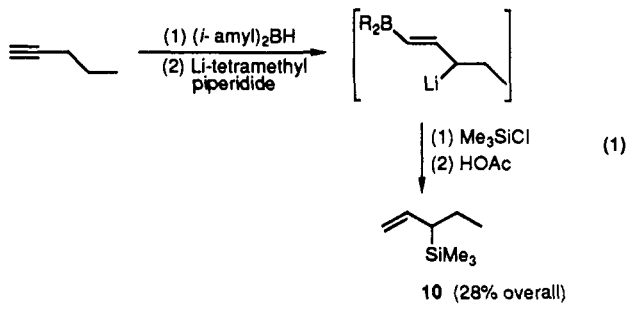
Scheme IV



Baeyer–Villiger oxidants: HO_2H–HOAc, CF_3CO_3H, and p-nitroperoxybenzoic acid.[12,13] Debenzylation of lactone ether **6** provided the crystalline alcohol **8** in 88% yield.

Oxidation of **8** under Swern[14] conditions followed by a nonaqueous workup[15] provided aldehyde **9** in essentially quantitative yield. This sensitive aldehyde decomposed when stored at room temperature and was immediately employed to develop the six-carbon side chain.

The *trans*-3-hexenyl side chain was elaborated by Sakurai reaction[16] of aldehyde **9** with 3-(trimethylsilyl)-1-pentene (**10**). Employing the general procedures of Rathke[17] and Zweifel,[18] this allylsilane was accessed from 1-pentyne by the one-pot sequence of transformations summarized in eq 1. Reaction of lactone



(1)

aldehyde **9** with 3-(trimethylsilyl)-1-pentene in the presence of BF_3·OEt_2 afforded a single, crystalline alcohol product **11** in 73% yield. The stereochemistry at the newly developed stereocenter of **11** was initially assigned on the expectation that the monodentate Lewis acid BF_3 would promote simple Cram stereoselection.[19] The stereochemistry at this center was subsequently confirmed by chemical correlation of **11** with a related intermediate which had yielded to X-ray crystallographic analysis.[20] Conventional silylation of **11** provided the silyl ether **12**.[21]

With the six-carbon side chain of kumausyne in place, manipulation of the lactone function to elaborate the five-carbon side chain was required. Accordingly, **12** was treated with 1.5 equiv of i-Bu_2AlH at −78 °C in toluene to provide the sensitive hydroxy aldehyde **13** (Scheme III). High-field ^{1}H NMR analysis indicated that this intermediate existed in $CDCl_3$ exclusively (>95%) in the open aldehyde form. After considerable experimentation, an efficient sequence was developed for converting **13** to the silyl-protected enal **15**. Dropwise addition of **13** to a solution containing 5 equiv of Me_3SiOTf and 5 equiv of i-Pr_2EtN (CH_2Cl_2, 23 °C) resulted in silylation of both the secondary hydroxyl and aldehyde functions, providing **14** as a ca. 3:1 mixture of geometrical isomers. Oxidation of the enoxysilane functionality of **14** with 1.5 equiv of $Pd(OAc)_2$ under Saegusa–Ito[22] conditions, followed by purification of the crude product on silica gel, afforded the desired (*E*)-enal **15** in 53% overall yield from **13**.

One-carbon homologation of the unsaturated aldehyde to the *trans*-enyne **17** was best accomplished by the general method of Normant.[23] Thus, treatment of **15** with the Horner–Emmons

(12) The migratory aptitude of *sec*-alkyl in Baeyer–Villiger oxidations is typically significantly greater than prim-alkyl.[13]

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

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

(15) See, e.g. Paquette, L. A.; Oplinger, J. A. *J. Org. Chem.* **1988**, *53*, 2953. Williams, D. R.; Harigaya, Y.; Moore, D. L.; D'sa, J. *J. Am. Chem. Soc.* **1984**, *106*, 2641.

(16) Hosomi, A.; Sakurai, H. *Tetrahedron Lett.* **1976**, 1295.

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(18) Rajagopalan, S.; Zweifel, G. *Synthesis* **1984**, 113.

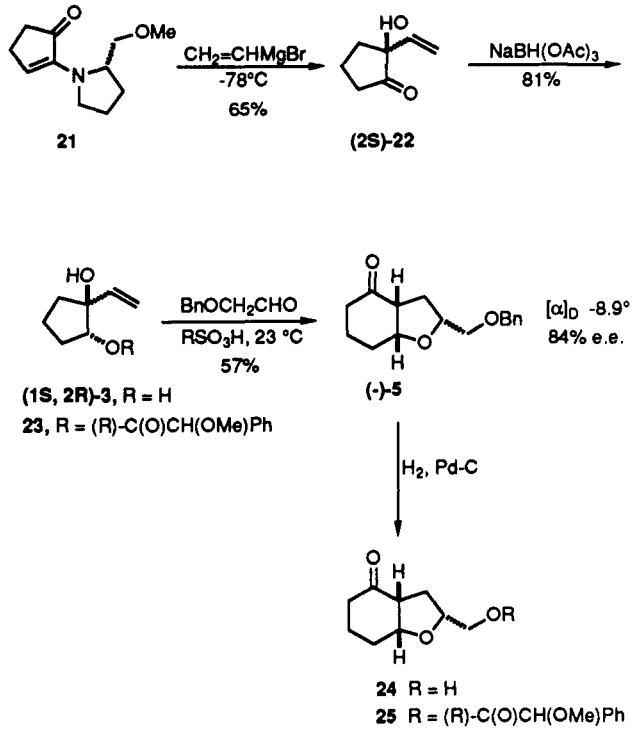
(19) For closely related examples; see: Danishefsky, S. J.; DeNinno, M. P.; Phillips, G. B.; Zelle, R. E.; Lartey, P. A. *Tetrahedron* **1986**, *42*, 2809. Danishefsky, S. J.; Selnick, H. G.; Zelle, R. E.; DeNinno, M. P. *J. Am. Chem. Soc.* **1988**, *110*, 4368.

(20) Hutchinson, K. D. Ph.D. Dissertation, University of California, Irvine, 1991.

(21) Corey, E. J.; Cho, H.; Reucker, C.; Hua, D. H. *Tetrahedron Lett.* **1981**, *22*, 3455.

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

Scheme V



reagent generated from diethyl trichloromethanephosphonate provided the dichloro diene **16** in 88% yield. Exposure of **16** to *n*-BuLi followed by a protic quench afforded the enyne **17** with 98% efficiency. Selective cleavage of the trimethylsilyl ether, followed by conventional acylation, provided **18** in 92% overall yield from **17**.

With all the carbon atoms of *trans*-kumausyne in place, the stage was set to address the crucial bromination step. Desilylation of **18** was effected in quantitative yield by treatment with HF·pyridine in CH_3CN (Scheme IV). Under these conditions no cleavage of the acetate was observed. Extensive model studies had demonstrated that bromination of alcohol **19** would not be trivial. These studies had also targeted the triphenylphosphine–carbon tetrabromide reagent system as being most suitable for this challenging functional group interconversion.[24] In the event, treatment of alcohol **19** with 5 equiv of Ph_3P and 5 equiv of freshly sublimed CBr_4 in the presence of 2.5 equiv of 2,6-di-*tert*-butylpyridine (PhH, 40 °C, 1 h) provided (±)-*trans*-kumausyne (**1**) in 40% yield after purification on silica gel. In addition to **1**, ca. 15% of the diene **20** was isolated. A comparison of the NMR and IR characteristics of synthetic **1** with spectra of natural *trans*-kumausyne[25] confirmed the identity of the synthetic product.

