β-Hydroxy-*γ*-lactones as Chiral Building Blocks for the Enantioselective Synthesis of Marine Natural Products†

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The enantioselective synthesis of *trans*-(+)-laurediol, (2*S*,3*S*,5*R*)-5-[(1*R*)-1-hydroxy-9-decenyl]-2-pentyltetrahydro-3-furanol, and (2*S*,3*S*,5*S*)-5-[(1*S*)-1-hydroxy-9-decenyl]-2-pentyltetrahydro-3-furanol are described. In addition, a formal synthesis of *trans*-(−)-kumausyne is also developed. All the synthetic procedures have in common the use of enantiomerically enriched *β*-hydroxy-*γ*-lactones, easily available by Sharpless asymmetric dihydroxylation (AD) from the suitable *β*,*γ*-unsaturated ester. The use of Katsuki−Sharpless asymmetric epoxidation (AE) as an additional enantioselective reaction provides cyclic compounds of high enantiomeric purity.

Introduction

Red and brown algae have been considered to be very important sources of marine natural products, which exhibit a large number of biological properties including antitumor, antimicrobial, immunosuppressant, antifeedant, pesticide activity, etc.[1] Red algae of the genus *Laurencia* produce a multitude of unique compounds, such as a series of nonterpenoid C15 metabolites generally named *lauroxanes* that are derived from fatty acid metabolism (acetogenins).[1] Thus, from *Laurencia nipponica* linear compounds such as the enantiomers of (3*E*,9*Z*,12*E*)-pentadeca-3,9,12-trien-1-yne-6,7-diol (*trans*-laurediol) and (3*Z*,9*Z*,12*E*)-pentadeca-3,9,12-trien-1-yne-6,7-diol (*cis*-laurediol)[2] and cyclic products such as *trans*-(−)-kumausyne (**2**) and *trans*-(+)-deacetylkumausyne (**3**) (Figure 1) have been isolated.[3] *Lauroxanes* have in common the presence of polysubstituted cyclic ethers with a defined stereochemistry in the substituents and a ring size changing from five to nine members. The cyclic ethers are considered to be biogenetically originated from laurediols (**1**) through intramolecular electrophilic cyclizations, usually induced by bromonium ion.[1]

On the other hand, (2*S*,3*S*,5*R*)-5-[(1*R*)-1-hydroxy-9-decenyl]-2-pentyltetrahydro-3-furanol (**4**)[4] and (2*S*,3*S*,5*S*)-5-[(1*S*)-1-hydroxy-9-decenyl]-2-pentyltetrahydro-3-furanol (**5**)[5] are C19 diols isolated from *Notheia anomala*, a member of the Notheiaceae family, a taxonomically unique brown alga found along the southern Australian coasts. These tetrahydrofurans have been considered to be biosynthesized via a cyclization of a natural methylene-interrupted bisepoxide and, within this context, a biomimetic synthesis of the racemic compounds has been reported (Figure 2).[6] They are potent and selective inhibitors of the larval development of parasitic nematodes.[5]

Within our program directed at the asymmetric total synthesis of bioactive substances of marine origin,[7] we focused our attention on the metabolites containing a highly functionalized tetrahydrofuran ring and their linear biogenetic precursors. We considered the possibility of developing a common methodology for both kinds of metabolites. In this contribution, we describe the enantioselective synthesis of these compounds, *trans*-(+)-**1**, (−)-**2**, (+)-**4**, and (+)-**5**, using as precursors functionalized *β*-hydroxy-*γ*-lactones **8**.[8] Basically, our idea is to synthesize the tetrahydrofuran ring by an intramolecular opening of an epoxide **6** available from the suitable alkene via asymmetric epoxidation. The stereoselective synthesis of the necessary linear unsaturated precursors could be envisioned by using Wittig-type reactions from the corresponding lactol **7** accessible from the key *γ*-lactone **8**. This methodology would be also the base for the synthesis of the linear laurediols (**1**). Finally, **8** could be

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† This paper is dedicated to Professor K. Barry Sharpless in recognition of his outstanding contribution to the art and science of organic chemistry.

(1) (a) Moore, R. E. In *Marine Natural Products*; Scheuer, P. J., Ed.; Academic Press: New York, 1978; Vol. 1, pp 43−121. (b) Erickson, K. L. In *Marine Natural Products*; Scheuer, P. J., Ed.; Academic Press: New York, 1983; Vol. V, pp 131−257. (c) Faulkner, D. J. *Nat. Prod. Rep.* **1984**, *1*, 251. (d) Faulkner, D. J. *Nat. Prod. Rep.* **1986**, *3*, 1. (e) Faulkner, D. J. *Nat. Prod. Rep.* **1987**, *4*, 539. (f) Faulkner, D. J. *Nat. Prod. Rep.* **1988**, *5*, 613. (g) Faulkner, D. J. *Nat. Prod. Rep.* **1990**, *7*, 269. (h) Faulkner, D. J. *Nat. Prod. Rep.* **1991**, *8*, 97. (i) Faulkner, D. J. *Nat. Prod. Rep.* **1992**, *9*, 323. (j) Faulkner, D. J. *Nat. Prod. Rep.* **1993**, *10*, 497. (k) Faulkner, D. J. *Nat. Prod. Rep.* **1994**, *11*, 355. (l) Faulkner, D. J. *Nat. Prod. Rep.* **1995**, *12*, 223. (m) Faulkner, D. J. *Nat. Prod. Rep.* **1997**, *14*, 259. (n) Faulkner, D. J. *Nat. Prod. Rep.* **1998**, *15*, 113. (o) Faulkner, D. J. *Nat. Prod. Rep.* **1999**, *16*, 155.

(2) Kurosawa, E.; Fukuzawa, A.; Irie, T. *Tetrahedron Lett.* **1972**, *21*, 2121.

(3) Suzuki, T.; Koizumi, K.; Suzuki, M.; Kurosawa, E. *Chem. Lett.* **1983**, 1643.

(4) Warren, R. G.; Wells, R. J.; Blount, J. F. *Aust. J. Chem.* **1980**, *33*, 891.

(5) Capon, R. J.; Barrow, R. A.; Rochfort, S.; Jobling, M.; Skene, C. *Tetrahedron* **1998**, *54*, 2227.

(6) (a) Capon, R. J.; Barrow, R. A.; Skene, C.; Rochfort, S. *Tetrahedron Lett.* **1997**, *38*, 7609. (b) Capon, R. J.; Barrow, R. A. *J. Org. Chem.* **1998**, *63*, 75.

(7) (a) Martín, T.; Soler, M. A.; Betancort, J. M.; Martín, V. S. *J. Org. Chem.* **1997**, *62*, 1570. (b) Betancort, J. M.; Martín, V. S.; Padrón, J. M.; Palazón, J. M.; Ramírez, M. A.; Soler, M. A. *J. Org. Chem.* **1997**, *62*, 4570. (c) Ramírez, M. A.; Padrón, J. M.; Palazón, J. M.; Martín, V. S. *J. Org. Chem.* **1997**, *62*, 4584. (d). Martín, T.; Martín, V. S. *Tetrahedron Lett.* **2000**, *41*, 2503. (e) García, C.; Soler, M. A.; Martín, V. S. *Tetrahedron Lett.* **2000**, *41*, 4127.

(8) For a very recent application of *β*-hydroxy-*γ*-lactones to the enantioselective synthesis of natural products, see: Han, X.; Corey, E. J. *Org. Lett.* **2000**, *2*, 2543.

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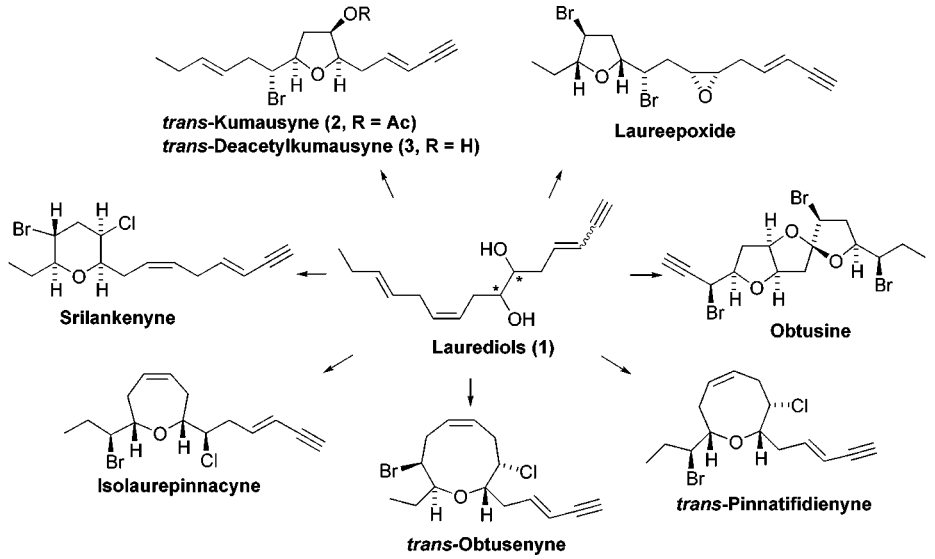


Figure 1. Representative *lauroxanes* isolated from *Laurencia*.

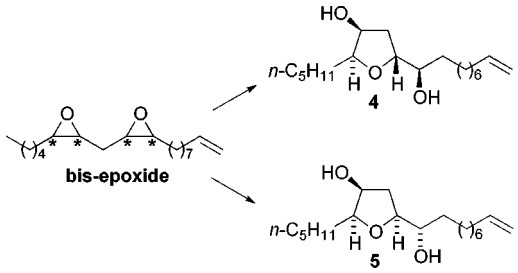
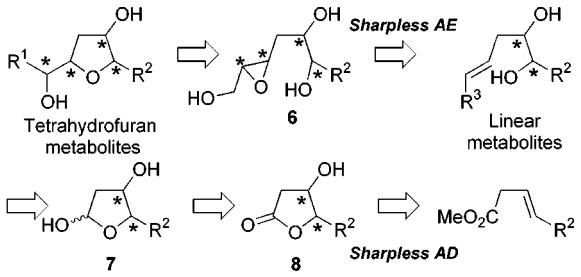


Figure 2. Hypothetic biosynthetic origin of C19 diols.

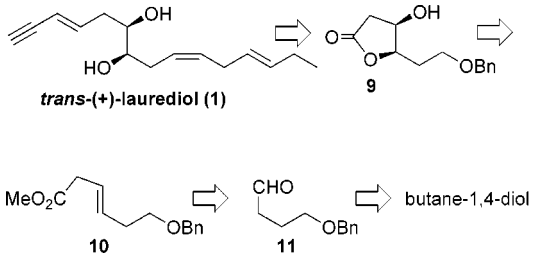
Scheme 1



obtained in both excellent yield and enantiomeric purity by asymmetric dihydroxylation of β,γ-unsaturated esters (Scheme 1).[9]

Synthesis of Linear Metabolites. Enantioselective Synthesis of *trans*-(+)-Laurediol (1). Considering the possible biologic origin of *lauroxanes* (Figure 1), we envisioned a synthesis of these compounds by intramolecular cyclization of hydroxyalkenes induced by a bromonium ion.[7a] Because of the necessity to perform these cyclization studies with laurediol (**1**), we needed to improve the two reported syntheses of **1** that in both cases were impractical to scale the production of the natural diol.[10,11] In this paper, we describe a shorter and highly convergent synthesis of *trans*-(+)-laurediol (**1**) based on the general strategy outlined above (Scheme 1)

Scheme 2



in which we disconnect to the β-hydroxy-γ-lactone **9** with the correct stereochemical requirements (Scheme 2).[12]

Selective monobenzylation of commercially available butane-1,4-diol provided **12** which was oxidized to the corresponding aldehyde **11**. Modified Knoevenagel condensation with malonic acid and piperidine as catalyst under nonpolar conditions[13] provided, after esterification, the (*E*)-β,γ-unsaturated-ester **10**. The application of the Sharpless asymmetric dihydroxylation reaction using AD-mix-β yielded the chiral β-hydroxy-γ-lactone **9** (93% ee).[14] With this step we simultaneously achieved two important goals: first, we introduced the correct stereochemistry in two stereocenters of the final molecules; second, by the lactonization we performed the chemical differentiation between the two hydroxy groups. Protection of the free secondary alcohol as a silyl ether and cleavage of the benzyl ether afforded the protected β-hydroxy-γ-lactone **14** (Scheme 3).

