Studies on Mimicry of Naturally Occurring Annonaceous Acetogenins: Non-THF Analogues Leading to Remarkable Selective Cytotoxicity against Human Tumor Cells

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Abstract: A class of structurally simplified analogues of the naturally occurring annonaceous acetogenins were developed, amongst which some non-THF analogues showed remarkable cytotoxicities against tumor cell lines, as well as good selectivity between human tumor cells and normal cells. The synthetic routes were significantly shortened because of the removal of the chiral centers bearing the THF rings on the natural templates. This simplification also provides access to the parallel synthesis of these mimics by a combinatorial strategy. The remaining stereogenic centers at the positions α to the ethereal links were introduced by the Chiron approach from the easily accessible chiral building blocks **6a** and/or **6b**, made in turn from L-ascorbic acid or D-mannitol, while the one in the butenolide segment was taken from L-lactate. All four diastereomeric non-THF analogues **2a**–**2d** showed remarkable activity against the HCT-8 cell line, and better differentiation was found when testing against the HT-29 cell line. It was also discovered that both the butenolide and ethylene glycol subunits play essential roles in the cytotoxicities against tumor cell lines, while the 10-substituted hydroxy group and the absolute configuration of methyl group at the butenolide moiety are less important for their activity.

Keywords: annonaceous acetogenins · asymmetric synthesis · cytotoxicity · natural products · structure–activity relationships

Introduction

Annonaceous acetogenins, a relatively newly discovered class of natural products found in Annonaceae in the 1980s, have been attracting worldwide attention because of their potent biological activities, especially as growth inhibitors[1] of a wide range of tumor cells. They have been shown[2] to function by blocking complex I in mitochondria as well as ubiquinone-linked NADH oxidase in the cells of specific tumor cell lines, including some multidrug-resistant[3] ones. These features make the acetogenins potential leads for new antitumor agents. However, the natural resource is scarce, so the substantial amounts of enantiomerically pure samples required for further biological and clinical studies appear to be attainable only by means of chemical synthesis. All the total syntheses[4] of annonaceous acetogenins that have so far appeared in the literature require more than 10 steps, which makes scaling-up very difficult. A further challenge in the total synthesis comes from the multiple chiral centers: usually there are at least five oxygen-linked carbon chiral centers in the target molecules. Their derivation and the related studies on structure–activity relationships are therefore very difficult. Herein we wish to report a potential solution to the problem, which relies on structural simplification while retaining the activity of the acetogenins.

It has been postulated[5] that the acetogenins' antitumor activities are associated with their ionophoric ability, although it has also been mentioned in a brief communication that acetogenins have no ionophoric effects in biological studies with living cell.[6] In fact, Ca^{2+} complexes of acetogenins have been detected, and the activity of acetogenins was assumed to be due to a role in the bioavailability of such cations in the cell membranes.[7] Besides, it has long been known that bis-THF annonaceous acetogenins containing more ethereal oxygen usually are more active than mono-THF annonaceous acetogenins, and acetogenins containing free hydroxy groups are more active than their ether, ester, or ketone counterparts. Therefore, the hydroxy and ethereal oxygen atoms in the acetogenins appear to be essential for the biological activities, and thus the THF rings, especially their ethylene bridge, do not seem to be necessary for the activities. As a preliminary

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0947-6539/03/0901-0282 $ 20.00+.50/0 *Chem. Eur. J.* **2003**, *9*, No. 1

experiment, we synthesized a highly simplified analogue, in which the THF part of annonaceous acetogenins was replaced by a diethylene or triethylene glycol unit and all the chiral centers of the THF region were eliminated. Testing of these analogues showed activities comparable to those of mono-THF natural templates.[8] These interesting results greatly encouraged us to design more new analogues based on this general consideration. A further means of such a structural simplification is to remove the ethylene bridge in these THF rings and reserve the flanking hydroxy groups (Figure 1). This eliminates only two chiral centers for each THF ring, but still greatly simplifies the synthesis in comparison with those of the natural molecules.

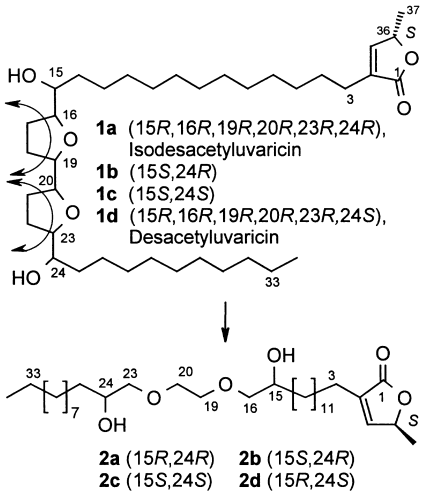
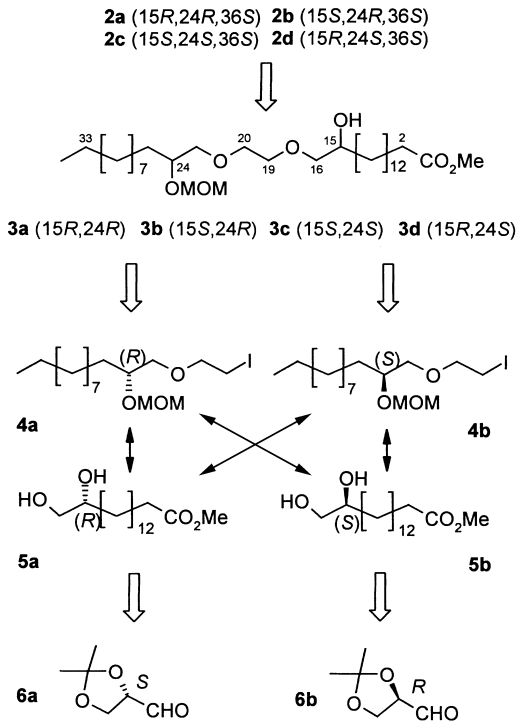


Figure 1. Design for simplifying bis-THF natural annonaceous acetogenins into linear mimics.

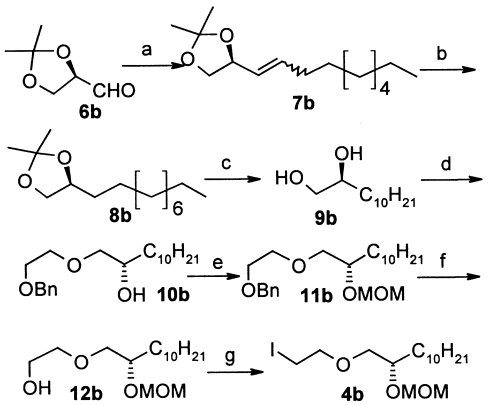
As a natural template, the bis-THF annonaceous acetogenin isodesacetyluvaricin (**1a**) and its isomers could be transformed into the linear[9] mimics **2**. Thus four chiral centers will be removed from the lead molecule. Also, it will greatly reduce the difficulty encountered in the synthetic endeavors and promises easier scaling-up in future processes.[10]

Parallel syntheses of all four enantiomerically pure analogues 2: To explore the potential influence of the configurations of hydroxy groups on biological activities, the syntheses of all four possible isomers of the simplified analogue **2** were planned (Scheme 1). First of all, the three-carbon unit of the chiral butenolide was removed from the skeleton, which could be built up by our previously reported methodology from ethyl lactate.[11] The protected dihydroxy esters **3a–d** could be further disconnected at the O–C_{19} bond (numbering according to bis-THF acetogenins) to give two segments **4** and **5**, each containing one chiral center. The *R* isomers of compounds **4a** and **5a** could be transformed to the commonly available (*S*)-glyceraldehyde acetonide **6a**. Correspondingly, the *S* isomers of compounds **4b** and **5b** could be prepared from (*R*)-glyceraldehyde acetonide **6b**. Our synthetic protocol for all four targets **2a–d** was highly concise, starting from a pair of enantiomeric glyceraldehyde acetonides through a simple combination of the two pairs of enantiopure intermediates **4** and **5**, and finally finishing the building of the chiral butenolides by a reliable sequence of aldol condensation, lactonization, and dehydration.



Scheme 1. The butenolide part of the targets is induced at the last stage of synthesis and all four precursor methyl esters can be attained from the combination of **4a,b** and **5a,b**, which are derived from the corresponding protected glyceraldehydes **6a** or **6b**. MOM = methoxymethyl.

The execution of the synthesis has three parts. Generally, the synthesis included the independent preparations of the segments **4** and **5**, and then combination of both segments to the target molecules. The synthesis of segment **4b** started from the chiral building block (*R*)-glyceraldehyde acetonide (**6b**) prepared from D-mannitol (Scheme 2). After the chain extension[12] at the aldehyde **6b** by a Wittig reaction followed by hydrogenation, the acetonide **8b** was converted into diol **9b** and then condensed with 2-benzyloxyethyl iodide regio-



Scheme 2. Reagents and conditions: a) $C_8H_{17}CH{=}PPh_3$, 90%; b) H_2/EtOH/Pd–C, 96%; c) HCl/MeOH; d) 1) $Bu_2SnO/CHCl_3$/MeOH (10:1:1)/reflux; 2) CsF/ICH_2CH_2OBn/DMF, 81% over two steps; e) MOMCl/iPr_2NH/CH_2Cl_2, 85%; f) Na/NH_3 (liq), 97%; g) I_2/imidazole/PPh_3, 92%.

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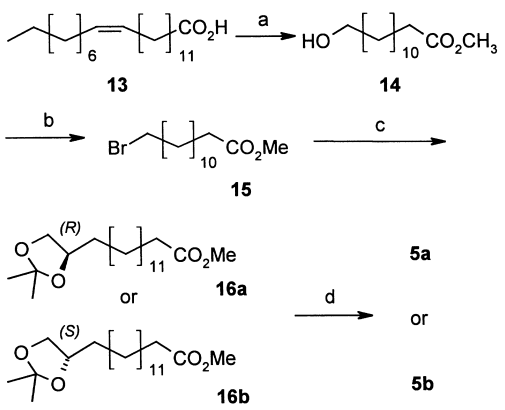
selectively via a cyclic stannate intermediate.[13] The secondary hydroxy group of **10b** was masked as a methoxymethyl (MOM) ether and the terminal benzyl protective group was then removed by Na/NH_3 (liquid). The resultant primary hydroxy group of **12b** was transformed into the desired iodide **4b**. Following the same reaction sequence, the segment **4a** was synthesized from the (*S*)-glyceraldehyde acetonide **6a**, which could be prepared from L-ascorbic acid.