Demonstration of an Asymmetric Route for the Synthesis of *Laurencia* Metabolites. The preparation of hydrobenzofuranone **5** in chiral, nonracemic form should enable asymmetric synthesis of *trans*-kumausyne and related *Laurencia* metabolites.[26] The (1*S*,2*R*)-diol precursor **3** of this key bicyclic intermediate was readily assembled as outlined in Scheme V. Employing the method of Fujisawa,[27] the keto enamine **21** was prepared from 1,2-cyclopentanedione[28] and (*S*)-*O*-methylprolinol.[29] Slow addition of vinylmagnesium bromide at −78 °C to a THF–Et_2O (1:9) solution of **21** followed by hydrolytic workup provided (2*S*)-**22**.[27] Stereoselective reduction[8] of this intermediate with $NaBH(OAc)_3$[30] provided the (1*S*,2*R*)-diol **3**, $[\alpha]_D$ −58.4°, in 53% overall yield from **21**. The enantiomeric purity of this intermediate (84% ee) was determined by ^1H NMR analysis after esterification with (*R*)-methylmandelic acid.[3] The degree of face selectivity in the reaction of **21** with vinylmagnesium bromide was quite sensitive to the reaction solvent. For example, use of THF alone yielded (2*S*)-**22** in only 33% enantiomeric excess. The choice of a 9:1 mixture of Et_2O–THF as the reaction medium was arrived at as the minimum amount of THF necessary to dissolve vinylmagnesium bromide at −78 °C.

Acid-promoted reaction of (1*S*,2*R*)-**3** with α-(benzyloxy)-acetaldehyde at room temperature, as described in the racemic series,[8] provided (−)-**5** in 57% yield. Debenzylation of (−)-**5** followed by analysis of the alcohol product as its (*R*)-methylmandelate ester confirmed that there had been no measurable loss of enantiomeric purity in the conversion of (1*S*,2*R*)-**3** to (−)-**5**.

The preparation of hydrobenzofuranone (−)-**5** in useful enantiomeric purity defines a convenient asymmetric approach for the synthesis of *trans*-kumausyne and related metabolites (Figure 1). It does not strictly constitute a formal total synthesis of (+)-kumausyne, since only racemic **5** has been converted on to the natural metabolite.[26] As a result of the low reported rotation of *trans*-kumausyne and the fact that its absolute configuration rests on rigorous degradative correlations,[3] we did not deem it worthwhile in the present context to convert (−)-**5** to optically active *trans*-kumausyne.

Conclusion

The first total synthesis of a C_{15} tetrahydrofuranoid lipid of the *Laurencia* genus, specifically (±)-*trans*-kumausyne, has been accomplished. The hydrobenzofuranone **5**, which is available on a large scale by the "ring-enlarging tetrahydrofuran annulation" chemistry recently developed in these laboratories,[8] is the key intermediate in the synthesis sequence. The bicyclic lactone aldehyde **2**, readily obtainable from **5**, is potentially a general intermediate for preparing a wide variety of *Laurencia* C_{15} lipid metabolites as suggested in Figure 1.

This completely stereocontrolled total synthesis of (±)-*trans*-kumausyne proceeded in 13 steps and 5.4% overall yield from hydrobenzofuranone **5**. This latter intermediate is available in racemic form in three steps and 40% overall yield from commercially available starting materials. Hydrobenzofuranone **5** is also obtainable in useful enantiomeric purity (ca. 85% ee) by a convenient four-step asymmetric synthesis. We anticipate that the new strategy for stereocontrolled assembly of tetrahydrofurans, which was developed as a prelude to this total synthesis,[8,9] will find other applications in the arena of complex tetrahydrofuranoid synthesis.

Experimental Section[32]

(3a*R,8a*R*)-2(*R**)-[(Benzyloxy)methyl]-5-oxotetrahydrofuro[3,2-*b*]oxepane (6) and (3a*R**,8a*R**)-2(*R**)-[(Benzyloxy)methyl]-4-oxotetrahydrofuro[3,2-*c*]oxepane (7).** To a stirring solution of hydrobenzofuranone **5** (5.47 g, 21.0 mmol)[8] in CH_2Cl_2 (150 mL) was added *m*-chloroperoxybenzoic acid (85%, 13.6 g, 67.3 mmol). The reaction mixture was stirred at 23 °C for 72 h and then was poured *carefully* into a cooled (0 °C) solution of Me_2S (12 mL) in CH_2Cl_2 (120 mL). Saturated $NaHCO_3$ (200 mL) was added, the organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 100 mL). The combined organic phases were dried ($MgSO_4$) and concentrated to leave a pale yellow oil. Purification by flash chromatography (hexanes–EtOAc 1:1) gave 3.38 g (58%) of **6** as a clear oil and 0.83 g (14%) of **7** as a white solid, mp 91–92 °C.

Spectral data for **6**: ^1H NMR (500 MHz, $CDCl_3$) δ 7.28–7.38 (m, Ph), 4.88 (apparent quintet, H(3a)), 4.58 (AB q, J = 12.1 Hz, $\Delta\nu$ = 39.6 Hz, CH_2Ph), 4.06 (dddd, J = 4.2, 4.2, 6.9, 8.6 Hz, H(2)), 3.93 (apparent quintet, H(8a)), 3.60 (dd, J = 6.9 Hz, 10.1 Hz, C*H*HOBn), 3.55 (dd, J = 4.2 Hz, 10.1 Hz, CH*H*OBn), 2.56–2.67 (m, 2 H, C(6)), 2.46 (ddd, J = 6.8, 7.6, 14.2 Hz, H(3β)), 2.16–2.20 (m, 1 H, C(8)), 1.96 (ddd, J

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(25) Provided by Professor E. Kurosawa, Department of Chemistry, Hokkaido University, Sapporo, Japan.
(26) The synthesis of **1** from hydrobenzofuranone **5** (Schemes II and III) contains no obvious stages where the enantiomeric integrity of an intermediate would be in jeopardy.
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(30) (a) Gribble, G. W.; Ferguson, D. C. *J. Chem. Soc., Chem. Commun.* **1975**, 535. (b) Saksena, A. K.; Mangiaracina, P. *Tetrahedron Lett.* **1983**, *24*, 273. (c) Evans, D. A.; Chapman, K. T.; Carreira, E. M. *J. Am. Chem. Soc.* **1988**, *110*, 3560.
(31) Trost, B. M.; Curran, D. P. *Tetrahedron Lett.* **1981**, *22*, 4929.
(32) General experimental details may be found in refs 8 and 9.