At this stage of the synthesis we were ready to homologate in both directions in order to build the carbon framework. Thus, oxidation of **14** produced an aldehyde that was converted to the corresponding (*Z*)-olefin **15** through a stereoselective Wittig reaction. For the completion of the synthesis, the γ-lactone was reduced with 1 equiv of DIBAL-H and the lactol submitted to Wittig

(9) (a) Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483. (b) Harcken, C.; Brückner, R. *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2750.

(10) Masamune et al. accomplished a synthesis of trans-**1** in 21 steps from (2*R*, 3*R*)−(+)-tartaric acid: Fukuzawa, A.; Sato, H.; Miyamoto, M.; Masamune, T. *Tetrahedron Lett.* **1986**, *27*, 2901.

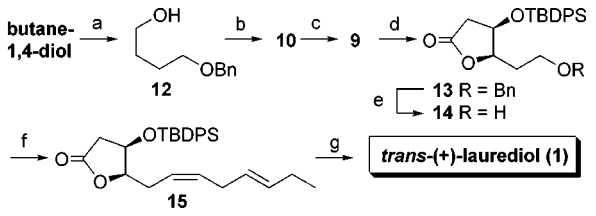
(11) From our laboratory was published also an enantioselective synthesis of both *cis*- and *trans*-laurediol in 28 steps from propargylic alcohol: Añorbe, B.; Martín, V. S.; Palazón, J. M.; Trujillo, J. M. *Tetrahedron Lett.* **1986**, *27*, 4991.

(12) For a preliminary communication of this work, see ref 7d.

(13) Ragoussis, N. *Tetrahedron Lett.* **1987**, *28*, 93.

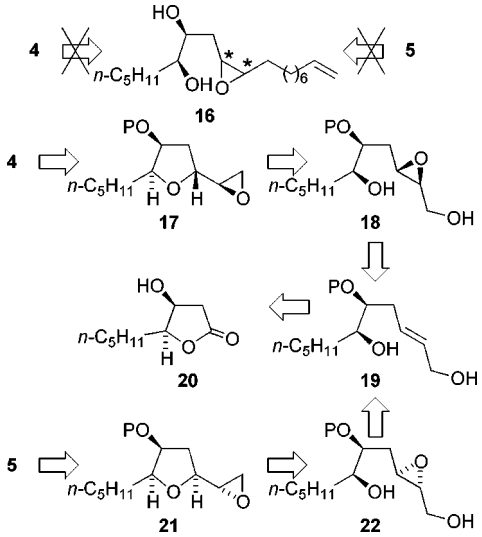
(14) The enantiomeric excess was determined by the ^{1}H NMR analysis of the corresponding (*R*)- and (*S*)-Mosher esters. Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543.

Scheme 3



(a) NaH, BnBr, *n*-Bu_4NI (cat.), THF, 0 °C, 78%. (b) (i) SO_3·Py, DMSO, Et_3N, CH_2Cl_2; (ii) malonic acid, piperidine (cat.), xylene, reflux; (iii) TMSCl, MeOH, room temperature, 58% overall. (c) AD-mix-*β*, $CH_3SO_2NH_2$, *t*-BuOH: H_2O (1:1), 0 °C, 90%. (d) TBDPSCl, imidazole, CH_2Cl_2, room temperature, 95%. (e) H_2, Pd−C 10%, EtOAc, 98%. (f) (i) PCC, NaOAc, CH_2Cl_2, 4 Å MS; (ii) (*E*)-$EtCH{=}CHCH_2CH_2PPh_3^+I^-$,[15] $KN(TMS)_2$, THF, −78 °C, 4 Å MS, 36% overall. (g) (i) DIBAL-H (1 equiv), Et_2O, −78 °C; (ii) $TMSC{\equiv}CCH_2PPh_3{+}Br^-$, KOBu-*t*, Et_2O, 0 °C to room temperature; (iii) *n*-Bu_4NF, THF, rt, 78% overall.

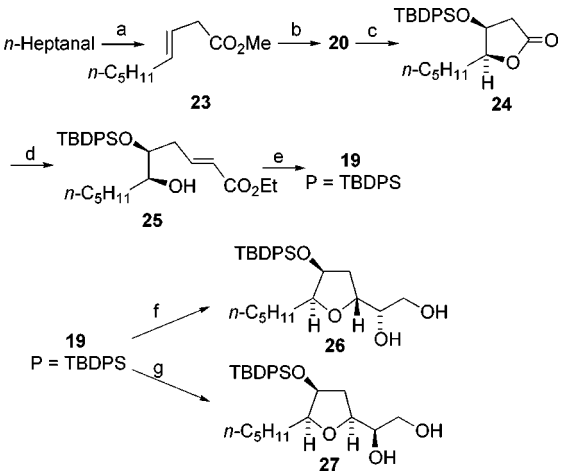
Scheme 4



olefination with the ylide derived from commercially available [3-(trimethylsilyl)-2-propynyl]triphenylphosphonium bromide to yield the *trans*-enyne. Fluoride-induced cleavage of the silyl-protecting groups furnished *trans*-(+)-laurediol (**1**): $[\alpha]^{25}_D = +19.8$ (*c* 1.2, CCl_4).[16]

Synthesis of Metabolites Having a Tetrahydrofuran Ring. Considerable efforts have been directed to the synthesis of **4**,[17] but, to the best of our knowledge, no asymmetric synthesis of **5** has hitherto been reported. In this paper, we describe our approach to the enantiomeric synthesis of these compounds, based on the retrosynthetic analysis outlined in Scheme 4.[18] We aimed to achieve stereochemical control in the ring formation from a common precursor with both high stereoselectivity and flexibility. A possible solution to the problem could

Scheme 5



(a) (i) malonic acid, piperidine (cat.), xylene, reflux; (ii) TMSCl, MeOH, room temperature, 80% overall. (b) AD-mix-α, $CH_3SO_2NH_2$, *t*-BuOH: H_2O (1:1), 0 °C, 82%. (c) TBDPSCl, imidazole, CH_2Cl_2, room temperature, 96%. (d) (i) DIBAL-H (1 equiv), Et_2O, −78 °C; (ii) $Ph_3P{=}CHCO_2Et$, benzene, 50 °C, 89% overall. (e) DIBAL-H, Et_2O, 0 °C, 5 min, 77%. (f) Ti(OPr-*i*)$_4$, (*R*,*R*)-(+)-DET, TBHP, CH_2Cl_2, −20 °C, 82%. (g) Ti(OPr-*i*)$_4$, (*S*, *S*)-(−)-DET, TBHP, CH_2Cl_2, −20 °C, 82%.

be the intramolecular opening of the suitable epoxy alcohols **16** with the proper stereochemistry. However, this approach implies the stereoselective synthesis of epoxides derived from *Z*-olefins which, in general terms, is difficult to achieve.[19,20] Considering the synthesis of **4** and to overcome this difficulty, we first disconnected the unsaturated chain from the terminal epoxide **17**, bearing in mind the possibility of introducing such a chain by a nucleophilic opening of the terminal ring. Now, this epoxide with the correct stereochemistry would be built from the suitable 2,3-epoxy alcohol **18**, available by a Katsuki−Sharpless asymmetric epoxidation (AE) of the corresponding allylic alcohol **19** obtained by homologation from the *β*-hydroxy-*γ*-lactone **20**. Two major advantages derive from this strategy: first, the synthesis of the diastereoisomer **5** would be simply achieved by changing the chiral auxiliary at the AE step; second, the application of two enantioselective reactions ensures the high enantiomeric purity of the final products.

Our synthesis of **4** and **5** started with the unsaturated ester **23**, available by a modified Knoevenagel condensation of malonic acid and *n*-heptanal and further esterification (Scheme 5).[13] The application to **23** of the AD reaction using AD-mix-α yielded the *γ*-lactone **20** in 96% ee.[9,14] The protection of the free secondary hydroxy group led to the silyl ether **24**, which was converted to the (*E*)-unsaturated ester **25** by selective reduction to the corresponding lactol followed by a Horner−Wadsworth−Emmons reaction.[21] The reduction of **25** provided the common allylic alcohol **19**, useful to introduce the two remaining stereocenters in both **4** and **5**. For the synthesis of **4**, the asymmetric epoxidation of **19** using (*R*,*R*)−(+)-DET provided by concomitant epoxide opening the *anti*-tetrahydrofuran **26** as the sole detected stereoisomer.[22] In a similar manner the use of the enantio-

(15) The phosphonium salt was prepared by refluxing $(Ph)_3P$ and (*E*)-$C_2H_5CH{=}CHCH_2CH_2I$ in CH_3CN. The iodide was synthesized from the commercially available alcohol [$(Ph)_3P$, imidazole, I_2, C_6H_6, room temperature].

(16) The α reported in the literature for natural *trans*-(+)-laureddiol (ref 2) was 27.2, but no concentration and temperature data were provided.

(17) (a) Williams, D. R.; Harigaya, Y.; Moore, J. L.; D'sa, A. *J. Am. Chem. Soc.* **1984**, *106*, 2641. (b) Hatakeyama, S.; Sakurai, K.; Saijo, K.; Takano, S. *Tetrahedron Lett.* **1985**, *26*, 1333. (c) Gurjar, M. K.; Mainkar, P. S. *Heterocycles* **1990**, *31*, 407. (d) Chikashita, H.; Nakamura, Y.; Uemura, H.; Itoh, K. *Chem. Lett.* **1993**, 477. (e) Wang, Z.-M.; Shen, M. *J. Org. Chem.* **1998**, *63*, 1414. (f) Mori, Y.; Sawada, T.; Furukawa, H. *Tetrahedron Lett.* **1999**, *40*, 731.

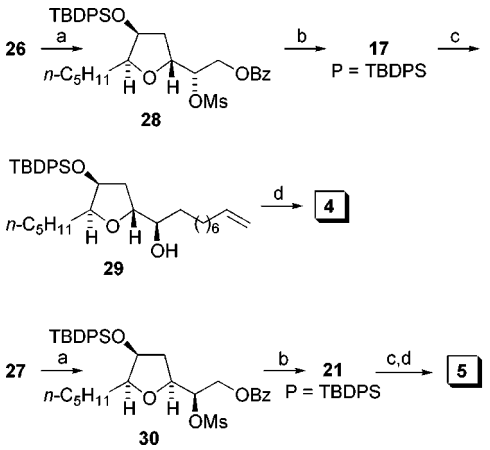
(18) For a preliminary communication of this work, see ref 7e.

(19) Katsuki, T.; Martín, V. S. In *Organic Reactions*; Paquette, L. A., et al., Eds.; John Wiley & Sons: New York, 1996; Vol. 48, pp 1−299.

(20) *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: New York, 1999; Vol. II and references therein.

(21) Boland, W.; Ney, P.; Jaenieke, L. *Synthesis* **1980**, 1015.

Scheme 6



(a) (i) BzCl (1.2 equiv), TEA, CH_2Cl_2, 0 °C; (ii) MsCl, TEA, 0 °C, 75%. (b) NaH, MeOH, CH_2Cl_2, 0 °C, 80%. (c) $H_2C{=}CH{-}(CH_2)_6MgBr$, CuI, THF, −30 °C. (d) TBAF, THF, room temperature, 78% overall.

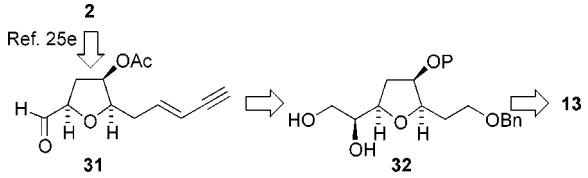
meric chiral auxiliary provided the corresponding *syn*-diastereoisomer **27**.[23]

To fulfill the synthesis of the natural compounds, first we addressed our efforts to the synthesis of **4** considering that the formation of **5** would be a simple extension of the methodology. Thus, the diol **26** was monoprotected as the benzoyl ester and the secondary free alcohol was transformed into the corresponding mesylate **28**. Basic hydrolysis of the ester then provided the terminal epoxide **17** (P = TBDPS) by intramolecular displacement of the secondary mesylate group with the primary alkoxide (Scheme 6). Opening of the terminal epoxide with the Grignard reagent derived from commercially available 8-bromo-1-octene, in the presence of CuI, furnished compound **29** which, after cleavage of the silyl protecting group, provided (2*S*,3*S*,5*R*)-5-[(1*R*)-1-hydroxy-9-decenyl]-2-pentyltetrahydro-3-furanol (**4**): mp 50−52 °C, $[\alpha]^{25}_D$ = +15.2 (*c* 0.8, $CHCl_3$) [lit[4] mp 54.5−55.0 °C, $[\alpha]^{25}_D$ = +15 (*c* 1, $CHCl_3$)].

