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First Total Synthesis of the Potent Anticancer Natural Product Dideoxypetrosynol A: Preparation of the "Skipped" (*Z*)-Enediyne Moiety by Oxidative Coupling of Homopropargylphosphonium Ylide

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Dideoxypetrosynol A is a C30 polyacetylenic alcohol with C_2 symmetry. The first total synthesis of both enantiomers of the potent anti-cancer natural product (+)- and (–)-dideoxypetrosynol A is reported. The key step is an oxidative coupling of a homopropargylphosphonium ylide to prepare the "skipped" (*Z*)-enediyne moiety. The natural dideoxypetrosynol A was isolated as a racemic mixture as shown in structure **1**. The absolute configurations of the chiral centers are established for the (+)- and (–)-enantiomers using Burgess' enzymatic resolution procedure with *Pseudomonas* AK lipase.

Introduction

Along with three similar polyacetylenic alcohols, dideoxypetrosynol A (**1**) was isolated by Jung and co-workers off the Komun Island, Korea from the marine sponge *Petrosia sp.* guided by a brine shrimp assay.[1] These compounds (Figure 1) have structural features related to duryne (**2**)[2] and petrosynol (**3**),[3,4] both of which have been found to possess anticancer and other interesting biological activities.[5] Dideoxypetrosynol A (**1**) was also found to have potent anticancer activity and exhibited an ED_{50} of 0.02 μg/mL against human ovarian cancer cells and of 0.01 μg/mL against human skin cancer cells.[1] It is noteworthy that the cytotoxic activities of compound **1** is one order of magnitude higher than those found for doxorubicin, which is one of the most commonly used chemotherapeutic drugs and exhibits a wide spectrum of activity against solid tumors, lymphomas, and leukemias.[6] Dideoxypetrosynol A (**1**) was also found to inhibit DNA replication at the initiation stage.[7] However, due to the minute yield (23 mg out of 14.5 kg of dry sponge) from the natural source, only limited studies of biological activity have been performed. To the best of our knowledge, no synthetic study of dideoxypetrosynol A has been reported.

Recently we reported a total synthesis of duryne (**2**) and assigned the geometry of the central C=C olefin and the absolute stereochemistry of the chiral centers.[8] Although the structures of compounds **1** and **2** are similar, the central (*Z*)-enedipropargyl moiety (which was first coined the "skipped" enediyne by Gleiter)[9] in **1** posed a new problem for an efficient synthesis. Here we are pleased to report a successful total synthesis of dideoxypetrosynol A with an oxidative coupling strategy to prepare the "skipped" enediyne moiety.

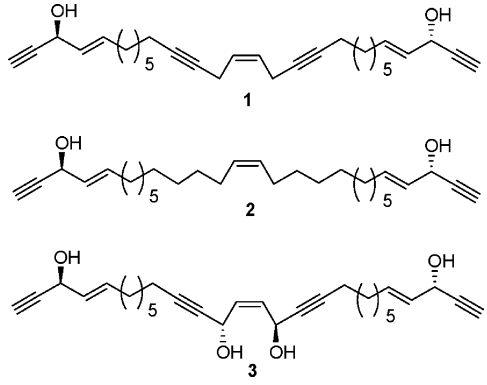

Figure 1. Anticancer C_{30} polyacetylenic alcohols, dideoxypetrosynol A (**1**), duryne (**2**), and petrosynol (**3**). Compound **1** contains a central (*Z*)-enedipropargyl moiety, also known as a "skipped" enediyne.

Results and Discussion

Current literature method for constructing the "skipped" (*Z*)-enediyne system such as compound **4**, Scheme 1, is an S_N2 alkylation of (*Z*)-1,4-dichloro-2-butene with a Grignard reagent made from alkyne.[9–11] The concurrent formation of the S_N2' product **5** and the elimination product **6**, as shown in Scheme 1, are the main problems for this approach. So far only poor yields have been reported.[11,12]

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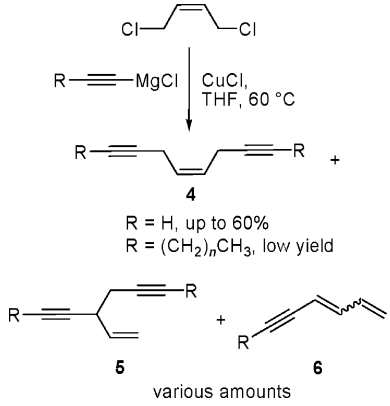
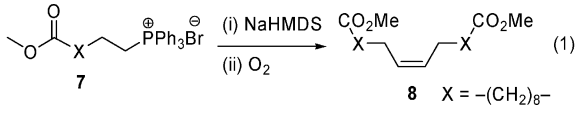


Scheme 1. Results from the existing method.