= 3.6, 8.7, 13.9 Hz, H(3α)), 1.89–1.91 (m, 1 H, C(7)), 1.68–1.73 (m, 1 H, C(7); 1 H, C(8)); ^{1}H NMR (500 MHz, C_6D_6) δ 7.17–7.39 (m, Ph), 4.45 (AB q, J = 12.1 Hz, Δν = 16.2 Hz, CH_2Ph), 3.97 (apparent quintet, H(3a)), 3.88–3.94 (m, H(2)), 3.62 (dd, J = 4.9, 11.1 Hz, C*H*HOBn), 3.48 (dd, J = 5.0, 9.9 Hz, CH*H*OBn), 3.26 (ddd, J = 4.9, 4.9, 11.1 Hz, H(8a)), 2.24 (apparent dd, J = 8.9, 13.5 Hz, 1 H, C(6)), 1.83–2.02 (m, 1 H, C(7)), 0.93–1.02 (m, 1 H, C(7)); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.8 (s), 137.9 (s), 128.3 (d), 127.8 (d), 127.6 (d), 80.4 (d), 79.8 (d), 77.1 (d), 73.4 (t), 72.1 (t), 35.8 (t), 31.5 (t), 26.5 (t), 16.7 (t); IR (CCl_4) 2956, 2875, 2863, 1751, 1459, 1266, 1235, 1156, 1098, 1082 cm^{-1}; MS (CI) m/z 277 (MH), 187, 169, 91; HRMS (EI) m/z 276.1358 (276.1361 calcd for $C_{16}H_{20}O_4$).

Spectral data for **7**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29–7.35 (m, Ph), 4.59 (AB q, J = 12.1 Hz, Δν = 51.8 Hz, CH_2Ph), 4.29 (app dd, J = 7.6, 12.8 Hz, 1 H, C(6)), 4.19 (ddd, J = 7.6, 7.6, 12.8 Hz, 1 H, C(6)) 4.09 (ddd, J = 3.0, 9.2, 12.0 Hz, H(8a)), 3.99–4.04 (m, H(2)), 3.56–3.62 (m, CH_2OBn), 3.45 (apparent quintet, J = 8.8 Hz, H(3a)), 2.18–3.00 (m, 2 H), 2.05–2.15 (m, 2 H), 1.64–1.72 (m, 1 H), 1.52–1.60 (m, 1 H); ^{1}H NMR (500 MHz, C_6D_6) δ 7.33–7.54 (m, Ph), 4.61, (AB q, J = 12.1 Hz, Δν = 25.6 Hz, CH_2Ph), 4.01–4.06 (m, H(2)), 3.80 (dd, J = 6.4, 10.1 Hz, C*H*HOBn), 3.74 (dd, J = 7.3, 12.8 Hz, 1 H), 3.68 (dd, J = 4.3, 10.1 Hz, CH*H*OBn), 3.55 (ddd, J = 3.5, 8.5, 12.0 Hz, H(8a)), 3.47 (ddd, J = 4.7, 12.8, 12.8 Hz, 1 H), 2.67–2.74 (m, 2 H), 1.97–2.05 (m, 2 H), 1.49–1.72 (m, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.3 (s), 137.9 (s), 128.3 (d), 127.8 (d), 127.6 (d), 77.9 (d), 76.6 (d), 73.5 (t), 72.0 (t), 64.9 (t), 46.4 (d), 31.1 (q), 27.1 (t), 22.6 (t); IR (CCl_4) 2952, 2881, 2861, 1751, 1454, 1357, 1278, 1179, 1157, 1147, 1098, 1091 cm^{-1}; MS (CI) m/z 277 (MH), 187, 169; MS (EI) m/z 276.1353 (276.1364 calcd for $C_{16}H_{20}O_4$). Anal. Calcd for $C_{16}H_{20}O_4$: C, 69.55; H, 7.29. Found: C, 69.44; H, 7.33.

(3a*R,8a*R**)-2(*R**)-(Hydroxymethyl)-5-oxotetrahydrofuro[3,2-*b*]-oxepane (8).** A mixture of **6** (3.15 g, 11.4 mmol) and 10% Pd/C (0.39 g) in EtOAc (70 mL) was stirred under a hydrogen atmosphere for 6 h. After filtration through a pad of Celite, the solvent was removed in vacuo and the residue purified by flash chromatography (20:1 EtOAc–EtOH) to give **8** (1.87 g, 88%) as a white crystalline solid.

An analytical sample was obtained by washing this solid with 5:1 hexane–CH_2Cl_2 and drying in vacuo (0.1 mm) over P_2O_5 for 24 h: mp 49–51 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.90 (ddd, J = 3.6, 4.5, 7.9 Hz, H(3a)), 3.90–4.03 (m, H(8a) and H(2)), 3.74 (ddd, J = 3.4, 6.3, 11.8 Hz, C*H*HOH), 3.63 (apparent quintet, CH*H*OH), 2.53–2.67 (m, 2 H), 2.43 (apparent quintet, 1 H), 2.33 (apparent t, J = 5.8 Hz, OH), 2.11–2.18 (m, 1 H), 1.87–2.06 (m, 2 H), 1.63–1.74 (m, 2 H). Addition of D_2O results in loss of the apparent t at δ 2.33, collapse of the ddd at δ 3.74 to a dd (J = 3.3, 11.8 Hz), and collapse of the apparent quintet at δ 3.63 to a dd (J = 6.3, 11.8 Hz): ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.8, 80.3, 80.0, 78.5, 64.2, 34.5, 31.4, 26.5, 16.6; IR (CCl_4) 3430, 2947, 2877, 1736, 1461, 1351, 1293, 1270, 1241, 1158, 1074 cm^{-1}; MS (CI) m/z 187 (MH), 169. Anal. Calcd for $C_9H_{14}O_4$: C, 58.05; H, 7.58. Found: C, 58.11; H, 7.58.

3-(Trimethylsilyl)-1-pentene (10). Following the general procedure of Brown,[33] to a solution of borane–methyl sulfide (8.07 mL of a 10 M solution in methyl sulfide, 80.7 mmol) in THF (40 mL) at −10 °C (CH_3OH, ice) was added dropwise a solution of 2-methyl-2-butene (80.7 mL of a 2 M solution in THF, 0.161 mmol). The reaction mixture was allowed to warm to 25 °C over a period of 2 h and then was cooled to 0 °C, and 1-pentyne (5 g, 73.5 mmol) was added dropwise. After 30 min, the ice bath was removed, and the reaction mixture was allowed to stand for 30 min.

