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Syntheses of Two Enantiomers of Eicos-(4E)-en-1-yn-3-ol, a Bioactive Component of the Marine Sponge *Cribrochalina vasculum*

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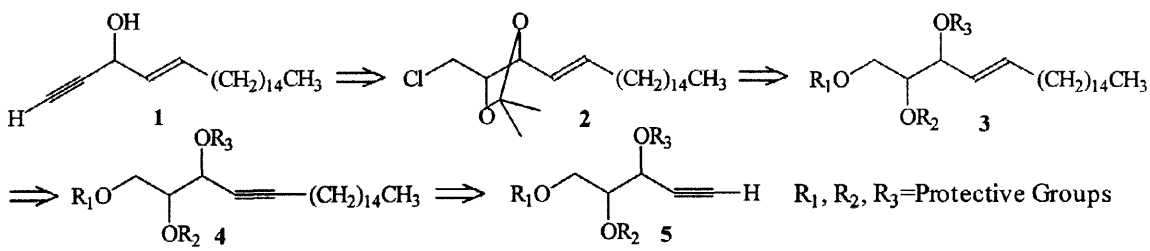
Abstract: Two enantiomers of eicos-(4E)-en-1-yn-3-ol (**1**), a bioactive component of the marine sponge *Cribrochalina vasculum*, were prepared using sugars as chiral pool starting materials.

Several classes of non-cyclic acetylenic compounds have been isolated from terrestrial plants as well as from marine organisms. The acetylenic compounds exhibit many biological activities, but they have not received much attention from a synthetic point of view. Recently, some acetylenic alcohols possessing a characteristic 4-en-1-yn-3-ol skeleton have been isolated from marine sponge *Cribrochalina vasculum* and exibit *in vitro* immunosuppressive and antitumor activities.[1,2,3] Aiello *et al.* assigned the configuration at C-3 of these acetylenic alcohols as *R* using the CD spectra of the corresponding *p*-bromobenzoate derivatives,[2] and Guo *et al.* also confirmed this stereochemical assignment *via* Mosher ester NMR method.[4] However, Hallock *et al.* recently determined the configuration at C-3 of these acetylenic alcohols as *S* using the Mosher's methods. They also reported that these types of acetylenic alcohols were scalemic mixtures, and the 3*S* enantiomer was the major constituent.[3] Eicos-(4E)-en-1-yn-3-ol (**1**) is typical of these compounds. It was reported that compound **1** exhibited cytotoxic activity in the NCI's 60 cell lines human tumor screens, especially a non-small lung cancer cell line (H-522) and an ovarian cell line (IGROV-1).[3] To our knowledge, there is only a racemic synthesis of compound **1** has been reported by Mamdapur *et al.*[5] In order to discover the correlation between the absolute configuration and the bioactivities, we developed an enantioselective synthesis of compound **1**. In this paper, we report syntheses of the two enantiomers of compound **1**, using sugars as chiral pool starting materials, and the 3*S* enantiomer should be the major constituent in the natural product.



Scheme 1

Our synthetic strategy is outlined in Scheme **1**. This route involves a double elimination[6,7] of the β-alkyloxy chloride **2**, the *trans* olefinic bond is obtained through the stereocontrolled reduction of the triple bond, and the stereochemistry of C-3 is afforded using sugars as chiral pool starting materials.