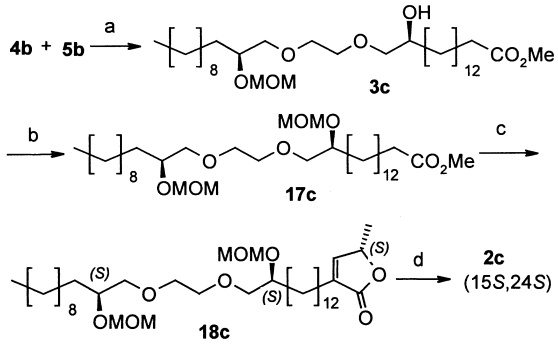
The preparation of the other segment, **5**, started from *cis*-eruic acid (**13**, Scheme 3). At first, the C–C double bond of **13** was cleaved by ozonization following a literature procedure[14] to give the hydroxy acid, which was esterified to the



Scheme 3. Reagents and conditions: a) 1) O_3/0–5 °C/EtOH/cyclohexane (1:5); 2) KBH_4; 3) MeOH/$SOCl_2$, 87% from **13**; b) $CBr_4/PPh_3/C_6H_6$, 87%; c) 1) PPh_3; 2) *t*BuOK, then **6a** or **6b**; 3) H_2/EtOH/Pd–C, 67% over three steps; d) H^+/MeOH, 91%.

corresponding methyl ester **14** in methanol in the presence of $SOCl_2$. Smooth bromination of the hydroxy with CBr_4 and PPh_3 provided the bromo ester **15** as the intermediate to the corresponding phosphonium salt for the following Wittig reaction in the same pot. Practically, the in situ formation of phosphonium salt from **15** could be achieved by reaction with PPh_3 without solvents at elevated temperature. The Wittig olefination with **6a** or **6b**, hydrogenation of the C–C double bond and removal of the acetonide protective group led to **5a** or **5b**, respectively.

With both segments in hand, the parallel syntheses of these stereomeric analogues were executed straightforwardly by combination of these intermediates. By selective etherification with dibutyltin oxide and cesium fluoride, both segments were successfully condensed by a selective ether bond formation at the primary position. For example compound **3c** was obtained from the intermediates **4b** and **5b** in good yields (Scheme 4). The newly produced secondary hydroxy group was then protected as a MOM ether before the chiral unit of the methylated γ-butenolide was introduced by an aldol strategy. After removal of the THP protective group with concurrent lactone ring-closure, the β-hydroxy was converted into its trifluoroacetate and then eliminated quickly into the methylated γ-butenolide in the presence of triethylamine. Finally, the MOM-masked hydroxy groups were released by acidified methanol to afford the target **2c**. Other target molecules were synthesized in a similar sequence by choosing appropriate precursors **4** and **5**. In short, coupling of



Scheme 4. Reagents and conditions: a) 1) $Bu_2SnO/CHCl_3$/MeOH (10:1)/reflux; 2) CsF/DMF, 54% over two steps; b) MOMCl/*i*Pr_2NH/CH_2Cl_2, 93%; c) 1) LDA/(*S*)-Me(OTHP)CHCHO; 2) 9% H_2SO_4/THF; 3) $(F_3CCO)_2O/NEt_3/CH_2Cl_2$, 43%; d) HCl/MeOH, 68%. LDA = lithium diisopropylamide.

4a and **5b** led to **2b**, reaction of **4b** with **5a** led to **2d**, and condensation of **4a** with **5a** yielded **2a**.

It is worthy noting that the strategy presented here to construct the butenolide moiety[15] after the completion of the chain extension gave much better yields than the one previously adopted,[16] in which the butenolide unit was introduced at the earlier stage of synthesis.

Syntheses of (36*R*)-analogue and (10*R*)-hydroxy-substituted analogue of 2c: The successful synthesis of simplified bis-THF annonaceous acetogenins and their remarkable selective inhibition effects on tumor cell lines (vide infra) prompted us to exploit a further structure modification. In this section, we describe how two more structural modifications based on the most active analogue **2c** were synthesized and investigated.

The bis-THF annonaceous acetogenin trilobin (**19**) was isolated from *Asimina triloba* in 1995. It shows very potent cytotoxicity against human tumor cells.[17] Following our methodology, removal of the ethylene bridges of THF rings gives a new, analogous (10*R*)-hydroxylated **2a**. Because **2c** is the most potent compound among the series of compounds **2**, the stereochemistry of the analogue was then tuned into the 10*R*-hydroxylated **2c** (**20**), whose structure is shown in Figure 2.

Reaction of compound **12b** with (*R*)-epichlorohydrin gave the epoxide **21** in the presence of phase transfer catalyst. Epoxy opening with monotrimethylsilyl acetylene lithium followed by TMS deprotection and MOM protection afforded one segment, **22**, of the target molecule. The other segment, **27**, was synthesized from methyl undecylenate (**23**), according to our previously reported hydrolytic kinetic resolution method.[18] Treatment of **22** with butyllithium followed by reaction with **27** in the presence of BF_3 etherate at −78 °C gave the whole skeleton **28** in 53% yield. The triple bond of **28** was selectively reduced by reaction with diimide. Deprotection of MOM ethers by boron trifluoride and dimethylsulfide gave the final product **20** (Scheme 5).

The same sequence was applied to the synthesis of the (36*R*)-isomer of compound **2c**, starting from the same intermediate **17c**. (*R*)-Me(OTHP)CHCHO was used to yield the *R*-methylated γ-butenolide and thus finally the target compound (15*S*,24*S*,36*R*)-**2** (**30**) (Scheme 6).

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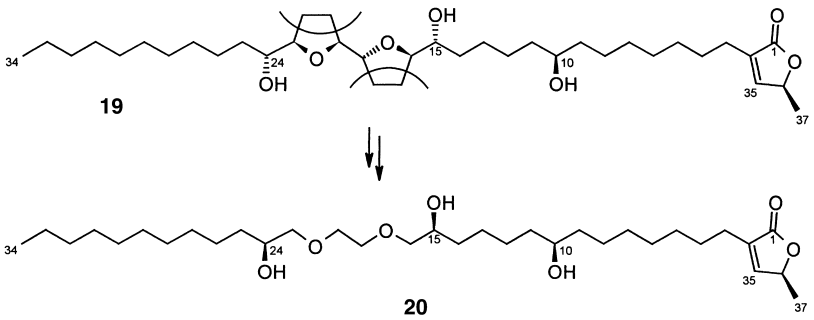
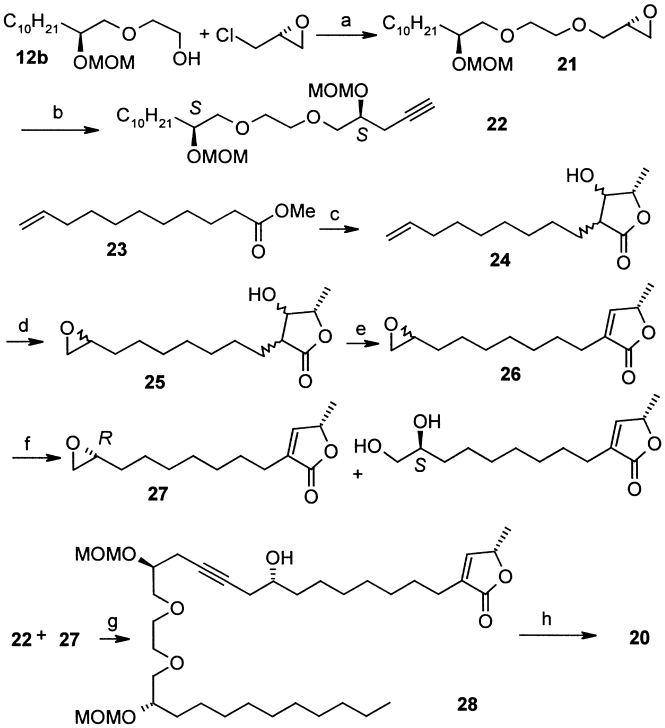
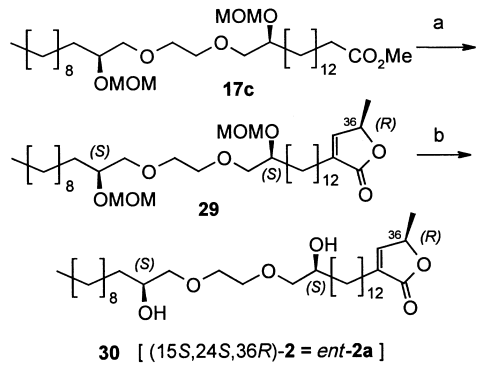


Figure 2. The molecular design of **20** uses natural trilobin as the template, removing the ethylene bridge of THF ring and inverting the configuration of the two flanking hydroxy groups.



Scheme 5. Reagents and conditions: a) 50% NaOH, Bu_4NHSO_4 (cat), 92.7%; b) 1) $(CH_3)_3SiCCLi$, $BF_3 \cdot Et_2O$, $-78\,^{\circ}C$; 2) Bu_4NF, THF; 3) MOMCl, $(iPr)_2NEt$, CH_2Cl_2, $0\,^{\circ}C$–RT, 66% for three steps; c) 1) LDA/HMPA, THF, then (*S*)-Me(OTHP)CHCHO; 2) 9% H_2SO_4, THF, 81%; d) *m*-CPBA, CH_2Cl_2, 92%; e) $(CF_3CO)_2O$, Et_3N, CH_2Cl_2, $0\,^{\circ}C$–RT, 87%; f) 0.5 mol% (*R,R*)-salen-Co^{III}-OAc, 0.5 equiv H_2O, 36% for **27;** g) *n*BuLi/$BF_3 \cdot Et_2O$, THF, $-78\,^{\circ}C$; h) 1) $TsNHNH_2$, NaOAc, DME/H_2O, reflux; 2) $BF_3 \cdot Et_2O$, DMS, 64%. HMPA = hexamethylphosphoramide, *m*-CPBA = *m*-chloroperoxybenzoic acid.



Scheme 6. Reagents and conditions: a) 1) LDA; 2) 9% H_2SO_4/THF; 3) $(F_3CCO)_2O/NEt_3/CH_2Cl_2$, 60%; b) $BF_3 \cdot Et_2O$, DMS, 60%.