Following the general procedure of Rathke,[17] a solution of *n*-BuLi (32.3 mL of a 2.5 M solution, 80.7 mmol) was cooled to 0 °C, and 2,2,6,6-tetramethylpiperidine (13.6 mL, 80.7 mmol) was added dropwise. The resulting mixture was allowed to reach 23 °C, and the volatiles were removed in vacuo (approximately 13 mm). The residue was cooled to 0 °C, and the above solution of disiamyl-1-pentenylborane was added via cannula, giving rise to an orange solution upon mixing and warming to 23 °C. The mixture was cooled to 0 °C, Me_2SiCl (15.4 mL, 0.122 mol) was added, and the mixture was stirred at this temperature for 30 min. According to the general procedure of Zweifel,[18] glacial AcOH (20 mL) was added and the reaction mixture was heated to 60 °C for 2 h. After being cooled to 23 °C, this solution was added to 30% H_2O_2 (44 mL) in 3 M NaOAc (200 mL), which exotherms mildly. This mixture was allowed to stand for 30 min and then was extracted with pentane (3 × 100 mL). The combined organic extracts were washed with 1 M K_2CO_3 (100 mL) and brine (100 mL) and concentrated by distillation (70 °C, 760 mm initially, and then 40 °C, 50 mm). The residue was dissolved in pentane and filtered, first through silica gel and then through alumina. After concentration, the residue was distilled (54–58 °C, 45 mm) to give 2.94 g (28%) of **10** as clear colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.61 (ddd, J = 9.1, 10.3, 17.2 Hz, *H*C=CH_2), 4.89 (dd, J = 2.1, 10.3 Hz, HC=C*H*H), 4.83 (ddd, J = 0.8, 2.1, 10.3 Hz, HC=CH*H*), 1.53–1.57 (m, C*H*$SiMe_3$), 1.34–1.40 (m, CH_2), 0.92 (t, J = 7.1 Hz, CH_3), −0.019 (s, 9 H, $SiMe_3$); IR (film) 3078, 2959, 2931, 2901, 2873, 1627, 1453, 1249, 1134, 1066 cm^{-1}.

(3a*R,8a*R**)-2(*R**)-(1(*S**)-Hydroxy-3(*E*)-hexenyl-5-oxotetrahydrofuro[3,2-*b*]oxepane (11).** To a solution of oxalyl chloride (0.188 mL, 2.16 mmol) in CH_2Cl_2 (4 mL) at −78 °C was added dropwise over 3 min Me_2SO (0.182 mL, 2.56 mmol). The reaction mixture was maintained at −78 °C for 20 min, and then a solution of the alcohol **8** (0.2 g, 1.08 mmol) in dry CH_2Cl_2 (2 mL) was added dropwise over 5 min. Stirring was continued at −78 °C for 1 h, then Et_3N (0.6 mL, 4.30 mmol) was added, and the reaction mixture was allowed to warm to 23 °C during 30 min. The reaction mixture was diluted with a mixture of EtOAc and acetone (2:1, 5 mL) and filtered through a plug of silica gel with EtOAc–acetone (2:1) as eluant. Concentration of the filtrate followed by flash chromatography on silica gel using EtOAc–acetone (4:1 and then 1:1) as eluant gave **9** (0.197 g, 100%) as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.70 (d, J = 1 Hz, HC=O), 4.89 (apparent t, J = 1 Hz, H(2), 4.29–4.36 (m), 4.17–4.23 (m); IR (film) 1739 cm^{-1}; MS (CI) m/z 185 (MH).

To a solution of aldehyde **9** (0.197 g, 1.07 mmol) in CH_2Cl_2 (10 mL) at −78 °C was added dropwise over 3 min BF_3·OEt_2 (0.197 mL, 1.61 mmol). A solution of allylsilane **10** (228 mg, 1.61 mmol) in CH_2Cl_2 (2 mL) was added dropwise over 3 min, and the clear, colorless solution was allowed to warm to 23 °C during 1 h. The reaction mixture was quenched by the addition of brine (10 mL), the organic phase was separated, and the aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phases were washed with brine (1 × 10 mL), then dried ($MgSO_4$), and concentrated in vacuo. Purification of the residue by flash chromatography using EtOAc–hexane (1:1) as eluant gave **11** (200 mg, 73%) as a white solid.

An analytical sample was obtained by recrystallization from 2:1 hexane–EtOAc: mp 121–122 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.59 (ddd, J = 6.3, 6.3, 15.4 Hz, *H*C=CH), 5.37–5.44 (m, HC=C*H*), 4.90 (apparent quintet, C(3a)), 3.89–3.93 (m, 1 H), 3.75–3.81 (m, 2 H), 2.56–2.66 (m, 2 H), 2.37–2.42 (ddd, J = 7.8, 6.4, 14.2 Hz, 1 H), 2.12–2.27 (m, 4 H), 2.00–2.06 (m, 3 H), 1.90–1.96 (m, 1 H), 1.67–1.74 (m, 2 H), 0.97 (t, J = 7.4 Hz, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.8, 136.1, 124.0, 80.3, 80.1, 80.0, 70.9, 36.5, 33.2, 31.5, 26.3, 25.6, 16.7, 13.7; IR ($CHCl_3$) 3581, 1737, 1075 cm^{-1}; MS (CI) m/z 255 (MH), 237, 219. Anal. Calcd for $C_{14}H_{22}O_4$: C, 66.12; H, 8.72. Found: C, 66.04; H, 8.77.

(3a*R,8a*R**)-2(*R**)-[1(*S**)-[[Dimethyl(1,1-dimethylethyl)silyl]-oxy]-3(*E*)-hexenyl]-5-oxotetrahydrofuro[3,2-*b*]oxepane (12).** To a stirring solution of **11** (400 mg, 1.57 mmol) and 2,6-lutidine (0.731 mL, 6.28 mmol) in CH_2Cl_2 (17 mL) at 0 °C was added dropwise over 3 min TBSOTf (0.721 mL, 3.14 mmol). After being stirred at 0 °C for 1 h, the reaction mixture was diluted with a mixture of hexanes (40 mL) and ether (10 mL), washed with 1 M HCl (1 × 10 mL) and saturated $NaHCO_3$ solution (1 × 10 mL), dried ($MgSO_4$), and concentrated in vacuo. Purification of the residue by flash chromatography (20:1 to 1:1 hexanes–EtOAc) gave **12** (524 mg, 90%) as a viscous, colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.50 (ddd, J = 6.1, 6.1, 15.3 Hz, *H*C=CH), 5.40 (ddd, J = 7.0, 7.0, 15.3 Hz, HC=C*H*), 4.87 (ddd, J = 4.9, 4.9, 8.3 Hz, H(3a)), 3.83–3.87 (m, 2 H), 3.68 (ddd, J = 4.6, 5.9, 9.8 Hz, 1 H), 2.54–2.64 (m, 2 H), 2.34 (ddd, J = 5.9, 8.0, 13.8 Hz, 1 H), 2.15–2.20 (m, 3 H), 2.05–2.14 (m, 1 H), 1.97–2.04 (m, 2 H), 1.87–1.95 (m, 1 H), 1.67–1.76 (m, 2 H), 0.97 (t, J = 7.4 Hz, CH_2CH_3), 0.89 (s, $C(CH_3)_3$), 0.07 (s, $SiCH_3$), 0.06 (s, $SiCH_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.0, 134.8, 124.6, 80.3, 80.2, 79.7, 72.5, 38.1, 33.8, 31.7, 26.0, 25.9, 25.6, 18.1, 17.1, 13.6, −4.3, −4.4; IR (CCl_4) 2960, 2931, 2857, 1754, 1461, 1264, 1252, 1235, 1154, 1078 cm^{-1}; MS (CI) m/z 369 (MH), 237; MS (EI) m/z 311.1696 (13%, 311.1678 calcd for $C_{16}H_{27}O_4Si$, loss of *t*-Bu), 219 (15%), 213 (24%), 199 (21%), 187 (14%), 167 (95%).