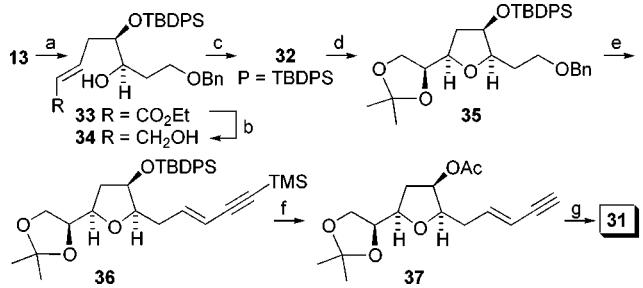
As mentioned before and with these satisfactory results in our hands, the synthesis of the diastereoisomer **5**, mp 35−37 °C, $[\alpha]^{25}_D$ = +20.5 (*c* 0.4, $CHCl_3$),[24] was performed in a straightforward and similar manner from **27** (Scheme 6).

Upon resolving the synthesis of **4** and **5** as examples of compounds having a tetrahydrofuran ring in their structures, we considered the possibility of using our methodology also for the synthesis of compounds with a halide in their structure. Thus, we addressed our attention to *trans*-(−)-kumausyne (**2**) considering the development of a new synthesis of such compounds. In recent

Scheme 7



Scheme 8



(a) (i) DIBAL-H (1 equiv), Et_2O, −78 °C; (ii) $Ph_3P{=}CHCO_2Et$, benzene, 50 °C, 89% overall. (b) DIBAL-H, Et_2O, 0 °C, 82%. (c) $Ti(OPr\text{-}i)_4$, (*R*,*R*)-(+)-DET, TBHP, CH_2Cl_2, −20 °C, 80%. (d) 2, 2-dimethoxy-propane, CSA (cat.), CH_2Cl_2, 93%. (e) (i) H_2, Pd−C 10%, EtOAc; (ii) PCC, NaOAc, CH_2Cl_2, 4 Å MS; (iii) $TMSC{\equiv}CCH_2PPh_3{+}Br^-$, *n*-BuLi, THF, −78 °C to room temperature, 50% overall. (f) (i) *n*-Bu_4NF, THF, room temperature; (ii) Ac_2O, Et_3N, DMAP (cat.), CH_2Cl_2, 87% overall. (g) (i) CSA (cat.), MeOH; (ii) $NaIO_4$, THF/H_2O (5:1), 85% overall.

years, a number of approaches to the syntheses of these compounds have been reported.[7a,25] Boukouvalas et al.,[25e] synthesized *trans*-(−)-kumausyne (**2**) using as a precursor the aldehyde **31**. Here we present an alternative enantioselective synthesis of **31** following the general strategy used above. The aldehyde function could be obtained from a diol cleavage of the tetrahydrofuran **32**, which could be straightforwardly obtained from the protected β-hydroxy-γ-lactone **13** (Scheme 7).

The synthesis of **31** started with the β-hydroxy-γ-lactone **13**. The application of a series of steps similar to those used in the syntheses of both **26** and **27** yielded **32** (P = TBDPS) as a pure stereoisomer. In this way, we constructed the desired tetrahydrofuran ring having controlled the three stereocenters (Scheme 8). Protection of the 1,2-diol functionality as its isopropylidene **35**, followed by cleavage of the benzyl ether and subsequent oxidation provided the corresponding aldehyde which, without purification, was treated with the ylide derived from commercially available [3-(trimethylsilyl)-2-propynyl]triphenylphosphonium bromide to afford the *trans*-enyne **36** as the only geometrical isomer. Removal of the silyl groups and further acetylation of the secondary alcohol yielded **37**. Finally, the hydrolysis of the dimethyl acetal and oxidative cleavage of the diol afforded the aldehyde **31**.[26] Since this aldehyde has been transformed into *trans*-(−)-kumausyne (**2**),[25e] this approach constitutes a formal new synthesis of this natural product.

(22) (a) Rusell, S. T.; Robinson, J. A.; Williams, D. J. *J. Chem. Soc., Chem. Commun.* **1987**, 351. (b) Hashimoto, M.; Kan, T.; Nozaki, K.; Yanagiya, M.; Shirahama, H.; Matsumoto, T. *J. Org. Chem.* **1990**, *55*, 5088.

(23) Although the enantiomeric excess of **20** was 96% ee, we did not observe any other diastereoisomers after both epoxidation steps. We also checked the Mosher's diesters of both enantiomers of **27** founding no traces of the minority enantiomers. We concluded that at this stage of the synthesis our products could be considered to be pure enantiomers, at least, within the limits of the accuracy of NMR analysis.

(24) (2*S*,3*S*,5*S*)-5-[(1*S*)-1-Hydroxy-9-decenyl]-2-pentyltetrahydro-3-furanol (**5**) was reported (ref 5) upon isolation as a colorless oil, $[\alpha]^{25}_D$ = +75.5 (*c* 0.4, $CHCl_3$). Although the spectroscopic data coincide with those reported, the discrepancy with our specific rotation value suggests the necessity to reisolate the natural compound in order to perform a comparative study. See the Supporting Information for a ^1H NMR spectrum of natural **5**.

(25) (a) Brown, M. J.; Harrison, T.; Overman, L. E. *J. Am. Chem. Soc.* **1991**, *113*, 5378. (b) Osumi, K.; Sugimura, H. *Tetrahedron Lett.* **1995**, *36*, 5789. (c) Lee, E.; Yoo, S.-K.; Cho, Y.-S.; Cheon, H.-S.; Chong, Y. H. *Tetrahedron Lett.* **1997**, *38*, 7757. (d) Andrey, O.; Glanzmann, C.; Landais, Y.; Parra-Rapado, L. *Tetrahedron* **1997**, *53*, 2835. (e) Boukouvalas, J.; Fortier, G.; Radu, I.-I. *J. Org. Chem.* **1998**, *63*, 916. (f) Fernández de la Pradilla, R.; Montero, C.; Priego, J.; Martínez-Cruz, L. A. *J. Org. Chem.* **1998**, *63*, 9612. (g) Mereyala, H. B.; Gadikota, R. R. *Tetrahedron: Asymmetry* **2000**, *11*, 743.

(26) Because aldehyde **31** was difficult to purify, we also characterized the corresponding known alcohol (ref 25e) obtained by reduction with $NaBH_4$ in methanol (see Supporting Information).

Conclusions

In summary, we have described a general methodology to gain access to a broad kind of both linear and cyclic natural products based on the use of enantiomerically enriched β-hydroxy-γ-lactones as the key intermediates. A short and highly convergent synthesis of *trans*-(+)-laurediol (**1**) with an 11% overall yield (12 steps) is described. In addition, we have developed a divergent route to *anti*- or *syn*-3-hydroxy-2,5-dialkyl tetrahydrofurans from a common precursor and applied it to the enantioselective synthesis of two C19 diols **4** and **5** isolated from *Notheia anomala*. Also, from a related intermediate we performed a new formal synthesis of the lauroxane *trans*-(−)-kumausyne (**2**). In this last case, the use of two consecutive enantioselective reactions that ensure very high enantiomeric purities in the final products is especially noteworthy. Moreover, the described methodology can be applied to other natural products with a similar structure.

Experimental Section

Materials and Methods. NMR spectra were measured at 400 or 300 MHz (^{1}H) and 75 MHz (^{13}C), and chemical shifts are reported relative to internal Me_4Si ($\delta = 0$). Optical rotations were determined for solutions in chloroform or carbon tetrachloride. Melting points are reported in degrees Celsius and are uncorrected. Column chromatography was performed on Merck silica gel, 60 Å and 400−500 mesh. Compounds were visualized by use of UV light and/or 2.5% phosphomolybdic acid in ethanol with heating. All solvents were purified by standard techniques.[27] Reactions requiring anhydrous conditions were performed under argon. Anhydrous magnesium sulfate was used for drying solutions.

Preparation of 4-Benzyloxy-butan-1-ol (12). To a suspension of NaH (6.7 g, 166 mmol, 60% in mineral oil) in dry THF (400 mL) was added dropwise butane-1,4-diol (14.7 mL, 166 mmol) at 0 °C. After complete addition, the mixture was stirred for 30 min and benzyl bromide (16 mL, 133 mmol) was added dropwise. Then a catalytic amount of *tetra*-butylammonium iodide was added and the reaction mixture was allowed to warm to room temperature and was stirred for 3 h. The reaction was poured into HCl aqueous solution (5% w/v, 200 mL), ice, and Et_2O (200 mL) and was vigorously stirred. After 5 min, the mixture was extracted with Et_2O and the combined organic phases were washed with a saturated aqueous solution of $NaHCO_3$ and brine and were dried and concentrated. Purification by column chromatography gave the alcohol **12** (23.4 g, 78% yield) as an oil: ^{1}H NMR ($CDCl_3$) δ 1.59−1.75 (m, 4H), 2.88 (br s, 1H), 3.50 (dd, $J = 5.9$, 5.9 Hz, 2H), 3.59 (dd, $J = 6.0$, 6.0 Hz, 2H), 4.51 (s, 2H), 7.33 (s, 5H); ^{13}C NMR ($CDCl_3$) δ 26.5 (t), 29.8 (t), 62.4 (t), 70.3 (t), 73.0 (t), 127.7 (d), 127.7 (d), 128.4 (d), 138.1 (s); IR (film) $\tilde{\nu}_{max}$ (cm^{-1}) 3376, 3063, 2939, 1496, 1363, 1098; MS *m*/*z* (relative intensity) 181 $(M + 1)^+$ (1), 180 $(M)^+$ (9), 108 (18), 107 (72), 91 (100); HRMS calcd for $C_{11}H_{16}O_2$ $(M)^+$ 180.11503, found 180.11568.

General Method for the Preparation of β,γ-Unsaturated Esters. Preparation of Methyl 6-Benzyloxy-hex-3(*E*)-enate (10). To a solution of the alcohol **12** (8 g, 44.4 mmol) in dry CH_2Cl_2 (125 mL) was added Et_3N (43 mL, 311 mmol) and DMSO (30 mL) at 0 °C. After the mixture was stirred for 15 min, SO_3·Py (21.2 g, 133 mmol) was added. The reaction was allowed to warm to room temperature and monitored by TLC until complete conversion (2 h). The reaction mixture was diluted with CH_2Cl_2 (100 mL) and washed with HCl aqueous solution (5% w/v) and a saturated aqueous solution of $NaHCO_3$ and brine and was dried and concentrated. The crude obtained was filtered through a pad of silica gel, and the aldehyde **11** was used in the next reaction without any purification.

In a flask equipped with a Dean−Star trap, a mixture of malonic acid (18.7 g, 133 mmol) and piperidine (5 μL, 0.044 mmol) in dry xylene (36 mL) was refluxed for 30 min. Then the crude aldehyde **11** was added slowly, and the mixture was refluxed for 5 h with H_2O elimination.[28] After dilution with EtOAc, the mixture was washed with H_2O, dried, filtered, and concentrated, yielding an oil of the crude β,γ-unsaturated acid, which was used without purification.