Biological activity: The synthesized samples were evaluated with MTT assays (MTT = 3-(4,5-cimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide) for their cytotoxicities against several human solid tumor cell lines. The results for all the four compounds **2a–c** showed potent activities (Table 1), as well as interesting cell line selectivity. No activities were found in the experiments against KB and A2780 cell lines. However, impressive positive effects were observed with HCT-8, in which the EC_{50} values are all on the order of nanomolar. More interesting results were obtained from the testing with HT-29 cell line: different stereochemistry combinations of the mimics showed remarkable differences in the activities. In comparison with the positive control adriamycin, these analogues were cytotoxic to HCT-8 and HT-29 cells, but somewhat less so than those of adriamycin. However, they show selectivity among different cell lines, and no comparable selectivity was observed in the case of adriamycin.

Table 1. Biological activity of structures **2** compared with adriamycin.

Compound	EC_{50} [$\mu g\,mL^{-1}$]			
	KB	A2780	HCT-8	HT-29
2a	>1	>1	0.066	0.272
2b	>1	>1	0.097	1.12
2c	>1	>1	0.032	0.11
2d	>1	>1	0.065	7.83
Adriamycin	0.00289	0.00102	0.00465	0.00098

Two series of compounds with partial structures of compounds **2** were also investigated. One series of compounds is similar to compounds **2** but for the γ-methyl butenolide subunits, such as compounds **31** (Figure 3). The other is the

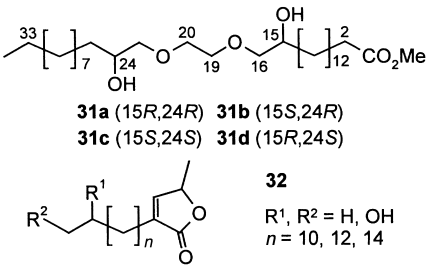


Figure 3. Two series of compounds with partial structures of **2** show almost no cytotoxicity.

α-alkyl or hydroxylated alkyl-substituted derivative of butenolides (3-substituted (5*S* or 5*R*)-methyl-2(5*H*)-furanone). For example, the chiral center of compounds **32** may be *S* or *R* (Figure 3). The corresponding EC_{50} values for both series were measured and all were more than 10 $\mu g\,mL^{-1}$. Based on all the above information, it is clear that both the butenolide and ethylene glycol subunits are essential structural features for the cytotoxicity toward tumor cell lines.

The activity studies of (36*R*)-analogue **30** and (10*R*)-hydroxy-substituted analogue **20** have similar selectivities and cytotoxicities to their parent compound **2c** (Table 2), and

Table 2. Biological activity of selected compounds against human cell lines.

Compound	EC_{50} [$\mu g\,mL^{-1}$]		
	KB	HCT-8	HT-29
20	10–20	≈0.1	0.7
30	>10	1.4	2.0
2c	>10	0.3	1.5

the EC_{50} values of (10*R*)-hydroxy-substituted analogue **20** are slightly larger than those of **2c**. Since similar EC_{50} values were observed for **30** and **2c**, the absolute configuration of the methyl group at the butenolide subunit is not a key point.

Cytotoxicity on the human normal cell HELF has also been studied. All of our synthetic samples gave negative results, with an EC_{50} value over 10 $\mu g\,mL^{-1}$. A preliminary antitumor assay in mice (Lewis lung cancer) with compound **2c** has been carried out, too. A dose of 10 $mg\,kg^{-1} \times 5$ times + 20 $mg\,kg^{-1} \times 4$ times was administered orally and 60% inhibition of tumor was observed compared with the control. Furthermore, in vivo inhibition of colon cancer is being studied right now.

Conclusion

In conclusion, a class of structurally simplified analogues of natural annonaceous acetogenins has been developed. The synthetic route has been significantly shortened by the removal of the chiral centers of the THF rings in natural templates, which opens the way for a parallel synthesis of stereomeric mimics. The remaining stereogenic centers in these analogues were derived from easily accessible chiral building blocks. All four analogues **2** showed remarkable activity against the HCT-8 cell line, while better differentiation was found when testing them against the HT-29 cell line.

Further synthetic work for the study of the structure–activity relationship is also described in this report. All the results disclose a very interesting piece of information, namely that both the butenolide and ethylene glycol subunits play essential roles in the cytotoxicities against tumor cell lines, in a way that is not yet clear. Additionally, the hydroxy group substituted at position 10 and the absolute configuration of the methyl group at the butenolide moiety are less important for their activity. Further studies along these general lines are currently under way in our laboratory, and the results will be reported in due time.

Experimental Section

Melting points are uncorrected. All NMR spectra were recorded at 300 MHz and 600 MHz (^1H NMR) or 75 MHz and 150 MHz (^{13}C NMR) in $CDCl_3$, respectively. Unless otherwise indicated, chemical shifts are reported in ppm, and coupling constants (*J*) are reported in Hertz. Mass spectra were recorded by EI and ESI modes on HP 59890A and Finnigan 4021 mass spectrometers, and HRMS were measured on a Finnigan MAT or Finnigan FTMS-2000 mass spectrometer. Optical rotations were recorded at ambient temperature. Organic solvents (such as didiethyl ether and THF) were freshly distilled over sodium/benzophenone under nitrogen. Commercially obtained reagents were used without further purification. All the reactions were monitored by TLC with GF254 silica-gel-coated plates. Flash column chromatography was carried out on silica gel (300–400 mesh) under pressure.

Compound 7b: A mixture of *n*-bromononane (20.7 g, 100.0 mmol) and triphenylphosphine (26.2 g, 100.0 mmol) was heated at 140 °C under nitrogen for 2.5 h. Dry THF (100 mL) and *n*-butyllithium (100.0 mmol) were added to the resultant slurry at −20 °C. After the mixture had been stirred for 0.5 h, (*R*)-glyceraldehyde acetonide (**6b**, 13.0 g, 100.0 mmol) was added to the red solution. After being stirred at room temperature for an additional 4 h, the reaction was quenched with saturated aqueous NH_4Cl solution. The mixture was extracted with diethyl ether (50 mL × 3). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated to yield the crude product, which was further purified by flash column chromatography with 10:1 petroleum hexanes/acetate as eluent to give pure product (*S*)-**7b** as a colorless oil in 91% yield. ^1H NMR (300 MHz, $CDCl_3$): $\delta = 0.88$ (t, $J = 6.7$ Hz, 3H), 1.27–1.40 (m, 12H), 1.40 (s, 3H), 1.425 (s, 3H), 2.10 (m, 2H), 3.51 (t, $J = 8.0$ Hz, 1H), 4.06 (dd, $J =$ 6.0 Hz, 8.0 Hz, 1H), 4.84 (dt, $J = 6.3$ Hz, 8.1 Hz, 1H), 5.40 (t, $J = 9.8$ Hz, 1H), 5.63 ppm (m, 1H); MS (EI): *m*/*z* (%): 240 ([M^+], 6.58), 225 (4.11), 195 (1.07), 183 (1.62); elemental analysis calcd (%) for $C_{15}H_{26}O_2$ (238.4): C 74.95, H 11.74; found: C 74.96, H 12.00.

Compound 7a: The preparation was carried out according to the procedure of (*S*)-**7b** but with (*S*)-glyceraldehyde acetonide **6a** as the starting material. (*R*)-**7a**: ^1H NMR (300 MHz, $CDCl_3$): $\delta = 0.88$ (t, $J = 6.6$ Hz, 3H), 1.27–1.53 (m, 12H), 1.40 (s, 3H), 1.43 (s, 3H), 2.12 (m, 2H), 3.51 (t, $J = 8.1$ Hz, 1H), 4.06 (dd, $J = 6.1$ Hz, 8.0 Hz, 1H), 4.84 (dt, $J = 6.2$ Hz, 8.1 Hz, 1H), 5.40 (t, $J = 9.8$ Hz, 1H), 5.64 (m, 1H); MS (EI): *m*/*z* (%): 240 ([M]$^+$, 0.09), 226 (8.14), 313 (2.99), 210 (1.04), 195 (2.14), 183 (8.70), 165 (10.90); elemental analysis calcd (%) for $C_{15}H_{28}O_2$ (240.4): C 74.95, H 11.74; found: C 74.95, H 11.88.

Compound 8b: A mixture of (*S*)-**7b** (12.0 g, 50.0 mmol), palladium on charcoal (10%, 500 mg), and MeOH (80 mL) containing 0.5% triethylamine was stirred at room temperature for 24 h under hydrogen. After filtration and removal of the solvent, the residue was purified by column chromatography on silica gel to afford a waxy solid in 96% yield: $[\alpha]_D^{20} = +15.2$ ($c = 1.18$ in $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): $\delta = 0.88$ (t, $J =$ 7.1 Hz, 3H), 1.20–2.02 (m, 18H), 1.38 (s, 3H), 1.40 (s, 3H), 3.49 (t, $J =$ 7.0 Hz, 1H), 4.04 (m, 2H).

Compound 8a: Hydrogenation of (*S*)-**7a** was carried out as for the procedure of **8b**. **8a**: $[\alpha]_D^{20} = -15.1$ ($c = 1.11$ in $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): $\delta = 0.94$ (t, $J = 6.8$ Hz, 3H), 1.20–2.02 (m, 18H), 1.38 (s, 3H), 1.40 (s, 3H), 3.49 (t, $J = 7.2$ Hz, 1H), 4.05 (m, 2H).

Compound 9b: During the work-up for preparation of compound **8b**, the filtrate was treated with 10% HCl (10 mL) and stirred overnight at room temperature. The reaction was quenched by adding dilute aqueous NaOH to pH 7. After removal of the solvent, the residue was extracted with ethyl acetate. The combined organic layers were dried over $MgSO_4$, concentrated and crystallized from ethyl acetate to give (*S*)-**9b** (9.5 g, 94%). $[\alpha]_D^{20} = +9.36$ ($c = 1.1$ in CH_3OH); IR (film): $\tilde{\nu} = 3316$, 2920, 2851, 1470, 1438 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 0.88$ (t, $J = 6.6$ Hz, 3H), 1.26–1.88 (m, 18H), 3.43 (m, 1H), 3.65 (t, $J = 3.0$ Hz, 1H), 3.69 (m, 1H); MS (EI): *m*/*z* (%): 202 ([M]$^+$, 3.09), 185 ([M − OH]$^+$, 1.00), 171 ([M − CH_2OH]$^+$, 11.48); elemental analysis calcd (%) for $C_{12}H_{26}O_2$ (202.3): C 71.23, H 12.95; found: C 70.97, H 12.90.