(2*R,3*R**,5*R**)-5-[1(*S**)-[[Dimethyl(1,1-dimethylethyl)silyl]oxy]-3-(*E*)-hexenyl]-2-(4-oxobutyl)-3-hydroxytetrahydrofuran (13).** To a solution of **12** (520 mg, 1.41 mmol) in toluene (20 mL) at −78 °C was added dropwise over 5 min *i*-Bu_2AlH (0.377 mL, 2.12 mmol). The reaction mixture was maintained at −78 °C for 1.5 h and then quenched at −78 °C by the addition of MeOH (2 mL) followed by saturated NH_4Cl solution (20 mL). The organic layer was separated, and the aqueous layer was extracted with Et_2O (3 × 20 mL). The combined organic phases were washed with brine (1 × 15 mL), dried ($MgSO_4$), and concentrated in vacuo to leave **13** (508 mg, 97%) as a colorless oil, which was used without further purification: ^{1}H NMR (300 Mz, $CDCl_3$) δ 9.76 (t, J = 1.7 Hz, C*H*O), 5.45 (m, 1 H), 5.28 (m, 1 H), 4.06 (app dt, J = 3.0, 10.6 Hz, 1 H), 3.55 (m, 1 H), 3.35 (d, J = 11.4 Hz, O*H*), 2.57 (app

(33) Brown, H. C.; Mandal, A. K.; Kulkarni, S. U. *J. Org. Chem.* **1977**, *42*, 1392.

t, J = 12.1 Hz, 2 H), 2.3–1.85 (m, 6 H), 1.8–1.6 (m, 4 H), 0.95 (t, J = 7.5 Hz, CH_2CH_3), 0.91 (s, $C(CH_3)_3$), 0.13 (s, $SiCH_3$), 0.12 (s, $SiCH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.3, 135.1, 123.6, 83.2, 78.5, 73.3, 71.1, 43.7, 38.4, 34.0, 28.1, 25.7, 25.4, 18.9, 18.0, 13.4, −4.3, −4.9; IR (film) 3420 (br), 2958, 1730, 1255, 1078, 1050, 1028; MS (CI) m/z 371.2624 (MH, 371.2617 calcd for $C_{20}H_{39}O_4Si$).

(2*R,3*R**,5*R**)-5-[1(*S**)-[[Dimethyl(1,1-dimethylethyl)silyl]oxy]-3-(*E*)-hexenyl]-2-(4-oxo-2-(*E*)-butenyl)-3-[(trimethylsilyl)oxy]tetrahydrofuran (15).** To a stirring solution of $Me_3SiOSO_2CF_3$ (0.044 mL, 0.23 mmol), i-Pr_3NEt (0.040 mL, 0.23 mmol), and CH_2Cl_2 (0.4 mL) was added dropwise over 15 min a solution of **13** (18 mg, 0.046 mmol) in CH_2Cl_2 (1 mL). The reaction mixture was stirred at 23 °C for 2 h, diisopropylamine (0.5 mL) was added, stirring was continued for 5 min, and the solvent was removed in vacuo. The residue was triturated with dry hexanes (10 mL), then filtered through a pad of anhydrous $CaSO_4$, and concentrated to give enoxysilane **14** as a clear, colorless oil (23 mg). This material was used without purification in the subsequent oxidation: ^1H NMR (300 MHz, $CDCl_3$) δ 6.20 (d, J = 12 Hz, 0.33 H, *trans*-(TMS)OC*H*=), 6.14 (d, J = 6.5 Hz, 0.66 H, *cis*-(TMS)OC*H*=), 5.5–5.4 (m, C*H*=C*H*), 5.03 (m, 0.3 H, *trans*-(TMS)OCH=C*H*), 4.51 (app q, J = 6.5 Hz, 0.66 H, *cis*-(TMS)OCH=C*H*), 4.20 (m, (TMS)-OC*H*), 3.75 (m, 1 H), 3.60 (m, 1 H), 3.55 (m, 1 H), 2.25–1.5 (m, 10 H), 0.96 (t, J = 7 Hz, 3 H), 0.88 (s, 9 H), 0.16 (s), 0.14 (s), 0.095 (s), 0.085 (s), 0.07 (s), 0.05 (s); IR (film) 1650, 1248 cm^{-1}.

A mixture of this sample of **14** (23 mg), Pd $(OAc)_2$ (15 mg, 0.06 mmol), and CH_3CN (1 mL) was stirred at 23 °C for 1.5 h, then the solvent was evaporated in vacuo, and the residue was diluted with hexane (10 mL) and filtered through a pad of Celite. Concentration of the filtrate followed by purification of the residue by flash chromatography using hexanes–EtOAc (20:1) as eluant gave the enal **15** (10.6 mg, 53% from **13**) as a colorless oil: ^1H NMR (500 MHz, $CDCl_3$) δ 9.52 (d, J = 8.0 Hz, HC=O), 6.94 (ddd, J = 7.0, 7.0, 15.6 Hz, *H*C=CHC=O), 6.18 (dddd, J = 1.4, 1.4, 8.0, 15.6 Hz, HCC=O), 5.49 (ddd, J = 6.1, 6.1, 15.3 Hz, C=C*H*Et), 5.38–5.44 (m, *H*C=CHEt), 4.30 (ddd, J = 4.2, 4.7, 6.8 Hz, H(3)), 3.82 (apparent dd, J = 5.5, 10.7 Hz, CHO-(TBS)), 3.75 (ddd, J = 4.9, 4.9, 8.1 Hz, H(5)), 3.68 (ddd, J = 5.0, 7.2, 8.2 Hz, H(2)), 2.64 (dddd, J = 1.5, 6.8, 8.4, 15.2 Hz, *H*HCHC=CHC=O), 2.54 (dddd, J = 1.4, 5.0, 7.4, 15.4 Hz, H*H*CHC=CHC=O), 2.13–2.22 (m, 3 H), 1.98–2.03 (m, 2 H), 1.86 (ddd, J = 4.2, 8.5, 12.9 Hz, 1 H), 0.97 (t, J = 7.5 Hz, CH_2CH_3), 0.90 (s, $C(CH_3)_3$), 0.11 (s, $SiC(CH_3)_3$), 0.07 (s, $SiCH_3$), 0.06 (s, $SiCH_3$); IR (CCl_4) 2963, 2931, 2894, 2856, 1700, 1469, 1456, 1256 cm^{-1}; ^{13}C NMR (75 MHz, $CDCl_3$) δ 194.1, 156.5, 134.6, 134.0, 124.8, 80.8, 80.1, 73.3, 72.6, 38.1, 36.7, 33.4, 25.9, 25.6, 18.2, 13.7, −0.1, −4.2; MS (CI) m/z 441 (MH), 309, 291, 219, 201; MS (EI) m/z 440.2739 (440.2778 calcd for $C_{23}H_{44}O_4Si_2$).

