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Total synthesis of panaxydol and its stereoisomers as potential anticancer agents

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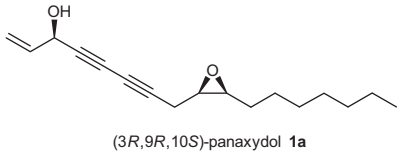
ABSTRACT

An efficient total synthesis of natural panaxydol **1a** and its seven stereoisomers **1b–h** was accomplished; four diastereomers of the natural form were prepared for the first time. Our strategy involves the Cadiot-Chodkiewicz cross-coupling reaction of chiral terminal alkynes with bromoalkynes, the asymmetric alkynylation of aldehydes, and the enantioselective Sharpless epoxidation of allylic alcohols. Preliminary in vitro cytotoxicity evaluation indicated that some synthetic panaxydols possess anticancer activities, and (3*S*,9*R*,10*S*)-panaxydol **1e** showed a particularly promising cytotoxic effect.

1. Introduction

As one of the most important traditional Asian medicines, red ginseng, the root of *Panax ginseng* C. A. Meyer, is commonly used for the treatment of cardiovascular disease, diabetes, and various cancers.[1] Panaxydol **1a** (Fig. 1) is an important chiral polyacetylenic alcohol isolated from red ginseng,[2] which has been proven to possess significant antitumor activities.[3–5] For instance, panaxydol showed cytotoxicity against various cancer cells, such as human breast cancer (MCF-7)[4] and human melanoma (SK-MEL-1).[5]



(3*R*,9*R*,10*S*)-panaxydol **1a**

Figure 1. The structure of natural Panaxydol **1a**.

Since the isolation of panaxydol **1a** from red ginseng and the confirmation of its structure and absolute configuration,[6,7] its total synthesis has attracted much attention and interest from chemists. In 1998, Cai et al. achieved the first total synthesis of (3*R*,9*R*,10*R*)-panaxydol **1a** from chiral (+)-diethyl tartrate.[8] To date, the main synthetic strategies to **1a** include derivation from a chiral template[8,9] and Sharpless asymmetric dihydroxylation.[10]

Considering the important bioactivity of natural panaxydol and the potential antitumor activities of its stereoisomers, we decided to search for more efficient and convenient asymmetric synthetic strategies. The enantioselective alkynylation of aldehydes is the most convenient protocol to obtain chiral propargyl alcohols.[11,12] However to the best of our knowledge, there are no reports which synthesize these polyacetylenic alcohols using this asymmetric catalytic methodology. Herein, we report an efficient total synthesis of natural panaxydol and its seven stereoisomers via enantioselective alkynylation of aldehydes; four diastereomers of the natural form were prepared for the first time. Furthermore, their preliminary antitumor activity was also investigated.

2. Results and discussion

Our retrosynthetic analysis of (3*R*,9*R*,10*R*)-panaxydol **1a** is outlined in Figure 2. The chiral polyacetylenic alcohol **1a** could be formed by the Cadiot-Chodkiewicz coupling reaction of terminal alkyne **13a** with bromoalkyne **7a**. We envisaged that the chiral propargyl alcohol moiety of fragment **7a** could be introduced via the enantioselective addition of trimethylsilylacetylene to acrolein **3**. Correspondingly, the Sharpless asymmetric epoxidation of **10a** was expected to give chiral epoxy alcohol **11a**, whose triflate was envisioned to generate the key intermediate **13a**.

Our study began with the preparation of chiral bromoalkynes **7** (Scheme 1). The enantioselective addition reaction of alkynylzinc

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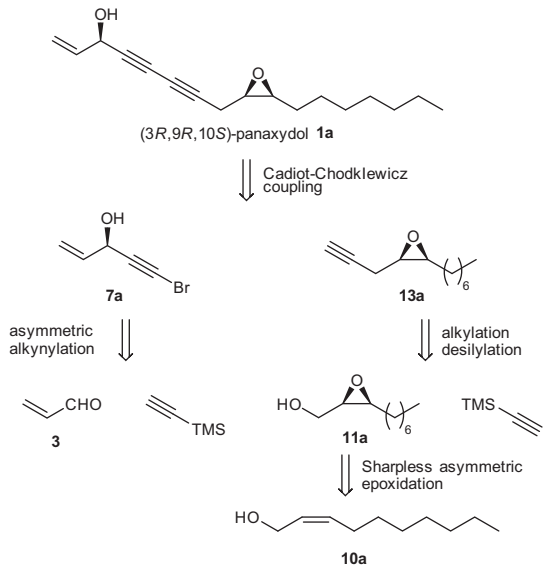
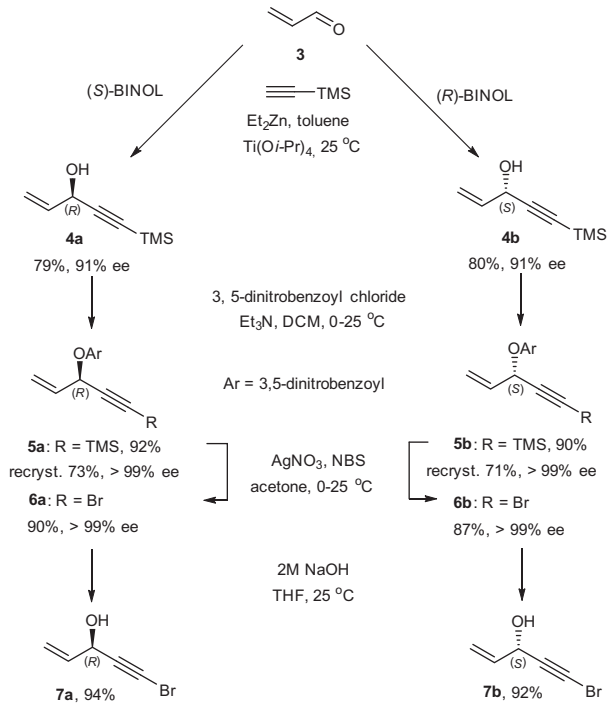