To a stirred solution of the crude β,γ-unsaturated acid in dry MeOH (110 mL) was added Me_3SiCl (12.4 mL, 97.6 mmol) at 0 °C. The mixture was allowed to reach room temperature and then was stirred for 2 h. The reaction was then concentrated and purified by column chromatography to afford **10** (6.05 g, 58% overall yield) as an oil: ^{1}H NMR ($CDCl_3$) δ 2.34−2.40 (m, 2H), 3.05 (d, $J = 5.9$ Hz, 2H), 3.51 (dd, $J = 6.7$, 6.7 Hz, 2H), 3.68 (s, 3H), 4.51 (s, 2H), 5.59−5.67 (m, 2H), 7.33 (s, 5H); ^{13}C NMR ($CDCl_3$) δ 32.9 (t), 37.9 (t), 51.7 (q), 69.6 (t), 72.9 (t), 123.6 (d), 127.5 (d), 127.6 (d), 128.2 (d), 131.0 (d), 138.4 (s), 172.3 (s); IR (film) $\tilde{\nu}_{max}$ (cm^{-1}) 3030, 2950, 1739, 1496, 1362, 1102; MS *m*/*z* (relative intensity) 219 $(M - CH_3)^+$ (1), 160 (37), 130 (17), 91 (100); HRMS calcd for $C_{13}H_{15}O_3$ $(M - CH_3)^+$ 219.10212, found 219.10246.

General Method for the Preparation of Enantiomerically Enriched β-Hydroxy-γ-lactones. Preparation of (4*R*,5*R*)-5-(2-Benzyloxy-ethyl)-4-hydroxy-dihydro-furan-2-one (9). The β,γ-unsaturated ester **10** (3 g, 12.8 mmol) was added to a mixture of *t*-BuOH (65 mL), H_2O (65 mL), AD-mix-β (18 g, 1.4 g/mmol of **10**), and methanesulfonyl amide (1.22 g, 12.8 mmol) at 0 °C. The solution was stirred for 20 h at 0 °C. After the addition of saturated solution of Na_2SO_3 (100 mL), the mixture was extracted with EtOAc. The extracts were dried, and the solvent was removed. Flash chromatography on silica gel yielded **9** (2.73 g, 90% yield) as a white solid: mp 78−79 °C; $[\alpha]^{25}_D = +43.2$ (*c* 0.99, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 2.06−2.22 (m, 2H), 2.49 (d, $J = 17.8$ Hz, 1H), 2.72 (dd, $J = 17.8$, 5.6 Hz, 1H), 3.54 (ddd, $J = 9.9$, 9.9, 3.0 Hz, 1H), 3.61 (br s, 1H), 3.66−3.72 (m, 1H), 4.39−4.49 (m, 2H), 4.51 (s, 2H), 7.24−7.37 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 28.6 (t), 38.3 (t), 66.1 (t), 68.6 (d), 73.5 (t), 83.5 (d), 127.7 (d), 127.9 (d), 128.6 (d), 137.2 (s), 176.1 (s); IR (film) $\tilde{\nu}_{max}$ (cm^{-1}) 2929, 2865, 1765, 1454, 1164, 1023; MS *m*/*z* (relative intensity) 218 $(M - H_2O)^+$ (11), 159 (23), 107 (33), 91 (100); HRMS calcd for $C_{13}H_{14}O_3$ $(M - H_2O)^+$ 218.09429, found 218.09495.

Preparation of (4*R*,5*R*)-5-(2-Benzyloxy-ethyl)-4-(*tert*-butyl-diphenyl-silanyloxy)-dihydro-furan-2-one (13). To a stirred solution of the alcohol **9** (2.5 g, 10.6 mmol) in dry CH_2Cl_2 (106 mL) under argon were added imidazole (940 mg, 13.8 mmol) and *tert*-butylchlorodiphenylsilane (3.6 mL, 13.8 mmol) at 0 °C. The reaction was allowed to warm to room temperature and was stirred overnight. Then it was poured into H_2O and extracted with CH_2Cl_2. The combined organic phases were washed with brine (100 mL), dried, filtered, and concentrated. The crude obtained was purified by flash chromatography yielding **13** (4.78 g, 95% yield) as an oil: $[\alpha]^{25}_D = +30.3$ (*c* 1.02, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.07 (s, 9H), 2.01−2.09 (m, 1H), 2.16−2.26 (m, 1H), 2.33 (dd, $J = 17.5$, 2.4 Hz, 1H), 2.41 (dd, $J = 17.5$, 4.9 Hz, 1H), 3.65 (dd, $J = 7.4$, 4.6 Hz, 2H), 4.44−4.50 (m, 2H), 4.53−4.59 (m, 2H), 7.26−7.48 (m, 11H), 7.61 (d, $J = 7.4$ Hz, 4H); ^{13}C NMR ($CDCl_3$) δ 19.3 (s), 26.9 (q), 29.8 (t), 39.1 (t), 66.5 (t), 70.9 (d), 73.2 (t), 81.8 (d), 127.8 (d), 128.0 (d), 128.4 (d), 130.2 (d), 132.4 (s), 133.0 (s), 135.7 (d), 135.8 (d), 138.2 (s), 175.2 (s); IR (film) $\tilde{\nu}_{max}$ (cm^{-1}) 3070, 2931, 2858, 1779, 1427, 1362, 1157, 1105; MS *m*/*z* (relative intensity) 417 $(M - Bu\text{-}t)^+$ (1), 249 (9), 207 (72), 199 (41), 91 (100); HRMS calcd for $C_{25}H_{25}O_4Si$ $(M - Bu\text{-}t)^+$ 417.15221, found 417.14956.

Preparation of (4*R*,5*R*)-4-(*tert*-Butyl-diphenyl-silanyloxy)-5-(2-hydroxyethyl)-dihydro-furan-2-one (14). A mixture of **13** (3 g, 6.3 mmol) and Pd−C 10% (150 mg) in dry EtOAc (63 mL) was stirred at room temperature under atmosphere of H_2 (≈1 atm). The reaction was stirred overnight,

(27) Armarego, W. L. F.; Perrin, D. D. *Purification of Laboratory Chemicals*, 4th ed.; Butterworth-Heinemann: Oxford, 1996.

(28) To avoid the formation of the α,β-unsaturated acid instead of the desired β,γ-compound, it is necessary to avoid the presence of bases such as pyridine, Et_3N, etc., that may remain from the oxidation step.

after which time TLC showed the end of the reaction. The solution was filtered through a pad of Celite, and the filter was washed with EtOAc. The combined organic phases were concentrated, and the crude obtained was purified by flash chromatography, yielding **14** (2.38 g, 98% yield) as a white solid: mp 106−107 °C; $[\alpha]^{25}_D = +24.4$ (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.08 (s, 9H), 1.73 (br s, 1H), 1.88−1.98 (m, 1H), 2.14−2.24 (m, 1H), 2.35 (dd, *J* = 17.5, 2.3 Hz, 1H), 2.43 (dd, *J* = 17.5, 4.7 Hz, 1H), 3.83 (dd, *J* = 7.0, 5.0 Hz, 2H), 4.48−4.56 (m, 2H), 7.38−7.49 (m, 6H), 7.60−7.64 (m, 4H); ^{13}C NMR ($CDCl_3$) 19.3 (s), 26.9 (q), 32.0 (t), 39.0 (t), 59.0 (t), 70.9 (d), 82.1 (d), 128.0 (d), 128.0 (d), 130.2 (d), 130.2 (d), 132.3 (s), 133.0 (s), 135.7 (d), 135.7 (d), 175.5 (s); IR (film) $\tilde{\nu}_{max}$ (cm^{-1}) 3429, 3071, 2932, 1777, 1428, 1113; MS *m*/*z* (relative intensity) 327 (M − Bu-*t*)$^+$ (5), 249 (14), 207 (76), 199 (100), 177 (15); HRMS calcd for $C_{18}H_{19}O_4Si$ (M − Bu-*t*)$^+$ 327.10526, found 327.09932.

Preparation of (4*R*,5*R*)-4-(*tert*-Butyl-diphenyl-silanyloxy)-5-[octa-2(*Z*),5(*E*)-dienyl]-dihydro-furan-2-one (15). Crushed, activated 4 Å molecular sieves were added to a stirred mixture of NaOAc (10 mg, 0.124 mmol) and the alcohol **14** (160 mg, 0.41 mmol) in dry CH_2Cl_2 (4.1 mL, 0.1 M) under argon at room temperature. The flask was cooled to 0 °C and PCC (180 mg, 0.83 mmol) was added to the mixture. The reaction was allowed to warm to room temperature and was stirred for 2 h. After dilution with Et_2O (20 mL), the mixture was filtered through a pad of Celite and silica gel and washed with Et_2O. The resulting solution was concentrated, yielding an oil of the crude aldehyde, which was used without purification.

Crushed, activated 4 Å molecular sieves were added to a stirred solution of (*E*)-EtCH=CHCH$_2$CH$_2$PPh$_3$ + I$^-$ (350 mg, 0.74 mmol) in dry THF (3.1 mL) under argon at room temperature. The flask was cooled to 0 °C and KN(TMS)$_2$ (1.5 mL, 0.5 M solution in toluene, 0.74 mmol) was added dropwise. After 15 min, the flask was cooled to −78 °C and the crude aldehyde in THF (1 mL) was added dropwise. The reaction mixture was stirred for 3 h, after which time TLC showed the end of the reaction. Then the reaction mixture was quenched with a saturated aqueous solution of NH_4Cl (10 mL) and extracted with Et_2O. The combined organic phases were washed with brine, dried, and filtered, and the solvent was evaporated. The crude was purified by silica gel column chromatography to give **15** (62 mg, 36% yield) as an oil: $[\alpha]^{25}_D = +31.2$ (*c* 0.6, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.97 (dd, *J* = 7.4, 7.4 Hz, 3H), 1.09 (s, 9H), 2.02 (ddd, *J* = 14.0, 6.9, 6.9 Hz, 2H), 2.42 (d, *J* = 4.1 Hz, 2H), 2.43−2.48 (m, 1H), 2.63−2.68 (m, 1H), 2.71 (dd, *J* = 5.8, 5.8 Hz, 2H), 4.24 (ddd, *J* = 8.6, 4.3, 4.3 Hz, 1H), 4.50 (ddd, *J* = 4.2, 4.2, 4.2 Hz, 1H), 5.29−5.57 (m, 4H), 7.39−7.50 (m, 6H), 7.63−7.68 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 13.8 (q), 19.3 (s), 25.5 (t), 26.9 (q), 27.2 (t), 30.6 (t), 38.9 (t), 70.5 (d), 84.5 (d), 124.3 (d), 126.5 (d), 127.7 (d), 128.0 (d), 130.2 (d), 131.2 (d), 132.4 (s), 132.8 (d), 133.0 (s), 135.8 (d), 175.0 (s); IR (film) $\tilde{\nu}_{max}$ (cm^{-1}) 2960, 2931, 2857, 1784, 1427, 1154, 1112, 965; MS *m*/*z* (relative intensity) 392 (M + H − Bu-*t*)$^+$ (18), 391 (M − Bu-*t*)$^+$ (56), 349 (35), 225 (45), 199 (100); HRMS calcd for $C_{24}H_{27}O_3Si$ (M − Bu-*t*)$^+$ 391.17295, found 391.17317.

Preparation of *trans*-(+)-Laurediol (1). To a stirred solution of **15** (74 mg, 0.16 mmol) in dry Et_2O (1.7 mL) was added dropwise DIBAL-H (0.19 mL, 1.0 M in hexane, 0.19 mmol) at −78 °C. The reaction mixture was stirred for 5 min. Then the reaction was quenched with H_2O (50 μL), allowed to warm to room temperature, and additionally stirred for 30 min. The mixture was dried over $MgSO_4$ and filtered through a pad of Celite and the solvent was evaporated. The residue was used without further purification.