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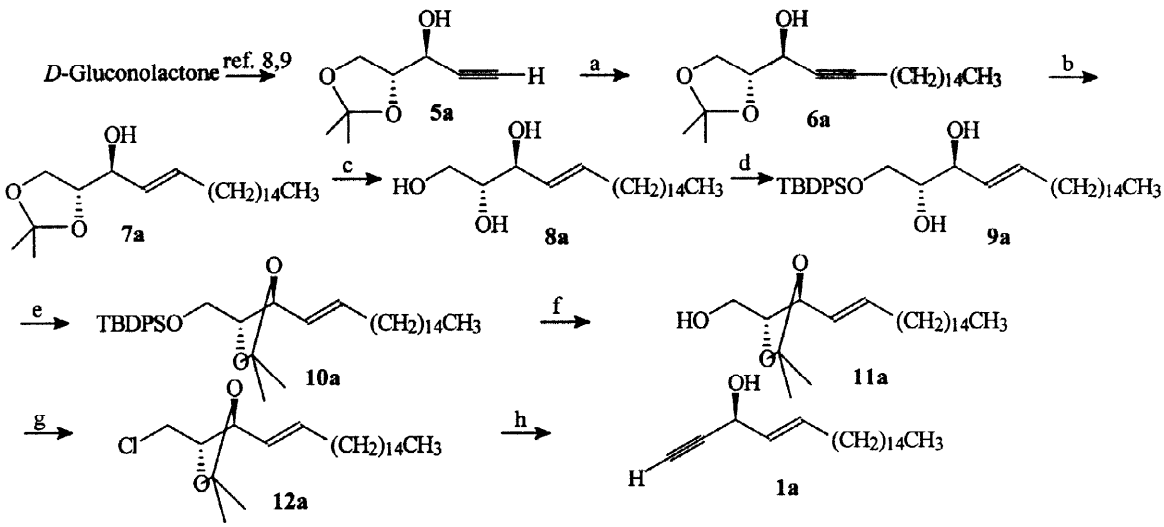
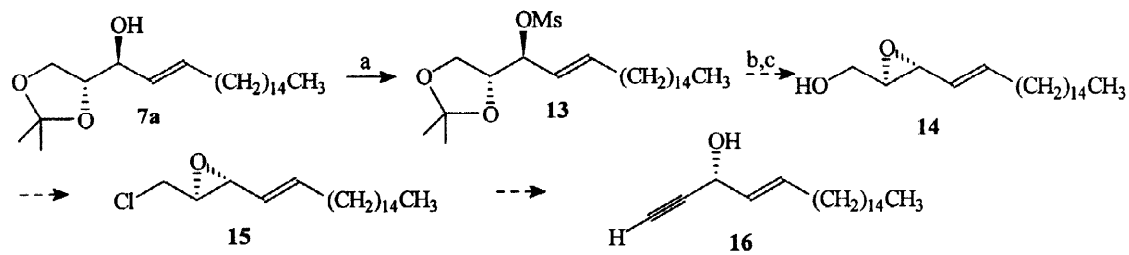
For the synthesis of (*S*)-eicos-(4E)-en-1-yn-3-ol **1a**, alkyne alcohol **5a** was prepared from *D*-gluconolactone according to a known procedure.[8,9] It was then alkylated at its terminal with 1-bromopentadecane to afford compound **6a** in 84% yield. Reduction of the triple bond by $LiAlH_4$ in THF gave the *trans* olefinic bond in compound **7a** in high yield. Deprotection of **7a** produced the triol **8a**, selective protection of the primary hydroxyl group with TBDPS, followed by treatment with 2,2-dimethoxypropane (DMOP) in the presence of camphorsulfonic acid (CSA), furnished the compond **10a**. Removal of the silyl group with *n*-Bu_4NF afforded the primary alcohol **11a**, which was subjected to subsequent chlorination by PPh_3/CCl_4 to yield chloride **12a**. Finally, double elimination[6,7] of **12a** with LDA gave the desired (*S*)-eicos-(4E)-en-1-yn-3-ol (**1a**) (Scheme 2).



Reagents and conditions: a) n-BuLi (2eq), *n*-$C_{15}H_{31}Br$, THF-HMPA, -20-0°C, 84%; b) $LiAlH_4$, THF, reflux, 93%; c) *p*-TsOH, MeOH, rt; d) TBDPSCl, imidazole, DMF, rt; e) 2,2-dimethoxypropane, CSA, CH_2Cl_2, rt, 82% in three steps; f) Bu_4NF, THF, rt, 97%; g) PPh_3, CCl_4, reflux, 87%; h) LDA (5eq), THF, -78°C, 65%.