Compound 9a: The above procedure for **9b** was employed. (*R*)-**9a**: $[\alpha]_D^{19} = -9.6$ ($c = 3.54$ in CH_3OH); IR (KBr): $\tilde{\nu} = 3713$, 3224, 1468, 1076 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 0.88$ (t, $J = 6.0$ Hz, 3H), 1.26–1.44 (m, 18H), 3.44 (m, 1H), 3.69 (m, 2H); MS (EI): *m*/*z* (%): 202 ([M]$^+$, 0.52), 186 (11.20), 171 (12.68), 153 (0.75), 111 (35.20), 97 (100.00); elemental analysis calcd (%) for $C_{12}H_{26}O_2$ (202.3): C 71.23, H, 12.95; found: C 71.17, H 12.81.

Compound 10b:

Preparation of ethylene glycol monobenzyl ether: Sodium hydride (80%, 15.0 g) was added in portions to a mixture of DMF/MeOH (200 mL, 1:1) and ethylene glycol (264 g, 4.0 mol). After the mixture had been stirred for 10 h, benzyl bromide (68.4 g, 0.4 mol) was added dropwise. The reaction mixture was stirred for an additional 10 h and then quenched with 10% HCl. The mixture was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated. The residue was distilled under reduced pressure to provide ethylene glycol monobenzyl ether (52.4 g, 86%). ^1H NMR (300 MHz,

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$CDCl_3$): $\delta = 3.62$ (t, $J = 6.6$ Hz, 2H), 3.76 (t, $J = 6.8$ Hz, 2H), 4.58 (s, 2H), 7.33 (m, 5H); MS (EI): m/z (%): 202 ($[M]^+$, 3.09), 185 ($[M - OH]^+$, 1.00), 171 ($[M - CH_2OH]^+$, 11.48).

Preparation of 2-iodoethyl benzyl ether: Iodine (43.5 g, 170 mmol) was added in portions to a solution of ethylene glycol monobenzyl ether (15.2 g, 100.0 mmol), imidazole (20.4 g, 300 mmol) and triphenylphosphine (44.9 g, 170 mmol) in 150 mL of dry benzene over 2 h at 0 °C. MeOH (2.0 mL) was added to quench the reaction when the starting material could no longer be detected by TLC. After the reaction mixture had been stirred for 1 h, silica gel (40–50 g) was added and stirred for an additional 20 min. The mixture was filtered through a pad of silica gel and the filtrate was concentrated to afford the iodide (24.2 g, 92%), which was used directly in the next step without purification. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 3.35$ (t, $J = 6.6$ Hz, 2H), 3.72 (t, $J = 6.8$ Hz, 2H), 4.61 (s, 2H), 7.33 (m, 5H).

*Preparation of compound **10b**:* A suspension of alcohol (*S*)-**9b** (2.02 g, 5.0 mmol) and dibutyltin oxide (2.5 g, 10.0 mmol) in $CHCl_3$/MeOH (50 mL, 10:1) was refluxed for 2 h. After the solvents had been removed under reduced pressure, the residue was dried under high vacuum for 6 h. To this residue in dry DMF (50 mL) were added 2-iodoethyl benzyl ether (2.9 g, 11.0 mmol) and cesium fluoride (2.4 g) under nitrogen. The reaction mixture was stirred for 18 h at 50 °C, and then the reaction mixture was poured into ethyl acetate (40 mL) and brine (200 mL). The mixture was stirred for 30 min and filtered through a pad of silica gel. The filtrate was extracted with ethyl acetate, and the combined organic layers were washed with saturated aqueous NH_4Cl and brine, dried over Na_2SO_4, and concentrated. The residue was further purified by column chromatography on silica gel to afford compound **10b** (2.73 g, 81%). $[\alpha]_D^{19} = +4.08$ ($c = 10.6$ in $CHCl_3$); IR (film): $\tilde{\nu} = 3426$, 3028, 2924, 1100, 702 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$): $\delta = 0.88$ (t, $J = 6.9$ Hz, 3H), 1.26–1.45 (m, 18H), 2.20 (br s, 1H), 3.31 (t, $J = 9.6$ Hz, 1H), 3.52 (dd, $J = 9.6$, 2.4 Hz, 1H), 3.61–3.72 (m, 4H), 3.79 (m, 1H), 4.57 (s, 2H), 7.34 (m, 5H); MS (EI): m/z (%): 337 ($[M]^+$+1), 149 (21.33), 91 (100.00).

Compound 10a: The procedure followed that for **10b**. **10a**: $[\alpha]_D^{20} = -4.05$ ($c = 5.83$ in $CHCl_3$); IR (film): $\tilde{\nu} = 3422$, 2922, 2854, 1450, 1102 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.88$ (t, $J = 7.1$ Hz, 3H), 1.26–1.51 (m, 18H), 2.35 (s, 1H), 3.30 (t, $J = 9.0$ Hz, 1H), 3.54 (dd, $J = 9.7$, 2.6 Hz, 1H), 3.66–3.81 (m, 5H), 4.57 (s, 2H), 7.33 (m, 5H); MS (EI): m/z (%): 336 ($[M]^+$, 0.13), 183 (0.59), 166 (3.8), 149 (20.0); elemental analysis calcd (%) for $C_{21}H_{36}O_3$ (336.5): C 74.95, H 10.78; found: C 74.82, H 10.97.

Compound 11b: Chloromethyl methyl ether (1.5 mL) was added to a solution of alcohol **10b** (1.68 g, 5 mmol) and DIPEA (2.0 mL) in CH_2Cl_2 (5 mL) at 0 °C. The mixture was stirred at 4 °C overnight and then quenched with saturated aqueous NH_4Cl and extracted with CH_2Cl_2. The organic layer was washed with water and brine, and dried over Na_2SO_4. Removal of the solvent followed by column chromatography (hexane/EtOAc 10:1) gave compound **11b** (1.62 g, 85%) as a colorless oil. $[\alpha]_D^{20} = -13.7$ ($c = 6.06$ in $CHCl_3$); IR (film): $\tilde{\nu} = 2922$, 1448, 1108, 1042 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.87$ (t, $J = 6.7$ Hz, 3H), 1.22–1.52 (m, 18H), 3.36 (s, 3H), 3.50 (d, $J = 5.1$ Hz, 2H), 3.62–3.75 (m, 4H), 3.69 (m, 1H), 4.55 (s, 2H), 4.63 (d, $J = 6.8$ Hz, 1H), 4.76 (d, $J = 6.8$ Hz, 1H), 7.32 ppm (m, 5H); MS (EI): m/z (%): 202 ($[M]^+$, 3.09), 185 ([M – OH], 1.00), 171 ([M – CH_2OH], 11.48).

Compound 11a: The same procedure as for **11b** was employed. **11a**: $[\alpha]_D^{20} = +12.9$ ($c = 2.87$ in $CHCl_3$); IR (film): $\tilde{\nu} = 2924$, 2854, 1454, 1356, 1108, 1044, 922, 738, 700 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$): $\delta = 0.88$ (t, $J =$ 6.9 Hz, 3H), 1.260–1.528 (m, 18H), 3.38 (s, 3H), 3.52 (m, 2H), 3.63–3.66 (m, 5H), 4.57 (s, 2H), 4.66 (d, $J = 7$ Hz, 1H), 4.76 (d, $J = 7$ Hz, 1H), 7.34 ppm (m, 5H); MS (EI): m/z (%): 380 ($[M]^+$, 0.11), 350 (4.78), 320 (6.95), 227 (22.44), 91 (98.84).

Compound 12b: A solution of **11b** (1.90 g) in dry THF (5 mL) was added dropwise to a solution of lithium/naphthalene (1.0 M in THF, 20 mL) at −25 °C over 15 min. The reaction mixture was stirred at −25 °C for 2 h, quenched by saturated aqueous NH_4Cl, and extracted with ether. The combined extracts were washed with brine, dried over Na_2SO_4, filtered and concentrated. The crude product was purified by column chromatography on silica gel to give compound **12b** (1.21 g, 84% yield): $[\alpha]_D^{20} = +9.8$ ($c = 6.3$ in $CHCl_3$); IR (film): $\tilde{\nu} = 3453$, 2926, 2856, 1467, 1215, 1040, 919 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.87$ (t, $J = 6.6$ Hz, 3H), 1.25 (m, 16H), 1.50 (t, $J = 6.6$ Hz, 2H), 2.21 (br s, 1H), 3.39 (s, 3H), 3.51 (d, $J = 4.9$ Hz, 2H), 3.58 (dd, $J = 8.5$, 3.5 Hz, 2H), 3.70 (m, 3H), 4.68 (d, $J = 6.8$ Hz, 1H), 4.75 ppm (d, $J = 6.8$ Hz, 1H); MS (EI): m/z (%): 273 ($[M+1 - H_2O]^+$, 0.03), 259 (0.60), 229 (3.61); elemental analysis calcd (%) for $C_{16}H_{34}O_4$ (290.4): C 66.04, H 11.80; found: C 66.02, H 11.93.

Compound 12a: Compound **12a** was obtained from **11a** using the procedure for **12b**. **12a**: $[\alpha]_D^{20} = -9.3$ ($c = 3.7$ in $CHCl_3$); IR (film): $\tilde{\nu} =$ 3450, 2926, 2856, 1467, 1131, 1041, 919 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.86$ (t, $J = 6.7$ Hz, 3H), 1.25 (m, 16H), 1.50 (t, $J = 6.6$ Hz, 2H), 2.38 (br s, 1H), 3.38 (s, 3H), 3.51 (d, $J = 4.9$ Hz, 2H), 3.57 (m, 2H), 3.71 (m, 3H), 4.67 (d, $J = 7.0$ Hz, 1H), 4.74 ppm (d, $J = 7.0$ Hz, 1H); MS (EI): m/z (%): 290 ($[M]^+$, 0.03), 273 (0.25), 2.59 (14.78), 229 (36.65).