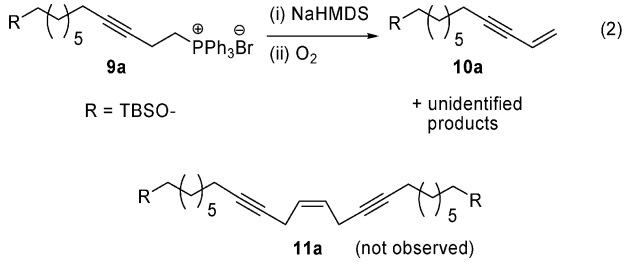
Gleiter and Merger reported an improvement of yield from 20% to 60% by using ethynylmagnesium chloride in stead of ethynylmagnesium bromide.[9]

Unfortunately reactions of long-chain alkynylmagnesium chloride did not seem to give any better yields.[11,12] In our hands, little of the desired product was obtained when using the alkynylmagnesium chloride reagent prepared from compound **12** (see Scheme 3).

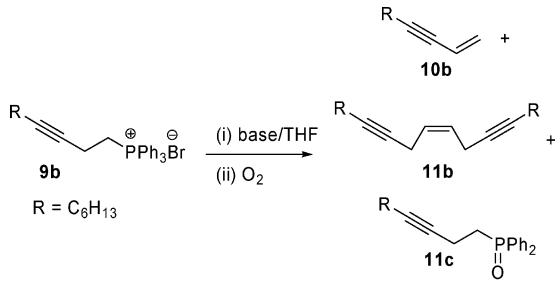
We turned our attention to an alternate strategy after failing to improve the yields with the alkynylation of *cis*-1,4-dichloro-2-butene. In our recent effort in the synthesis of duryne (**2**),[8] the (*Z*)-geometry of the central double bond was established by an autooxidation of the Wittig reagent **7** generated in situ as reported by Poulain and coworkers, Equation (1).[13] The reaction mixture was saturated with oxygen before refluxing for 16 h to produce the *cis*-olefin **8**.[14]



However, when the same condition was applied to the phosphonium salt **9a** in an attempt to prepare the *cis*-olefin **11a**, the only identifiable product was the enyne **10**, along with mixtures of unidentified products, Equation (2). It appeared that a proton abstraction from the propargylic position, at least in part, had occurred in compound **9a** when sodium hexamethyldisilazide (NaHMDS) was used as the base in the reaction.



The most acidic proton in the phosphonium salt **9a** should be the CH_2 attached to the positively charged phosphorus atom ($Ph_3P^+CH_2$, p$K_a \approx 22$).[15] However, the adjacent propargylic CH_2 in compound **9a** could lose a proton to give the elimination product **10**. Propargylic CHs are well known to be acidic and amide bases have been used to remove propargylic protons,[16–18] though there is little data to be found concerning the pK_a of propargylic CH groups.[19] Propargyllithium is known to have an allene-like structure,[20] suggesting that propargylic CH groups are less acidic than allenylic CH groups, which is consistent with gas phase acidity orders of allene and propyne.[21] Thus the CH_2 bonded to the positively charged phosphorus atom in **9a** should be more acidic than the propargylic CH_2. Therefore, it should be possible to selectively remove the $Ph_3P^+CH_2$ proton in compound **9a**. A survey of different bases was performed and the results are shown in Scheme 2.



base	10b	11b	11c
	% yield		
*n*BuLi	0	88	0
KO*t*Bu	54	22	0
NaHMDS	77	0	0
NaOMe[a]	0	0	88