Scheme 2

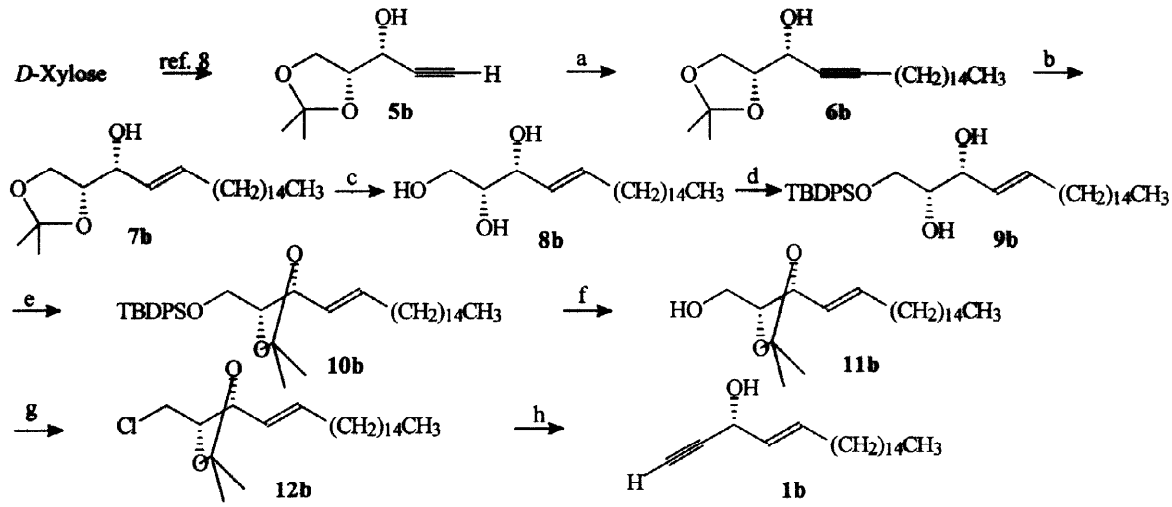
With compound **7a** in hand, we tried to invert the C-3 configuration of it to prepare the (*R*)-eicos-(4E)-1 yn-3-ol (**1b**) as showed in Scheme 3. Unfortunately, mesylation of **7a** gave a poor yield, and hydrolysis of the terminal iospropylidine acetal and subsequent treatment with K_2CO_3 failed to give any desired product.



Reagents and conditions: a) MsCl, pyridine, rt, 40%; b) TsOH, MeOH; c) K_2CO_3, MeOH, no product.

Scheme 3

For the synthesis of **1b**, alkyne alcohol **5b** was prepared from *D*-xylose,[8] and using the same synthetic process as the preparation of **1a**, (*R*)-eicos-(4E)-en-1-yn-3-ol (**1b**) was obtained (Scheme 4).



Reagents and conditions: the same as in **scheme 2.**

Scheme 4

The optical rotation was found to be +19.5 (*c*, 1.12, MeOH) for **1a** and -21.8 (c, 2.20, MeOH) for **1b**, respectively. Gunasekera *et al.* firstly reported the rotation value of naturally occurring **1** was +3.8 (*c*, 0.9, MeOH),[1] and laterly, Hallock *et al.* reported their sample's optical rotation was +18.3 (*c*, 0.37, MeOH).[3] Comparison of their values with those of **1a** and **1b** confirmed that Gunasekera's sample was a scalemic mixture, and Hallock's sample might be optically pure, and that the 3*S* enantiomer was the major constituent of the natural product.

EXPERIMENTAL

All melting points (Mp) are uncorrected. Optical rotations were measured with a Perkin-Elmer 241MS Autopol polarimeter. IR spectra were taken with Perkin-Elmer 598B or Nicolt Magan 750 infrared spectrometer. NMR spectra were recorded with Gemini-300 spectrometer. MS spectra were obtained on MAT-711, MAT-95, MAT-8430 and HT5989 instruments. Flash colum chromatography was performed on silica gel H(10-40um) and with petroleum ether-ethyl acetate system as eluent.