Compound 4b: Iodine (2.18 g, 8.5 mmol) was added in small portions to a solution of **12b** (1.45 g, 5.0 mmol), imidazole (1.02 g, 15 mmol) and triphenylphosphine (2.35 g, 9 mmol) in dry benzene at 0 °C over 2 h. The reaction mixture was stirred until TLC indicated complete consumption of the starting material. MeOH (0.5 mL) was then added into the reaction mixture. The mixture was stirred for 30 min, silica gel (4–5 g) was added and the mixture was stirred for a further 20 min. Filtration and concentration of filtrate afforded the iodide **4b** (1.68 g, 96%), which was used for the next step without further purification. **Compound 4a** was prepared from **12a** according to the same procedure.

Compound 16b:

*Preparation of methyl α-hydroxytridecanoate (**14**):* A stream containing O_3 was bubbled through a solution of *cis*-13-docosenoic acid (25 g, 74 mmol) in the mixture of ethanol (15 mL) and cyclohexane (65 mL) for 4 h at 0–5 °C till a drop of reaction solution no longer decolorized bromide/acetic acid. The ozonide solution was then added dropwise to potassium borohydride (8.2 g, 134 mmol) in MeOH (70 mL) at 0 °C, and the mixture was stirred for 8 h, acidified with 6 N HCl to pH 2, and extracted with chloroform. The combined extracts were dried over Na_2SO_4 and concentrated under reduced pressure. Freshly distilled thionyl chloride (30 mL) was added dropwise to the solution of the residue in methanol (100 mL) at 0 °C; the reaction mixture was then stirred for 1 h and neutralized with saturated aqueous $NaHCO_3$ to pH > 7.0. After removal of methanol under reduced pressure, the residue was extracted with ethyl acetate. The combined extracts were washed with brine, dried over anhydrous Na_2SO_4, and concentrated. The crude product was further purified by column chromatography on silica gel to give compound **14** (16.3 g, 90%). M.p. 47–49 °C; IR (KBr): $\tilde{\nu} = 3300$, 2920, 2851, 1743, 1474, 1179 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.24$ (m, 16H), 1.56 (m, 4H), 2.28 (t, $J = 7.6$ Hz, 2H), 3.6 (t, $J =$ 6.6 Hz, 2H), 3.64 ppm (s, 3H); MS (EI): m/z (%): 245 ($[M+H]^+$, 3.38), 227 ($[M - H_2O]^+$, 1.29), 214 (11.27), 195 (6.09).

*Preparation of methyl ω-bromotridecanoate (**15**):* Carbon tetrabromide (20.0 g, 60 mmol) was added to a solution of alcohol **14** (12.2 g, 50 mmol) in dry benzene (40 mL) at room temperature. After being stirred for 20 min, the solution was cooled to 0 °C, and triphenylphosphine (15.7 g, 60 mmol) was added. The mixture was stirred for 2 h at room temperature. Petroleum ether (200 mL) was added. The mixture was filtered through a short pad of silica gel and the filtrates were concentrated to give the crude product, which was further purified by column chromatography on silica gel to provide the pure bromide **15** (14.1 g, 92%); IR (KBr): $\tilde{\nu} = 2920$, 2851, 1737, 1474, 1464, 1214, 1174 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.25$ (m, 14H), 1.40 (m, 2H), 1.59 (m, 2H), 1.82 (m, 2H), 2.28 (t, $J = 7.6$ Hz, 2H), 3.38 (t, $J = 6.9$ Hz, 2H), 3.64 ppm (s, 3H); MS (EI): m/z (%): 309 ($[M+H]^+$, 3.90), 307 ($[M+H]^+$, 4.10), 227 (6.74), 263 (7.37), 227 (10.92), 143 (12.20).

*Preparation of compound **16b**:* A mixture of **15** (7.68 g, 25.0 mmol) and triphenylphosphine (6.55 g, 25.0 mmol) was heated at 80 °C under nitrogen atmosphere for 5 h. The residue was cooled to 30 – 40 °C, and dry THF (100 mL) was then added. The solution was cooled to −40–50 °C, and potassium *tert*-butoxide (3.136 g, 28.0 mmol) was added and stirred for 10 min. (*R*)-Glyceraldehyde acetonide (**6b**, 4.0 g, 31.0 mmol) in dry THF was added to the resultant red solution of ylide at −70 °C, and the mixture was stirred for 2 h. The reaction was quenched with saturated aqueous NH_4Cl solution and diluted with diethyl ether. The aqueous layer was extracted with diethyl ether (3 × 50 mL), and the combined organic layers were washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure. A solution of the above residue in methanol (20 mL) was hydrogenated in the presence of 10% palladium on charcoal (100 mg) overnight. After removal of the catalyst and the solvent, the residue was purified by flash column chromatography to give the pure product (*S*)-**16b** (54–72%): $[\alpha]_D^{18} = +10.25$ ($c = 3.8$ in $CHCl_3$); IR (KBr): $\tilde{\nu} = 2986$, 2916, 2850, 1739, 1476, 1380, 1172 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.25$ –

1.64 (m, 24H), 1.36 (s, 3H), 1.41 (s, 3H), 2.30 (t, $J=7.6$ Hz, 2H), 3.50 (t, $J=7.5$ Hz, 1H), 3.67 (s, 3H), 4.04 ppm (m, 2H); MS (EI): m/z (%): 342 ($[M]^+$), 328 ($[M+1-CH_3]^+$, 55.39), 313 (2.99), 286 (5.28), 267 (1.57), 254 (15.11); elemental analysis calcd (%) for $C_{20}H_{38}O_4$ (332.5): C 70.13, H 11.18; found: C 70.14, H 11.26.

Compound 16a: The above protocol for **16b** was adapted by starting with (*S*)-glyceraldehyde acetonide **6b**. **16a**: $[\alpha]_D^{18}=-9.82$ ($c=3.36$ in $CHCl_3$); IR (KBr): $\tilde{\nu}=2986$, 2917, 2851, 1739, 1476, 1198, 1172 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta=1.26-1.62$ (m, 24H), 1.36 (s, 3H), 1.41 (s, 3H), 2.30 (t, $J=7.6$ Hz, 2H), 3.50 (t, $J=7.5$ Hz, 1H), 3.67 (s, 3H), 4.04 ppm (m, 2H); MS (EI): m/z (%): 342 ($[M]^+$, 3.29), 328 ($[M+1-CH_3]^+$, 57.0), 313 (2.08), 286 (5.77), 267 (1.68), 254 (15.98); elemental analysis calcd (%) for $C_{20}H_{38}O_4$ (332.5): C 70.13, H 11.18; found: C 70.15, H 11.61.

Compound 5b: A solution of compound (*S*)-**16b** (3.42 g, 10 mmol) in THF (30 mL) and 50% acetic acid (30 mL) was stirred for 5 h at 60 °C. The solvent was removed in vacuum and the crude product was purified by column chromatography on silica gel to afford diol (*S*)-**5b** (2.85 g, 94%). $[\alpha]_D^{20}=+10.6$ ($c=10.6$ in $CHCl_3$); IR (KBr): $\tilde{\nu}=3487$, 2918, 2851, 1737, 1472 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): $\delta=1.28$ (m, 22H), 1.64 (m, 2H), 1.79 (br s, 2H), 2.32 (t, $J=7.2$ Hz, 2H), 3.47 (m, 1H), 3.69 (m, 1H), 3.69 (s, 3H), 3.74 ppm (m, 1H).

Compound 5a: Compound **5a** was prepared from **16a** by the same procedure as **5b**. **5a**: $[\alpha]_D^{20}=-9.7$ ($c=2.51$ in $CHCl_3$); IR (KBr) 3487, 2918, 2851, 1737, 1473, 1437 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): $\delta=1.28$ (m, 22H), 1.64 (m, 2H), 1.81 (br s, 2H), 2.32 (t, $J=7.2$ Hz, 2H), 3.47 (m, 1H), 3.69 (m, 1H), 3.70 (s, 3H), 3.73 ppm (m, 1H).

Compound 3c: A suspension of alcohol (*S*)-**5b** (1.51 g, 5.0 mmol) and dibutyltin oxide (1.25 g, 5.0 mmol) in $CHCl_3$/MeOH (50 mL, 10:1) was refluxed for 2 h. After the solvents were removed under reduced pressure, the residue was dried under high vacuum for 2 h. To the solution of above residue in DMF (25 mL) were added iodide (*S*)-**4b** (2.1 g, 5.25 mmol) and cesium fluoride (1.4 g, 9.2 mmol) under nitrogen. After the reaction mixture was stirred overnight at 40–50 °C, the reaction was quenched by adding ethyl acetate (40 mL) and brine (200 mL). After being stirred for 30 min, the mixture was filtered through a pad of silica gel. The aqueous layer was extracted with ethyl acetate, and the combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated. The resultant residue was purified by column chromatography on silica gel to give (15*S*,24*S*)-**3c** (1.56 g, 54%). $[\alpha]_D^{20}=+12.6$ ($c=7.7$ in $CHCl_3$); IR (film): $\tilde{\nu}=3472$, 2924, 2854, 1736, 1464, 1042 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): $\delta=0.88$ (t, $J=7.2$ Hz, 3H), 1.25–1.48 (m, 38H), 1.52 (m, 2H), 1.67 (m, 2H), 1.94 (br s, 1H), 2.30 (t, $J=7.2$ Hz, 2H), 3.30 (t, $J=7.8$ Hz, 1H), 3.39 (s, 3H), 3.51 (m, 3H), 3.58–3.66 (m, 4H), 3.66 (s, 3H), 3.71 (m, 1H), 3.77 (m, 1H), 4.66 (d, $J=6.9$ Hz, 1H), 4.77 ppm (d, $J=6.9$ Hz, 1H); HRMS for $C_{33}H_{66}O_7$+Na: 597.4700; found: 597.4695.

Compound 3d: The above protocol for **3c** was applied to the coupling of segments **4b** and **5a** to afford **3d**: $[\alpha]_D^{18}=+5.9$ ($c=0.38$ in $CHCl_3$); IR (film): $\tilde{\nu}=3472$, 2924, 2854, 1736, 1464, 1112, 1042, 922 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta=0.87$ (t, $J=6.6$ Hz, 3H), 1.2–1.7 (m, 42H), 2.30 (t, $J=7.6$ Hz, 2H), 2.40 (br s, 1H), 3.23–3.34 (m, 1H), 3.38 (s, 3H), 3.48–3.56 (m, 3H), 3.6–3.8 (m, 6H), 3.66 (s, 3H), 4.66 (d, $J=6.9$ Hz, 1H), 4.77 ppm (d, $J=6.9$ Hz, 1H); HRMS for $C_{33}H_{66}O_7$+Na: 597.4700; found: 597.4707.