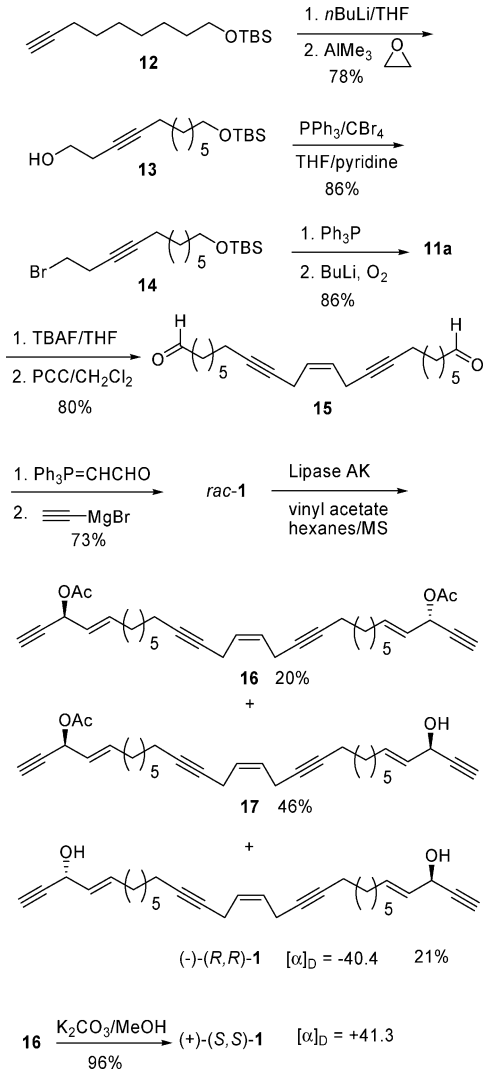
[a] The solvent contained methanol.

Scheme 2. Base effect on Wittig reagent formation and oxidative coupling.

The use of *n*-butyllithium in place of NaHMDS led to a much better yield of the desired product **11b** than the S_N2 alkynylation procedure shown in Scheme 1. Interestingly, the less strong bases are all inferior in this reaction compared to *n*-butyllithium. A previous report also indicated that *n*-butyllithium gave smooth formation of the desired Wittig reagent on a similar phosphonium salt.[22] On the basis of these observations, the formation of the by products such as enyne **10** might be due to (1) the steric bulk of the base used and (2) the reversibility of the deprotonation step when the less strong bases such as NaHMDS are used. Thus, a significant amount of the elimination product **10** could occur through a shift of the reaction equilibrium even only a small percentage of the propargylic proton was initially removed. The following elimination and the formation of enyne **10** are not reversible. This explains why enyne **10** was produced when KO*t*Bu and NaHMDS were used.

When the reaction was performed in a mixed solvent system containing methanol, the homopropargyl(diphenyl)-phosphane oxide **11c** was produced in 88% yield. The formation of **11c** did not require the presence of oxygen. It is presumably formed through a CH_3O^- attack on the phosphonium salt at the phosphorus atom followed by protonation of a phenyl anion and an S_N2 attack on the resulting $Ph_2RP{=}O^+{-}CH_3$ by a CH_3O group.

Once we found the proper base to use in the preparation of the Wittig reagent, the synthesis of the target started with the known terminal acetylene **12**, Scheme 3.[23] Homopropargyl alcohol **13** was prepared following a procedure reported by Brummond.[24] This procedure employs Me_3Al as an additive in the ethylene oxide opening reaction and gives a reproducible yield of the desired product. Compound **13** was converted into the homopropargyl bromide by a modification of the Appel reaction.[25] The preparation of the phosphonium salt **9a** [Equation (2)] follows the reported procedure by Dawson.[26] *n*BuLi treatment of **9a** followed by saturating the reaction mixture with oxygen and reflux in THF produced the *cis*-enediyne **11a** in 86% yield. With the key intermediate **11a** in hand, dial **15** was obtained through a two-step sequence: (1) removal of the TBS protecting group with TBAF in THF and (2) PCC oxidation of the resulting diol, Scheme 3. The Wittig reaction of the dialdehyde with $Ph_3P{=}CHCHO$ yielded a α,β-unsaturated dial and the addition of acetylenic magnesium bromide to the dial produced the racemic natural product **1**.



Scheme 3. Synthesis of dideoxypetrosynol A.

Although the natural product dideoxypetrosynol A was reported as a possible racemic mixture, it was unclear whether racemization had occurred during the isolation-identification process.[1] It is important to identify the efficacy of each enantiomer's action on cancer cells. Therefore, we decided to carry out an enzymatic resolution to assign the absolute configurations to each enantiomer.