(2*R*, 3*S*)-1, 2-Isopropylidenedioxyeicos-4-yn-3-ol (6a) Under nitrogen atomosphere, a solution of *n*-butyllithium (1.6M in hexane, 6.6mL, 10.6mmol) was added to a THF soultion (30mL) of alkyne alcohol **5a** (825mg, 5.29mmol) at -20°C, and the mixture was stirred for 30 min. Then a HMPA solution (8mL) of *n*-bromopentadecane (1.54g, 5.3mmol) was added to the solution, and the mixture was warmed to 0°C and stirred for 3 h. Then the reaction was quenched by adding aqueous NH_4Cl (20mL), the aqueous solution was extracted with ether (20mL×3). The organic layer was washed with brine (40mL), and dried over $MgSO_4$. After removal of the solvent, compound **6a** (1.63g, 84%) was obtained by silica gel column chromatography (petroleum ether/ ethyl acetate, 10:1 v/v) as a white waxy solid. Mp: 39-40.5°C. $[\alpha]_D$ +20.3 (*c*, 1.10, $CHCl_3$), IR(KBr): 3348, 2920, 2855, 2231, 1471, 1367, 1070, 852. 717 cm^{-1}. ^{1}HNMR($CDCl_3$): 0.88 (3H, t, *J*=6.8Hz), 1.20-1.50 (26H, m), 1.38 (3H, s), 1.46 (3H, s), 2.20 (2H, dt, *J*=2.0, 7.0Hz), 4.05 (2H, m), 4.20 (1H, m), 4.48 (1H, m). EIMS(m/z): 366(M^+), 351(M^+-CH_3). HREIMS(m/z): (M^+-CH_3) cacld. for $C_{22}H_{39}O_3$, 351.2899; found: 351.2877.

(2*R*, 3*R*)-1, 2-Isopropylidenedioxyeicos-4-yn-3-ol (6b) By the same procedure for **6a** from **5a**, **5b** was converted into **6b** (81%) as a colorless oil. $[\alpha]_D$ +8.6 (*c*, 0.3, $CHCl_3$). IR(film): 3444, 2924, 2853, 2230, 1458, 1371, 1073, 856, 721 cm^{-1}. ^{1}HNMR($CDCl_3$): 0.88 (3H, t, *J*=6.8Hz), 1.20-1.50 (26H, m), 1.38 (3H, s), 1.44 (3H. s), 2.19 (2H, dt, *J*=1.9, 6.9Hz), 3.87 (1H, dd, *J*=5.0, 8.0Hz), 4.10 (2H, m), 4.39 (1H, dt, *J*=1.9, 6.9Hz). EIMS(m/z): 366(M^+), 351(M^+-CH_3). HREIMS(m/z): (M^+-CH_3) cacld. for $C_{22}H_{39}O_3$: 351.2899; found: 351.2903.

(2*R*, 3*S*)- 1, 2-Isopropylidenedioxyeicos-4(E)-en-3-ol (7a) To a suspension of $LiAlH_4$ (0.4g, 10.54mmol) in THF (10mL) was added a solution of compound **6a** (1.98g, 5.41mmol) in THF (10mL) at 0°C. After being stirred at 0°C for 1 h, the reaction mixture was stirred under reflux for 6 h, and the excess $LiAlH_4$ was hydrolyzed by dropwise addition of H_2O. The mixture was filtered and the white precipitate was washed with ether. The combined filtrates were dried over $MgSO_4$ and concentrated in vacuum. Silica gel column chromatography (petroleum ether/ ethyl acetate, 10:1 v/v) of the residue gave compound **7a** (1.85g, 93%) as a white solid. Mp: 40-41°C. $[\alpha]_D$ +13.8 (*c*, 1.20, $CHCl_3$). IR(KBr): 3392, 2920, 2850, 1471, 1367, 1211, 1070, 854, 717 cm^{-1}. ^{1}HNMR($CDCl_3$): 0.88 (3H, t, *J*=6.8Hz), 1.18-1.60 (26H, m), 1.38 (3H, s), 1.47 (3H, s), 2.05 (2H, m), 3.90 (2H, m), 4.10 (1H, m), 4.26 (1H, m), 5.38 (1H, ddt, *J*=1.4, 15.5, 6.5Hz), 5.78 (1H, m). EIMS(m/z): 368(M^+), 353(M^+-CH_3), 325, 267, 101. Anal. cacld. for $C_{23}H_{44}O_3$: C, 74.95; H, 12.03, found: C, 75.04, H, 12.05