Compound 3b: The above protocol for **3c** was applied to the coupling of segments **4a** and **5b** to afford **3b**: $[\alpha]_D^{20}=-6.6$ ($c=4.6$ in $CHCl_3$); IR (KBr): $\tilde{\nu}=2924$, 2854,1734, 1364, 1148, 1044, 922, 726 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): $\delta=0.88$ (t, $J=6.9$ Hz, 3H), 1.25–1.48 (m, 38H), 1.52 (m, 2H), 1.67 (m, 2H), 1.98 (br s, 1H), 2.30 (t, $J=7.6$ Hz, 2H), 3.30 (dd, $J=12.6$ Hz, 11.4 Hz, 1H), 3.38 (s, 3H), 3.48–3.56 (m, 3H), 3.60–3.8 (m, 4H), 3.66 (s, 3H), 3.71 (m, 1H), 3.78 (m, 1H), 4.66 (d, $J=6.9$ Hz, 2H), 4.76 ppm (d, $J=6.9$ Hz, 2H); MS (EI): m/z (%): 555 ($[M+1]^+$, 0.48), 353 (5.08), 309 (20.6), 295 (100.0); HRMS for $C_{33}H_{66}O_7$+Na: 597.4700; found: 597.4693.

Compound 3a: The above protocol for **3c** was applied to the coupling of segments **4a** and **5a** to afford **3a**: $[\alpha]_D^{20}=-11.8$ ($c=3.2$ in $CHCl_3$); IR (KBr): $\tilde{\nu}=3466$, 2924, 2854, 1736, 1464, 1112, 1042, 922 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): $\delta=0.88$ (t, $J=7.2$ Hz, 3H), 1.25–1.48 (m, 38H), 1.53 (m, 2H), 1.62 (m, 2H), 2.30 (t, $J=7.2$ Hz, 2H), 3.30 (t, $J=7.8$ Hz, 1H), 3.38 (s, 3H), 3.48–3.54 (m, 3H), 3.58–3.78 (m, 6H), 3.67 (s, 3H), 4.66 (d, $J=6.9$ Hz, 1H), 4.77 ppm (d, $J=6.9$ Hz, 1H); HRMS for $C_{33}H_{66}O_7$+Na: 597.4700; found: 597.4704.

Compound (15*S*,24*S*)-17c: MOMCl (1.2 mL, 5.8 mmol) was added to a mixture of **(15*S*,24*S*)-3c** (1.148 g, 2 mmol) and diisopropyl ethylamine (3 mL, 17.2 mmol) in dry CH_2Cl_2 (5 mL) at 0 °C. The mixture was stirred at room temperature for 12 h, quenched with saturated aqueous NH_4Cl, and extracted with ether. The extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel to afford **17c** (0.16 g, 90%) as a colorless oil. $[\alpha]_D^{20}=-9.04$ ($c=7.9$ in $CHCl_3$); ^1H NMR (600 MHz, $CDCl_3$): $\delta=0.81$ (t, $J=7.2$ Hz, 3H), 1.18–1.56 (m, 42H), 2.23 (t, $J=7.2$ Hz, 2H), 3.31 (s, 6H), 3.41–3.44 (m, 4H), 3.51–3.57 (m, 4H), 3.60 (s, 3H), 3.62 (quint, $J=6.0$ Hz, 2H), 4.59 (d, $J=6.6$ Hz, 2H), 4.68 ppm (d, $J=6.6$ Hz, 2H).

Compound 17d: Protection of compound **3d** followed the same procedure for **17c** to give **17d**: $[\alpha]_D^{19}=-6.0$ ($c=6.6$ in $CHCl_3$); IR (film): $\tilde{\nu}=2922$, 1750, 1042 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): $\delta=0.81$ (t, $J=7.2$ Hz, 3H), 1.17–1.58 (m, 42H), 2.30 (t, $J=7.2$ Hz, 2H), 3.31 (s, 6H), 3.41–3.44 (m, 4H), 3.51–3.56 (m, 4H), 3.60 (s, 3H), 3.60–3.64 (m, 2H), 4.59 (d, $J=6.6$ Hz, 2H), 4.69 ppm (d, $J=6.6$ Hz, 2H).

Compound 17b: Protection of compound **3b** followed the same procedure for **17c** to give **17b**: $[\alpha]_D^{20}=+5.9$ ($c=4.3$ in $CHCl_3$); IR (film): $\tilde{\nu}=2924$, 2854, 1736, 1466, 1110, 1042, 922 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): $\delta=0.87$ (t, $J=7.2$ Hz, 3H), 1.20–1.62 (m, 42H), 2.29 (t, $J=7.2$ Hz, 2H), 3.37 (s, 6H), 3.48–3.50 (m, 4H), 3.58–3.63 (m, 4H), 3.66 (s, 3H), 3.66–3.67 (m, 2H), 4.65 (d, $J=6.6$ Hz, 2H), 4.76 ppm (d, $J=6.6$ Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$): $\delta=174.257$, 96.002, 76.226, 74.115, 70.757, 55.387, 51.350, 34.081, 32.027, 31.885, 29.732, 29.590, 29.420, 29.307, 29.222, 29.123, 25.939, 24.929, 22.649, 14.064 ppm.

Compound 17a: Protection of compound **3a** followed the same procedure for **17c** to give **17a**: $[\alpha]_D^{18}=+8.67$ ($c=1.3$ in $CHCl_3$); IR (film): $\tilde{\nu}=2924$, 2854, 1736, 1466, 1042, 922 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): $\delta=0.87$ (t, $J=7.2$ Hz, 3H), 1.22–1.64 (m, 42H), 2.29 (t, $J=7.2$ Hz, 2H), 3.37 (s, 6H), 3.46–3.52 (m, 4H), 3.57–3.63 (m, 4H), 3.66 (s, 3H), 3.66–3.70 (m, 2H), 4.65 (d, $J=6.6$ Hz, 2H), 4.75 ppm (d, $J=6.6$ Hz, 2H).

Compound (15*S*,24*S*,36*S*)-18c: *n*BuLi (1.6 M in hexane, 1.25 mL, 2 mmol) was added to a solution of diisopropylamine (0.31 mL, 2.22 mmol) in THF (9 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 30 min and cooled to −78 °C. A solution of ester **(15*S*,24*S*)-17c** (0.55 g, 1 mmol) in dry THF (2.0 mL) was then added. After 30 min, a solution of *O*-THP-(*S*)-lactaldehyde (368 mg, 1.95 mmol) in dry THF (5 mL) was added. The reaction mixture was stirred for 2 h and then quenched with saturated aqueous NH_4Cl and diluted with diethyl ether. The aqueous layer was extracted with diethyl ether three times and the combined extracts were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. A 9% solution of H_2SO_4 (3.0 mL) was added to the resultant residue and the mixture was stirred for 48 h. The reaction was quenched with 10% $NaHCO_3$ and extracted with ether three times. The extracts were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. Then $(CF_3CO)_2O$ (2.0 mL) was added to the solution of the above crude intermediate in dry CH_2Cl_2 (5 mL) and Et_3N (3.0 mL) at 0 °C. The mixture was stirred at room temperature for 8 h, quenched with $NaHCO_3$, and extracted with diethyl ether. The extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by column chromatography on silica gel (elution with EtOAc/hexane = 5:1–2:1) afforded **18c** (272 mg, 43%) as a yellow oil. IR (film): $\tilde{\nu}=2922$, 2852, 1750, 1466, 1042, 922 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): $\delta=0.88$ (t, $J=7.2$ Hz, 3H), 1.22–1.40 (m, 34H), 1.40 (d, $J=6.6$ Hz, 3H), 1.48–1.58 (m, 6H) 2.26 (t, $J=7.8$ Hz, 2H), 3.38 (s, 6H), 3.48–3.51 (m, 4H), 3.58–3.64 (m, 4H), 3.67–3.71 (m, 2H), 4.65 (d, $J=6.9$ Hz, 2H), 4.76 (d, $J=6.9$ Hz, 2H), 4.99 (qd, $J=6.6$ Hz, 1.2 Hz, 1H), 6.98 ppm (d, $J=1.2$ Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): $\delta=173.885$, 148.11, 134.414, 96.059, 77.397, 76.280, 74.162, 71.042, 70.799, 69.225, 55.457, 55.214, 32.058, 31.929, 31.843, 29.768, 29.639, 29.553, 29.339, 29.210, 27.435, 25.489, 25.203, 22.684, 19.235, 14.111 ppm.

Compound 18d: The above protocol for **18c** was employed for the transformation of **17d** to **18d**: IR (film): $\tilde{\nu}=2922$, 2852, 1750, 1466, 1042, 922 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta=0.88$ (t, $J=7.2$ Hz, 3H), 1.2–1.6 (m, 40H), 1.40 (d, $J=6.6$ Hz, 3H), 2.26 (t, $J=7.8$ Hz, 2H), 3.38 (s, 6H), 3.48–3.70 (m, 10H), 4.66 (d, $J=6.9$ Hz, 2H), 4.75 (d, $J=6.9$ Hz, 2H), 4.99 (qd, $J=6.6$ Hz, 1.2 Hz, 1H), 6.98 ppm (d, $J=1.2$ Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): $\delta=173.88$, 148.81, 134.44, 96.703, 96.059, 77.397, 76.280,

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74.162, 71.042, 70.799, 69.826, 69.225, 55.457, 55.214, 32.058, 31.929, 31.843, 29.768, 29.639, 29.553, 29.339, 29.210, 27.435, 25.489, 25.203, 22.684, 19.235, 14.111 ppm.

Compound 18b: The above protocol for **18c** was employed for the transformation of **17b** to **18b**: IR (film): $\tilde{\nu}=2924$, 2854, 1752, 1466, 1112, 1042, 922 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): $\delta=0.88$ (t, $J=6.9$ Hz, 3H), 1.2–1.6 (m, 40H), 1.40 (d, $J=6.6$ Hz, 3H), 2.26 (t, $J=7.8$ Hz, 2H), 3.38 (s, 6H), 3.5–3.7 (m, 10H), 4.65 (d, $J=6.9$ Hz, 2H), 4.76 (d, $J=6.9$ Hz, 2H), 4.99 (q, $J=6.6$ Hz, 1H), 6.98 ppm (s, 1H).