The general procedures of Burgess were followed using lipase AK from *pseudomonas sp* for the enzymatic resolution of the acetylenic alcohol **1**.[27,28] The progress of the reaction was followed by both thin-layer chromatography and ^1H NMR to ensure a clean kinetic resolution of the enantiomers. The separation of the diacetate **16**, the *meso* monoacetate **17**, and the diol (–)-**1** was done by column chromatography.

The (*R*,*R*)-diol **1** has a negative optical rotation of $[\alpha]_D$ = –40.4. The removal of the acetate group from **16** yields (*S*,*S*)-diol **1**, which gives a positive optical rotation of $[\alpha]_D$ = +41.3. The assignment of the absolute configurations is based on Burgess active site model for the lipases from *Pseudomonas sp*.[27] This model predicts that alcohols resolved most efficiently have one small and one relatively large group attached to the hydroxylmethine carbon. Dideoxypetrosynol A (**1**) is similar in structure to several C_2-symmetric polyacetylenic alcohols including adociacetylene, duryne, and a C20 acetylenic alcohol, all of which we have successfully resolved using lipase from *Pseudomonas* sp.[8,23,29] For most secondary alcohols, the rate of acylation is faster for the (*R*)-configuration than for the (*S*)-configuration. However, for the acetylenic alcohol **1**, the isomer with (*S*,*S*) configuration is acylated faster because the small acetylenic group has a higher priority in the nomenclature system. From these considerations and the data obtained, we assign the (3*S*,28*S*) configurations to the enantiomer with a positive optical rotation and the (3*R*,28*R*) to the enantiomer with a negative optical rotation. To corroborate this assignment, several known C_2-symmetric acetylenic alcohols isolated from marine sources[3,4,30,31] are listed in Table 1 for comparison purpose.

Table 1. Absolute configurations of naturally occurring C_2-symmetric acetylenic alcohols.

Name	Chain length	$[\alpha]_D$	Configuration	Origin
Adociacetylene	30	+21.7	*S*,*S*	*Adocia sp.*
Petrosynol	30	+107	*S*,*S*	*Petrocia sp.*
C20 alkynol	20	+26	*S*,*S*	*Callyspongia pseudoreticulata*
Duryne	30	+29	*S*,*S*	*Cribrochalina dura*
Dideoxy-petrosynol A (**1**)	30	+41.3	*S*,*S*	*Petrocia sp.*

Conclusions

A total synthesis of the potent anticancer polyacetylenic alcohol dideoxypetrosynol A (**1**) has been achieved. The key step involves the coupling of a homopropargylphosphonium ylide to produce the *cis*-"skipped" enediyne moiety.

n-Butyllithium was found to be the most effective base in the preparation of the Wittig reagent from the triphenylphosphonium salt containing a homopropargyl substituent. Two-directional synthesis is executed in the remaining steps to obtain the racemic polyacetylenic natural product **1** in an efficient 8 steps and 33.7% overall yield starting from the known compound **12**. The absolute configurations of the (+)- and (–)-dideoxypetrosynol have been established through the total synthesis of **1** and the subsequent enzymatic resolution of the racemic mixture.

Experimental Section

General: All reactions were carried out under nitrogen in oven-dried glassware with magnetic stirring. Reagents were purchased from commercial sources and used directly without further purification. Purification of reaction products was carried out by flash chromatography using silica gel 40–63 μm (230–400 mesh), unless otherwise stated. Reactions were monitored by ^{1}H NMR and/or thin-layer chromatography. Visualization was accomplished with UV light, staining with 5% $KMnO_4$ solution followed by heating. Chemical shifts are recorded in ppm (δ) using tetramethylsilane (H, C) as the internal reference. Data are reported as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet; integration, coupling constant(s) in Hz.