(2*R*, 3*R*)- 1, 2-Isopropylidenedioxyeicos-4(E)-en-3-ol (7b) By the same procedure for **7a** from **6a**, **6b** was converted into **7b** (96%) as a white solid. $[\alpha]_D$ -2.19 (*c*, 0.4, $CHCl_3$). IR(Film): 3398, 2910, 2860, 1664, 1467, 1371, 1228, 1072, 852, 721 cm^{-1}. ^{1}HNMR($CDCl_3$): 0.88 (3H, t, *J*=6.8Hz), 1.20-1.50 (26H, m), 1.38 (3H, s), 1.46 (3H, s), 2.05 (2H, m), 3.72 (1H, m), 4.00 (3H, m), 5.39 (1H, ddt, *J*=1.3, 15.4, 8.0Hz), 5.80 (1H, m). EIMS(m/z): 368(M^+), 351(M^+-CH_3), 325, 267, 101. Anal. cacld. for $C_{23}H_{44}O_3$: C, 74.95; H, 12.03, found: C, 74.54; H, 11.89.

(2*R*, 3*S*)-1-*tert*-Butyldiphenylsilyloxyeicos-4(E)-en-2, 3-diol (10a) Compound **7a** (430mg, 1.17mmol) was dissolved in MeOH (15mL) and *p*-TsOH (100mg) was added to the solution. After being stirred at room temperature for 12 h, the mixture was extracted with EtOAc. The extract was dried and concentrated to give the crude triol **8a** as a white solid.

The crude triol **8a** was then dissolved in DMF (10mL), imidazole (200mg, 2.93mmol) and *t*-butyldiphenyl chlorosilane (322mg, 1.17mmol) were added to the solution. After the mixture had been stirred for 10 h, it was diluted with CH_2Cl_2 (25mL) and washed with H_2O (20mL) and brine (20mL). The organic extracts were dried over $MgSO_4$ and concentrated to give the crude silyl ether **9a** as a colorless oil which was used in next step without purification.

To a solution of the above silyl ether and 2,2-dimethoxypropane (0.5mL) in CH_2Cl_2 (10mL) was added camphorsulfonic acid (15mg) at room temperature. After the mixture had been stirred for 10 h, it was diluted with ether (30mL) and washed with 10% aqueous $NaHCO_3$ (20mL)and brine (20mL). After drying ($MgSO_4$) and removal of the solvent, compound **10a** (580mg, 82%) was obtained by silica gel column chromatography (petroleum ether/ ethyl acetate, 100:1 v/v) as a colorless oil. $[\alpha]_D$ +6.7 (*c*, 2.35, $CHCl_3$). IR(film) 2920, 2860, 1464. 1429, 1387, 1215, 1113, 702 cm^{-1}. ^{1}HNMR($CDCl_3$): 0.88 (3H, t, *J*=6.8Hz), 1.05 (9H, s), 1.18-1.50 (26H, m), 1.36 (3H, s), 1.43 (3H, s), 2.03 (2H, m), 3.62 (1H, dd, *J*=5.1, 10.6Hz), 3.71 (1H, dd, *J*=6.4, 10.6Hz), 4.21 (1H, m), 4.62 (1H, dd, *J*=6.2, 7.7Hz), 5.56 (1H, ddt, *J*=1.3, 15.3, 8.0Hz), 5.77 (1H, m), 7.39, 7.68 (10H, Ar-H). EIMS(m/z): 591(M^+-CH_3), 491(M^+-$C(CH_3)_3$), 199. HREIMS(m/z) (M^+-CH_3) calcd. for $C_{38}H_{59}SiO_3$ 591.4233; Found: 591.4216.

(2*R*, 3*R*)-1-*tert*-Butyldiphenylsilyloxyeicos-4(E)-en-2, 3-diol (10b) By the same procedure for **10a** from **7a**, **7b** was converted into **10b** (84%) as a colorless oil. $[\alpha]_D$ +3.52 (*c*, 2.30, $CHCl_3$). IR(film) 2920, 2860, 1464. 1429, 1387,

1215, 1113, 702 cm^{-1}. ^{1}HNMR($CDCl_3$): 0.88 (3H, t, *J*=6.8Hz), 1.05 (9H, s), 1.20-1.50 (26H, m), 1.43 (6H, s), 2.02 (2H, m), 3.80 (3H, m), 4.40 (1H, t, *J*=7.7Hz), 5.40 (1H, ddt, *J*=1.3, 15.4, 8.0Hz), 5.75 (1H, m), 7.39, 7.66 (10H, Ar-H). EIMS(m/z): 591(M^+-CH_3), 491(M^+-$C(CH_3)_3$), 199. HREIMS(m/z) (M^+-CH_3) calcd. for $C_{38}H_{59}SiO_3$ 591.4233; Found: 591.4243.