To a suspension of commercially available TMSC≡CCH$_2$-PPh$_3$ + Br$^-$ (0.15 g, 0.33 mmol) in dry Et_2O (1.5 mL) was added potassium *tert*-butoxide (35 mg, 0.33 mmol) under argon at 0 °C. The mixture was stirred for 1 h. Then the crude lactol was added in dry Et_2O (0.2 mL) and the mixture was allowed to warm to room temperature and was monitored by TLC until complete conversion (4 h). The mixture was filtered through a pad of Celite and washed with Et_2O. The resulting solution was concentrated and the obtained residue was dissolved in dry THF (1.7 mL) and tetra-*n*-butylammonium fluoride (0.5 mL, 1 M in THF, 0.49 mmol) was added under argon at room temperature. The reaction mixture was stirred for 1 h, after which time TLC showed a completed reaction. The mixture was poured into H_2O (10 mL) and extracted with Et_2O. The combined organic solutions were concentrated and purified by column chromatography, yielding *trans*-(+)-laurediol (**1**) (30 mg, 78% overall yield) as an oil: $[\alpha]^{25}_D = +19.8$ (*c* 1.2, CCl_4);[16] ^{1}H NMR ($CDCl_3$) δ 0.95 (dd, *J* = 7.4, 7.4 Hz, 3H), 1.96−2.03 (m, 2H), 2.28−2.40 (m, 6H), 2.75 (dd, *J* = 6.6, 6.6 Hz, 2H), 2.82 (d, *J* = 2.0 Hz, 1H), 3.47−3.51 (m, 1H), 3.52−3.57 (m, 1H), 5.33−5.63 (m, 5H), 6.27 (ddd, *J* = 15.9, 8.0, 7.4 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 13.7 (q), 25.4 (t), 30.4 (t), 31.5 (t), 37.4 (t), 72.5 (d), 73.0 (d), 76.4 (d), 81.9 (s), 111.4 (d), 124.8 (d), 126.7 (d), 131.5 (d), 132.7 (d), 142.0 (d); IR (film) $\tilde{\nu}_{max}$ (cm^{-1}) 3290, 2926, 1654, 1429, 1057, 964; MS *m*/*z* (relative intensity) 217 (M − OH)$^+$ (2), 205 (1), 187 (4), 133 (13); HRMS calcd for $C_{13}H_{15}O$ (M − CH$_2$CH$_3$ − H$_2$O)$^+$ 187.11229, found 187.11278.

Preparation of Methyl Non-3(*E*)-enoate (23). The general procedure used above to obtain β,γ-unsaturated esters was applied to *n*-heptanal on a 52 g (0.46 mmol) scale, yielding **23** (77 g, 80% overall yield) as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 0.87 (dd, *J* = 6.6, 6.6 Hz, 3H), 1.26−1.37 (m, 6H), 2.01 (dd, *J* = 13.0, 6.1 Hz, 2H), 3.02 (d, *J* = 5.3 Hz, 2H), 3.67 (s, 3H), 5.54 (dd, *J* = 11.3, 5.7 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 14.0 (q), 22.5 (t), 28.0 (t), 31.3 (t), 32.4 (t), 37.9 (t), 51.7 (q), 121.3 (d), 135.0 (d), 172.6 (s); IR ($CHCl_3$) $\tilde{\nu}_{max}$ (cm^{-1}) 3450, 2900, 1720, 1415, 1150, 960; MS (*m*/*z* relative intensity) 170 (M)$^+$ (6), 138 (74), 96 (89), 74 (100); HRMS calcd for $C_{10}H_{18}O_2$ (M$^+$) 170.13068, found 170.13310.

Preparation of (4*S*,5*S*)-4-Hydroxy-5-pentyl-dihydro-furan-2-one (20). The general procedure used above to obtain enantiomerically enriched β-hydroxy-γ-lactones was applied to **23** on a 4 g (23.5 mmol) scale, yielding **20** (3.2 g, 82% yield) as a colorless oil: $[\alpha]^{25}_D = -49.37$ (*c* 0.8, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.92 (dd, *J* = 6.9, 6.9 Hz, 3H), 1.29−1.47 (m, 6H), 1.69−1.85 (m, 2H), 2.54 (d, *J* = 17.7 Hz, 1H), 2.79 (dd, *J* = 17.7, 5.4 Hz, 1H), 4.36 (ddd, *J* = 5.4, 4.2, 3.6 Hz, 1H), 4.47 (dd, *J* = 4.2, 4.2 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 13.9 (q), 22.4 (t), 25.2 (t), 28.2 (t), 31.6 (t), 39.5 (t), 69.0 (d), 85.0 (d), 175.9 (s); IR ($CHCl_3$) $\tilde{\nu}_{max}$ (cm^{-1}) 3400, 2900, 1760, 1590, 1150; MS (*m*/*z* relative intensity) 144 (M − CO)$^+$ (7), 101 (66), 88 (13), 83 (100), 71 (4), 55 (81); HRMS calcd for $C_8H_{16}O_2$ (M − CO)$^+$: 144.11503, found 144.11937.

Preparation of (4*S*,5*S*)-4-(*tert*-Butyl-diphenyl-silanyloxy)-5-pentyl-dihydro-furan-2-one (24). The procedure used above to obtain **13** from **9** was applied to **20** on a 7.46 g (43 mmol) scale, yielding **24** (17 g, 96% yield) as a colorless oil: $[\alpha]^{25}_D = -14.35$ (*c* 2.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.90 (dd, *J* = 6.9, 6.9 Hz, 3H), 1.08 (s, 9H), 1.29−1.38 (m, 5H), 1.48−1.50 (m, 1H), 1.63−1.71 (m, 1H), 1.88−1.93 (m, 1H), 2.39 (s, 1H), 2.40 (d, *J* = 1.5 Hz, 1H), 4.24 (ddd, *J* = 8.7, 4.3, 4.3 Hz, 1H), 4.45 (dd, *J* = 7.8, 3.9 Hz, 1H), 7.36−7.48 (m, 6H), 7.60−7.66 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 14.0 (q), 19.3 (s), 22.5 (t), 25.4 (t), 26.9 (q), 29.0 (t), 31.7 (t), 39.0 (t), 70.7 (d), 85.0 (d), 127.9 (d), 130.2 (d), 132.6 (s), 133.1 (s), 134.8 (d), 135.8 (d), 175.3 (s); IR ($CHCl_3$) $\tilde{\nu}_{max}$ (cm^{-1}) 3650, 2900, 1760, 1590, 1450, 1100; MS (*m*/*z* relative intensity) 353 (M − Bu-*t*)$^+$ (56), 311 (100), 225 (16), 199 (37), 183 (18), 139 (7). Anal. Calcd for $C_{25}H_{34}O_3Si$: C, 73.13; H, 8.35. Found: C, 73.20; H, 8.32.

Preparation of Ethyl (2*E*)(5*S*,6*S*)-5-(*tert*-Butyl-diphenyl-silanyloxy)-6-hydroxy-dec-2-enoate (25). To a cooled solution of the lactone **24** (17.8 g, 43.3 mmol) in dry Et_2O (433 mL) under argon atmosphere was added dropwise DIBAL-H (60 mL, 1M in cyclohexane, 60 mmol) at −78 °C. The mixture was stirred at −78 °C until no starting material was presented by TLC. The reaction was quenched by the addition of 6 mL of H_2O and then to the same flask was added $MgSO_4$. The gelatinous solution was filtered through a pad of Celite and washed with Et_2O. The solvent was removed under reduced pressure, and the residue was used in the next reaction without further purification.

To a solution of the crude lactol in benzene (870 mL) under argon atmosphere was added carbethoxymethylene triphenylphosphorane (23.1 g, 66 mmol). The mixture was stirred at 50 °C until TLC showed completion of the reaction (ca. 2 h).

The reaction was allowed to reach room temperature and was quenched with a saturated aqueous solution of NaCl. The layers were partitioned, and the aqueous phase was extracted with EtOAc. The combined organic layers were dried, filtered, and concentrated. Flash chromatography of the residue on a silica gel column gave **25** (18.5 g, 89% yield) as a colorless oil: $[\alpha]^{25}_D = +17.32$ (*c* 5.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.86 (dd, *J* = 6.8, 6.8 Hz, 3H), 1.07 (s, 9H), 1.22−1.31 (m, 8H), 1.33−1.42 (m, 3H), 2.03 (br s, 1H), 2.16−2.26 (m, 1H), 2.45−2.55 (m, 1H), 3.40 (br s, 1H), 3.69 (ddd, *J* = 7.8, 4.3, 3.5 Hz, 1H), 4.13 (ddd, *J* = 7.1, 7.1, 7.1 Hz, 2H), 5.63 (d, *J* = 15.6 Hz, 1H), 6.70 (ddd, *J* = 15.3, 7.8, 7.5 Hz, 1H), 7.35−7.48 (m, 6H), 7.60−7.68 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 14.0 (q), 14.2 (q) 19.4 (s), 22.5 (t), 25.4 (t), 27.1 (q), 31.8 (t), 33.6 (t), 36.4 (t), 60.1 (t), 72.9 (d), 75.1 (d), 123.8 (d),127.6 (d), 127.8 (d), 129.9 (d), 130.0 (d), 133.0 (s), 133.5 (s), 135.9 (d), 144.4 (d), 166.1 (s); IR ($CHCl_3$) $\tilde{\nu}_{max}$ (cm^{-1}) 3550, 2900, 1760, 1450, 1360, 960; MS (*m*/*z* relative intensity) 425 (M − Bu-*t*)$^+$ (14), 347 (39), 199 (100). Anal. Calcd for $C_{29}H_{42}O_4Si$: C, 72.15; H, 8.77. Found: C, 72.27; H, 9.12.

Preparation of (2*E*)(5*S*,6*S*)-5-(*tert*-Butyl-diphenyl-silanyloxy)-undec-2-ene-1,6-diol (19). To a solution of **25** (20.9 g, 43.3 mmol) in dry Et_2O (433 mL) under argon atmosphere was added dropwise DIBAL-H (95 mL, 1 M in cyclohexane, 95 mmol) at 0 °C. The mixture was stirred until TLC showed complete conversion of the lactone. Then, the reaction was quenched with H_2O (10 mL) and additionally stirred for 20 min at room temperature. To the flask was added $MgSO_4$ and the gelatinous mixture was filtered through a pad of Celite and washed with EtOAc. The solvent was removed under reduced pressure. Purification of the residue by flash chromatography afforded the allylic alcohol **19** (14.6 g, 77% yield) as a white solid: mp 73−79 °C; $[\alpha]^{25}_D = +10.46$ (*c* 1.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.88 (dd, *J* = 6.7, 6.7 Hz, 3H), 1.08 (s, 9H), 1.21−1.30 (m, 5H), 1.38−1.48 (m, 3H), 2.07−2.15 (m, 1H), 2.23 (br s, 1H), 2.33−2.42 (m, 1H), 3.47 (br s, 1H), 3.65 (ddd, *J* = 7.5, 4.5, 3.3 Hz, 1H), 3.90 (d, *J* = 4.5 Hz, 2H), 5.32−5.49 (m, 2H), 7.35−7.46 (m, 6H), 7.68−7.71 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 14.0 (q), 19.5 (s), 22.6 (t), 25.5 (t), 27.1 (q), 31.9 (t), 33.2 (t), 36.5 (t), 63.3 (t), 72.7 (d), 75.8 (d), 127.5 (d), 127.7 (d), 127.9 (d), 129.8 (d), 129.9 (d), 132.0 (d), 133.3 (s), 134.0 (s), 135.9 (d); IR ($CHCl_3$) $\tilde{\nu}_{max}$ (cm^{-1}) 3650, 3400, 2900, 1590, 1450, 1410; MS (*m*/*z* relative intensity) 365 (M − Bu-*t* − H_2O)$^+$ (9), 311 (100); HRMS calcd for $C_{23}H_{29}O_2Si$ (M − Bu-*t* − H_2O)$^+$ 365.19368, found 365.19458.