11-(*tert*-Butyldimethylsilanyloxy)undec-3-yn-1-ol (13): *n*BuLi (7.2 mL, 11.5 mmol) wass added dropwise to a solution of the alkyne **12** (2.45 g, 9.6 mmol) in THF (10 mL) at –78 °C. After 45 min the flask was placed in an ice bath for 15 min then Me_3Al (1 mL, 1.92 mmol) was added followed by ethylene oxide (0.6 mL, 11.5 mmol). The ice bath was removed and the reaction mixture was stirred at room temperature for 36 h after which it was quenched by the addition of H_2O and diethyl ether. The biphasic mixture was transferred into a separatory funnel and 10% HCl was added until it eliminated the aluminum emulsion. The aqueous layer was extracted using EtOAc. The combined organics were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Purification was effected by column chromatography to afford **13** as clear oil (2.2 g, 78%): IR: $\tilde{\nu}$ = 1045, 1097, 1254, 1471, 2244, 2856, 2929, 3380 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$, 23 °C): δ = 0.02 (s, 6 H), 0.86 (s, 9 H), 1.27–1.49 (m, 10 H), 1.81 (br., 1 H), 2.13 (t, J = 2.3 Hz, 2 H), 2.41 (t, J = 4.1 Hz, 2 H), 3.58 (t, J = 6.7 Hz, 2 H), 3.66 (dt, J = 6.2, 4.3 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 23 °C): δ = 0.04, 18.4, 18.7, 23.4, 23.2, 25.6, 25.9, 28.8, 28.9, 32.8, 61.3, 63.2, 76.3, 82.5 ppm. HRMS: calcd. for $C_{17}H_{34}O_2Si$ [M + Na] 321.2226; found 321.2204.

(11-Bromoundec-8-ynyloxy)-*tert*-butyl(dimethyl)silane (14): A reaction mixture containing **13** (2.2 g, 7.34 mmol) in dry THF (18 mL) was treated with Ph_3P (3.9 g, 14.68 mmol), dry pyridine (0.6 mL, 7.34 mmol) and CBr_4 (2.42 g, 7.34 mmol). After stirring for 4 h at room temperature the reaction mixture was diluted with H_2O and the aqueous solution was extracted with EtOAc. The combined organic solution was washed with 1 M HCl, H_2O and brine in that order. This was then dried ($MgSO_4$) filtered and concentrated in vacuo. The resulting oil was triturated with hexanes and the combined washings were concentrated in vacuo. Purification was effected by column chromatography to give **14** as clear oil (2.4 g, 86%): IR: $\tilde{\nu}$ = 1005, 1097, 1253, 1471, 2856, 2928 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$, 23 °C): δ = 0.02 (s, 6 H), 0.86 (s, 9 H), 1.27–1.45 (m, 10 H), 2.12 (t, J = 2.3 Hz, 2 H), 2.69 (t, J = 5.1 Hz, 2 H), 3.38 (t, J = 7.4 Hz, 2 H), 3.57 (dt, J = 6.6 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 23 °C): δ = 0.04, 18.4, 18.7, 23.4, 25.7, 25.9, 28.7, 28.8, 28.9, 30.3, 32.8, 63.2, 77.3, 82.7 ppm.

1,22-Bis[*tert*-butyl(dimethyl)silanyloxy]docos-11-ene-8,14-diyne (11a): A solution of **14** (2.4 g, 6.4 mmol) and Ph_3P (1.65 g, 6.4 mmol) in CH_3CN (15 mL) was stirred at reflux for 16 h and then concentrated under reduced pressure to afford the crude product which was triturated with hexanes several times to afford **9a** (3.2 g, 88%): IR: $\tilde{\nu}$ = 1110, 1254, 1437, 1471, 1587, 1824, 2176, 2855, 2928, 3055 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$, 23 °C): δ = 0.02 (s, 6 H), 0.86 (s, 9 H), 1.12–1.26 (m, 8 H), 1.57 (t, J = 2.1 Hz, 2 H), 1.67 (br., 2 H), 2.81 (br. d, 2 H), 3.57 (t, J = 6.6 Hz, 2 H), 4.12 (dt, J = 12.2, 6.3 Hz, 2 H) 7.67 (dd, J = 7.9, 3.4 Hz, 6 H), 7.85 (dt, J = 8.2, 4.2 Hz, 3 H), 7.88 (dt, J = 8.5, 7.3, 6 H5 Hz) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 23 °C): δ = 0.04, 13.2, 18.3, 18.4, 22.6, 23.0, 25.7, 25.8, 25.9, 28.3, 28.8, 32.8, 63.2, 76.9, 85.4, 128.7, 130.2, 130.3, 133.9, 134.9 ppm.