(2*R*, 3*S*)- 2, 3-Isopropylidenedioxyeicos-4(E)-en-1-ol (11a) To an ice-cooled solution of **10a** (672mg, 1.07mmol) in THF (10mL) was added Bu_4NF (1.0M in THF, 2.1mL, 2.1mmol). The mixture was allowed to warm to room temperature and then stirred for a further 10 h. After completion of the reaction, the mixture was quenched by adding aqueous NH_4Cl (10mL), and extracted with ether (20mL×3). The organic layer was washed with H_2O (20mL) and brine (20mL), dried over $MgSO_4$ and concentrated to afford the crude **11a**, which was chromatographed over silica gel (petroleum ether/ ethyl acetate, 10:1 v/v) to give the pure alcohol **11a** (392mg, 97%) as a white wax. $[\alpha]_D$ +27.5 (*c*, 1.30, $CHCl_3$). IR(film): 3392, 2910, 2840, 1471, 1209, 1055, 976, 860, 719 cm^{-1}. ^{1}HNMR($CDCl_3$): 0.88 (3H, t, *J*=6.8Hz), 1.12-1.50 (26H, m), 1.46 (3H, s), 1.49 (3H, s), 2.05 (2H, m), 3.57 (2H, d, *J*=5.6Hz), 4.20 (1H, dd, *J*= 5.6, 7.3Hz), 4.61 (1H, t, *J*=7.5Hz), 5.48 (1H, ddt, *J*=1.4, 15.4, 8.2Hz), 5.82 (1H, m). EIMS(m/z): 368(M^+), 353(M^+-CH_3), 293, 267, 97. Anal. cacld. for $C_{23}H_{44}O_3$: C, 74.95; H, 12.03, Found: C, 75.21; H, 12.42.

(2*R*, 3*S*)- 2, 3-Isopropylidenedioxyeicos-4E-en-1-ol (11b) By the same procedure for **11a** from **10a**, **10b** was converted into **11b** (97%) as a white wax. $[\alpha]_D$ +6.9 (*c*, 1.0, $CHCl_3$). IR(film): 3394, 2920, 2860, 1463, 1371, 1224, 1045, 966, 865 cm^{-1}. ^{1}HNMR($CDCl_3$): 0.88 (3H, t, *J*=6.8Hz), 1.14-1.50 (26H, m), 1.41 (3H, s), 1.42 (3H, s), 2.05 (2H, m), 3.57 (1H, dd, *J*=3.8, 11.9Hz), 3.77 (2H, m), 4.26 (1H, t, *J*= 8.2Hz), 5.42 (1H, ddt, *J*=1.4, 15.3, 8.0Hz), 5.82 (1H, m). EIMS(m/z): 368(M^+), 353(M^+-CH_3), 293, 267, 97. Anal. cacld. for $C_{23}H_{44}O_3$: C, 74.95; H, 12.03, Found: C, 75.25; H, 12.33

(2*S*, 3*S*)-1-Chloro-2, 3-isopropylidenedioxyeicos-4(E)-ene (12a) To a solution of alcohol **11a** (297mg, 0.807mmol) in CCl_4 (15mL) was added PPh_3 (433mg, 1.62mmol). The mixture was stirred under reflux for 48 h. After being cooled to room temperature, the white precipitate was filtered off, washed with ether (50mL), and the filtrate was concentrated, the residue was chromatographed on silica gel (petroleum ether/ ethyl acetate, 50:1 v/v) to give chloride **12a** (270mg, 87%) as a colorless oil. $[\alpha]_D$ +14.5 (*c*, 1.35, $CHCl_3$). IR(film) 2930, 2840, 1670, 1465, 1380, 1217, 055, 89, 717 cm^{-1}. ^{1}HNMR($CDCl_3$): 0.88 (3H, t, *J*=6.8Hz), 1.14-1.50 (26H, m), 1.37 (3H, s), 1.49 (3H, s), 2.06 (2H, m), 3.47 (2H, m), 4.30 (1H, dd, *J*=6.2, 2.3Hz), 4.62 (1H, m), 5.44 (1H, ddt, *J*=1.4, 15.3, 8.1Hz), 5.82 (1H, m), . EIMS(m/z): 386(M^+), 371(M^+- CH_3), 308. Anal. cacld. for $C_{23}H_{43}ClO_2$: C, 71.37; H, 11.20, Found: C, 71.18; H, 11.38.