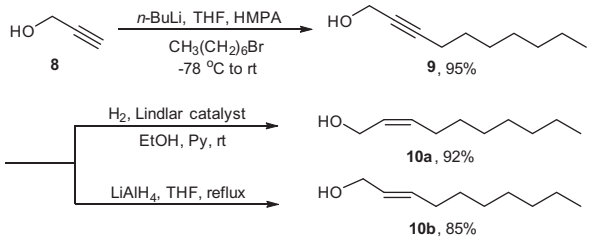
Figure 2. Retrosynthetic analysis of (3*R*,9*R*,10*S*)-panaxydol **1a**.



Scheme 1. Enantioselective synthesis of bromoalkynes **7a** and **7b**.

reagent, which was prepared in situ from trimethylsilylacetylene and diethylzinc, to acrolein **3** catalyzed by (*S*)-BINOL/Ti(O^{i}Pr)$_4$ generated (*R*)-5-(trimethylsilyl)pent-1-en-4-yn-3-ol **4a** in 79% yield and with 91% ee.[11a] The specific rotation of **4a**[13] and the governing precedents in the enantioselective alkynylation of acroleins[11a] also favored its absolute (*R*)-configuration. Our previous study[14] demonstrated that recrystallization of the benzoate derived from the chiral alcohol could improve the enantiomeric purity. 3,5-Dinitrobenzoate **5a** was prepared from alcohol **4a** and recrystallized from *n*-hexane–dichloromethane. The enantiomeric purity of **5a** was improved from 91% to over 99%. Subsequent in situ desilylation and bromination of alkyne **5a** using NBS and $AgNO_3$ afforded optically active **6a** in 90% yield.[13] Finally, treating **6a** with 2 M sodium hydroxide in tetrahydrofuran resulted in the formation of bromoalkyne **7a** in 94% yield.[15] A similar procedure for the synthesis of **7b** was developed from the enantioselective alkynylation of acrolein **3** with (*R*)-BINOL/Ti(O^{i}Pr)$_4$ catalyst.

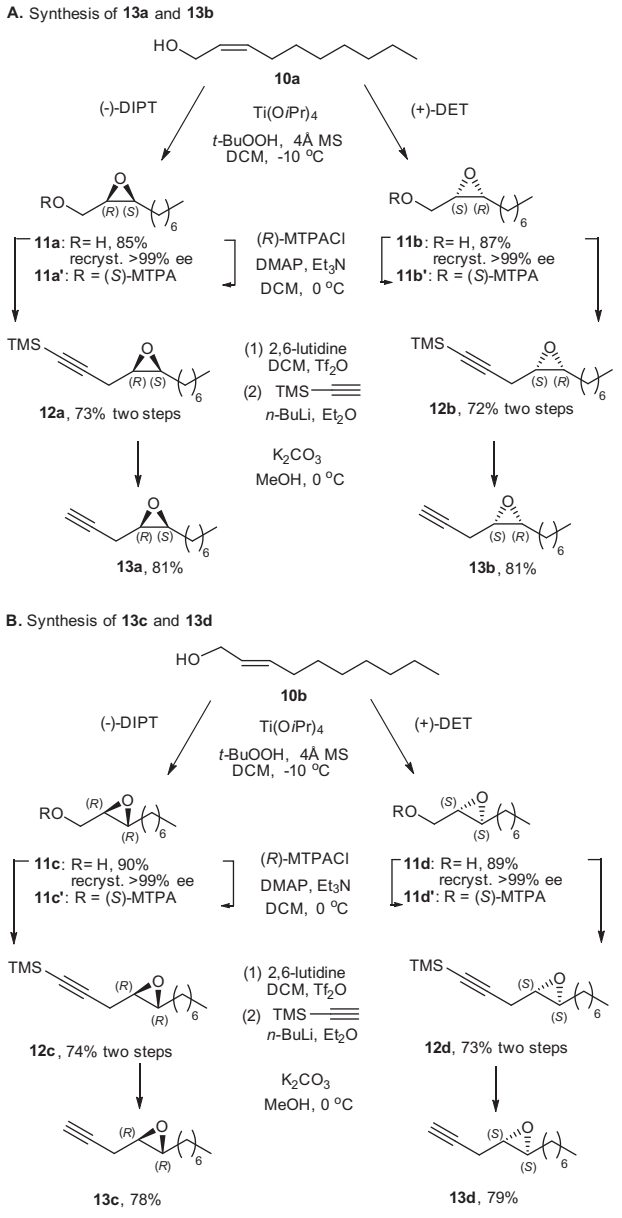
Next, the key intermediate allylic alcohols **10a** and **10b** were prepared (Scheme 2). The alkylation of commercially available propargyl alcohol **8** with 1-bromoheptane gave dec-2-yn-1-ol **9** in 95% yield.[16] Propargyl alcohol **9** was hydrogenated with Lindlar catalyst to form (*Z*)-dec-2-en-1-ol **10a** in 92% yield.[17] By contrast, reduction of **9** with $LiAlH_4$ afforded (*E*)-2-decen-1-ol **10b** in 85% yield.[18]



