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Molecular Simplification in Bioactive Molecules: Formal Synthesis of (+)-Muconin

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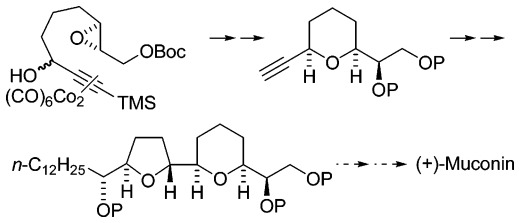

The concept of molecular simplification as a drug design strategy to shorten synthetic routes, while keeping or enhancing the biological activity of the lead drug, has been applied to (+)-muconin, an acetogenin with remarkable cytotoxicity. A novel approach that enables the stereoselective synthesis of such a natural compound or its enantiomer from a common precursor is described. An additional advantage of the method is complete stereochemical control and the decrease in the number of chemical steps required, thus providing an enhancement of the overall yield. Antiproliferative studies against the human solid tumor cell lines showed that the aliphatic chain-THF/THP fragment of (+)-muconin has modest cytotoxic activity. The strategy opens the way to preparing novel bioactive acetogenin analogues by shorter synthetic routes.

Introduction

Acetogenins constitute a broad family of compounds with interesting biological properties. From the plant family *Annonaceae*, a large number of natural acetogenins have been isolated. These compounds have attracted the attention of many research groups as a result of their interesting structural complexity and the important biological activities (anticancer, pesticidal, immunosuppressive, and antifeedant) they exert.[1] The four main classes of structural features of annonaceous acetogenins are mono-tetrahydrofuran, adjacent bis-tetrahydrofuran, nonadjacent bis-tetrahydrofuran, and nonclassical acetogenins.[1]

(+)-Muconin (**1**), a nonclassical acetogenin, was isolated for the first time by McLaughlin et al. in 1996.[2] This natural product can be split up into three parts: a long carbon chain, sequential THF and THP rings, and a 2,4-disubstituted α,β-unsaturated γ-lactone (Figure 1). Furthermore, this compound has eight stereogenic centers, six of which are found in the middle part (THF/THP rings). Focusing on the biological activity, (+)-muconin (**1**) showed a potent in vitro cytotoxicity against human pancreatic and breast tumor cells.[2] In light of the interesting biological results and its backbone novelty, some groups dedicated their efforts to achieve its total synthesis.[3]

The critical issue encountered in the diverse reported total syntheses has been to introduce in a straightforward manner

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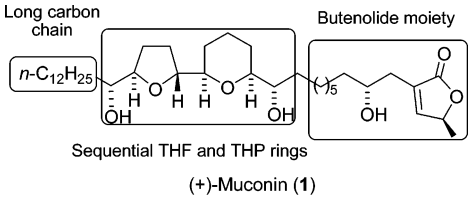
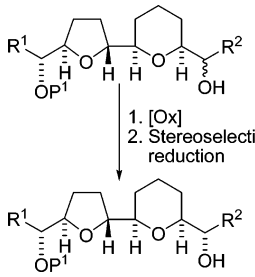


FIGURE 1. Main structural blocs in (+)-muconin.

SCHEME 1. Common Step in Several Synthetic Approaches to (+)-Muconin (1)

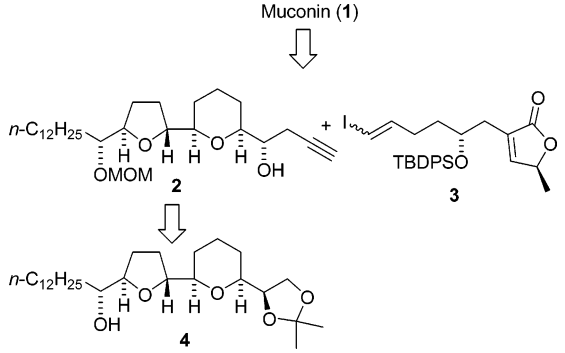


the six stereogenic carbons present in the sequential THF/THP moiety. In most reported syntheses,[3] a common strategy is the oxidation and subsequent stereoselective reduction of a secondary alcohol (Scheme 1). Although the sequence of oxidation/reduction reactions works well and with moderate stereocontrol, it represents an increase in the total number of synthetic steps.

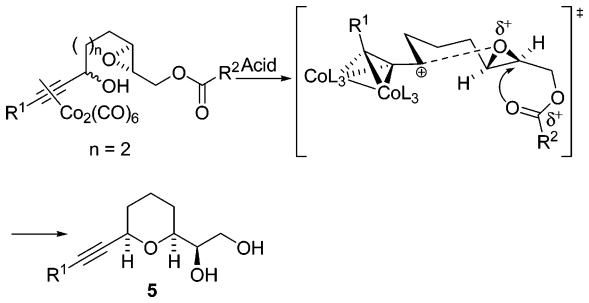
Structural simplification represents a drug design strategy to shorten synthetic routes while keeping or enhancing the biological activity of the natural template. The concept has been applied successfully in naturally occurring acetogenins, leading to analogues with remarkable cytotoxicity against human solid tumor cells.[4] In acetogenins in general, the 2,4-disubstituted α,β-unsaturated γ-lactone fragment is claimed to be essential for the biological activity.[1a] However, the contribution of the other structural fragments of these molecules to the cytotoxic activity has not been studied in detail. We addressed our attention toward the synthetic strategy developed by Takahashi's group,[3e] since such studies should permit analysis of the influence of the aliphatic chain and THF/THP fragments in the cytotoxic activity of muconin. Their strategy relies on the Sonogashira coupling between the building blocks **2** and **3** (Scheme 2). The building block **2** was synthesized from compound **4**, which represents a very advanced intermediate in the synthesis and in which the six stereogenic centers are installed. Therefore, this molecular block represents an interesting synthetic target inasmuch as its synthesis achieved in some alternative manner represents a new formal synthesis of the natural compound.

Within our research program directed toward the synthesis of cyclic ethers[5] and biologically active molecules,[6] we report herein on the synthesis of intermediate **4**. In addition, a preliminary structure−activity relationship (SAR) study of the

SCHEME 2. Retrosynthetic Analysis Developed by Takahashi's Group for the Synthesis of (+)-Muconin (1)



SCHEME 3. Epoxides as Nucleophiles in the Intramolecular Nicholas Reaction; Strategy for the Key THP Ring



synthetic intermediates against the human ovarian cancer cell line A2780 and the human non-small cell lung cancer (NSCLC) cell line SW1573 is described. The application of molecular simplification in this class of compounds is also discussed.