(2*R,3*R**,5*R**)-2-(5,5-Dichloro-2(*E*),4-pentadienyl)-5-[1(*S**)-[[dimethyl(1,1-dimethylethyl)silyl]oxy]-3(*E*)-hexenyl]-3-[(trimethylsilyl)-oxy]tetrahydrofuran (16).** To a solution of diethyl trichloromethanephosphonate (70 mg, 0.28 mmol) in THF (0.4 mL) and Et_2O (0.6 mL) cooled to −100 °C (N_2/methylcyclohexane) was added *n*-BuLi (0.10 mL of a 2.5 M solution in hexane, 0.25 mmol). After 15 min at −100 °C, a solution of aldehyde **15** (7.0 mg, 0.016 mmol) in THF (0.5 mL) was added, and the temperature of the reaction mixture was allowed to reach 0 °C. The black mixture was then diluted with a saturated solution of $NaHCO_3$ (1 mL) followed by addition of $MeOBu^t$ (1 mL). The organic extracts were separated, and the aqueous layer was washed with $MeOBu^t$ (2 × 1 mL). The combined organic extracts were washed with brine (1 mL), dried (Na_2SO_4), and concentrated. Purification of the residue on silica gel (20:1 hexane–EtOAc) gave 7 mg (88%) of **16**: ^1H NMR (500 MHz, $CDCl_3$) δ 6.40 (d, J = 10.5 Hz, Cl_2C=CH), 6.25 (dddd, J = 1.3, 1.3, 10.5, 15.3 Hz, Cl_2C=CHC*H*), 5.89 (apparent quintet, J = 7.5 Hz, Cl_2C=CHCH=C*H*), 5.49 (ddd, J = 6.0, 6.0, 15.3 Hz, C=CHEt), 5.38–5.45 (m, *H*C=CEt), 4.24 (ddd, J = 3.7, 4.4, 6.8 Hz, H(3)), 3.81 (apparent dd, J = 5.4, 10.8 Hz, $CHOSiMe_2Bu^t$), 3.61–3.66 (m, H(5) and H(2)), 2.41–2.47 (m, 1 H), 2.34–2.39 (m, 1 H), 2.11–2.24 (m, 3 H), 1.98–2.06 (m, 2 H), 1.82 (ddd, J = 3.7, 8.1, 13.1 Hz, 1 H), 0.97 (t, J = 7.5 Hz, CH_2CH_3), 0.90 (s, $C(CH_3)_3$), 0.11 (s, $SiC(CH_3)_3$), 0.08 (s, $SiCH_3$), 0.07 (s, $SiCH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.5, 134.4, 129.0, 126.1, 125.0, 119.2, 81.9, 79.9, 73.4, 72.5, 38.1, 37.0, 33.3, 26.0, 25.7, 18.2, 13.7, 0.0, −4.2, −4.3; IR (CCl_4) 2962, 2931, 2856, 1250, 1106, 1081, 969 cm^{-1}; MS (CI) m/z 509 (MH), 507 (MH), 377, 375, 307, 305, 295, 293, 287, 285, 269, 267, 255, 149, 133.

(2*R*,3*R,5*R**)-2-(2(*E*)-Penten-4-ynyl)-5-[1(*S**)-[[dimethyl(1,1-dimethylethyl)silyl]oxy]-3(*E*)-hexenyl]-3[(trimethylsilyl)oxy]tetrahydrofuran (17).** To a solution of *n*-BuLi (0.05 mL of a 2.5 M solution in hexane, 0.13 mmol), Et_2O (0.6 mL) and THF (0.6 mL) at −70 °C was added dropwise a solution of diene **16** (19 mg, 0.038 mmol) in THF (0.5 mL). The reaction mixture was stirred at −70 °C for 10 min, then was warmed to −20 °C, and after an additional 10 min was quenched by the addition of saturated NH_4Cl solution (1 mL). The organic layer was separated, and the aqueous phase was extracted with Et_2O (3 × 5 mL). After drying (Na_2SO_4) and concentration, the residue was purified on silica gel (4:1 hexane–EtOAc) to provide 16 mg (98%) of **17** as a colorless oil: ^1H NMR (500 MHz, $CDCl_3$) δ 6.29 (ddd, J = 7.2, 7.2, 15.8 Hz, C≡CCH=C*H*), 5.54 (ddd, J = 1.6, 3.5, 15.9 Hz, C≡CCH), 5.39–5.51 (m, *H*C=C*H*Et) 4.24 (ddd, J = 3.7, 4.7, 6.9 Hz, H(3)), 3.80 (apparent dd, J = 5.5, 10.9 Hz, $CHOSiMe_2Bu^t$), 3.59–3.66 (m, H(2) and H(5)), 2.80 (d, J = 2.1 Hz, *H*C≡C), 2.33–2.44 (m, 2 H), 2.17–2.21 (m, 2 H), 2.13 (ddd, J = 6.9, 6.9, 13.5 Hz, 1 H), 1.99–2.04 (m, 2 H), 1.81 (ddd, J = 3.7, 8.1, 13.1 Hz, 1 H), 0.97 (t, J = 7.5 Hz, CH_2CH_3), 0.80 (s, $C(CH_3)_3$), 0.11 (s, $SiC(CH_3)_3$), 0.08 (s, $SiCH_3$), 0.06 (s, $SiCH_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.8, 134.5, 125.0, 110.1, 82.5, 81.6, 79.8, 75.8, 73.5, 72.4, 38.1, 37.1, 33.4, 26.0, 25.7, 18.2, 13.7, 0.0, −4.22, −4.24; IR (CCl_4) 3316, 2959, 2930, 2899, 2858, 2105, 1472, 1462, 1252, 1110, 1040 cm^{-1}; MS (CI) m/z 437 (MH), 367.2132 (367.2125 calcd for $C_{19}H_{35}O_3Si_2$, loss of C_5H_9), 305, 239, 133.

(2*R,3*R**,5*R**)-3-Acetoxy-5-[1(*S**)-[[dimethyl(1,1-dimethylethyl)-silyl]oxy]-3(*E*)-hexenyl]-2-(2-(*E*)-penten-4-ynyl)tetrahydrofuran (18).** To a stirred solution of **17** (78 mg, 0.179 mmol) in anhydrous MeOH (10 mL) was added anhydrous citric acid (166 mg, 0.86 mmol). The reaction mixture was stirred at 23 °C for 15 min, and then the solvent was removed in vacuo. The residue was partitioned between H_2O (5 mL) and Et_2O (20 mL), the organic layer was separated, and the aqueous layer was extracted with ether (2 × 15 mL). The combined organic phases were washed with saturated $NaHCO_3$ solution (2 × 5 mL) and brine (1 × 5 mL), dried ($MgSO_4$), and concentrated in vacuo to afford **18** (61.4 mg, 94%) as a colorless oil. ^1H NMR (500 MHz, $CDCl_3$) δ 6.30 (ddd, J = 7.5, 7.5, 15.8 Hz, C≡CCH=C*H*), 5.58 (ddd, J = 1.6, 3.7, 15.9 Hz, C≡CCH≡), 5.46–5.52 (m, 1 H), 5.26–5.32 (m, 1 H), 4.09 (ddd, J = 2.3, 3.1, 10.1 Hz, $CHOSiMe_2Bu^t$), 3.95 (app ddd, J = 2.3, 5.1, 11.2 Hz, 1 H), 3.91 (ddd, J = 2.1, 4.9, 9.4 Hz, H_5), 3.58 (ddd, J = 2.3, 6.9, 6.9 Hz, H(2)), 3.43 (d, J = 11.2 Hz, OH), 2.80 (d, J = 1.9 Hz, C≡CH), 2.47–2.50 (m, 2 H), 2.22–2.27 (m, 1 H), 2.2–2.17 (m, 1 H), 1.96–2.07 (m, 4 H), 0.97 (t, J = 7.4, CH_2CH_3), 0.93 (s, $C(CH_3)_3$), 0.08 (s, $Si(CH_3)_2$); IR (CCl_4) 3456, 3316, 2962, 2931, 2856, 2106, 1462, 1256 cm^{-1}; MS (CI) m/z 365.2504 (MH, 365.2512 calcd for $C_{21}H_{37}O_3Si$), 233, 151, 133.