Scheme 2. Synthesis of allylic alcohols **10a** and **10b**.

As with allylic alcohols **10a** and **10b,** the preparation of chiral epoxy alkynes **13a–d** was studied (Scheme 3). Sharpless asymmetric epoxidation with (−)-diisopropyl tartrate and Ti(O^{i}Pr)$_4$ converted *cis*-allylic alcohol **10a** into (2*R*,3*S*)-2,3-epoxy-1-decanol **11a** in 85% yield.[19a] Recrystallization of **11a** from petroleum ether improved the ee to over 99%, which was determined by ^{1}H NMR analysis of Mosher ester **11a**′ derived from **11a** and (*R*)-(−)-MTPACl. Analysis of the terminal methylene proton region of Mosher ester **11a**′ indicated that there was no diastereomeric (*S*)-MTPA ester of **11b** (Fig. 3).[19b] The comparison with reported specific rotation value and the governing precedents in the Sharpless asymmetric epoxidation of allylic alcohols **10a**[19a] both supported the (2*R*,3*S*)-configuration of **11a**. Similarly, optically active epoxy alcohol (2*S*,3*R*)-**11b** was obtained when (+)-diethyl tartrate was used. On the other hand, chiral epoxy alcohols (2*R*,3*R*)-**11c** and (2*S*,3*S*)-**11d** were synthesized from the enantioselective epoxidation of *trans*-allylic alcohol **10b** with (−)-diisopropyl tartrate/Ti(O^{i}Pr)$_4$ and (+)-diethyl tartrate/Ti(O^{i}Pr)$_4$ catalyst via a similar protocol, respectively.[19c] According to ^{1}H NMR analysis of the terminal methylene proton region of Mosher esters **11c**′,**d**′ derived from **11c**,**d** and (*R*)-(−)-MTPACl, the ee values for **11c** and **11d** were over 99%, within the detection limit of ^{1}H NMR (Fig. 4). We found that the alkylation of (trimethylsilylethynyl)lithium with the corresponding triflate generated from the treatment of **11a** with trifluoromethanesulfonic anhydride, furnished (4*R*,5*S*)-**12a** in 73% yield over two steps.[20] Finally, **12a** was converted into **13a** after desilylation with potassium carbonate in methanol.[10] Having obtained terminal alkyne **13a**, we prepared its enantiomer **13b** and diastereomeric isomers **13c** and **13d** by repeating the same procedures.

Having accessed chiral building blocks **7** and **13**, eight panaxydols **1a–h** were prepared (Scheme 4). The Cadiot-Chodkiewicz cross-coupling reaction of **7a** and **13a** resulted in the formation of panaxydol **1a** in 85% yield.[21,22] The specific rotation measured for **1a** {$[\alpha]_D^{20} = -94.8$ (*c* 1.1, $CHCl_3$)} was consistent with the value of natural (3*R*,9*R*,10*S*)-panaxydol {$[\alpha]_D = -81.8$ (*c* 1.52, $CHCl_3$)},[7] which matched the configurations of chiral intermediates **7a** and **13a**. Bromoalkyne **7a** and other epoxy alkynes **13b–d** were merged in Cadiot-Chodkiewicz cross-coupling reactions to afford (3*R*,9*S*,10*R*)-, (3*R*,9*R*,10*R*)-, and (3*R*,9*S*,10*S*)-panaxydol **1b–d** stereoisomers. In addition, another four stereoisomers of natural panaxydol **1e–h** were also synthesized in good yields using a similar approach from bromoalkyne **7b** and epoxy alkynes **13a–d**.



Scheme 3. Synthesis of epoxy alkynes **13**.