Recently, we have developed a reliable strategy to synthesize polysubstituted oxanes and oxepanes with a high degree of stereocontrol by a Nicholas reaction, based on the intramolecular nucleophilic attack of an epoxide to a carbocation generated by acid treatment of *exo*-$Co_2(CO)_6$ propargylic alcohols.[7] This synthetic tool allows us to introduce a new stereocenter at the propargylic position with total control of the stereochemistry (Scheme 3).

With the aforementioned methodology, we planned the retrosynthetic analysis of **4** outlined in Scheme 4, where the THP ring **5** (R^1 = H) would act as a scaffold. We first disconnected the saturated chain from the terminal epoxide **6**, bearing in mind the possibility of introducing such an alkyl chain by a nucleophilic opening of the terminal epoxide ring. The THF ring was envisioned through a regio- and stereoselective *exo*-cyclization in situ of the suitable epoxy alcohol, which in turn could be obtained through a Katsuki−Sharpless asymmetric

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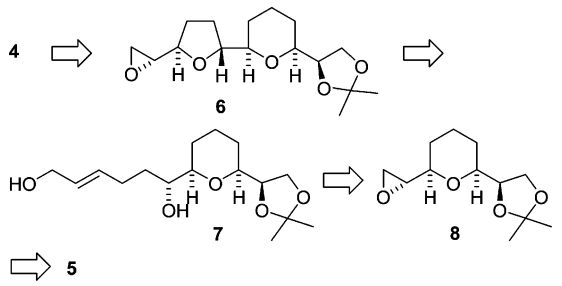
SCHEME 4. Retrosynthetic Analysis of Compound 4



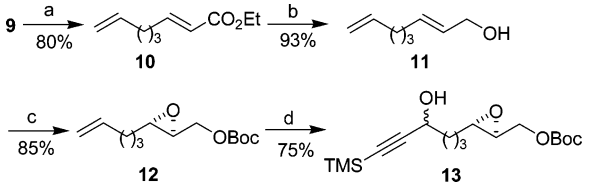
epoxidation (KSAE)[8] of the allylic alcohol **7**. Compound **7** could be synthesized by an allyl Grignard regioselective opening of epoxide **8** with further homologation and reduction. Compound **8** would be derived from **5** (R^1 = H) after a simple four-step sequence: hydrogenation of the triple bond, Sharpless asymmetric dihydroxylation (SAD) of the olefin,[9] selective tosylation of the primary alcohol, and terminal epoxide formation under basic conditions. Three major advantages derived from this strategy: first, the synthesis of the THF and THP stereoisomers would be modulated by simply changing the chiral auxiliary at the KSAE and SAD steps; second, the application of three consecutive enantioselective reactions ensures the high enantiomeric purity of the final products; third, the building block **8** could be homologated in both directions opening the possibility to synthesize the enantiomer of compound muconin (**1**) starting from the common intermediate **5**.

Results and Discussions

The synthesis of **5** (R^1 = H) began with the commercially available alcohol 5-hexen-1-ol (**9**), which was homologated by a protocol recently developed in our group.[10] Reduction of the α,β-unsaturated ester **10** with DIBAL-H generated the allylic alcohol **11**. With **11** in our hands, we performed a KSAE using as chiral auxiliary (+)-diethyl tartrate,[11] followed by alcohol protection as *tert*-butyl carbonate (Boc). The double bond present in compound **12** was cleaved with OsO_4/$NaIO_4$. Thus, the obtained aldehyde was submitted to the next step without further purification. The coupling of this aldehyde with the lithium salt of trimethylsilylacetylene furnished the diastereomeric propargylic alcohols **13**. This synthetic route to **13** represents an improvement in the overall yields and in the number of chemical steps (47% in 6 steps) on an earlier strategy (25% in 11 steps) (Scheme 5).[7]

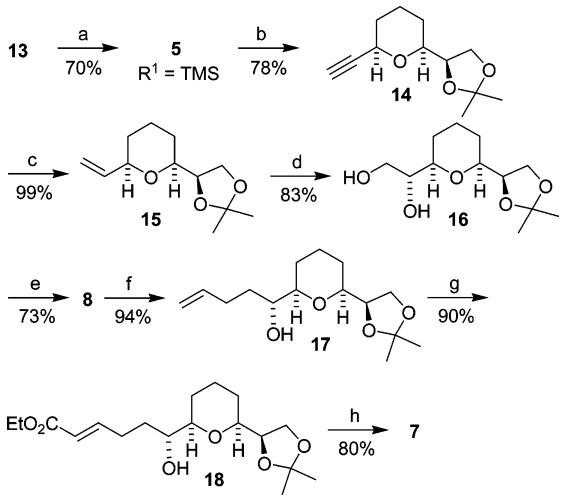
Compound **13** was then transformed into the THP **5** (R^1 = TMS) by a regio- and stereoselective intramolecular Nicholas reaction as described earlier.[6] K_2CO_3 treatment and diol protection with 2,2-dimethoxypropane led to the key compound **14**. The next step was the introduction of a secondary alcohol adjacent to the THP ring, a process that proceeded with total stereocontrol. To carry out this transformation a two-step sequence was applied: partial hydrogenation with Lindlar catalyst to generate the double bond in **15** and a SAD with AD-mix α affording diol **16** as an 8:1 inseparable epimeric mixture. Fortunately, when the primary alcohol was selectively tosylated and reacted with NaH, pure terminal epoxide **8** was obtained. The key epoxide **8** was then opened with allyl Grignard, in the presence of CuI, furnishing the allylic alcohol **17**. Application of the known OsO_4/$NaIO_4$ protocol to cleave double bonds, followed by Wittig reaction, led to the α,β-unsaturated ester **18** in good yields. Reduction with DIBAL-H allowed us to obtain intermediate **7** (Scheme 6).

SCHEME 5. Improved Synthesis of the Linear Precursor 13[a]



[a] Reagents and conditions: (a) SO_3·Py, DMSO, TEA, $Ph_3P{=}CHCO_2Et$, CH_2Cl_2; (b) DIBAL-H, toluene, 0 °C; (c) (i) (+)-DET, Ti(OPr-*i*)$_4$, TBHP, CH_2Cl_2, −20 °C (ii) toluene, DMAP, Boc_2O; (d) (i) OsO_4 cat., $NaIO_4$, NMO, THF/H_2O (1:1) (ii) TMS-acetylene, *n*-BuLi, THF, −78 °C.

SCHEME 6. Synthesis of the Allylic Alcohol 7 Precursor of the THF/THP Rings[a]



[a] Reagents and conditions: (a) see ref 6; (b) (i) K_2CO_3, MeOH (ii) 2,2-dimethoxypropane, CSA, CH_2Cl_2; (c) Lindlar catalyst, quinoleine, EtOAc; (d) AD-mix-α, *t*-BuOH/H_2O (1:1); (e) (i) TsCl, Py, 0 °C (ii) NaH, THF; (f) AllylMgBr, CuI, THF; (g) (i) OsO_4 cat., $NaIO_4$, NMO, THF/H_2O (1:1) (ii) $Ph_3P(O){=}CHCO_2Et$, CH_2Cl_2; (h) DIBAL-H, toluene, 0 °C.