A solution of this alcohol (10.0 mg, 0.0274 mmol), acetic anhydride (0.2 mL), pyridine (0.3 mL), and 4-(dimethylamino)pyridine (one crystal) in CH_2Cl_2 (1 mL) was stirred at 23 °C for 1 h. The mixture was diluted with CH_2Cl_2 (15 mL), washed successively with saturated $CuSO_4$ solution (1 × 2 mL), saturated $NaHCO_3$ solution (1 × 2 mL), and brine (1 × 2 mL), then dried ($MgSO_4$), and concentrated in vacuo. Purification of the residue by flash chromatography (20:1 hexanes–EtOAc) gave **18** (9.5 mg, 85%) as a colorless oil: ^1H NMR (500 MHz, $CDCl_3$) δ 6.25 (ddd, J = 7.2, 7.2, 16.0 Hz, C≡CCH=C*H*), 5.54 (ddd, J = 1.5, 3.6, 16.0 Hz, C≡CCH), 5.46–5.51 (m, 1 H), 5.35–5.41 (m, 1 H), 5.23 (ddd, J = 2.7, 4.5, 7.3 Hz, H(3)), 3.88 (ddd, J = 4.0, 6.0, 6.0 Hz, $CHOSiMe_2Bu^t$), 3.68–3.73 (m, H(2) and H(5)), 2.82 (d, J = 2.1 Hz, C≡CH), 2.44–2.48 (m, 1 H), 2.35–2.40 (m, 1 H), 2.27 (apparent quintet, J = 7.3 Hz, 1 H), 2.09–2.18 (m, 2 H), 2.06 (s, $OCOCH_3$), 1.89–2.04 (m, 3 H), 0.97 (t, J = 7.5 Hz, CH_2CH_3), 0.90 (s, $C(CH_3)_3$), 0.08 (s, $SiCH_3$), 0.07 (s, $SiCH_3$); IR (CCl_4) 3312, 2962, 2931, 2893, 2856, 1744, 1237 cm^{-1}; MS (CI) m/z 407.2625 (MH, 407.2617 calcd for $C_{23}H_{39}O_4Si$), 275, 255, 215, 133.

(2*R,3*R**,5*R**)-3-Acetoxy-5-(1(*S**)-hydroxy-3(*E*)-hexenyl)-2-(2-(*E*)-penten-4-ynyl)tetrahydrofuran (19).** A solution of silyl ether **18** (43 mg, 0.106 mmol) in dry CH_3CN (2 mL) containing HF·pyridine (Aldrich, ca. five drops) was maintained at 23 °C for 1 h. The reaction solution was then diluted with ether (30 mL), washed carefully with saturated $NaHCO_3$ solution (2 × 2 mL) and brine (1 × 2 mL), dried ($MgSO_4$), and concentrated. Purification of the residue by flash chromatography (9:1 and then 1:1 hexanes–EtOAc) gave **19** (31 mg, 100%) as a viscous, colorless oil: ^1H NMR (500 MHz, $CDCl_3$) δ 6.23 (ddd, J = 7.3, 7.3, 15.9 Hz, C≡CCH=C*H*), 5.56–5.61 (m, 2 H), 5.37–5.55 (m, 1 H), 5.24 (ddd, J = 2.3, 4.0, 6.5 Hz, H(3)), 3.86 (ddd, J = 3.7, 6.6, 8.1 Hz, 1 H), 3.81–3.83 (m, C*H*COH), 3.79 (ddd, J = 3.9, 5.7, 7.6 Hz, 1 H), 2.83 (d, J = 2.1 Hz, C≡CH), 2.39–2.51 (m, 2 H), 2.30 (ddd, J = 6.7, 8.0, 14.5 Hz, 1 H), 2.14–2.18 (m, 2 H), 1.98–2.09 (m, 4 H), 2.08 (s, $OCOCH_3$), 0.98 (t, J = 7.5, CH_2CH_3), addition of D_2O results in collapse of the multiplet at δ 3.81–3.83 to a ddd (J = 3.8, 6.1, 7.1 Hz) and loss of 1 H in the multiplet at δ 1.98–2.09; ^{13}NMR (125 MHz, $CDCl_3$) δ 170.33, 141.62, 135.72, 123.96, 111.01, 81.87, 80.05, 79.96, 76.63, 74.36, 71.02, 36.26, 32.66, 32.63, 25.54, 20.97, 13.64; IR (CCl_4) 3583, 3314, 2968, 2939, 2847, 1743, 1439, 1374, 1240 cm^{-1}; MS (CI) m/z 293, (MH), 233, 227, 215, 133; MS (EI) m/z 292.1690 (292.1674 calcd for $C_{17}H_{24}O_4$, M).

(±)-*trans*-Kumausyne (1). To a solution of **19** (13.5 mg, 0.046 mmol) in benzene (2 mL) were added, 2,6-di-*tert*-butylpyridine (0.026 mL, 0.11 mmol), Ph_3P (32 mg, 0.11 mmol), and freshly sublimed CBr_4 (41 mg,

0.11 mmol). The reaction mixture was warmed to 40 °C, and then a second batch of Ph_3P (32 mg, 0.11 mmol) and CBr_4 (41 mg, 0.11 mmol) was added. The solution was stirred for 30 min at 40 °C, allowed to cool to 23 °C, and then filtered through a plug of silica gel (1:1 hexanes–CH_2Cl_2). The filtrate was concentrated and purified by flash chromatography (4:1 hexanes–CH_2Cl_2) to give **1** (6.6 mg, 40%) as a colorless oil: ^1H NMR (500 MHz, $CDCl_3$) δ 6.24 (ddd, J = 7.4, 7.4, 15.8 Hz, C≡CCH=C*H*) 5.54–5.64 (m, 2 H), 5.27–5.36 (m, 1 H), 5.25 (ddd, J = 2.7, 4.2, 6.9 Hz, H(3)), 3.99–4.04 (m, 2 H), 3.85 (ddd, J = 4.4, 6.1, 7.2 Hz, 1 H), 2.83 (d, J = 2.1 Hz, C≡CH), 2.67–2.72 (m, 2 H), 2.41–2.56 (m, 3 H), 2.01–2.10 (m, 2 H), 2.09 (s, CH_3CO), 1.91 (ddd, J = 2.6, 7.1, 14.5 Hz, 1 H), 1.00 (t, J = 7.5 Hz, CH_2CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.44, 141.62, 135.88, 124.75, 111.05, 82.01, 80.20, 79.48, 76.59, 74.12, 56.59, 37.46, 36.48, 32.79, 25.57, 20.99, 13.63; IR (film) 3292, 2926, 1740, 1375, 1240 cm^{-1}; MS (CI) m/z 355.0912 (355.0830 calcd for $C_{17}H_{24}{}^{79}BrO_3$, MH), 357.0900 (357.0830 calcd for $C_{17}H_{24}{}^{81}BrO_3$, MH).