The in vitro cytotoxicities of natural panaxydol and its stereoisomers were evaluated against human colon cancer cell line (HCT-116), human lung cancer cell line (NCI-H1650), and human ovarian cancer cell line (A2780) using a 3-(dimethyl-thiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay (Table 1).[23] The results showed that the stereoisomers of natural panaxydol, except for **1b**, generally exhibited a stronger cytotoxic activity than the natural one. It is noteworthy that (3*S*,9*R*,10*S*)-panaxydol **1e** had a good cytotoxic effect against HCT-116, NCI-H1650, and A2780 cells with IC_{50} values of 2.13, 4.97, and 1.92 μM, respectively, which were close to the result with taxol, a well-known antitumor drug.[24] These results show that some synthetic panaxydols are of value for further exploration as potential anticancer agents.

3. Conclusion

In conclusion, we have conducted an efficient total synthesis of natural panaxydol and seven of its stereoisomers. Meanwhile, (3*R*,9*R*,10*R*)-, (3*R*,9*S*,10*S*)-, (3*S*,9*R*,10*R*)-, (3*S*,9*S*,10*S*)- panaxydol **1c**,

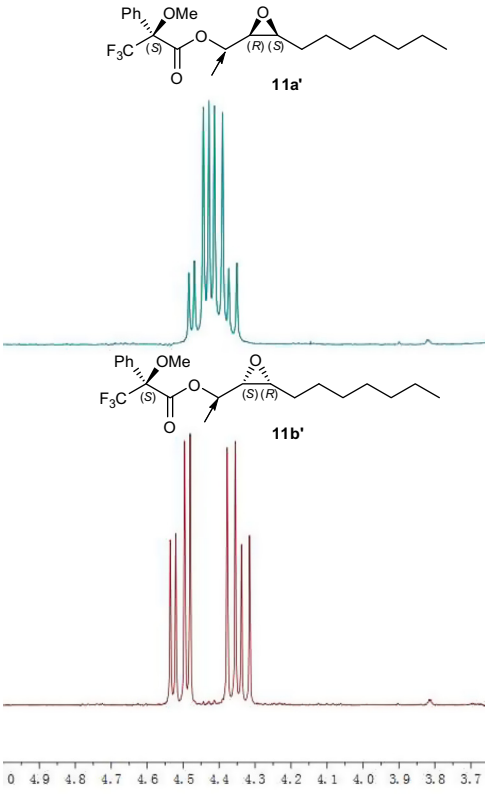


Figure 3. The representative ^1H NMR spectra (300 MHz, $CDCl_3$) of Mosher esters **11a**′ and **11b**′.

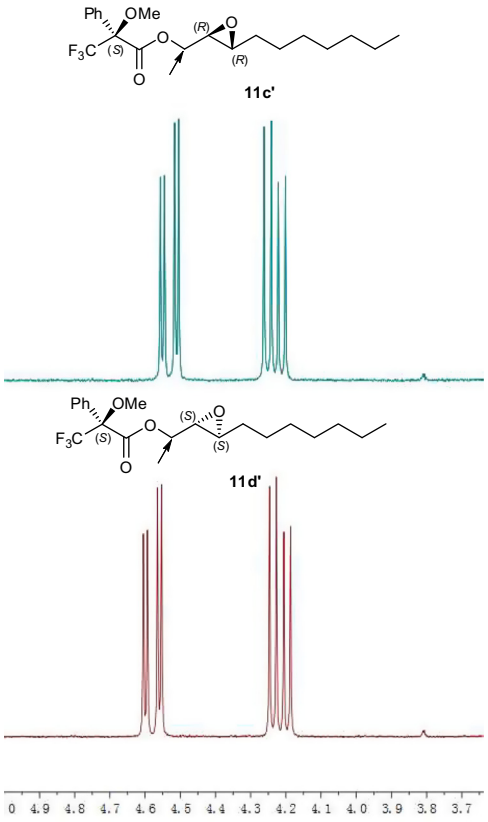
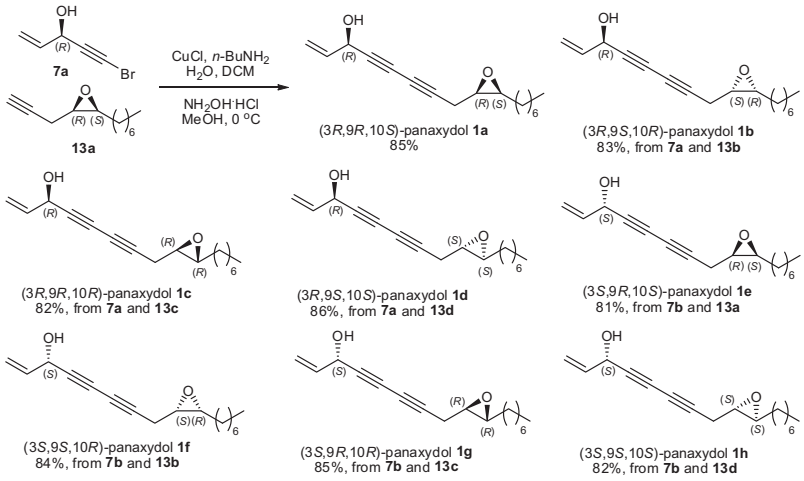


Figure 4. The representative ^1H NMR spectra (300 MHz, $CDCl_3$) of Mosher esters **11c**′ and **11d**′.