With compound **7** in hand we proceeded to the THF ring formation. Interestingly, the KSAE of **7** using (+)-diethyl tartrate as chiral auxiliary provided by concomitant epoxide opening the *anti*-tetrahydrofuran **19** as the sole detected stereoisomer (Scheme 7). The sequential THF/THP rings were then obtained as a single diastereoisomer. In addition, the six stereocenters were installed with complete stereocontrol. Compound **19** was subjected to selective benzoylation of the primary alcohol and further mesylation of the secondary alcohol. Basic hydrolysis of the benzoyl ester group provided the terminal epoxide **6** by intramolecular displacement of the secondary mesylate group with the primary alkoxide. Finally, the regioselective opening of the terminal epoxide with the Grignard reagent derived from commercially available 1-bromoundecane, in the presence of CuI, furnished the desired compound **4** achieving a formal synthesis of (+)-muconin (**1**).[3e]

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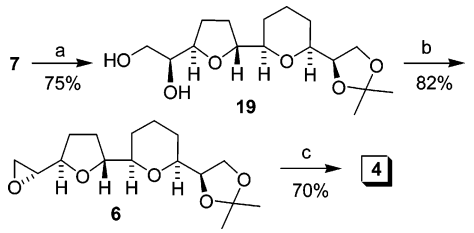
SCHEME 7. Completion of the Formal Synthesis of (+)-Muconin (1)[a]



[a] Reagents and conditions: (a) (+)-DET, Ti(OPr-*i*)$_4$, TBHP, CH_2Cl_2, −20 °C; (b) (i) TEA, benzoyl chloride, then MsCl, CH_2Cl_2 (ii) MeOH, NaH, CH_2Cl_2, 0 °C; (c) bromoundecane, Mg, CuI, THF, −78 °C.

TABLE 1. In Vitro Cytotoxic Activity (GI_{50}) against Human Solid Tumor Cells[a]

	cell line	
compound	A2780	SW1573
4	90 ± 18	85 ± 20
7	>100	>100
8	>100	>100
15	18 ± 11	24 ± 5
16	>100	>100
17	>100	>100
18	>100	>100
19	>100	>100

[a] Values are given in μM and are means of at least three experiments; standard deviation is given.

A series of the aforementioned intermediates was then screened for growth inhibition and cytotoxicity against the human solid tumor cell lines A2780 and SW1573 using the SRB assay of the NCI.[12] The sensitivities expressed as 50% growth inhibition (GI_{50}) are listed in Table 1. Interestingly, compounds **4** and **15** were the only products that reached a GI_{50} value within the experimental range. Compound **4**, which represents the left half of muconin (**1**), showed modest GI_{50} values of 90 and 85 μM against A2780 and SW1573 cells, respectively. Despite the absence of the 2,4-disubstituted α,β-unsaturated γ-lactone fragment, which is essential for the activity of acetogenins, intermediate **4** is able to inhibit cell growth. This effect is masked in muconin (**1**) by the extraordinarily potency of the butenolide fragment. Interestingly, compound **15** proved to be a more potent derivative with GI_{50} values in the low micromolar range, which are comparable to those of the anticancer drugs cisplatin[13] and 5-fluorouracil[14] currently used in NSCLC and ovarian cancer chemotherapy. Furthermore, compound **15** may be considered a molecular or structural simplification of the more complex intermediate **4**, where the long aliphatic chain and the THF ring have been replaced by a vinyl group.

Conclusions

In summary, we have accomplished a new formal and practical synthesis of (+)-muconin (**1**). Total control of the six stereocenters present in the THF/THP moiety is ensured by means of three enantioselective reactions, and the yield in each step is over 70%. In addition, intermediate **5** can serve as a scaffold to obtain both enantiomers of muconin (**1**). Moreover, the described methodology can be applied to other natural products with a similar structure. In addition, the developed methodology opens the way to synthesize other diastereoisomers/enantiomers by simply changing the chiral auxiliary used in the enantioselective reactions. Biological observations suggest that our data could lead to the development of a new class of structurally simplified anticancer agents. Further studies along these lines are currently under way in our laboratories, and the results will be reported elsewhere.

Experimental Section

Preparation of (*E*)-Ethyl Octa-2,7-dienoate (10). To a solution of 5-hexen-1-ol (**9**) (12 mL, 99.8 mmol) in dry CH_2Cl_2 (400 mL) under N_2 atmosphere were added DMSO (80 mL) and triethylamine (83 mL, 0.6 mol) at room temperature. Then, to the stirred solution was added $Ph_3P{=}CHCO_2Et$ (70 g, 0.2 mol), and after it was completely dissolved, $SO_3{\cdot}Py$ (48 g, 0.3 mol) was added. The reaction was monitored by TLC until the starting material could not be detected. Subsequently, 5% HCl solution was added until acidic pH. Extraction with CH_2Cl_2 was done. The combined organic phases were washed with water and brine, dried over $MgSO_4$, filtered, concentrated, and purified by column flash chromatography to yield 13 g (80% yield) of **10**. ^{1}H NMR (300 MHz) δ 1.28 (t, J = 7.1 Hz, 3H), 1.56 (m, 2H), 2.08 (m,2H), 2.20 (m, 2H), 4.17 (q, J = 7.1 Hz, 2 H), 4.99 (m, 2H), 5.79 (m, 2H), 6.95 (dt, J = 15.5, 6.9 Hz, 1H); ^{13}C NMR (75 MHz) δ 14.0 (q), 26.9 (t), 31.2 (t), 32.8 (t), 59.9 (t), 114.8 (t), 121.3 (d), 137.8 (d), 148.7 (d), 166.5 (s); IR (cm^{-1}) 1367, 1443, 1654, 1721, 2933, 2980, 3078; MS (EI) *m*/*z* (relative intensity) 54 (91), 81 (66), 95 (100), 123 (54), 140 (39), 168 (M)$^+$ (8); HRMS (EI) calcd for $C_{10}H_{16}O_2$ 168.1150, found 168.1152. Anal. Calcd for $C_{10}H_{16}O_2$ C 71.39, H 9.59. Found: C 71.38, H 10.02.