(2*S*)-2-Hydroxy-2-vinylcyclopentanone ((*S*)-22). To a stirring solution of ketoenamine **21** (500 mg, 2.56 mmol)[27] and Et_2O (30 mL) at −78 °C was added dropwise over 30 min a solution of vinylmagnesium bromide (1.0 M in THF, 6.4 mL, 6.4 mmol) and Et_2O (30 mL). The reaction was stirred at −78 °C for 30 min and then quenched by the addition of saturated NH_4Cl solution (30 mL). The organic layer was separated, and the aqueous layer was extracted with ether (3 × 30 mL). The combined organic phases were washed with brine (1 × 30 mL), dried ($MgSO_4$), and concentrated. Purification of the residue by flash chromatography using hexanes–Et_2O (1:1) as eluant gave (2*S*)-**22** (210 mg, 65%) as a pale yellow oil: $[\alpha]^{25}_D$ 32.7° (*c* 1.4, $CHCl_3$).

(1*S*,2*R*)-1-Vinylcyclopentane-1,2-diol ((1*S*),(2*R*)-3). Reduction of (2*S*)-**22** (210 mg, 1.67 mmol) under the conditions described previously for the reduction of the related racemic ketone[8] gave (1*S*,2*R*)-**3** (174 mg, 81%) as a viscous, colorless oil: $[\alpha]^{25}_D$ − 58.4° (*c* 1.25, $CHCl_3$).

A solution of this diol sample (10 mg, 0.078 mmol), (*R*)-(−)-α-methoxyphenylacetic acid (13.8 mg, 0.0819 mmol), dicyclohexylcarbodiimide (17 mg, 0.082 mmol), 4-pyrrolidinopyridine (1.1 mg, 0.078 mmol), and dry CH_2Cl_2 (0.5 mL) was maintained at 23 °C for 1.5 h.[31] Concentration followed by purification of the residue by flash chromatography (3:1 hexanes–Et_2O) gave the monoester **23** (18 mg, 86%) as a colorless oil. The enantiomeric excess of **3** was determined to be 84% by ^1H NMR integration of the vinylic hydrogen signals of the major and minor distereoisomers at δ 5.4 and 5.9, respectively.

(2*R*,3a*R*,7a*R*)-Hexahydro-2-[(benzyloxy)methyl]-4(2*H*)-benzofuranone ((−)-5). Reaction of a sample of (1*S*,2*R*)-**3** (55 mg, 0.41 mmol) with α-(benzyloxy)acetaldehyde, under conditions identical with those described[8] for the racemic diol, provided (−)-**5** (64 mg, 57%) as a colorless oil: $[\alpha]^{26}_D$ −8.9° (c, 1.28, $CHCl_3$).

Conversion of (−)-5 to (*R*)-Methylmandelate Ester 25. A mixture of (−)-**5** (64 mg, 0.25 mmol), 10% Pd/C (8 mg), and EtOAc (1.5 mL) was stirred at 23 °C under an atmosphere of H_2 for 18 h. The reaction mixture was then filtered through a pad of Celite, and the filtrate was concentrated. Purification of the residue by flash chromatography (EtOAc) gave alcohol **24** (39 mg, 93%) as a viscous, colorless oil: $[\alpha]^{26}_D$ − 38.4° (*c* 1.95, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 4.32 (m, 1 H), 4.00 (m, 1 H), 3.64 (m, 1 H), 3.47 (m, 1 H), 2.78 (m, 1 H), 2.45 (m, 1 H), 2.35 (m, 2 H), 2.08 (m, 1 H), 2.04–1.73 (m, 5 H); IR (film) 3423 (br, OH), 1706, 1048 cm^{-1}, MS (EI, 70 eV) m/z 170.0941 (170.0943 calcd for $C_9H_{14}O_3$, M).

A solution of alcohol **24** (19 mg, 0.188 mmol), (*R*)-(−)-α-methoxyphenylacetic acid (19.5 mg, 0.118 mmol), DCC (24 mg, 0.12 mmol), and 4-pyrrolidinopyridine (2.0 mg, 0.012 mmol) in dry CH_2Cl_2 (1.0 mL) was maintained at 23 °C for 1.5 h.[31] Evaporation of the solvent followed by purification of the residue by flash chromatography (1:1 hexanes–EtOAc) gave **25** (34 mg, 92%) as a colorless oil. The enantiomeric excess of **24** was determined to be 84% by ^1H NMR (500 MHz, $CDCl_3$) comparison of the integrals for the methoxy signlets at δ 3.39 and 3.42 and the methine singlets at δ 4.80 and 4.82 of the major and minor diastereomers of **25**, respectively.

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Registry No. 1, 126786-44-5; **3**, 133870-03-8; (1*S*,2*R*)-**3**, 133908-24-4; **5**, 133870-04-9; (−)-**5**, 133908-25-5; **6**, 133870-05-0; **7**, 133870-06-1; **8**, 133870-07-2; **9**, 133870-08-3; **10**, 133870-09-4; **11**, 133870-10-7; **12**, 133870-11-8; **13**, 133870-12-9; *cis*-**14**, 133870-13-0; *trans*-**14**, 133908-26-6; **15**, 133870-14-1; **16**, 133886-79-0; **17**, 133870-15-2; **18**, 133870-16-3; **19**, 133870-17-4; **20**, 133870-18-5; **21**, 96304-33-5; (2*S*)-**22**, 133870-19-6; **23**, 133870-20-9; **24**, 133870-21-0; **25**, 133870-22-1; 1,2-cyclopentanedione, 3008-40-0; (*S*)-*O*-methylprolinol, 63126-47-6.

Bis-Heteroannulation. 15. Enantiospecific Syntheses of (+)- and (−)-Norsecurinine

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Abstract: (−)-Norsecurinine (**2a**) has been prepared in a stereospecific fashion with the acetylenic oxazole **39** as the starting material. Diels–Alder cyclization of **39** afforded the furano ketone **45** that was transformed in five steps to the butenolide mesylate **52**. Transannular alkylation of **52** then afforded **2a**. In identical fashion, *ent*-**39** gave (+)-norsecurinine (**2b**).

Introduction

The *Securinega* alkaloids are a family of more than 20 compounds isolated from the *Securinega* and *Phyllanthus* genera of *Euphorbiaceae*,[1] most of which contain either a "securinine-type" skeleton I or a "norsecurinine-type" skeleton II (Figure 1). Members of skeletal class I are built upon an indolizidine nucleus, while those of class II are built upon a pyrrolizidine nucleus. All of these compounds contain an α,β-unsaturated-γ-lactone (butenolide) moiety, and they also share in common the interesting azabicyclo[3.2.1]octane ring system.

Securinine (**1**) is the most abundant of the *Securinega* alkaloids and it was the first member of this group to be isolated (1956) and characterized (1962).[2a-c] The degradative and spectroscopic

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