Scheme 4. Synthesis of panaxydols **1a**–**h** via Cadiot-Chodkiewicz cross-coupling.

Table 1
The in vitro cytotoxicities of natural panaxydol and their stereoisomers against three human cancer cell lines[a]

Compound	IC_{50} (μM)		
	HCT-116	NCI-H1650	A2780
Natural panaxydol **1a**	>10	>10	>10
(3*R*,9*S*,10*R*)-Panaxydol **1b**	>10	>10	>10
(3*R*,9*R*,10*R*)-Panaxydol **1c**	>10	7.2 ± 1.30	3.99 ± 0.10
(3*R*,9*S*,10*S*)-Panaxydol **1d**	>10	1.94 ± 0.30	9.38 ± 1.20
(3*S*,9*R*,10*S*)-Panaxydol **1e**	2.13 ± 0.42	4.97 ± 0.24	1.92 ± 0.14
(3*S*,9*S*,10*R*)-Panaxydol **1f**	3.58 ± 0.03	$>10 \times 10^{-6}$	3.58 ± 0.92
(3*S*,9*R*,10*R*)-Panaxydol **1g**	>10	$>10 \times 10^{-6}$	>10
(3*S*,9*S*,10*S*)-Panaxydol **1h**	>10	$>10 \times 10^{-6}$	>10
Taxol[b]	0.03	0.36	0.061

[a] MTT assay following 96 h inhibition. HCT-116 is a human colon cancer cell line. NCI-H1650 is human lung cancer cell line. A2780 is human ovarian cancer cell line.
[b] Positive control.

1d, **1g**, **1h** were prepared for the first time. The key steps of our approach include the asymmetric addition of alkynylzinc reagent to aldehydes, the enantioselective Sharpless epoxidation of allylic alcohols and the Cadiot-Chodkiewicz cross-coupling reactions. Moreover, preliminary in vitro cytotoxicity evaluations indicated that some synthetic panaxydols have potential utility in the development of antitumor drugs.

4. Experimental

4.1. General

All reactions were performed using standard Schlenk techniques, and under a nitrogen atmosphere unless otherwise noted. Solvents were dried following standard procedures and distilled before use. Melting points were measured on a STUART-SMP3 Melt-Temp apparatus and were uncorrected. Optical rotations were recorded on a Perkin–Elmer PE-341 polarimeter. Enantiomeric excesses (ee) were determined on an Agilent 1100 HPLC system with a chiral column (Chiralcel OJ-H, Chiralcel OD-H or Chiralpak AD-H column), and 2-propanol–*n*-hexane was the eluent. ^{1}H and ^{13}C NMR spectra were obtained on a Bruker DP-X300 spectrometer. Chemical shifts are reported in ppm, and tetramethylsilane (TMS) served as an internal standard for ^{1}H NMR and ^{13}C NMR. High resolution mass spectrometry (HRMS) data were collected on an Agilent instrument using the TOF MS technique, or a Waters LCT Premier™ with an ESI mass spectrometer.

4.2. Experimental procedures and spectroscopic data

4.2.1. (*R*)-5-Trimethylsilyl-1-penten-4-yn-3-ol 4a

To a stirred solution of trimethylsilylethyne (3.31 mL, 24 mmol) in toluene (12 mL), was slowly added diethylzinc (16 mL, 1.5 M in *n*-hexane, 24 mmol) under a nitrogen atmosphere at room temperature. The resulting mixture was refluxed for 1 h. After cooling to room temperature, (*S*)-BINOL (0.68 g, 2.4 mmol), Et_2O (96 mL), and $Ti(O^iPr)_4$ (1.71 g, 6.0 mmol) were added sequentially and the mixture was stirred for an additional 1 h. Acrolein **3** (0.4 mL, 6 mmol) was then added and the reaction solution was stirred for 4 h at room temperature. The reaction was quenched with saturated NH_4Cl (20 mL), and the aqueous phase was extracted with CH_2Cl_2 (3 × 40 mL). The combined organic phases were dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by silica gel chromatography (*n*-hexane/ethyl acetate 10:1) to provide **4a** (0.73 g, 79% yield, 91% ee) as a colorless oil. $[\alpha]_D^{20} = -37.6$ (*c* 1.3, $CHCl_3$), lit.[13] $[\alpha]_D^{20} = -24.1$ (*c* 1, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.97 (ddd, *J* = 17.0, 10.1, 5.3 Hz), 5.51–5.45 (m, 1H), 5.26–5.22 (m, 1H), 4.90–4.86 (m, 1H), 1.92–1.89 (m, 1H), 0.19 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.7, 116.6, 104.0, 91.1, 63.5, −0.23; HRMS (APCI-TOF) calcd for $C_8H_{15}OSi$ $[M+H]^+$ 155.0892, found: 155.0894. Enantiomeric excess was determined by HPLC with a Chiralcel OJ-H column (99:1 *n*-hexane/2-propanol, 0.8 mL/min, 220 nm); major (*R*)-enantiomer t_r = 10.96 min, minor (*S*)-enantiomer t_r = 12.91 min.