Preparation of (1*S*)-1-[(4*S*,5*S*,2*R*)-4-(*tert*-Butyl-diphenyl-silanyloxy)-5-pentyl-tetrahydro-furan-2-yl]-ethane-1, 2-diol (26). Crushed, activated 4 Å molecular sieves were added to stirred CH_2Cl_2 (66 mL) under argon. The flask was cooled to −20 °C, and Ti(OPr-*i*)$_4$ (2.4 mL, 8.1 mmol), (*R*,*R*)-(+)-DET (1.6 mL, 9.6 mmol), and the allylic alcohol **19** (3 g, 6.8 mmol) in CH_2Cl_2 (2 mL) were added sequentially with stirring. The mixture was stirred at the same temperature for 20 min, and TBHP (3.8 mL, 3.2 M in isooctane, 12.2 mmol) was added slowly. After the addition, the reaction was maintained with stirring for 2 h. Tartaric acid aqueous solution (15% w/v) was added at room temperature, and the stirring was continued until clear phases were reached (ca. 1 h). The phases were separated, and the aqueous phase was extracted with CH_2Cl_2. The combined organic phases were washed with brine, concentrated, diluted with Et_2O, and treated with precooled (0 °C) 15% (w/v) NaOH aqueous solution. The two-phase mixture was stirred vigorously for 15 min at 0 °C. The organic phase was separated, and the aqueous phase was extracted with CH_2Cl_2. The combined organic phases were washed with brine, dried, filtered, concentrated, and purified by silica gel column chromatography to yield **26** (2.55 g, 82% yield) as a colorless oil: $[\alpha]^{25}_D = +5.05$ (*c* 7.7, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.87 (dd, *J* = 6.3, 6.3 Hz, 3H), 1.07 (s, 9H), 1.26 (br s, 6H), 1.58−1.66 (m, 2H), 1.69−1.88 (m, 2H), 3.48 (dd, *J* = 11.2, 6.5 Hz, 1H), 3.60 (dd, *J* = 11.2, 3.7 Hz, 1H), 3.69 (d, *J* = 3.7 Hz, 2H), 4.19 (dd, *J* = 14.4, 6.4 Hz, 1H), 4.32 (s, 1H), 7.35−7.43 (m, 6H), 7.64−7.66 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 13.9 (q), 19.4 (s), 22.4 (t), 26.1 (t), 27.0 (q), 29.5 (t), 32.0 (t), 36.6 (t), 63.9 (t), 73.6 (d), 74.5 (d), 77.7 (d), 83.7 (d), 127.6 (d), 127.7 (d), 129.8 (d), 133.5 (s), 134.3 (s), 135.8 (d), 135.9 (d); IR ($CHCl_3$) $\tilde{\nu}_{max}$ (cm^{-1}) 3684, 3019, 2400, 1522, 1427, 1046; MS (*m*/*z* relative intensity) 399 (M − Bu-*t*)$^+$ (4), 381 (8), 321 (18), 311 (60), 253 (14), 199 (100). Anal. Calcd for $C_{27}H_{40}O_4Si$: C, 71.01; H, 8.83. Found: C, 71.03; H, 9.08.

Preparation of (1*R*)-1-[(4*S*,5*S*,2*S*)-4-(*tert*-Butyl-diphenyl-silanyloxy)-5-pentyl-tetrahydro-furan-2-yl]-ethane-1, 2-diol (27). The procedure used above to obtain **26** was applied again to **19** (3 g, 6.8 mmol), using the (*S*, *S*)-(−)-DET instead of the (*R*,*R*)-(+)-DET, to yield **27** (2.55 g, 82% yield) as a colorless oil: $[\alpha]^{25}_D = -7.8$ (*c* 1.2, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.85 (dd, *J* = 6.2, 6.2 Hz, 3H), 1.09 (s, 9H), 1.16−1.22 (m, 5H), 1.25−1.41 (m, 2H), 1.61−1.64 (m, 1H), 1.94 (ddd, *J* = 8.7, 6.2, 2.5 Hz, 2H), 3.46 (ddd, *J* = 8.0, 8.0, 4.0 Hz, 1H), 3.63 (d, *J* = 7.0 Hz, 2H), 3.83 (dd, *J* = 9.3, 4.5 Hz, 1H), 3.88 (ddd, *J* = 4.0, 4.0, 1.7 Hz, 1H), 4.29 (ddd, *J* = 6.0, 6.0, 3.0 Hz, 1H), 7.35−7.47 (m, 6H), 7.64−7.69 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 14.0 (q), 19.3 (s), 22.5 (t), 26.1 (t), 27.1 (q), 29.5 (t), 31.9 (t), 36.3 (t), 64.0 (t), 72.9 (d), 73.9 (d), 78.6 (d), 83.3 (d), 127.6 (d), 127.7 (d), 129.8 (d), 133.2 (s), 133.7 (s), 136.0 (d); IR ($CHCl_3$) $\tilde{\nu}_{max}$ (cm^{-1}) 3684, 3019, 2400, 1522, 1046; MS (*m*/*z* relative intensity)-395 (M − Bu-*t* - H_2O)$^+$ (1), 321 (19), 251 (44), 199 (100). Anal. Calcd for $C_{27}H_{40}O_4Si$: C, 71.01; H, 8.83. Found: C, 71.02; H, 8.79.

Preparation of (2*S*)-2-[(4*S*,5*S*,2*R*)-4-(*tert*-Butyl-diphenyl-silanyloxy)-5-pentyl-tetrahydro-furan-2-yl]-2-methanesulfonyloxy-ethyl Benzoate (28). To a solution of **26** (1.55 g, 3.4 mmol) in dry CH_2Cl_2 (34 mL) under argon atmosphere were sequentially added Et_3N (0.73 mL, 5.1 mmol) and benzoyl chloride (0.47 mL, 4.1 mmol) at 0 °C. The reaction was stirred for 2 h, after which time TLC showed that the starting material had disappeared. Then saturated aqueous solution of NaCl was added and the resulting mixture was extracted with CH_2Cl_2. The combined organic phases were dried, filtered, and evaporated in a vacuum to yield a crude that was used in the next step without any further purification.

To a stirred mixture of the crude monobenzoate in dry CH_2Cl_2 (34 mL) under argon atmosphere were added Et_3N (0.73 mL, 5.1 mmol) and methanesulfonyl chloride (0.32 mL, 4.1 mmol) at 0 °C. The reaction mixture was stirred for 1 h, after which time TLC showed no remaining alcohol. Then, a saturated aqueous solution of NaCl was added and the resulting mixture was extracted with CH_2Cl_2. The combined organic phases were dried, filtered, and evaporated in a vacuum. The residue was purified by column chromatography on silica gel to give **28** (1.6 g, 75% yield) as a colorless oil: $[\alpha]^{25}_D = +2.5$ (*c* 0.8, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.87 (dd, *J* = 6.4, 6.4 Hz, 3H), 1.07 (s, 9H), 1.26−1.27 (m, 5H), 1.34−1.40 (m, 1H), 1.54−1.60 (m, 1H), 1.66−1.71 (m, 1H), 1.89 (dd, *J* = 7.1, 1.8 Hz, 1H), 1.9 (d, *J* = 3.4 Hz, 1H), 2.99 (s, 3H), 3.73 (ddd, *J* = 7.9, 5.2, 3.0 Hz, 1H), 4.28 (dd, *J* = 12.2, 6.9 Hz, 1H), 4.36 (d, *J* = 3.0 Hz, 1H), 4.44 (ddd, *J* = 8.4, 8.4, 3.6 Hz, 1H), 4.51 (d, *J* = 3.4 Hz, 1H), 5.03 (ddd, *J* = 7.1, 3.6, 3.6 Hz, 1H), 7.33−7.46 (m, 8H), 7.55−7.67 (m, 5H), 8.01−8.03 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 14.0 (q), 19.4 (s), 22.5 (t), 26.1 (t), 27.0 (q), 29.6 (t), 32.0 (t), 36.3 (t), 38.4 (q), 63.3 (t), 74.4 (d), 75.5 (d), 80.7 (d), 84.2 (d), 127.7 (d), 128.5 (d), 129.4 (s), 129.8 (d), 129.9 (d), 133.3 (d), 134.0 (s), 135.7 (d), 135.8 (d), 166.0 (s); IR ($CHCl_3$) $\tilde{\nu}_{max}$ (cm^{-1}) 3684, 3019, 2400, 1522, 1230, 928; MS (*m*/*z* relative intensity) 581 (M − Bu-*t*)$^+$ (10), 199 (45), 165 (100); HRMS calcd for $C_{31}H_{37}O_7SiS$ (M − Bu-*t*)$^+$ 581.20292, found 581.20204.

Preparation of *tert*-Butyl-[5-(2*R*)-oxiran-2-yl)−(2*S*,3*S*,-5*R*)-2-pentyl-tetrahydro-furan-3-yloxy]-diphenyl-silane (17). To a cooled suspension of NaH (144 mg, 60% in mineral oil, 6.0 mmol) in dry CH_2Cl_2 (25 mL) under argon atmosphere was added dropwise dry MeOH (0.16 mL, 4.0 mmol) at 0 °C. The mixture was stirred for 15 min and **28** (1.53 g, 2.4 mmol) was added slowly. After the addition, the mixture was allowed to warm to room temperature until the TLC showed no remaining benzoate. Then a saturated aqueous solution of NaCl was added, the aqueous phase was extracted with CH_2Cl_2, and the combined organic phases were dried, filtered, and concentrated. Purification was effected by flash column chromatography to yield **17** (841 mg, 80% yield) as a colorless oil: $[\alpha]^{25}_D = +7.2$ (*c* 1.9, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.88 (dd, *J* = 6.4, 6.4 Hz, 3H), 1.07 (s, 9H), 1.27−1.28 (m, 6H), 1.59−1.80

(m, 3H), 1.87 (dd, J = 6.7, 1.5 Hz, 1H), 2.69 (br s, 2H), 2.87 (dd, J = 6.8, 3.7 Hz, 1H), 3.70 (ddd, J = 2.9, 1.8, 1.8 Hz, 1H), 4.13 (dd, J = 4.2, 2.2 Hz, 1H), 4.35 (s, 1H), 7.35−7.44 (m, 6H), 7.66−7.68 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 14.0 (q), 19.4 (s), 22.6 (t), 26.1 (t), 26.9 (q), 29.5 (t), 32.0 (t), 38.1 (t), 44.5 (t), 54.2 (d), 74.4 (d), 75.7 (d), 84.1 (d), 127.6 (d), 127.7 (d), 129.7 (d), 129.8 (d), 133.5 (s), 134.4 (s), 135.5 (d), 135.8 (d), 135.9 (d); IR ($CHCl_3$) $\tilde{\nu}_{max}$ (cm^{-1}) 3684, 3019, 2400, 1522, 1230, 928; MS (*m*/*z* relative intensity) 381 (M − Bu-*t*)$^+$ (18), 311 (63), 199 (100). Anal. Calcd for $C_{27}H_{38}O_3Si$: C, 73.92; H, 8.73. Found: C, 73.94; H, 8.93.

Preparation of (1*R*)-1-[(4*S*,5*S*,2*R*)-4-(*tert*-Butyl-diphenyl-silanyloxy)-5-pentyl-tetrahydro-furan-2-yl]-dec-9-en-1-ol (4). To a mixture of CuI (cat.) in dry THF (2.5 mL) under argon atmosphere was added *n*-$C_8H_{15}BrMg$ (0.38 mL, 1 M in THF, 0.38 mmol) at −30 °C. The mixture was stirred for 10 min, and the epoxide **17** (110 mg, 0.25 mmol) was added slowly. TLC showed almost instant conversion. The reaction was quenched with a saturated aqueous solution of NH_4Cl. The layers were partitioned, and the aqueous phase was extracted with Et_2O. The combined organic layers were dried, filtered, and concentrated to yield a crude oil that was used in the next reaction without purification.

To a stirred mixture of the crude in THF (2.5 mL) was added tetra-*n*-butylammonium fluoride (0.36 mL, 1 M in THF, 0.36 mmol). The mixture was stirred until TLC showed no remaining silyl ether. The residue was diluted with Et_2O (5 mL), and H_2O (5 mL) was added. The resulting mixture was extracted with Et_2O. The combined organic layers were dried, filtered, and concentrated. Silica gel flash chromatography of the residue afforded **4** (61 mg, 78% yield) as a white solid: mp 50−52 °C; $[\alpha]^{25}_D$ = +15.2 (*c* 0.8, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.70 (dd, J = 7.2, 7.2 Hz, 3H), 1.25−1.36 (m, 18H), 1.48−1.63 (m, 4H), 1.81 (ddd, J = 13.3, 9.0, 4.3 Hz, 1H), 2.01 (dd, J = 13.0, 6.7 Hz, 2H), 2.33 (br s, 1H), 3.36 (d, J = 5.6 Hz, 1H), 3.74 (ddd, J = 7.0, 7.0, 2.5 Hz, 1H), 4.02 (dd, J = 15.4, 6.7 Hz, 1H), 4.23 (s, 1H), 4.92 (d, J = 10.0 Hz, 1H), 4.97 (d, J = 17.0 Hz, 1H), 5.80 (dddd, J = 17.0, 10.0, 7.0, 7.0 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 14.0 (q), 22.5 (t), 25.6 (t), 25.9 (t), 28.8 (t), 28.9 (t), 29.0 (t), 29.4 (t), 29.6 (t), 31.9 (t), 33.1 (t), 33.7 (t), 37.9 (t), 73.4 (d), 74.1 (d), 80.2 (d), 82.5 (d), 114.1 (t), 139.2 (d); IR ($CHCl_3$) $\tilde{\nu}_{max}$ (cm^{-1}) 3684, 3620, 2930, 2400, 1522, 1046; MS (*m*/*z* relative intensity) 312 (M)$^+$ (2), 199 (3), 157 (100). Anal. Calcd for $C_{19}H_{36}O_3$: C, 73.03; H, 11.61. Found: C, 73.08; H, 12.10.