A solution of **9** (2.2 g, 3.91 mmol) in THF (20 mL) under N_2 was cooled to 0 °C followed by dropwise addition of *n*BuLi (2.44 mL, 3.91 mmol) by a syringe. The mixture was stirred at 0 °C for 2 h then warmed to room temperature and stirred for a further 1 h and then oxygen was bubbled into the reaction mixture. Stirring was continued at 60 °C for 16 h. The reaction mixture was quenched with saturated NH_4Cl and the mixture poured into H_2O. Purification was effected by column chromatography to give **11** as an oil (1.9 g, 86%): IR: $\tilde{\nu}$ = 1005, 1048, 1094, 1253, 1360, 1462, 2855, 2928 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$, 23 °C): δ = 0.02 (s, 6 H), 0.86 (s, 9 H), 1.28–1.50 (m, 20 H), 2.11 (t, J = 2.3 Hz, 2 H), 2.90 (br., 4 H), 3.57 (t, J = 6.6 Hz, 2 H), 5.47 (t, J = 4.5 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 23 °C): δ = 0.04, 17.1, 18.3, 18.8, 25.7, 25.9, 28.8, 28.9, 29.0, 32.8, 63.2, 77.6, 80.4, 126.5 ppm.

(*Z*)-Docos-11-ene-8,14-diynedial (15): TBAF (9.23 mL, 9.23 mmol) was added to a stirred solution of **11** (1.3 g, 2.3 mmol) in THF (21 mL) at 0 °C. The mixture was stirred at this temperature for 10 min then warmed to room temperature and stirred for 2 h. The reaction mixture was then filtered through a silica gel pad and washed with 80% EtOAc/hexanes. The filtrate was concentrated under high vacuum and the crude material was purified by column chromatography to afford the diol as a yellow solid (694 mg, 87%); m.p. 38–39 °C: IR: $\tilde{\nu}$ = 1057, 1096, 1255, 1462, 2855, 2929, 3339 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$, 23 °C): δ = 1.28–1.54 (m, 20 H), 2.09–2.13 (m, 4 H), 2.89 (br., 4 H), 3.60 (t, J = 6.7 Hz, 4 H), 5.45 (t, J = 4.5 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 23 °C): δ = 17.2, 18.7, 25.6, 28.8, 28.9, 29.0, 32.7, 62.9, 77.7, 80.4, 126.5 ppm.

The diol (690 mg, 1.77 mmol) was dissolved in CH_2Cl_2 (2 mL). This mixture was added to a stirred suspension consisting of PCC (1.2 g, 5.32 mmol) and Celite (1.2 g) in CH_2Cl_2 (15 mL) under N_2. After 2 h the starting material disappeared and the mixture was diluted with Et_2O then filtered through a pad of Celite. This was thoroughly rinsed with Et_2O followed by solvent removal under reduced pressure to afford **15** as an oil (634 mg, 92%): IR: $\tilde{\nu}$ = 1464, 1724, 2857, 2932 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$, 23 °C): δ = 1.35–1.67 (m, 16 H), 2.12 (t, J = 2.1 Hz, 4 H), 2.39 (dt, J = 7.2, 1.5 Hz, 4 H), 2.89 (br., 4 H), 5.45 (t, J = 4.5 Hz, 2 H), 9.73 (t, J = 1.8 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 23 °C): δ = 17.2, 18.7, 21.7, 21.9, 28.5, 28.6, 43.8, 77.8, 80.2, 126.5, 202.8 ppm. HRMS: calcd. for $C_{22}H_{32}O_2$ [M + Na] 351.2300; found 351.2297.

(2*E*,13*Z*,24*E*)-Hexacosa-2,13,24-triene-10,16-diynedial: To a stirred solution of the dialdehyde **15** (568 mg, 1.5 mmol) in benzene (15 mL) was added $Ph_3PCHCHO$ (1.8 g, 6 mmol) under N_2. The reaction mixture was refluxed in an oil bath until complete consumption of the starting material (TLC/^{1}H NMR). This was then

filtered through silica gel, concentrated, then purified by column chromatography to give the dienedialdehyde as an oil (510 mg, 79%): IR: $\tilde{\nu}$ = 1124, 1461, 1690, 2857, 2931 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$, 23 °C): δ = 1.32–1.51 (m, 16 H), 2.12 (t, J = 2.1 Hz, 4 H), 2.32 (dt, J = 7.2, 1.5 Hz, 4 H), 2.89 (br., 4 H), 5.45 (t, J = 4.5 Hz, 2 H), 6.10 (dd, J = 15.6, 7.9 Hz, 2 H), 6.83 (dt, J = 15.6, 6.8 Hz, 2 H), 9.48 (d, J = 7.9 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 23 °C): δ = 17.2, 18.7, 27.7, 28.6, 28.8, 32.6, 43.8, 77.7, 80.2, 126.5, 133.0, 158.8, 194.1 ppm.