Preparation of (*E*)-Octa-2,7-dien-1-ol (11). To a solution of **10** (13 g, 77.3 mmol) in dry toluene (400 mL) under N_2 atmosphere at 0 °C was added dropwise DIBAL-H (154 mL, 0.15 mol). When TLC indicated the complete reaction of the starting material, the reaction was quenched by the addition of H_2O. To the obtained slurry was added $MgSO_4$, and then the mixture was filtered through a pad of Celite. The solvent was evaporated, and the residue was purified by column chromatography to give 9 g (93% yield) of **11**. ^{1}H NMR (300 MHz) δ 1.48 (m, 2H), 2.04 (m, 4H), 4.07 (d, J = 4.6 Hz, 2H), 4.97 (m, 2H), 5.64 (m, 2H), 5.79 (m, 2H); ^{13}C NMR (75 MHz) δ 28.0 (t), 31.3 (t), 32.9 (t), 63.5 (t), 114.4 (t), 129.0 (d), 132.7 (d), 138.4 (d); IR (cm^{-1}) 1670, 1721, 2857, 2928, 3077, 3354; MS (EI) *m*/*z* (relative intensity) 55 (75), 67 (100), 79 (51), 93 (35), 107 (12), 125 (M − 1)$^+$ (4); HRMS (EI) calcd for $C_8H_{14}O$ 126.1045, found 126.1047. Anal. Calcd for $C_8H_{14}O$ C 76.14, H 11.18. Found: C 76.16, H 11.71.

Preparation of *tert*-Butyl[(2*S*,3*S*)-3-(pent-4-enyl)]oxidan-2-yl]-methyl Carbonate (12). To a solution of crushed molecular sieves (MS 4 Å) and (+)-DET (17 mL, 99 mmol) in dry CH_2Cl_2 under N_2 atmosphere at −20 °C was added Ti(OPr-*i*)$_4$ (25 mL, 85 mmol). After 15 min, compound **11** was added (8.4 g, 71 mmol,) and 30 min later a 6.1 M solution of TBHP in isooctane (21 mL, 127 mmol) was added. The reaction was stirred overnight. The reaction was quenched by the addition of tartaric acid solution (15% in water), and further extraction was done with CH_2Cl_2. The extracts were dried over $MgSO_4$, and the solvent was evaporated under reduced pressure. The residue obtained was dissolved in ether and washed with NaOH solution (15% in water). The organic phase was dried with $MgSO_4$ and filtered. Following solvent evaporation the residue was employed in the next step without further purification.

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To a solution of the aforementioned crude epoxy alcohol in dry toluene (280 mL) under N_2 atmosphere and at room temperature was added Boc anhydride (19 g, 85 mmol) followed by DMAP (867 mg, 7.1 mmol). The reaction was monitored by TLC and was complete after 2 h. The reaction mixture was treated with $CHCl_3$ and HCl solution (5% in water) and extracted with more $CHCl_3$. The organic phase was dried and concentrated. Chromatography on silica gel afforded 14.5 g (85% yield) of **12**. $[\alpha]^{25}_D = -19.9$ (*c* 1.1, $CHCl_3$); ^{1}H NMR (300 MHz) δ 1.48 (s, 9H), 1.47−1.57 (m, 4H), 2.08 (m, 2H), 2.85 (m, 1H), 2.97 (m, 1H), 4.00 (dd, $J = 5.8$, 12.0 Hz, 1H), 4.22 (dd, $J = 3.8$, 12.0 Hz, 1H), 4.97 (m, 2H), 5.76 (m, 1H);^{13}C NMR (75 MHz) δ 24.8 (t), 27.5 (q), 30.6 (t), 33.0 (t), 54.8 (d), 56.3 (d), 66.8 (t), 82.3 (s), 114.7 (t), 137.9 (d), 153.0 (s); IR (cm^{-1}) 1370, 1641, 1744, 2862, 2980, 3077; MS (FAB) *m*/*z* (relative intensity) 57 (100), 107 (41), 137 (14), 154 (9), 187 (33), 243 (M + 1)$^+$ (8); HRMS (FAB) calcd for $C_{13}H_{23}O_4$ (M + 1)$^+$ 243.1596, found 243.1595. Anal. Calcd for $C_{13}H_{22}O_4$ C 64.44, H 9.15. Found: C 64.44, H 9.53.

Preparation of *tert*-Butyl{(2*R*,3*R*)-3-[4-hydroxy-6-(trimethylsilyl)hex-5-ynyl]oxiran-2-yl}methyl Carbonate (13). Compound **12** (14 g, 57.8 mmol) was dissolved in THF/H_2O 1:1 (350 mL) at room temperature. To this solution were added NMO (17 g, 0.14 mol) and a catalytic amount of OsO_4. The reaction mixture was stirred overnight, quenched with a saturated solution of $Na_2S_2O_3$, and extracted with EtOAc. The organic phase was dried, and the solvent was evaporated under reduced pressure. The crude aldehyde obtained was used in the next step without purification.

To a solution of ethynyltrimethylsilane (9 mL, 63.5 mmol) in dry THF under N_2 atmosphere at −78 °C was added a solution of *n*-BuLi (2.1 M, 30 mL). After 30 min at the same temperature the crude aldehyde was added. The reaction was quenched by addition of a saturated solution of NH_4Cl, and the extraction was done with Et_2O. The organic phase was dried over $MgSO_4$, and the solvent was evaporated under reduced pressure. Purification by chromatographic column afforded 14.8 g (75% yield) of **13**. ^{1}H NMR (300 MHz) δ 0.17 (s, 9H), 1.49 (s, 9H), 1.57−1.86 (m, 6H), 2.88 (m, 1H), 2.99 (m, 1H), 4.01 (dd, $J = 5.8$, 12.0 Hz, 1H), 4.24 (dd, $J = 3.7$, 12.0 Hz, 1H), 4.36 (m, 1H); ^{13}C NMR (75 MHz) δ −0.4 (q), 21.4 (t), 27.5 (q), 30.8 (t), 36.9 (t), 57.7 (d), 56.2 (d), 62.4 (d), 66.7 (t), 82.3 (s), 89.5 (s), 106.2 (s), 153.0 (s); IR (cm^{-1}) 1281, 1370, 1745, 2170, 2957, 3459; MS (FAB) *m*/*z* (relative intensity) 57 (95), 73 (100), 137 (25), 154 (23), 181 (9), 269 (30); HRMS (FAB) calcd for $C_{17}H_{30}O_5SiNa$ (M + Na)$^+$ 365.1760, found 365.1768. Anal. Calcd for $C_{17}H_{30}O_5Si$ C 59.61, H 8.83. Found: C 59.61, H 8.89.