4.2.2. (*S*)-5-Trimethylsilyl-1-penten-4-yn-3-ol 4b

Similar asymmetric alkynylation as described for **4a** from trimethylsilylethyne (3.31 mL, 24 mmol), diethylzinc (16 mL, 1.5 M in *n*-hexane, 24 mmol), and acrolein **3** (0.4 mL, 6 mmol), catalyzed by (*R*)-BINOL (0.68 g, 2.3 mmol) and $Ti(O^iPr)_4$ (1.71 g, 6.0 mmol) afforded **4b** (0.74 g, 80% yield, 91% ee) as a colorless oil. $[\alpha]_D^{20} = +36.2$ (*c* 1.3, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.97 (ddd, *J* = 17.0, 10.1, 5.3 Hz, 1H), 5.50–5.44 (m, 1H), 5.25–5.21 (m, 1H), 4.88–4.86 (m, 1H) 2.12–2.10 (m, 1H), 0.19 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.7, 116.5, 104.1, 91.1, 63.5, −0.24; HRMS (APCI-TOF) calcd for $C_8H_{15}OSi$ $[M+H]^+$ 155.0892, found: 155.0896. Enantiomeric excess was determined by HPLC with a Chiralcel OJ-H column (99:1 *n*- hexane/2-propanol, 0.8 mL/min, 220 nm);

minor (*R*)-enantiomer t_r = 10.94 min, major (*S*)-enantiomer t_r = 12.51 min.

4.2.3. (*R*)-5-Trimethylsilyl-1-penten-4-yn-3-yl 3,5-dinitrobenzoate 5a

To a stirred solution of **4a** (2.07 g, 13.5 mmol), triethylamine (2.8 mL, 20 mmol) in CH_2Cl_2 (40 mL) was added 3,5-dinitrobenzoyl chloride (3.73 g, 16 mmol) at 0 °C under nitrogen atmosphere. The resulting mixture was stirred for 30 min at room temperature and the reaction was quenched with water (15 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL) and the combined organic layers were dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (*n*-hexane/diethyl ether 5:1) to furnish **5a** (4.32 g, 92% yield) as a white solid. Slow recrystallization of **5a** from *n*-hexane–dichloromethane (15:1, 80 mL) improved the enantiomeric purity to over 99% ee, and gave enantiomerically pure **5a** (3.15 g, 73% yield) as colorless crystals. Mp 99.0–100.0 °C; $[\alpha]_D^{20}$ = −49.6 (*c* 1.1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.25–9.20 (m, 3H), 6.20 (d, *J* = 5.9 Hz), 6.04 (ddd, *J* = 16.8, 10.0, 5.9 Hz), 5.71 (d, *J* = 16.9 Hz, 1H), 5.48 (d, *J* = 10.0 Hz, 1H), 0.22 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.3, 148.7, 133.6, 131. 8, 129.6, 122.6, 120.7, 98.5, 94.3, 67.3, −0.4; HRMS (ESI) calcd for $C_{15}H_{17}N_2O_6Si$ $[M+H]^+$ 349.0856, found: 349.0845. Enantiomeric excess was determined by HPLC with a Chiralcel OD-H column (95:5 *n*-hexane/2-propanol, 1.0 mL/min, 254 nm); major (*R*)-enantiomer t_r = 6.55 min.

4.2.4. (*S*)-5-Trimethylsilyl-1-penten-4-yn-3-yl 3,5-dinitrobenzoate 5b

A similar procedure as described for **5a** was accomplished from 3,5-dinitrobenzoyl chloride (3.92 g, 17.0 mmol) and **4b** (2.18 g, 14.2 mmol) to give **5b** (4.46 g, 90% yield) as a white solid. Slow recrystallization of **5b** from *n*-hexane–dichloromethane (10:1, 85 mL) improved the enantiomeric purity to over 99% ee, and gave enantiomerically pure **5b** (3.17 g, 71% yield) as colorless crystals. Mp 99.5–100.5 °C; $[\alpha]_D^{20}$ = +49.4 (*c* 1.3, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.25–9.20 (m, 3H), 6.22–6.19 (m, 1H), 6.10–6.00 (m, 1H), 5.74–5.68 (m, 1H), 5.50–5.46 (m, 1H), 0.22 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.3, 148.7, 133.6, 131.8, 129.6, 122.6, 120.7, 98.6, 94.3, 67.3, −0.39; HRMS (ESI) calcd for $C_{15}H_{17}N_2O_6Si$ $[M+H]^+$ 349.0856, found: 349.0843. Enantiomeric excess was determined by HPLC with a Chiralcel OD-H column (95:5 *n*-hexane/2-propanol, 1.0 mL/min, 254 nm); major (*S*)-enantiomer t_r = 6.53 min.