(4*E*,15*Z*,26*E*)-Triaconta-4,15,26-triene-1,12,18,29-tetrayne-3,28-diol (1): To a stirred solution of ethynylmagnesium bromide (6.2 mL, 3.06 mmol) in THF (11 mL) at 0 °C under N_2, was added the dienedialdehyde (490 mg, 1.1 mmol). The reaction mixture was stirred at this temperature for 2 h then quenched by the addition of saturated NH_4Cl solution. The aqueous layer was thoroughly extracted using EtOAc. The organics were combined, dried ($MgSO_4$) and purified by column chromatography to afford **1** as a solid (480 mg, 92%); m.p. 33–42 °C: IR: $\tilde{\nu}$ = 736, 970, 1282, 1433, 1661, 2856, 2920, 3298, 3355 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$, 23 °C): δ = 1.28–1.45 (m, 16 H), 2.03 (br., 2 H) 2.05–2.11 (m, 8 H), 2.54 (d, J = 2.1 Hz, 2 H), 2.90 (t, J = 2.4 Hz, 4 H), 4.80 (br., 2 H), 5.45 (t, J = 4.4 Hz, 2 H), 5.58 (dd, J = 15.3, 6.1 Hz, 2 H), 5.88 (dt, J = 14.3, 6.6 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 23 °C): δ = 17.2, 18.7, 28.6, 28.7, 28.8, 28.9, 31.9, 62.8, 74.0, 77.7, 80.4, 83.4, 126.5, 128.5, 134.0 ppm. HRMS: calcd. for $C_{30}H_{40}O_2$ [M + Na] 455.2926; found 455.2914.

Enzymatic Resolution of 1: A flask was charged with lipase AK Amano "20" (960 mg) molecular sieves (960 mg) vinyl acetate (1.6 mL, 17 mmol) hexanes (12 mL) and the racemic diol (480 mg, 1.12 mmol). The mixture was stirred at room temperature for several hours. Reaction progress was monitored by TLC and ^1H NMR spectroscopy. When the amount of the diacetate was about the same as the amount of the diol and half the amount of the monoacetate the reaction was stopped. The reaction mixture was filtered through a pad of silica then purified by column chromatography to give (–)-**1** as a viscous oil (99 mg, 21%). $[\alpha]_D$ = –40.4 (c = 0.04, $CHCl_3$). IR: $\tilde{\nu}$ = 737, 970, 1283, 1433, 1663, 2856, 2930, 3290, 3355 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$, 23 °C): δ = 1.30–1.48 (m, 16 H), 1.85 (br., 2 H) 2.04 (t, J = 7.1 Hz, 4 H) 2.11–2.12 (m, 4 H), 2.54 (d, J = 2.4 Hz, 2 H), 2.90 (br., 4 H), 4.81 (t, J = 5.1 Hz, 2 H), 5.46 (t, J = 4.7 Hz, 2 H), 5.61 (dd, J = 15.2, 6.4 Hz, 2 H), 5.87 (dt, J = 15.1, 6.7 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 23 °C): δ = 17.2, 18.7, 28.6, 28.7, 28.8, 28.9, 31.8, 62.7, 73.9, 77.7, 80.4, 83.3, 126.5, 128.4, 134.4 ppm. HRMS: calcd. for $C_{30}H_{40}O_2$ [M + Na] 455.2926; found 455.2914.