Preparation of (*R*)-1-{(2*S*,6*R*)-6-[2-(Trimethylsilyl)ethynyl]-tetrahydro-2*H*-pyra-2-yl}ethane-1,2-diol (5). To a solution of **13** (8.52 g, 24.9 mmol) in dry CH_2Cl_2 under N_2 atmosphere and at room temperature was added $Co_2(CO)_8$ (9.36 g, 27.3 mmol). The reaction was monitored by TLC until the starting material was completely consumed. To the solution of the hexacarbonyldicobalt complex of **13** was added $BF_3{\cdot}OEt_2$ (3.15 mL, 24.9 mmol) at room temperature. The reaction mixture was stirred for 3 h. The mixture was poured with vigorous stirring into a saturated solution of $NaHCO_3$ at 0 °C and extracted with CH_2Cl_2. The combined organic phases were washed with brine, dried ($MgSO_4$), and concentrated. The crude mixture was dissolved in acetone (2.1 mL) at 0 °C. Ceric ammonium nitrate (41.0 g, 74.7 mmol) was added in portions with stirring until evolution of CO ceased and the CAN color persisted (30 min). The solvent was removed under vacuum, and the pink solid residue was then partitioned between Et_2O and H_2O. The aqueous phase was extracted additionally twice with Et_2O. The combined organic extracts were dried, filtered, concentrated, and subjected to silica gel flash chromatography yielding compound **5** in 70% yield (4.2 g). $[\alpha]^{25}_D = -26.6$ (*c* 0.7, $CHCl_3$); ^{1}H NMR (300 MHz) δ 0.15 (s, 9H), 1.48−1.65 (m, 5H), 1.80−1.92 (m, 3H), 3.45 (m, 1H), 3.65 (m, 1H), 3.75 (m, 2H), 4.10 (dd, $J = 2.3$, 11.1 Hz, 1H); ^{13}C NMR (75 MHz) δ −0.4 (q), 22.6 (t), 26.0 (t), 32.3 (t), 63.1 (t), 68.7 (d), 73.3 (d), 79.8 (d), 89.0 (s), 104.2 (s); IR (cm^{-1}) 1063, 1250, 1715, 2179, 2954, 3384; MS (EI) *m*/*z* (relative intensity) 73 (100), 97 (29), 109 (15), 125 (84), 181 (34), 242 (M)$^+$ (3); HRMS (EI) calcd for $C_{12}H_{22}O_3Si$ (M)$^+$ 242.1338, found 242.1331. Anal. Calcd for $C_{12}H_{22}O_3Si$ C 59.46, H 9.15. Found: C 59.44, H 9.01.

Preparation of (2*S*,6*R*)-2-[(*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl]-6-ethynyl-tetrahydro-2*H*-pyran (14). To a solution of **5** (3.52 g, 14.5 mmol) in methanol (50 mL) at room temperature was added K_2CO_3 (1.0 g, 7.2 mmol). After 6 h the reaction was completed. To the reaction mixture was added CH_2Cl_2, and the mixture was filtered through a pad of Celite. The solvent was evaporated under reduced pressure, and the resulting residue was employed in the next step without purification.

This crude was dissolved in dry CH_2Cl_2 (50 mL) under N_2 atmosphere and at room temperature. To the solution were added 2,2-dimethoxypropane (2.7 mL, 21.7 mmol) and camphor-10-sulfonic acid (1.68 g, 7.2 mmol). The reaction was monitored by TLC, and after 3 h starting material was not observed. A saturated solution of $NaHCO_3$ was added to the reaction mixture, and the mixture was extracted with CH_2Cl_2. The organic phase was dried and the solvent evaporated. Column chromatography afforded 2.35 g (78% yield) of compound **14**. $[\alpha]^{25}_D = -44.1$ (*c* 1.1, $CHCl_3$); ^{1}H NMR (300 MHz) δ 1.33 (s, 3H), 1.39 (s, 3H), 1.26−1.68 (m, 3H), 1.80−1.87 (m, 3H), 2.45 (d, $J = 2.1$ Hz, 1H), 3.24 (m, 1H), 3.91−3.97 (m, 2H), 4.04−4.13 (m, 2H); ^{13}C NMR (75 MHz) δ 22.4 (t), 25.0 (q), 26.5 (q), 27.2 (t), 32.3 (t), 67.1 (t), 67.7 (d), 72.3 (d), 77.7 (d), 79.0 (d), 82.8 (s), 109.0 (s); IR (cm^{-1}) 1371, 1719, 2120, 2860, 2942, 3284; MS (FAB) *m*/*z* (relative intensity) 55 (100), 69 (65), 81 (73), 101 (75), 154 (52), 210 (M)$^+$ (4); HRMS (FAB) calcd for $C_{12}H_{18}O_3$ (M)$^+$ 210.1256, found 210.1258. Anal. Calcd for $C_{12}H_{18}O_3$ C 68.54, H 8.63. Found: C 68.64, H 8.85.

Preparation of (2*S*,6*R*)-2-[(*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl]-6-vinyl-tetrahydro-2*H*-pyran (15). A mixture of compound **14** (1.79 g, 8.5 mmol), Lindlar catalyst (89 mg, 5% w), and quinoline (4 μL, 0.2% w) in dry EtOAc (50 mL) was stirred at room temperature under H_2 atmosphere (1 atm) for 1 h. After this time, TLC showed complete conversion. The solution was filtered through a pad of Celite, and the filter cake was washed with EtOAc. After purification by chromatographic column, 1.79 g (99% yield) of compound **15** was obtained. $[\alpha]^{25}_D = -38.1$ (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz) δ 1.35 (s, 3H), 1.40 (s, 3H), 1.23−1.67 (m, 4H), 1.79−1.92 (m, 2H), 3.32 (m, 1H), 3.84 (m, 1H), 3.95 (m, 2H), 4.05 (m, 1H), 5.06 (dt, $J = 10.6$, 1.4 Hz, 1H), 5.19 (dt, $J = 17.3$, 1.6 Hz, 1H), 5.83 (ddd, $J = 17.3$, 10.6, 5.3 Hz, 1H); ^{13}C NMR (75 MHz) δ 22.6 (t), 25.0 (q), 26.4 (q), 27.5 (t), 31.0 (t), 66.8 (t), 77.9 (d), 78.0 (d), 78.2 (d), 108.8 (s), 114.1 (t), 138.8 (d); IR (cm^{-1}) 1075, 1212, 1370, 2859, 2936, 2986; MS (EI) *m*/*z* (relative intensity) 67 (100), 93 (95), 101 (52), 111 (79), 197 (54), 212 (M)$^+$ (1); HRMS (EI) calcd for $C_{12}H_{20}O_3$ (M − 1)$^+$ 211.1334, found 211.1342. Anal. Calcd for $C_{12}H_{20}O_3$ C 67.89, H 9.50. Found: C 67.87, H 9.67.