4.2.5. (*R*)-5-Bromo-1-penten-4-yn-3-yl 3,5-dinitrobenzoate 6a

To a stirred solution of *N*-bromosuccinimide (1.90 g, 10.7 mmol) and $AgNO_3$ (0.57 g, 3.4 mmol) in acetone (35 mL) was added **5a** (3.1 g, 8.9 mmol) at 0 °C. The reaction flask was covered with aluminum foil and the reaction mixture was stirred for 5 h at room temperature. The reaction was quenched with water (20 mL), and the aqueous layer was extracted with Et_2O (3 × 30 mL). The combined organic phases were dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (*n*-hexane/diethyl ether 5:1) to afford **6a** (2.84 g, 90% yield, >99% ee) as a white solid. Mp 89.0–90.0 °C; $[\alpha]_D^{20}$ = −45.2 (*c* 1.3, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.25–9.19 (m, 3H), 6.19 (d, *J* = 6.0 Hz, 1H), 6.04 (ddd, *J* = 16.6, 9.9, 6.0 Hz, 1H), 5.71 (d, *J* = 16.8 Hz, 1H), 5.51 (d, *J* = 9.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.3, 148.7, 133.2, 131.3, 129.6, 122.7, 121.1, 74.4, 67.5, 49.9; HRMS (APCI-TOF) calcd for $C_{12}H_7BrN_2O_6$ $[M]^-$ 353.9487, found: 353.9481. Enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (98:2 *n*-hexane/2-propanol, 1.0 mL/min, 254 nm); major (*R*)-enantiomer t_r = 16.29 min.

4.2.6. (*S*)-5-Bromo-1-penten-4-yn-3-yl 3,5-dinitrobenzoate 6b

A similar procedure as described for **6a** was accomplished from **5b** (5.9 g, 17 mmol), *N*-bromosuccinimide (3.63 g, 20.4 mmol), and $AgNO_3$ (0.57 g, 3.4 mmol) to afford **6b** (5.24 g, 87% yield, >99% ee) as a white solid. Mp 90.0–90.5 °C; $[\alpha]_D^{20}$ = +47.4 (*c* 1.2, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.26–9.19 (m, 3H), 6.20–6.18 (m, 1H), 6.05 (ddd, *J* = 16.8, 10.0, 6.0 Hz, 1H), 5.71 (d, *J* = 16.9 Hz, 1H), 5.51 (d, *J* = 10.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.3, 148.8, 133.3, 131.3, 129.7, 122.7, 121.2, 74.4, 67.6, 50.0; HRMS (APCI-TOF) calcd for $C_{12}H_7BrN_2O_6$ $[M]^-$ 353.9487, found: 353.9491. Enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (98:2 *n*-hexane/2-propanol, 1.0 mL/min, 254 nm); major (*S*)-enantiomer t_r = 14.39 min.

4.2.7. (*R*)-5-Bromo-1-penten-4-yn-3-ol 7a

To a stirred solution of **6a** (1.770 g, 5 mmol) in THF (20 mL) was added 2 M NaOH (12.5 mL, 25 mmol). The reaction mixture was stirred for 2 h at room temperature and then diluted with Et_2O (15 mL). The aqueous phase was extracted with Et_2O (3 × 20 mL). The combined organic phases were dried over $NaSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (*n*-hexane/ethyl acetate 10:1) to furnish **7a** (0.76 g, 94% yield) as a colorless oil. $[\alpha]_D^{20}$ = −41.8 (*c* 1.4, $CHCl_3$), lit.[13] $[\alpha]_D^{20}$ = −31.6 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CHCl_3$) δ 5.95 (ddd, *J* = 17.0, 10.2, 5.4 Hz, 1H), 5.50–5.44 (m, 1H), 5.28–5.24 (m, 1H), 4.92–4.88 (m, 1H), 2.18–2.16 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.2, 116.9, 78.8, 63.9, 46.8; HRMS (APCI-TOF) calcd for C_5H_4BrO $[M-H]^+$ 158.9446, found: 158.9439.

4.2.8. (*S*)-5-Bromo-1-penten-4-yn-3-ol 7b

A similar procedure as described for **7a** was accomplished from **6b** (3.97 g, 11.2 mmol) and 2 M NaOH (22.4 mL) to give **7b** (1.65 g, 92% yield) as a colorless oil. $[\alpha]_D^{20}$ = +36.0 (*c* 1.3, $CHCl_3$), lit.[25] $[\alpha]_D^{20}$ = 38.0 (*c* 1.9, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.95 (ddd, *J* = 17.0, 10.1, 5.3 Hz, 1H), 5.51–5.44 (m, 1H), 5.28–5.24 (m, 1H), 4.93–4.88 (m, 1H), 1.98 (d, 6.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.2, 117.0, 78.8, 64.0, 46.9; HRMS (APCI-TOF) calcd for C_5H_4BrO $[M-H]^+$ 158.9446, found: 158.9448.