Compound 18a: The above protocol for **18c** was employed for the transformation of **17a** to **18a**: IR (film): $\tilde{\nu}=2924$, 1752, 1466, 1042 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): $\delta=0.88$ (t, $J=7.2$ Hz, 3H), 1.22–1.58 (m, 40H), 1.40 (d, $J=6.6$ Hz, 3H), 2.26 (t, $J=7.2$ Hz, 2H), 3.38 (s, 6H), 3.46–3.72 (m, 10H), 4.65 (d, $J=6.6$ Hz, 2H), 4.76 (d, $J=6.6$ Hz, 2H), 4.98 (q, $J=6.6$ Hz, 1H), 6.98 ppm (s, 1H).

Compound (15*S*,24*S*,36*S*)-2c: MOM-protected compound **18c** (316 mg) in 6N HCl/THF/CH_3OH (2:1:2, 15 mL) was stirred for 16 h at room temperature. The reaction mixture was quenched with 10% $NaHCO_3$ and extracted with ether. The extracts were washed with saturated aqueous NH_4Cl and brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was further purified by column chromatography on silica gel to afford **2c** (186 mg, 68%). $[\alpha]_D^{18}=+16.3$ ($c=2.17$ in $CHCl_3$); IR (film): $\tilde{\nu}=2922$, 2852, 1750, 1466, 1042, 922cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): $\delta=0.87$ (t, $J=7.2$ Hz, 3H), 1.20–1.48 (m, 38H), 1.36 (d, $J=7.2$ Hz, 3H), 1.53 (quint, $J=7.8$ Hz, 2H), 2.26 (t, $J=7.8$ Hz, 2H), 2.50 (br s, 2H, OH), 3.31 (dd, $J=9.6$ Hz, 8.4 Hz, 2H), 3.52 (dd, $J=9.6$ Hz, 10.2 Hz, 2H), 3.61 (m, 4H), 3.75–3.81 (m, 2H), 4.98 (dq, $J=1.2$ Hz, 7.2 Hz, 1H), 6.97 ppm (d, $J=1.2$ Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): $\delta=$ 173.88, 148.81, 134.41, 78.11, 76.72, 71.27, 70.49, 34.44, 32.63, 29.85, 29.64, 29.55, 29.34, 29.21, 27.44, 25.49, 25.20, 22.68, 19.24, 14.11 ppm; MS (EI): *m*/*z* (%): 555 ([*M*+H]$^+$, 2.30), 353 (7.68), 309 (30.67), 295 (100.00); HRMS for $C_{33}H_{62}O_6$+Na: 577.4438; found: 577.4437.

Compound 2d: The above deprotection procedure was employed for the transformation of **18d** to **2d**: $[\alpha]_D^{20}=-87.4$ ($c=0.35$ in $CHCl_3$); ^1H NMR (600 MHz, $CDCl_3$): $\delta=0.88$ (t, $J=6.9$ Hz, 3H), 1.20–1.48 (m, 38H), 1.40 (d, $J=6.6$ Hz, 3H), 1.55 (quint, $J=7.2$ Hz, 2H), 2.15 (br s, 2H, OH), 2.26 (br t, $J=7.8$ Hz, 2H), 3.32 (dd, $J=9.6$ Hz, 8.4 Hz, 2H), 3.53 (dd, $J=9.6$ Hz, 2.4 Hz, 2H), 3.62–3.72 (m, 4H), 3.78 (m, 2H), 4.99 (dq, $J=1.2$ Hz, 6.6 Hz, 1H), 6.98 ppm (d, $J=1.2$ Hz, 1H); ^{13}C NMR (150 MHz, CD_3COCD_3): $\delta=$ 173.936, 150.757, 134.124, 78.016, 76.745, 71.323, 70.621, 70.504, 34.551, 32.651, 30.546, 29.435, 28.222, 26.337, 25.781, 23.341, 19.468, 14.352 ppm; MS (EI): *m*/*z* (%): 555 ([*M*+H]$^+$, 0.35), 353 (5.21), 309 (21.85), 295 (100.00); MS (FAB): *m*/*z* 578 ([*M*+1+Na]$^+$), 555 ([*M*+1]$^+$); HRMS for $C_{33}H_{62}O_6$Na: 577.4438; found: 577.4433.

Compound 2b: The above deprotection procedure was employed for the transformation of **18b** to **2b**: $[\alpha]_D^{20}=-6.9$ ($c=0.40$ in $CHCl_3$); IR (KBr): $\tilde{\nu}=3470$, 2927, 1748, 1464, 1042, 922 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): $\delta=0.88$ (t, $J=6.9$ Hz, 3H), 1.20–1.48 (m, 38H), 1.40 (d, $J=6.6$ Hz, 3H), 1.55 (quint, $J=7.2$ Hz, 2H), 2.15 (br s, 2H, OH), 2.26 (br t, $J=7.8$ Hz, 2H), 3.32 (dd, $J=9.6$ Hz, 8.4 Hz, 2H), 3.53 (dd, $J=2.4$ Hz, 9.6 Hz, 2H), 3.62–3.72 (m, 4H), 3.78 (m, 2H), 4.99 (dq, $J=1.2$ Hz, 6.6 Hz, 1H), 6.98 ppm (d, $J=1.2$ Hz, 1H); MS (EI): *m*/*z* (%): 555 ([*M*+1]$^+$, 0.48), 353 (5.08), 323 (0.30), 309 (20.55), 295 (100.00); ^{13}C NMR (150 MHz, CD_3COCD_3): $\delta=$ 173.936, 150.757, 134.124, 78.16, 76.745, 71.323, 70.504, 34.551, 34.507, 32.651, 30.545, 29.435, 28.222, 26.337, 25.781, 23.341, 19.468, 14.352 ppm; HRMS for $C_{33}H_{62}O_6$+Na: 577.4438; found: 577.4445.

Compound 2a: The above deprotection procedure was employed for the transformation of **18a** to **2a**: $[\alpha]_D^{20}=+3.4$ ($c=2.31$ in $CHCl_3$); IR (KBr): $\tilde{\nu}=3474$, 2922, 1748, 1464, 1108, 1040, 922 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): $\delta=0.88$ (t, $J=6.9$ Hz, 3H), 1.20–1.50 (m, 38H), 1.40 (d, $J=7.2$ Hz, 3H), 1.55 (quint, $J=6.6$ Hz, 2H), 2.26 (br t, $J=7.8$ Hz, 2H), 3.32 (dd, $J=9.6$ Hz, 8.4 Hz, 2H), 3.53 (dd, $J=9.6$, 10.2 Hz, 2H), 3.60–3.72(m, 4H), 3.74–3.83 (m, 2H), 4.99 (dq, $J=1.2$ Hz, 7.2 Hz, 1H), 6.98 ppm (d, $J=1.2$ Hz, 1H); ^{13}C NMR (150 MHz, CD_3COCD_3): $\delta=174.259$, 151.104, 134.272, 78.224, 75.136, 71.574, 70.297, 33.768, 32.611, 30.399, 29.702, 29.629, 29.584, 29.525, 29.348, 29.201, 27.430, 25.931, 25.708, 23.289, 19.430, 14.339 ppm; MS (EI): *m*/*z* (%): 505 ([*M*+1]$^+$, 0.38), 353 (5.86), 309 (22.75), 295 (100.00), 267 (4.39); HRMS for $C_{33}H_{62}O_6$+Na: 577.4438; found: 577.4437.

Compound 21: Tetrabutylammonium bisulfate (0.067 g) and aqueous 50% NaOH solution (2 mL) were added to a stirred mixture of compound **12b** (0.67 g, 4.24 mmol) and (*R*)-epichlorohydrin (0.36 g). After being stirred for 22 h at room temperature, the reaction mixture was diluted with ether (20 mL). The organic layer was washed with saturated NH_4Cl and brine, and dried over Na_2SO_4. Removal of solvent and purification by column chromatography gave **21** (0.7 g, 88%). $[\alpha]_D^{20}=-8.5$ ($c=7.67$ in $CHCl_3$); IR (KBr): $\tilde{\nu}=2924$, 2853, 1466, 1210, 1043, 920 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta=0.84$ (t, $J=6.6$ Hz, 3H), 1.20–1.52 (m, 18H), 2.57 (dd, $J=$ 2.6, Hz, 5.0 Hz, 1H), 2.78 (t, $J=4.5$ Hz, 1H), 3.15 (m, 1H), 3.35 (s, 3H), 3.33– 3.78 (m, 9H), 4.62 (d, $J=6.7$ Hz, 1H), 4.73 ppm (d, $J=6.7$ Hz, 1H); MS (EI): *m*/*z* (%): 346 ([*M*]$^+$), 306 (38.91), 285 (5.96), 225 (100.00), 207 (13.04), 188 (70.76), 91 (66.07); HRMS (FAB) for $C_{19}H_{38}O_5$+Na: 369.2611; found: 369.2607.

Compound 22: To a stirred solution of trimethylsilyl acetylene (1.3 mL, 9.16 mmol) in THF (5 mL) at $-78\,^\circ C$ were added *n*BuLi (1.6M, 5.73 mL, 9.16 mmol), $BF_3\cdot Et_2O$ (1.24 mL, 9.16 mmol), and compound **21** (1.2 g, 3.5 mmol) in THF (2 mL) successively. After being stirred for 2 h, the reaction was quenched by adding saturated $NaHCO_3$, and the mixture was extracted with ether. The combined organic layers were washed with saturated brine, concentrated and chromatographed to give the acetylene intermediate. $[\alpha]_D^{20}=-7.67$ ($c=1.25$ in $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): $\delta=0.14$ (s, 9H), 0.86 (t, $J=6.9$ Hz, 3H), 1.2–1.3 (m, 16H), 1.53 (m, 2H), 2.47 (t, $J=6.9$ Hz, 2H), 3.36 (s, 1H), 3.42–3.52 (m, 3H), 3.56–3.66 (m, 6H), 3.92 (m, 1H), 4.65 (d, $J=6.8$ Hz, 1H), 4.78 ppm (d, $J=$ 5.5 Hz, 1H); MS (EI): *m*/*z* (%): 413 ([*M* – OCH_3]$^+$, 1.68), 363 (0.85), 307 (3.50), 271 (5.61), 227 (6.63), 183 (4.46), 167 (43.55).