Preparation of (*R*)-1-{(2*R*,6*S*)-6-[(*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl]-tetrahydro-2*H*-pyran-2-yl}ethane-1,2-diol (16). Compound **15** was added to a mixture of *t*-BuOH (43 mL), H_2O (43 mL), and AD-mix-α (11.83 g, 1.4 g/mmol of **15**) at 0 °C. The solution was stirred for 12 h at 0 °C. After addition of a saturated Na_2SO_3 solution (50 mL) the mixture was extracted with EtOAc. The extracts were dried, and the solvent was removed. Flash chromatography yielded **16** (1.70 g, 83% yield). $[\alpha]^{25}_D = -6.6$ (*c* 1.1, $CHCl_3$); ^{1}H NMR (300 MHz) δ 1.32 (s, 3H), 1.40 (s, 3H), 1.17−1.53 (m, 3H), 1.72 (m, 2H), 1.93 (m, 1H), 3.35 (m, 1H), 3.43 (m, 1H), 3.56 (m, 1H), 3.68 (m, 2H), 3.85−4.02 (m, 3H); ^{13}C NMR (75 MHz) δ 22.2 (t), 25.0 (q), 26.3 (q), 27.0 (t), 27.6 (t), 63.2 (t), 66.2 (t), 73.5 (d), 77.9 (d), 78.2 (d), 79.3 (d), 109.1 (s); IR (cm^{-1}) 1212, 1371, 2861, 2936, 2985, 3417; MS (FAB) *m*/*z* (relative intensity) 81 (55), 132 (78), 189 (54), 231 (60), 247 (M + 1)$^+$ (100), 269 (M + Na)$^+$ (64); HRMS (FAB) calcd for $C_{12}H_{22}O_5$ (M)$^+$ 246.1467, found 246.1464. Anal. Calcd for $C_{12}H_{22}O_5$ C 58.52, H 9.00. Found: C 58.51, H 9.10.

Preparation of (2*S*,6*R*)-2-[(*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl]-6-[(*R*)-oxiran-2-yl]-tetrahydro-2*H*-pyran (8). To a stirred solution of **16** (1.5 g, 6.1 mmol) in dry pyridine (30.5 mL, 0.2 M) was added TsCl (1.39 g, 7.3 mmol) at 0 °C. The reaction mixture was stirred for 6 h, after which time TLC showed the end, and then diluted with H_2O, and the aqueous layer was extracted with Et_2O. The ethereal extracts were washed with H_2O, saturated $CuSO_4$ solution, and saturated NaCl solution (60 mL), dried, and concentrated. The residue monotosylated alcohol was used in the next step without purification.

The crude was dissolved in dry THF (61 mL) under N_2 atmosphere at room temperature, and NaH (60%, 175 mg, 12.2 mmol) was added. After 4 h, TLC showed that starting material was completely consumed. The reaction was quenched by addition of a saturated solution of NaCl, and the mixture was extracted with Et_2O. The organic phase was dried, and the solvent was evaporated under reduced pressure. Purification by chromatographic column gave 1.01 g (73% yield) of epoxide **8**. $[\alpha]^{25}_D = -6.0$ (*c* 0.7, $CHCl_3$); ^{1}H NMR (300 MHz) δ 1.35 (s, 3H), 1.41 (s, 3H), 1.24−1.91 (m, 6H), 2.67 (dd, J = 2.6, 5.2 Hz, 1H), 2.75 (dd, J = 4.1, 5.2 Hz, 1H), 2.94 (m, 1H), 3.25 (m, 2H), 3.88−4.05 (m, 3H); ^{13}C NMR (75 MHz) δ 22.1 (t), 25.1 (q), 26.4 (q), 27.5 (t), 44.9 (t), 53.2 (t), 53.5 (d), 66.7 (t), 77.2 (d), 77.9 (d), 78.4 (d), 109.3 (s); IR (cm^{-1}) 1092, 1370, 1456, 2861, 2937, 2986; MS (FAB) *m*/*z* (relative intensity) 55 (100), 69 (90), 83 (61), 95 (50), 213 (16), 229 $(M + 1)^+$ (16); HRMS (FAB) calcd for $C_{12}H_{21}O_4$ $(M + 1)^+$ 229.1440, found 229.1441. Anal. Calcd for $C_{12}H_{20}O_4$ C 63.14, H 8.83. Found: C 63.14, H 9.19.

Preparation of (1*R*)-1-{(2*R*,6*S*)-6-[(*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl]-tetrahydro-2*H*-pyran-2-yl}penten-4-en-1-ol (17). To a mixture of CuI (75 mg, 0.4 mmol) in dry THF (40 mL) under argon atmosphere was added allylmagnesium bromide (11.8 mL, 1 M in THF, 11.8 mmol) at −78 °C. The mixture was stirred for 10 min, and epoxide **6** (900 mg, 3.9 mmol) was added dropwise. 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, which was purified by chromatographic column to obtain 1.00 g (94% yield) of compound **17**. $[\alpha]^{25}_D = -8.3$ (*c* 0.6, $CHCl_3$); ^{1}H NMR (300 MHz) δ 1.35 (s, 3H), 1.40 (s, 3H), 1.18−1.65 (m, 6H), 1.80 (m, 1H), 1.91−2.13 (m, 3H), 2.25 (m, 1H), 3.31 (m, 2H), 3.62 (m, 1H), 3.91 (m, 2H), 4.02 (m, 1 H), 5.01 (m, 2H), 5.83 (m, 1H); ^{13}C NMR (75 MHz) δ 22.3 (t), 24.6 (t), 25.1 (q), 26.5 (q), 28.0 (t), 29.8 (t), 31.0 (t), 66.8 (t), 72.8 (d), 78.1(d), 78.6 (d), 80.1 (d), 109.0 (s), 114.6 (t), 138.2 (d); IR (cm^{-1}) 1370, 1640, 2858, 2937, 3076, 3472; MS (EI) *m*/*z* (relative intensity) 66 (84), 81 (96), 133 (44), 169 (69), 255 (100), 270 $(M + 1)^+$ (1); HRMS (EI) calcd for $C_{15}H_{26}O_4$ $(M)^+$ 270.1831, found 270.1835. Anal. Calcd for $C_{15}H_{26}O_4$ C 66.64, H 9.69. Found: C 66.56, H 9.86.

Preparation of Ethyl (2*E*,6*R*)-6-{(2*R*,6*S*)-6-[(4*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl]-tetrahydro-2*H*-pyran-2-yl}-6-hydroy-2-hexenoate (18). Compound **17** (900 mg, 3.33 mmol) was dissolved in a 1:1 mixture of THF/H_2O (35 mL) at room temperature. To this solution were added NMO (1.01 g, 8.32 mmol) and a catalytic amount of OsO_4. The reaction mixture was stirred overnight, quenched with a saturated solution of $Na_2S_2O_3$, and extracted with EtOAc. The organic phase was dried, and the solvent was evaporated under reduced pressure. The crude aldehyde obtained was used in the next step without purification.