Preparation of (2*R*)-2-[(4*S*,5*S*,2*S*)-4-(*tert*-Butyl-diphenyl-silanyloxy)-5-pentyl-tetrahydro-furan-2-yl]-2-methanesulfonyloxy-ethyl Benzoate (30). The procedure used above for the preparation of **28** from **26** was applied to **27** on a 1.49 g (3.26 mmol) scale, giving **30** (1.56 g, 75% yield) as a colorless oil: $[\alpha]^{25}_D$ = +16.84 (*c* 1.8, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.87 (dd, J = 6.6, 6.6 Hz, 3H), 1.10 (s, 9H), 1.16−1.23 (m, 5H), 1.31−1.45 (m, 2H), 1.61−1.63 (m, 1H), 2.06 (d, J = 6.7 Hz, 1H), 2.08 (dd, J = 7.5, 2.4 Hz, 1H), 3.07 (s, 3H), 3.50 (dd, J = 8.6, 4.3 Hz, 1H), 3.94 (ddd, J = 7.5, 7.5, 4.9 Hz, 1H), 4.34 (ddd, J = 9.9, 9.9, 4.3 Hz, 1H), 4.45 (dd, J = 12.4, 6.7 Hz, 1H), 4.68 (dd, J = 12.4, 3.0 Hz, 1H), 5.12 (ddd, J = 6.6, 4.5, 2.2 Hz, 1H), 7.35−7.46 (m, 8H), 7.57−7.70 (m, 5H), 8.03−8.06 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 14.0 (q), 19.2 (s), 22.5 (t), 26.1 (t), 27.1 (q), 29.5 (t), 31.8 (t), 37.2 (t), 38.9 (q), 63.6 (t), 73.7 (d), 75.5 (d), 80.6 (d), 83.9 (d), 127.7 (d), 128.5 (d), 129.6 (d), 129.8 (d), 133.2 (d), 133.3 (d), 133.7 (s), 135.7 (d), 136.0 (d), 166.1 (s); IR ($CHCl_3$) $\tilde{\nu}_{max}$ (cm^{-1}) 3683, 3019, 2400, 1722, 1230, 929; MS (*m*/*z* relative intensity) 581 (M − Bu-*t*)$^+$ (100), 303 (33), 277 (79), 165 (90); HRMS calcd for $C_{31}H_{37}O_7SiS$ (M − Bu-*t*)$^+$ 581.20292, found 581.20341.

Preparation of *tert*-Butyl-[5-(2*S*)-oxiran-2-yl)−(2*S*,3*S*,-5*S*)-2-pentyl-tetrahydro-furan-3-yloxy]-diphenyl-silane (21). The procedure used above for the preparation of **17** from **28** was applied to **30** on a 1.53 g (2.4 mmol) scale, affording **21** (840 mg, 80% yield) as a colorless oil: $[\alpha]^{25}_D$ = +4.83 (*c* 0.6, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.87 (dd, J = 6.4, 6.4 Hz, 3H), 1.08 (s, 9H), 1.25 (br s, 4H), 1.44 (br s, 1H), 1.49−1.61 (m, 2H), 1.65−1.80 (m, 2H), 1.99 (ddd, J = 13.4, 6.7, 6.7 Hz, 1H), 2.49 (br s, 1H), 2.72 (dd, J = 4.4, 4.4 Hz, 1H), 3.14 (dd, J = 3.0, 3.0 Hz, 1H), 3.43 (dd, J = 14.2, 6.9 Hz, 1H), 3.58 (ddd, J = 8.3, 4.2, 4.2 Hz, 1H), 4.34 (dd, J = 8.8, 4.3 Hz, 1H), 7.35−7.46 (m, 6H), 7.65−7.67 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 14.0 (q), 19.3 (s), 22.6 (t), 26.1 (t), 27.0 (q), 29.8 (t), 32.0 (t), 38.0 (t), 43.9 (t), 54.4 (d), 73.8 (d), 78.6 (d), 83.6 (d), 127.6 (d), 129.8 (d), 133.5 (s), 134.4 (s), 135.9 (d); IR ($CHCl_3$) (cm^{-1}) 3650, 3300, 2900, 1590, 1350, 1100; MS (*m*/*z* relative intensity) 381 (M − Bu-*t*)$^+$ (18), 311 (11), 199 (100); HRMS calcd for $C_{23}H_{29}O_3Si$ (M − Bu-*t*) 381.18860, found 381.18719.

Preparation of (1*S*)-1-[(4*S*,5*S*,2*S*)-4-(*tert*-Butyl-diphenyl-silanyloxy)-5-pentyl-tetrahydro-furan-2-yl]-dec-9-en-1-ol (5). Obtained from **21** (147 mg, 0.33 mmol) as described above for **4** from **17**, affording **5** (81 mg, 78% yield) as a white solid: mp 35−37 °C; $[\alpha]^{25}_D$ = +20.5 (*c* 0.4, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.88 (dd, J = 6.4, 6.4 Hz, 3H), 1.24−1.33 (m, 18 H), 1.50−1.65 (m, 4H), 1.83 (dd, J = 14.1, 3.4 Hz, 1H), 2.02 (dd, J = 13.0, 6.6 Hz, 2H), 2.36 (ddd, J = 14.0, 10.0, 5.5 Hz, 1H), 3.46 (ddd, J = 8.0, 5.0, 2.5 Hz, 1H), 3.61 (ddd, J = 7.0, 7.0, 2.7 Hz, 1H), 3.93 (dd, J = 9.8, 5.4 Hz, 1H), 4.03 (dd, J = 5.4, 2.7 Hz, 1H), 4.92 (d, J = 10.0 Hz, 1H), 4.98 (d, J = 17.0 Hz, 1H), 5.80 (dddd, J = 17.0, 10.0, 7.0, 7.0 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 14.0 (q), 22.6 (t), 26.0 (t), 28.7 (t), 28.9 (t), 29.0 (t), 29.4 (t), 29.5 (t), 29.7(t), 32.0 (t), 33.7 (t), 34.3 (t), 38.7 (t), 71.5 (d), 73.9 (d), 79.1 (d), 84.3 (d), 114.1 (t), 139.1 (d); IR ($CHCl_3$) $\tilde{\nu}_{max}$ (cm^{-1}) 3684, 2930, 2400, 1520, 1230, 1045; MS (*m*/*z* relative intensity) 297 (M − CH_3)$^+$ (4), 187 (4), 157 (100). Anal. Calcd for $C_{19}H_{36}O_3$: C, 73.03; H, 11.61. Found: C, 73.08; H, 11.53.

Preparation of Methyl (2*E*)(5*R*,6*R*)-8-Benzyloxy-5-(*tert*-butyl-diphenyl-silanyloxy)-6-hydroxy-oct-2-enoate (33). The procedure used above to obtain **25** from **24** was applied to **13** on a 5.82 g (12.26 mmol) scale, yielding **33** (5.98 g, 89% yield) as a colorless oil: $[\alpha]^{25}_D$ = −16.65 (*c* 2.7, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.06 (s, 9H), 1.24 (dd, J = 7.0, 7.0 Hz, 3H), 1.77 (ddd, J = 5.8, 5.8, 5.8 Hz, 2H), 2.25 (ddd, J = 14.0, 7.1, 6.4 Hz, 1H), 2.53 (ddd, J = 14.0, 7.1, 6.4 Hz, 1H), 2.49 (ddd, J = 9.1, 5.8, 5.8 Hz, 1H), 3.60−3.71 (m, 2H), 3.77 (ddd, J = 6.4, 6.4, 3.8 Hz, 1H), 4.13 (ddd, J = 7.0, 7.0, 7.0 Hz, 2H), 4.46 (s, 2H), 5.66 (d, J = 15.4 Hz, 1H), 6.77 (ddd, J = 15.4, 7.1, 7.1 Hz, 1H), 7.25−7.45 (m, 11H), 7.64−7.67 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 14.2 (q), 19.4 (s), 27.1 (q), 32.6 (t), 35.7 (t), 60.0 (t), 68.5 (t), 72.0 (d), 73.2 (t), 75.0 (d), 123.6 (d), 127.6 (d), 127.7 (d), 128.4 (d), 129.8 (d), 129.9 (d), 132.9 (s), 133.5 (s), 135.9 (d), 138.1 (s), 145.0 (d), 166.2 (s); IR (film) $\tilde{\nu}_{max}$ (cm^{-1}) 3450, 2900, 1710, 1100; MS *m*/*z* (relative intensity) 489 (M − Bu-*t*)$^+$ (0.3), 275 (12), 207 (14), 91 (100). Anal. Calcd for $C_{33}H_{42}O_5Si$: C, 72.49; H, 7.74. Found: C, 72.49; H, 7.99.

Preparation of (2*E*)(5*R*,6*R*)-8-Benzyloxy-5-(*tert*-butyl-diphenyl-silanyloxy)-oct-2-ene-1,6-diol (34). The procedure used above to obtain **19** from **25** was applied to **33** on a 5.98 g (10.93 mmol) scale, yielding **34** (4.53 g, 82% yield) as an oil: $[\alpha]^{25}_D$ = −8.28 (*c* 0.25, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.05 (s, 9H), 1.77 (ddd, J = 6.0, 6.0, 6.0 Hz, 2H), 2.11 (ddd, J = 13.0, 6.5, 6.5 Hz, 1H), 2.37 (ddd, J = 13.0, 6.5, 6.5 Hz, 1H), 2.55 (br s, 1H), 3.52 (ddd, J = 9.0, 6.0, 6.0 Hz, 1H), 3.63 (ddd, J = 9.0, 6.0, 6.0 Hz, 1H), 3.67−3.72 (m, 2H), 3.88 (d, J = 4.7 Hz, 2H), 4.46 (s, 2H), 5.29−5.49 (m, 2H), 7.18−7.45 (m, 11H), 7.60−7.68 (m, 4H);^{13}C NMR ($CDCl_3$) δ 19.5 (s), 27.1 (q), 33.0 (t), 35.9 (t), 63.5 (t), 68.3 (t), 71.5 (d), 73.1 (t), 75.8 (d), 127.5 (d), 127.6 (d), 127.7 (d), 128.4 (d), 128.6 (d), 129.7 (d), 129.9 (d), 131.8 (d), 133.4 (s), 133.9 (s), 135.9 (s), 135.9 (d), 138.2 (s); MS *m*/*z* (relative intensity) 447 (M − Bu-*t*)$^+$ (5), 309 (19), 154 (70), 91 (100); IR (film) $\tilde{\nu}_{max}$ (cm^{-1}) 3350, 3050, 1415, 1100. Anal. Calcd for $C_{31}H_{40}O_4Si$: C, 73.77; H, 7.99. Found: C, 73.73; H, 8.16.

Preparation of (2*S*)-1-[(2*R*,4*R*,5*R*)-5-(2-Benzyloxy-ethyl)-4-(*tert*-butyl-diphenyl-silanyloxy)-tetrahydro-furan-2-yl]-ethane-1,2-diol (32). The procedure used above to obtain **26** from **19** was applied to **34** on a 1.4 g (2.77 mmol) scale, yielding **32** (1.15 g, 80% yield) as a colorless oil: $[\alpha]^{25}_D$ = +18.8 (*c* 1.84, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.10 (s, 9H), 1.77−1.88 (m, 1H), 1.90 (dd, J = 9.0, 6.0 Hz, 2H), 1.95−2.02 (m, 1H), 2.44 (br s, 1H), 3.19 (br s, 1H), 3.50−3.61 (m, 4H), 3.75 (ddd, J = 9.5, 4.0, 4.0 Hz, 1H), 3.80−3.88 (m, 2H), 4.37 (ddd, J = 4.7, 4.7, 4.7 Hz, 1H), 4.46 (br s, 2H), 7.25−7.47 (m, 11H), 7.61−7.70 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 19.3 (s), 27.1 (q), 30.2 (t), 35.6 (t), 63.8 (t), 67.7 (t), 72.8 (d), 72.9 (t), 74.0 (d), 78.4 (d), 79.7 (d), 127.6 (d), 127.7 (d), 127.8 (d), 128.3 (d), 129.9 (d), 133.2

(s), 133.6 (s), 135.9 (d), 136.0 (d), 138.4 (s); IR (film) $\tilde{\nu}_{max}$ (cm^{-1}) 3400, 2850, 1420, 1060; MS *m/z* (relative intensity) 443 ($M - C_6H_5$)$^+$ (0.2), 303 (2.63), 207 (11.73), 199 (100). Anal. Calcd for $C_{31}H_{40}O_5Si$: C, 71.50; H, 7.74. Found: C, 71.76; H, 7.56.