Tetrabutylammonium fluoride (1.0M, 3.8 mL) was added to a solution of the above intermediate in THF (10 mL). The reaction mixture was stirred for 2 h, diluted with ether and worked up as usual to give the crude terminal acetylene intermediate. Into the solution of this crude intermediate and diisopropylethyl amine (2.8 mL) was injected MOMCl (2 mL). After being stirred for 8 h, the mixture was diluted with ether, washed with water and with saturated brine, dried over Na_2SO_4, concentrated, and purified by column chromatography to give compound **22** in 66% overall yield. $[\alpha]_D^{20}=+9.69$ ($c=0.46$ in $CHCl_3$); IR (film): $\tilde{\nu}=3300$, 2925, 1466, 1043, 922 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): $\delta=0.90$ (t, $J=7.2$ Hz, 3H), 1.20–1.62 (m, 18H), 1.98 (t, $J=2$ Hz, 1H), 2.38–2.52 (m, 2H), 3.37 (s, 3H), 3.38 (s, 3H), 3.4–3.9 (m, 10H), 4.65 (d, $J=6.9$ Hz, 1H), 4.73 (s, 2H), 4.75 ppm (d, $J=$ 6.9 Hz, 1H); HRMS for $C_{23}H_{44}O_6$+Na: 439.3029; found: 439.3024.

Compound 28: In succession, *n*BuLi (1.6M, 1.375 mL, 2.2 mmol), $BF_3\cdot Et_2O$ (0.3 mL, 2.2 mmol) and **27**17 (262 mg, 1.1 mmol) in THF (3 mL) were added to a stirred solution of compound **22** (922 mg, 2.2 mmol) in THF (4 mL) at $-78\,^\circ C$ over a 20–30-minute interval. After being stirred for 3 h, the reaction was quenched by adding saturated $NaHCO_3$, and the mixture was extracted with diethyl ether. The combined organic layers were washed with saturated brine, dried over $MgSO_4$, concentrated under vacuum, and purified by column chromatography to afford **28** (350 mg, 51%): $[\alpha]_D^{20}=-10.9$ ($c=2.19$ in $CHCl_3$); IR (KBr): $\tilde{\nu}=3467$, 2924, 1753, 1460, 1039, 922 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta=0.88$ (t, $J=6.9$ Hz, 3H), 1.26–1.60 (m, 30H), 1.41 (d, $J=6.9$ Hz, 3H), 2.24 (t, $J=7$ Hz, 2H), 2.4–2.6 (m, 4H), 3.39 (s, 3H), 3.41 (s, 3H), 3.3–4.0 (m, 11H), 4.63 (d, $J=6.6$ Hz, 1H), 4.7–4.8 (m, 3H), 4.98 (q, $J=6.9$ Hz, 1H), 6.99 ppm (d, $J=1.7$ Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=14.061$, 19.161, 20.982, 22.135, 22.621, 25.110, 25.414, 25.596, 27.341, 27.812, 29.269, 29.405, 29.557, 29.694, 31.849, 31.985, 36.235, 55.434, 70.034, 70.626, 70.868, 72.644, 74.101, 74.708, 76.165, 77.334, 95.895, 134.278, 148.832 ppm; MS (EI): *m*/*z* (%): 615 (7.11), 460 (5.57), 225 (66.74), 207 (8.64); HRMS (FAB) for $C_{37}H_{66}O_9$+Na: 677.4599; found: 677.4603.

Compound 20: A solution of NaOAc (0.88 g, 28 mmol) in H_2O (15 mL) was added dropwise to a solution of **28** (90 mg, 0.138 mmol) and *para*-toluenesulfonyl hydrazone (1.77 g, 9.5 mmol) in dimethoxylethane (15 mL) under reflux over 5 h. The reaction mixture was then cooled to room temperature and poured into water. The mixture was extracted with ether and the extracts were washed with brine, dried, and concentrated to give a crude intermediate. The crude product obtained was then dissolved into dimethyl sulfide (8 mL), cooled in an ice–water bath and treated with $BF_3\cdot Et_2O$ (0.78 mL, 6.15 mmol). After being stirred for 30 min, the reaction mixture was quenched with saturated $NaHCO_3$, and extracted with ethyl acetate. The combined extracts were washed with water and then saturated brine, dried, concentrated, and purified by column chromatog-

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raphy to give **20** (50 mg, 64 %): $[\alpha]_D^{20} = +18.7$ ($c = 0.57$ in $CHCl_3$); IR (KBr): $\tilde{\nu} = 3420, 2922, 2852, 1741, 1465, 1325, 1150, 1084\ cm^{-1}$; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 0.88$ (t, $J = 6.7$ Hz, 3H), 1.26 – 1.60 (m, 38H), 1.41 (d, $J = 6.9$ Hz, 3H), 2.27 (dt, $J = 1.7$ Hz, 6.6 Hz, 2H), 2.86 (br s, 3OH), 3.32 (dt, $J = 2.8$ Hz, 8.9 Hz, 2H), 3.52 – 3.73 (m, 7H), 3.79 (m, 2H), 5.01 (dq, $J =$ 1.7 Hz, 6.9 Hz, 1H), 6.99 ppm (d, $J = 1.4$ Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 14.128$, 19.237, 22.703, 25.185, 25.495, 25.568, 25.633, 27.410, 29.130, 29.281, 29.346, 29.559, 29.584, 29.630, 29.710, 31.924, 32.885, 33.036, 37.346, 37.497, 70.094, 70.315, 70.510, 70.561, 71.736, 75.855, 75.903, 76.614, 134.317, 148.908, 173.895 ppm; MS (EI): m/z: 571 ($[M+1]^+$); HRMS (FAB) for $C_{33}H_{62}O_7$+Na: 593.4387; found: 593.4397.

Compound 29: A solution of *n*BuLi in hexane (1.23 mL, 1.6 M, 1.96 mmol) was added to a solution of diisopropylamine (0.41 mL, 2.94 mmol) in THF (6 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 30 min and cooled down to −78 °C, and **(15*S*,24*S*)-17c** (0.606 g, 0.981 mmol) in dry THF (2.0 mL) was then added. After 30 min, *O*-THP-(*R*)-lactaldehyde (232 mg, 1.47 mmol) in dry THF (6 mL) was added. The reaction mixture was stirred for 2 h, quenched with saturated aqueous NH_4Cl and diluted with diethyl ether. The aqueous layer was extracted with diethyl ether three times and the combined extracts were washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. To the resultant residue was added 9 % H_2SO_4 (5 mL), and the mixture was stirred for 48 h, quenched with 10 % $NaHCO_3$, and extracted with ether three times. The extracts were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. $(CF_3CO)_2O$ (0.26 mL) was added to the solution of the above residue in dry CH_2Cl_2 (5 mL) and Et_3N (0.52 mL) at 0 °C. The reaction mixture was stirred at room temperature for 8 h, quenched with $NaHCO_3$, and extracted with ether. The extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by column chromatography on silica gel (EtOAc/hexane = 5:1 to 2:1) afforded **29** (0.378 mg, 60 %) as a yellow oil. $[\alpha]_D^{20} = -25.8$ ($c = 0.39$ in $CHCl_3$); IR (film): $\tilde{\nu} = 2927, 2855, 1760, 1467, 1319, 1145, 1111, 1040, 919\ cm^{-1}$; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 0.89$ (t, $J = 6.9$ Hz, 3H), 1.21 – 1.58 (m, 40H), 1.42 (d, $J = 6.9$ Hz, 3H), 2.28 (t, $J =$ 7.5 Hz, 2H), 3.39 (s, 6H), 3.46 – 3.76 (m, 10H), 4.67 (d, $J = 6.9$ Hz, 2H), 4.77 (d, $J = 6.9$ Hz, 2H), 5.01 (qd, $J = 7.1$ Hz, 1.5 Hz, 1H), 7.00 ppm (d, $J =$ 1.8 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): $\delta = 168.129$, 148.830, 134.382, 96.677, 96.034, 79.235, 76.607, 76.264, 74.141, 71.030, 70.779, 55.465, 55.220, 32.059, 31.934, 31.835, 29.784, 29.644, 29.559, 29.352, 29.217, 27.443, 25.487, 25.206, 22.702, 19.238, 14.132 ppm; MS (ESI): m/z: 665 ($[M+Na]^+$); HRMS (ESI) calcd for $C_{37}H_{70}O_8Na$ $[M+Na]^+$: 665.4923; found 665.4963.

Compound 30: To a solution of **29** (0.161 g, 0.174 mmol) in dimethyl sulfide (4 mL) was added $BF_3 \cdot Et_2O$ (0.47 mL, 3.15 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 40 min and quenched with saturated aqueous $NaHCO_3$ (5.4 mL). The mixture was extracted with ethyl acetate (3 × 15 mL), and the extracts were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography to afford compound **30** (83 mg, 60 %) as a waxy solid. $[\alpha]_D^{25} = -7.7$ ($c = 0.78$ in $CHCl_3$); IR (film): $\tilde{\nu} = 3506, 3415, 2916, 2850, 1751, 1738, 1655, 1470, 1327, 1141, 1118, 1100, 1031, 909, 881, 720\ cm^{-1}$; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 0.88$ (t, $J = 6.9$ Hz, 3H), 1.19 – 1.52 (m, 40H), 1.41 (d, $J = 6.9$ Hz, 3H), 2.26 (t, $J = 7.8$ Hz, 2H), 3.32 (dd, $J = 8.4$, 9.8 Hz, 2H), 3.54 (dd, $J = 2.7$, 9.9 Hz, 2H), 3.61 – 3.73 (m, 4H), 3.76 – 3.83 (m, 2H), 5.00 (dq, $J = 1.8$, 6.8 Hz, 1H), 6.99 ppm (d, $J = 1.5$ Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 173.897$, 148.837, 134.353, 76.597, 75.901, 70.515, 70.271, 33.019, 31.909, 29.689, 29.606, 29.559, 29.513, 29.327, 29.307, 29.186, 27.413, 25.555, 25.180, 22.687, 19.223, 14.107 ppm; MS (ESI): m/z: 577 ($[M+Na]^+$); HRMS (ESI) calcd for $C_{33}H_{62}O_6Na$ $[M+Na]^+$: 577.4438; found 577.4438.

Acknowledgements

We are grateful to the National Natural Science Foundation of China (29790126), the Chinese Academy of Sciences (95-A1-504-03) and the Ministry of Science and Technology of China (G2000077502) for financial support.

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Received: August 2, 2002 [F4311]