To a solution of the crude aldehyde in CH_2Cl_2 (35 mL) under N_2 atmosphere at room temperature was added $Ph_3P{=}CHCO_2Et$ (2.32 g, 6.66 mmol). After 4 h the reaction was completed. The reaction was quenched with H_2O, and extraction was done with CH_2Cl_2. The organic phase was dried, and the solvent was evaporated under reduced pressure. Chromatographic purification gave 1.02 g (90% yield) of the ester **18**. $[\alpha]^{25}_D = -2.8$ (*c* 1.1, $CHCl_3$); ^{1}H NMR (300 MHz) δ 1.26 (t, J = 7.1 Hz, 3H), 1.33 (s, 3H), 1.38 (s, 3H), 1.16−1.59 (m, 5H), 1.79 (m, 1H), 1.91 (m, 1H), 2.09−2.40 (m, 3H), 3.29 (m, 2H), 3.58 (m, 1H), 3.87 (m, 2H), 4.02 (m, 1H), 4.16 (q, J = 7.1 Hz, 2H), 5.82 (d, J = 15.6 Hz, 1H), 6.96 (dt, J = 6.9, 15.4 Hz, 1H); ^{13}C NMR (75 MHz) δ 14.0 (q), 22.2 (t), 24.8 (t), 25.1 (q), 26.4 (q), 27.9 (t), 28.3 (t), 30.2 (t), 59.9 (t), 66.7 (t), 72.5 (d), 78.0 (d), 78.6 (d), 80.0 (d), 109.0 (s), 121.4 (d), 148.5 (d), 166.4 (s); IR (cm^{-1}) 1370, 1652, 1719, 2860, 2938, 3487; MS (FAB) *m*/*z* (relative intensity) 55 (83), 67 (65), 83 (58), 101 (50), 327 (65), 343 $(M + 1)^+$ (100); HRMS (FAB) calcd for $C_{18}H_{31}O_6$ $(M + 1)^+$ 343.2121, found 343.2120. Anal. Calcd for $C_{18}H_{30}O_6$ C 63.14, H 8.83. Found: C 63.14, H 9.67.

Preparation of (2*E*,6*R*)-6-{(2*R*,6*S*)-6-[(*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl]-tetrahydro-2*H*-pyran-2-yl}hex-2-ene-1,6-diol (7). To a solution of **18** (900 mg, 2.6 mmol) in toluene (26 mL) under N_2 atmosphere at 0 °C was added DIBAL-H (7.9 mL, 7.9 mmol). When TLC indicated the complete conversion of the starting material, the reaction was quenched by addition 0.25 mL of H_2O. To the slurrish solution obtained was added $MgSO_4$, and it was filtered through a pad of Celite. The solvent was evaporated, and the residue was purified by chromatographic column to give 630 mg of **7** (80% yield). $[\alpha]^{25}_D = -6.4$ (*c* 1.9, $CHCl_3$); ^{1}H NMR (300 MHz) δ 1.34 (s, 3H), 1.39 (s, 3H), 1.22−1.59 (m, 6H), 1.76−2.24 (m, 6H), 3.29 (m, 2H), 3.60 (m, 1H), 3.86−4.08 (m, 5H), 5.67 (m, 2H); ^{13}C NMR (75 MHz) δ 22.3 (t), 24.6 (t), 25.1 (q), 26.4 (q), 27.9 (t), 28.3 (t), 31.2 (t), 63.3 (t), 66.6 (t), 72.7 (d), 78.0 (d), 78.5 (d), 80.1 (d), 109.0 (s), 129.2 (d), 132.3 (d); IR (cm^{-1}) 1074, 1371, 1669, 2858, 2936, 3415; MS (FAB) *m*/*z* (relative intensity) 55 (100), 73 (98), 147 (43), 221 (16), 281 (13), 300 $(M)^+$ (1); HRMS (FAB) calcd for $C_{16}H_{28}O_5$ $(M)^+$ 300.1937, found 300.1926. Anal. Calcd for $C_{16}H_{28}O_5$ C 63.97, H 9.40. Found: C 63.84, H 9.08.

Preparation of (*S*)-1-((2*R*,5*R*)-5-{(2*R*,6*S*)-6-[(*R*)-2,2-Dimethyl-1,3,dioxolan-4-yl]-tetrahydro-2*H*-pyran-2-yl}-tetrahydrofuran-2-yl)ethane-1,2-diol (19). Crushed, activated 4 Å molecular sieves were added to stirred CH_2Cl_2 (2.5 mL) under argon. The flask was cooled to −20 °C, and Ti(OPr-*i*)$_4$ (0.16 mL, 0.5 mmol), (+)-DET (0.11 mL, 0.6 mmol), and the allylic alcohol **7** (134 mg, 0.45 mmol) in CH_2Cl_2 (2.5 mL) were added sequentially with stirring. The mixture was stirred at the same temperature for 20 min, and TBHP (0.15 mL, 6.1 M in isooctane, 0.80 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 **19** (106 mg, 75% yield). $[\alpha]^{25}_D = -3.0$ (*c* 0.7, $CHCl_3$); ^{1}H NMR (300 MHz) δ 1.21 (m, 2H), 1.34 (s, 3H), 1.39 (s, 3H), 1.46 (m, 1H), 1.68−1.99 (m, 7H), 2.32 (m, 1H), 2.46 (m, 1H), 3.25 (m, 2H), 3.67 (m, 3H), 3.89 (m, 4H), 4.00 (m, 1H); ^{13}C NMR (75 MHz) δ 22.4 (t), 25.1 (q), 26.5 (q), 26.9 (q), 27.5 (t), 27.7 (t), 28.0 (t), 63.7 (t), 66.7 (t), 72.7 (d), 78.1 (d), 78.4 (d), 79.9 (d), 80.4 (d), 81.6 (d), 109.0 (s); IR (cm^{-1}) 1211, 1371, 1648, 2935, 2983, 3421; MS (FAB) *m*/*z* (relative intensity) 55 (89), 69 (100), 81 (59), 109 (27), 154 (14), 339 $(M + Na)^+$ (10); HRMS (FAB) calcd for $C_{16}H_{28}O_6Na$ $(M + Na)^+$ 339.1784, found 339.1798. Anal. Calcd for $C_{16}H_{28}O_6$ C 60.74, H 8.92. Found: C 60.82, H 8.67.