(2*S*, 3*R*)-1-Chloro-2, 3-isopropylidenedioxyeicos-4(E)-ene (12b) By the same procedure for **12a** from **11a**, **11b** was converted into **12b** (91%) as a colorless oil. $[\alpha]_D$ +6.2 (*c*, 1.40, $CHCl_3$). IR(film) 2920, 2840, 1672, 1466, 1379, 1240, 1063, 899, 750 cm^{-1}. ^{1}HNMR($CDCl_3$): 0.88 (3H, , *J*=6.8Hz), 1.20-1.50 (26H, m), 1.44 (6H, s), 2.10 (2H, m), 3.58 (1H, dd, *J*=5.2, 11.8Hz), 3.67 (1H, dd, *J*=4.0, 11.8Hz), 3.92 (1H, m), 4.37 (1H, t, *J*=8.0Hz), 5.46 (1H, ddt, *J*=1.4, 15.3, 8.0Hz), 5.85 (1H, m). EIMS(m/z): 386(M^+), 371(M^+-CH_3), 308. HREIMS(m/z) (M^+-CH_3) calcd. for $C_{22}H_{40}ClO_2$ 371.2717; Found: 371.2698.

3(*S*)-Hydroxyeicos-4(E)-en-1-yne (1a) Under nitrogen atomosphere, a solution of *n*-butyllithium (1.6M in hexane, 1.8mL, 2.88mmol) was added to a THF solution (4mL) of diisopropylamine (0.44ml, 3.14mmol) at -78°C, and the mixture was stirred for 30 min to form the LDA solution. Then a THF solution (4mL) of chloride **12a** (220mg, 0.57mmol) was added at -78°C and after stirring for 3 h, the reaction was quenched by adding aqueous NH_4Cl (5mL). The aqueous solution was extracted with ether (5mL×3), and the organic layer was washed with brine (10mL) and

dried over $MgSO_4$. After removal of the solvent, 3(*S*)-hydroxyeicos-4(E)-en-1-yne (**1a**) (108mg, 65%) was obtained by silica gel column chromatography (petroleum ether/ ethyl acetate, 10:1 v/v) as a white solid. Mp. 49-50°C. $[\alpha]_D$ +19.5 (*c*, 1.12, MeOH). IR(KBr) 3280, 2930, 2840, 2116, 1670, 1462, 1014 cm^{-1}. ^{1}HNMR($CDCl_3$): 0.88 (3H, t, *J*=6.8Hz), 1.13-1.50 (26H, m), 2.05 (2H, m), 2.53 (1H, d, *J*=2.1Hz), 4.82 (1H, m), 5.60 (1H, ddt, *J*=1.3, 15.2, 6.1Hz), 5.90 (1H, m) . ^{13}CNMR ($CDCl_3$, 75MHz): 14.3, 22.9, 29.0, 29.6, 29.7, 29.8, 29.9 (8C), 32.1, 63.0, 74.1, 83.4, 128.6, 134.8. EIMS(m/z): 291(M^+-1), 263, 249. Anal. cacld. for $C_{20}H_{36}O$: C, 82.13; H, 12.40, Found: C, 82.44; H, 12.84.

3(*R*)-Hydroxyeicos-4(E)-en-1-yne (1b) By the same procedure for **1a** from **12a**, **12b** was converted into **1b** (60%) as a white solid. Mp. 49-50°C. $[\alpha]_D$ -21.8 (*c*, 2.18, MeOH). The data of IR, ^{1}H NMR, ^{13}C NMR and EIMS were the same as for **1a**, Anal. cacld. for $C_{20}H_{36}O$: C, 82.13; H, 12.40, Found: C, 81.99; H, 12.44.

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