Preparation of (2*R*,3*R*,5*R*)-[2-(2-Benzyloxy-ethyl)-5-(2,2-dimethyl-[1,3]dioxolan-(4*S*)-4-yl)-tetrahydro-furan-3-yloxy]-*tert*-butyl-diphenyl-silane (35). To a solution of **32** (1.02 g, 1.96 mmol) in dry CH_2Cl_2 (19 mL) under argon was added 2,2-dimethoxy-propane (0.32 mL, 2.60 mmol) and a catalytic amount of CSA (40 mg) at 0 °C. The reaction was allowed to warm to room temperature and was stirred until TLC showed completed conversion (ca. 2 h). The mixture was diluted with CH_2Cl_2, quenched with Et_3N until pH ≈ 7 was reached, and washed with H_2O. The organic phase was dried, concentrated, and purified by column chromatography to give **35** (1.02 g, 93% yield): $[\alpha]^{25}_D = +3.31$ (*c* 1.48, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.07 (s, 9H), 1.34 (s, 3H), 1.36 (s, 3H), 1.81−1.99 (m, 3H), 2.06 (ddd, *J* = 13.5, 7.5, 6.0 Hz, 1H), 3.51 (dd, *J* = 6.4, 6.4 Hz, 2H), 3.70 (ddd, *J* = 7.5, 7.5, 6.0 Hz, 1H), 3.76 (ddd, *J* = 8.7, 4.0, 4.0 Hz, 1H), 3.84 (dd, *J* = 14.0, 6.0 Hz, 1H), 4.08 (dd, *J* = 14.0, 7.5 Hz, 1H), 4.13 (ddd, *J* = 7.5, 7.5, 6.0 Hz, 1H), 4.33 (ddd, *J* = 6.0, 4.0, 4.0 Hz, 1H), 4.43 (br s, 2H), 7.25−7.45 (m, 11H), 7.63−7.67 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 19.3 (s), 25.4 (q), 26.7 (q), 27.0 (q), 30.4 (t), 38.3 (t), 67.6 (t), 67.8 (t), 72.8 (t), 74.2 (d), 78.2 (d), 78.5 (d), 79.8 (d), 109.1 (s), 127.4 (d), 127.6 (d), 127.7 (d), 128.3 (d), 129.7 (d), 133.4 (s), 133.8 (s), 135.8 (d), 135.9 (d), 136.0 (d), 138.6 (s); IR (film) $\tilde{\nu}_{max}$ (cm^{-1}) 3417, 2930, 1650, 1110; MS *m/z* (relative intensity) 560 $(M)^+$ (0.13), 545 $(M - CH_3)^+$ (2.50), 277 (22.7), 91 (100). Anal. Calcd for $C_{34}H_{44}O_5Si$: C, 72.82; H, 7.91. Found: C, 72.82; H, 8.10.

Preparation of (4*S*)-4-[(2*R*,4*R*,5*R*)-4-(*tert*-Butyl-diphenyl-silanyloxy)-5-(5-trimethylsilanyl-pent-2-(*E*)-en-4-ynyl)-tetrahydro-furan-2-yl]-2,2-dimethyl-[1,3]dioxolane (36). A mixture of **35** (957 mg, 1.70 mmol) and Pd−C 10% (5% w) in dry EtOAc (17 mL) was stirred at room temperature under an atmosphere of H_2 (≈ 1 atm). The reaction was stirred overnight, after which time TLC showed the end of the reaction. The solution was filtered through a pad of Celite, and the filter was washed with EtOAc. The combined organic phases were concentrated, and the crude obtained was used without purification.

To a solution of the crude in dry CH_2Cl_2 (17 mL) was added crushed, activated 4 Å molecular sieves and NaOAc (42 mg, 0.51 mmol) under argon. The flask was cooled to 0 °C, and PCC (735 mg, 3.41 mmol) was added with stirring. The reaction was allowed to warm to room temperature and was stirred for 2 h. After dilution with Et_2O, the mixture was filtered through a pad of Celite and silica gel and washed with Et_2O. The resulting solution was concentrated, yielding an oil of the crude aldehyde, which was used without purification.

To a suspension of commercially available $TMSC{\equiv}CCH_2PPh_3{+}Br^-$ (1.08 g, 2.38 mmol) in dry THF (12 mL) was added *n*-butyllithium (1.16 mL, 1.9 M in *n*-hexane, 2.21 mmol) under argon at 0 °C. The mixture was stirred for 1 h and cooled at −78 °C. Then the aldehyde was added in dry THF (5 mL), and the mixture was allowed to warm to room temperature and monitored by TLC until complete conversion (ca. 4 h). The mixture was filtered through a pad of Celite and washed with Et_2O. The resulting solution was concentrated and purified by flash chromatography, yielding **36** (480 mg, 50% overall yield) as an oil: $[\alpha]^{25}_D = +56.7$ (*c* 3.13, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.17 (s, 9H), 1.08 (s, 9H), 1.34 (s, 3H), 1.37 (s, 3H), 1.92 (ddd, *J* = 13.5, 6.4, 4.1 Hz, 1H), 2.07 (ddd, *J* = 13.5, 7.4, 6.2 Hz, 1H), 2.23 (ddd, *J* = 14.8, 8.0, 4.3 Hz, 1H), 2.38 (ddd, *J* = 14.8, 8.2, 6.8 Hz, 1H), 3.59 (ddd, *J* = 8.7, 4.4, 4.4 Hz, 1H), 3.70 (br dd, *J* = 7.0, 3.0 Hz, 1H), 3.83 (ddd, *J* = 8.4, 7.2, 3.5 Hz, 1H), 4.07−4.13 (m, 2H), 4.33 (ddd, *J* = 6.0, 4.5, 4.5 Hz, 1H), 5.46 (dd, *J* = 15.9, 1.3 Hz, 1H), 6.13 (ddd, *J* = 15.9, 7.1, 7.1 Hz, 1H), 7.35−7.46 (m, 6H), 7.63−7.66 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 0.0 (q), 19.2 (s), 25.4 (q), 26.7 (q), 27.0 (q), 34.1 (t), 38.0 (t), 67.8 (t), 73.9 (d), 78.3 (d), 78.4 (d), 81.8 (d), 93.0 (s), 104.0 (s), 109.1 (s), 111.4 (d), 127.7 (d), 127.8 (d), 129.8 (d), 129.9 (d), 133.3 (s), 133.6 (s), 135.8 (d), 136.0 (d), 142.8 (d); IR (film) $\tilde{\nu}_{max}$ (cm^{-1}) 2900, 2075, 1720, 1420; MS *m/z* (relative intensity) 562 $(M)^+$ (0.6), 547 $(M - CH_3)^+$ (5.44), 505 (12.83), 199 (100). Anal. Calcd for $C_{33}H_{46}O_4Si_2$: C, 70.41; H, 8.24. Found: C, 70.45; H, 8.34.

Preparation of (2*R*,3*R*,5*R*)-5-{(4 *S*)-2,2-Dimethyl-[1,3]-dioxolan-4-yl}-2-[pent-2(*E*)-en-4-ynyl]-tetrahydro-furan-3-yl Acetate (37). To a stirred solution of **36** (375 mg, 0.66 mmol) in dry THF (6.6 mL) under argon was added tetra-*n*-butylammonium fluoride (2.42 mL, 1.1 M in THF, 2.66 mmol) at 0 °C. The reaction was allowed to warm to room temperature and was stirred for 1 h. The reaction mixture was poured into H_2O and extracted with Et_2O. The combined organic solutions were washed with brine, dried, and concentrated to yield a crude oil.

To a solution of the crude alcohol in dry CH_2Cl_2 (6.6 mL) under argon was added Et_3N (130 μL, 1.0 mmol), acetic anhydride (94 μL, 1.0 mmol), and a catalytic amount of DMAP at 0 °C. The reaction was stirred for 2 h, after which time TLC showed that the starting material had disappeared. Then, a saturated aqueous solution of NaCl was added and the resulting mixture was extracted with CH_2Cl_2. The combined organic phases were dried, filtered, evaporated in a vacuum, and purified by silica gel chromatographic column to yield **37** as an oil (170 mg, 87% overall yield): $[\alpha]^{25}_D = -1.32$ (*c* 0.22, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.33 (s, 3H), 1.38 (s, 3H), 1.95 (ddd, *J* = 14.6, 5.4, 1.8 Hz, 1H), 2.06 (s, 3H), 2.37−2.49 (m, 3H), 2.79 (d, *J* = 1.7 Hz, 1H), 3.78−3.90 (m, 3H), 4.01−4.11 (m, 2H), 5.23 (ddd, *J* = 6.4, 3.7, 1.8 Hz, 1H), 5.51 (ddd, *J* = 15.8, 3.8, 1.7 Hz, 1H), 6.16 (ddd, *J* = 15.8, 7.4, 7.4 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 21.0 (q), 25.3 (q), 26.7 (q), 32.9 (t), 35.8 (t), 67.3 (t), 74.3 (d), 76.6 (d), 77.8 (d), 78.4 (d), 80.6 (d), 82.2 (s), 109.3 (s), 110.2 (d), 141.6 (d), 170.2 (s); IR (film) $\tilde{\nu}_{max}$ (cm^{-1}) 2950, 1730, 1360, 1230; MS *m/z* (relative intensity) 279 $(M - CH_3)^+$ (46.85), 229 (64.07), 171 (14.99), 101 (100); HRMS calcd for $C_{15}H_{19}O_5$ $(M - CH_3)^+$ 279.12324, found 279.13001.

Preparation of (2*R*,3*R*,5*R*)-5-Formyl-2-[pent-2(*E*)-en-4-ynyl]-tetrahydro-furan-3-yl Acetate (31). To a stirred solution of **37** (109 mg, 0.37 mmol) in MeOH (3.7 mL) was added a catalytic amount of CSA (17 mg, 0.07 mmol) at room temperature. The reaction mixture was vigorously stirred for 4 h, until TLC showed complete conversion. The mixture was diluted with CH_2Cl_2 and washed with H_2O. The organic phase was dried, filtered and concentrated, yielding the diol, which was used without purification.

To a stirred solution of the crude diol dissolved in THF/H_2O (5:1, 3.7 mL) was added $NaIO_4$ (200 mg, 0.93 mmol). After 1 h, the mixture was diluted with Et_2O and washed with H_2O. The resulting organic phase was dried, concentrated, and purified by column chromatography to give the aldehyde **31** as an oil (70 mg, 85% overall yield):[26] $[\alpha]^{25}_D = +32.0$ (*c* 0.53, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 2.02 (s, 3H), 2.24 (d, *J* = 14.4 Hz, 1H), 2.38−2.52 (m, 4H), 2.82 (br s, 1H), 4.02−4.07 (m, 1H), 4.32 (d, *J* = 9.9 Hz, 1H), 5.25−5.29 (m, 1H), 5.56 (d, *J* = 15.6 Hz, 1H), 6.21 (ddd, *J* = 15.6, 7.6, 7.6 Hz, 1H), 9.70 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 20.8 (q), 33.0 (t), 36.3 (t), 73.0 (d), 76.8 (s), 77.4 (d), 81.4 (d), 81.6 (d), 111.5 (d), 140.9 (d), 169.8 (s), 203.4 (d); IR (film) (cm^{-1}) 3442, 1644, 1246, 1040.

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Supporting Information Available: ^{1}H NMR and ^{13}C NMR spectra for all new compounds described in the Experimental Section, ^{1}H NMR spectra of natural **5**, Mosher's diesters of both enantiomers of **27,** and NOE spectrum of **5**. This information is available free of charge via the Internet at http://pubs.acs.org.

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