The monoacetate **17** was obtained as an oil (248 mg, 46%). $[\alpha]_D$ = +12.4 (c = 0.12, $CHCl_3$). IR: $\tilde{\nu}$ = 732, 911, 1015, 1228, 1370, 1739, 2856, 2930, 3291, 3449 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$, 23 °C): δ = 1.27–1.48 (m, 16 H), 2.04–2.08 (m, 4 H), 2.10 (s, 3 H), 2.11–2.12 (m, 4 H), 2.54 (d, J = 2.1 Hz, 2 H), 2.89 (br., 4 H), 4.81 (br. d, J = 5.1 Hz, 2 H), 5.45 (t, J = 4.5 Hz, 2 H), 5.51 (dd, J = 15.3, 6.5 Hz, 1 H), 5.57 (dd, J = 15.1, 6.1 Hz, 1 H), 5.79 (d, J = 6.3 Hz, 1 H) 5.87 (dt, J = 15.3, 6.1 Hz, 2 H), 5.97 (dt, J = 15.3, 6.5 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 23 °C): δ = 17.2, 18.7, 21.0, 24.8, 28.5, 28.6, 28.7, 28.9, 31.8, 31.9, 34.5, 62.7, 63.7, 64.1, 72.8, 73.9, 74.7, 77.7, 79.8, 80.4, 124.4, 126.5, 128.4, 134.4,137.0, 169.7 ppm. HRMS: calcd. for $C_{32}H_{42}O_3$ [M + Na] 497.3032; found 497.3025.

The diacetate **16** was obtained as an oil (92 mg, 20%). $[\alpha]_D$ = +22.9 (c = 0.04, $CHCl_3$): IR: $\tilde{\nu}$ = 969, 1015, 1228, 1370, 1433, 1741, 2857, 2931, 3290 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$, 23 °C): δ = 1.29–1.45 (m, 16 H), 2.04–2.07 (m, 4 H), 2.10 (s, 6 H), 2.11 (t, J = 4.6 Hz, 4 H), 2.54 (d, J = 2.1 Hz, 2 H), 2.90 (br., 4 H), 5.45 (t, J = 4.5 Hz, 2 H), 5.51 (dd, J = 15.2, 6.4 Hz, 2 H), 5.80 (d, J = 6.0 Hz, 2 H), 5.98 (dt, J = 15.3, 6.5 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 23 °C): δ = 18.7, 20.9, 24.0, 28.6, 28.7, 28.9, 31.8, 34.5, 64.1, 74.7, 77.7, 79.9, 80.4, 124.4, 126.5, 137.0, 169.7 ppm. HRMS: calcd. for $C_{34}H_{44}O_4$ [M + Na] 539.3137; found 539.3115.

(3*S*,4*E*,15*Z*,26*E*,28*S*)-Triaconta-4,15,26-triene-1,12,18,29-tetrayne-3,28-diol (+)-1: The diacetate (60 mg, 0.11 mmol) and K_2CO_3 (6 mg, 0.04 mmol) were dissolved in MeOH (2 mL) with stirring under N_2. The reaction was allowed to proceed at room temperature for several hours until the complete consumption of the starting material, the reaction mixture was then quenched using 1 N HCl and the organic layer was extracted with EtOAc. Purification was effected using column chromatography to give (+)-**1** as a viscous oil (45 mg, 96%). $[\alpha]_D$ = +41.3 (c = 0.03, $CHCl_3$): IR: $\tilde{\nu}$ = 736, 970, 1283, 1433, 1663, 2856, 2930, 3290, 3355 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$, 23 °C): δ = 1.30–1.48 (m, 16 H), 1.85 (br., 2 H) 2.06 (t, J = 6.4 Hz, 4 H) 2.12 (t, J = 2.3 Hz, 4 H), 2.54 (d, J = 2.1 Hz, 2 H), 2.90 (br., 4 H), 4.81 (t, J = 5.1 Hz, 2 H), 5.46 (t, J = 4.5 Hz, 2 H), 5.61 (dd, J = 15.2, 6.4 Hz, 2 H), 5.87 (dt, J = 15.1, 6.7 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 23 °C): δ = 17.2, 18.7, 28.6, 28.7, 28.8, 28.9, 31.8, 62.7, 73.9, 77.7, 80.4, 83.3, 126.5, 128.4, 134.4 ppm. HRMS: calcd. for $C_{30}H_{40}O_2$ [M + Na] 455.2926; found 455.2914.

Supporting Information (see also the footnote on the first page of this article): ^1H and ^{13}C NMR, and HRMS spectra for compounds **1**, **9**, **11**, **13**–**17**.

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