Preparation of (2*S*,6*R*)-2-[(*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl]-6-{(2*R*,5*R*)-5-[(*R*)-oxiran-2-yl]-tetrahydrofuran-2-yl}-tetrahydro-2*H*-pyran (6). To a solution of **19** (95 mg, 0.30 mmol) in dry CH_2Cl_2 (6 mL) under argon atmosphere were sequentially added Et_3N (0.06 mL, 0.45 mmol) and benzoyl chloride (0.047 mL, 0.36 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 under reduced pressure to yield a residue, which was used in the next step without any further purification. To a stirred mixture of the crude monobenzoate in dry CH_2Cl_2 (6 mL) under argon atmosphere were added Et_3N (0.06 mL, 0.45 mmol) and methanesulfonyl chloride (0.05 mL, 0.72 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 under reduced pressure.

To a cooled suspension of NaH (36 mg, 60% in mineral oil, 0.9 mmol) in dry CH_2Cl_2 (6 mL) under argon atmosphere was added dropwise dry MeOH (0.4 mL, 0.9 mmol) at 0 °C. The mixture was stirred for 15 min, and the residue obtained above 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 **6** (73 mg, 82% yield). $[\alpha]^{25}_D = -9.0$ (*c* 0.5, $CHCl_3$); ^{1}H NMR (300 MHz) δ 1.21 (m, 3H), 1.34 (s, 3H), 1.39 (s, 3H), 1.64−1.86 (m, 6H), 2.02 (m, 2H), 2.66 (dd, J = 2.7, 5.1 Hz, 1H), 2.74 (dd, J = 4.2, 5.1 Hz, 1H), 2.95 (m, 1H), 3.24 (m, 1H), 3.81−3.91 (m, 4H), 3.99 (m, 1H); ^{13}C NMR (75 MHz) δ 22.4 (t), 25.2 (q), 26.5 (q), 27.5 (t), 28.0 (t), 28.1 (t), 28.4 (t), 43.8 (t), 53.9 (d), 66.8 (t), 78.1 (d), 78.4 (d), 78.7 (d), 79.9 (d), 82.1 (d), 109.0 (s); IR (cm^{-1}) 1210, 1370, 1456, 2860, 2934, 2984; MS (FAB) *m*/*z* (relative intensity) 55 (100), 69 (73), 81 (60), 109 (29), 132 (16), 297 $(M - 1)^+$ (6); HRMS (FAB) calcd for $C_{16}H_{25}O_5$ $(M - 1)^+$ 297.1702, found 297.1709. Anal. Calcd for $C_{16}H_{26}O_5$ C 64.41, H 8.78. Found: C 64.39, H 9.40.

Preparation of (1*R*)-1-((2*R*,5*R*)-5-{(2*R*,6*S*)-6-[(4*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl]tetrahydro-2*H*-pyran-2-yl}tetrahydro-2-furanyl)-1-tridecanol (4). To a mixture of CuI (4 mg, 0.02 mmol) in dry THF (2 mL) under argon atmosphere at −78 °C was added undecanemagnesium bromide, previously formed from bromoundecane (195 mg, 0.83 mmol) and magnesium turnings (20 mg, 0.8 mmol) at room temperature. The mixture was stirred for 10 min, and epoxide **6** (62 mg, 0.2 mmol) dissolved in dry THF (2 mL) 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, which was purified by chromatographic column to obtain 66 mg (70% yield) of compound **4**. $[\alpha]^{25}_D = +16.5$ (*c* 0.4, $CHCl_3$) {lit. $[\alpha]^{25}_D = +17.8$ (*c* 0.23, $CHCl_3$)}[3e]; ^{1}H NMR (300 MHz) δ 0.87 (t, J = 4.7 Hz, 3H), 1.34 (s, 3H), 1.39 (s, 3H), 1.18−1.91 (m, 34 H), 3.28 (m, 2H), 3.79 (m, 2H), 3.93 (m, 2H), 4.05 (m, 1H); ^{13}C NMR δ (75 MHz) δ 13.9 (q), 22.3 (t), 22.4 (t), 25.1 (q), 25.4 (t), 26.5 (q), 27.9 (t), 28.0 (t), 28.3 (t), 29.1 (t), 29.4 (t), 29.5 (t), 31.7 (t), 33.3 (t), 66.8 (t), 73.8 (d), 78.1 (d), 78.5 (d), 80.0 (d), 81.3 (d), 82.6 (d), 109.0 (s); IR (cm^{-1}) 1371, 1460, 2856, 2926, 2983, 3495; MS (EI) *m*/*z* (relative intensity) 127 (22), 197 (49), 255 (100), 353 (13), 440 (4), 454 $(M)^+$ (0.4); HRMS (EI) calcd for $C_{27}H_{50}O_5$ $(M)^+$ 454.3658, found 454.3669.

Biological Tests. Cells, Culture, and Plating. The human solid tumor cell lines A2780 (ovarian and SW1573 (nonsmall cell lung cancer) were used in this study. Cells were maintained in 25 cm^2 culture flasks in RPMI 1640 supplemented with 5% heat-inactivated fetal calf serum and 2 mM l-glutamine in a 37 °C, 5% CO_2, 95% humidified air incubator. Exponentially growing cells were trypsinized and resuspended in antibiotic containing medium (100 units penicillin G and 0.1 mg of streptomycin/mL). Single cell suspensions displaying >97% viability by trypan blue dye exclusion were subsequently counted. After counting, dilutions were made to give the appropriate cell densities for inoculation onto 96-well microtiter plates. Cells were inoculated in a volume of 100 mL per well at densities of 7,000 (A2780) and 6,000 (SW1573) cells per well, based on their doubling times.

Chemosensitivity Testing. Chemosensititvity tests were performed using the SRB assay of the NCI.[12] Pure compounds were initially dissolved in DMSO at 400 times the desired final maximum test concentration. Control cells were exposed to an equivalent concentration of DMSO (negative control). Each agent was tested in triplicates at different dilutions in the range 1−100 μM. The drug treatment was started on day 1 after plating. Drug incubation times were 48 h, after which time cells were precipitated with 25 μL ice-cold 50% (w/v) trichloroacetic acid and fixed for 60 min at 4 °C. Then the SRB assay was performed. The optical density (OD) of each well was measured at 490 nm, using BioTek's ELx800NB absorbance microplate reader. Values were corrected for background OD from wells only containing medium. The effect is defined as percentage of growth (PG) and was calculated with respect to untreated control cells (C) at each of the drug concentration levels based on the difference in OD at the start (T_0) and end of drug exposure (T), according to NCI formulas. Briefly, if T is greater than or equal to T_0 the calculation is $100 \times [(T - T_0)/(C - T_0)]$. If T is less than T_0 denoting cell killing the calculation is $100 \times [(T - T_0)/(T_0)]$. With these calculations a PG value of 0 corresponds to the amount of cells present at the start of drug exposure, while negative PG values denote net cell kill. Thus, 50% growth inhibition (GI_{50}) represents the concentration at which PG is +50.

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Supporting Information Available: General experimental conditions and ^{1}H NMR and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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