4.2.9. 2-Decyn-1-ol 9

To a solution of propargyl alcohol **8** (5.32 mL, 90 mmol) and HMPA (39.5 mL, 225 mmol) in THF (50 mL) was added *n*-BuLi (72 mL, 2.5 M in *n*-hexane, 180 mmol) at −78 °C. The resulting mixture was warmed to −30 °C and stirred for 3 h. Next, 1-bromoheptane (7 mL, 45 mmol) was added and the reaction mixture was warmed to room temperature and stirred for another 21 h. The reaction mixture was quenched with saturated aqueous NH_4Cl (30 mL). The aqueous layer was extracted with Et_2O (3 × 50 mL). The combined organic layers were dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by flash chromatography (*n*-hexane/diethyl ether 5:1) to give **9** (6.6 g, 95% yield) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.27–4.23 (m, 2H), 2.24–2.18 (m, 2H), 1.68 (t, *J* = 6.0 Hz, 1H), 1.56–1.46 (m, 2H), 1.39–1.27 (m, 8H), 0.89 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 86.4, 78.3, 51.2, 31.7, 28.8, 28.7, 28.6, 22.6, 18.7, 14.0; HRMS (APCI-TOF) calcd for $C_{10}H_{19}O$ $[M+H]^+$ 155.1436, found: 155.1428.

4.2.10. (*Z*)-2-Decen-1-ol 10a

To a solution of pyridine (22 mL) and Lindlar catalyst (0.67 g) in EtOH (120 mL) was added alkyne **9** (6.93 g, 45 mmol) under a hydrogen gas atmosphere. Next, the reaction mixture was stirred at room temperature for 1 h. The mixture was filtered through a Celite pad, and the filtrate was concentrated under reduced pressure. The crude product was purified by silica gel chromatography (*n*-hexane/diethyl ether 5:1) to provide **10a** (6.52 g, 92% yield) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.64–5.50 (m, 2H), 4.21–4.18 (m, 2H, 2.10–2.04 (m, 2H), 1.38–1.27 (m, 11H), 0.88 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 133.2, 128.3, 58.5,

31.8, 29.6, 29.1, 29.1, 27.4, 22.6, 14.0; HRMS (ESI) calcd for $C_{10}H_{20}KO$ $[M+K]^+$ 195.1151, found: 195.1146.

4.2.11. (*E*)-2-Decen-1-ol 10b

To a suspension of $LiAlH_4$ (3.42 g, 90 mmol) in dry THF (100 mL) was added alkyne **9** (9.24 g, 60 mmol) at 0 °C. After the addition was completed, the reaction mixture was refluxed for 20 h and cooled to 0 °C. Next, 5% aqueous HCl (30 mL) was slowly added to the mixture, and the aqueous layer was extracted with Et_2O (3 × 50 mL). The combined organic layers were dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by flash chromatography (petroleum ether/ethyl acetate 7:1) to give **10b** (7.95 g, 85% yield) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.75–5.58 (m, 2H), 4.10–4.07 (m, 2H), 2.07–2.00 (m, 2H), 1.39–1.27 (m, 11H), 0.88 (t, J = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 133.5, 128.8, 63.7, 32.2, 31.8, 29.1, 22.6, 14.0 (Two resonances were not observed due to overlapping resonances); HRMS(TOF) calcd for $C_{10}H_{20}NaO$ $[M+Na]^+$ 179.1412, found: 179.1409.

4.2.12. (2*R*,3*S*)-2,3-Epoxy-1-decanol 11a

To a cooled solution of powered activated 4 Å molecular sieves (5 g) in CH_2Cl_2 (140 mL), were added (−)-diisopropyl tartrate (2.1 g, 9.0 mmol) and $Ti(O^iPr)_4$ (1.8 g, 6.4 mmol) sequentially at 0 °C. After the mixture was cooled to −23 °C, *tert*-butyl hydroperoxide (TBHP) (23 mL, 5.6 M in decane, 128 mmol) was added slowly. The resulting mixture was stirred for 1 h, and (*Z*)-2-decen-1-ol **10a** (1.0 g, 64 mmol) was added. The reaction mixture was warmed to −10 °C and stirred for 72 h. The reaction was quenched with water (10 mL) at 0 °C, and the resulting mixture was stirred for 1 h. After the mixture was warmed to room temperature, a solution of 30% aqueous NaOH (40 mL) was added. The solution was stirred vigorously until phase separation occurred. The aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by flash chromatography (*n*-hexane/diethyl ether 2:1) to afford **11a** (9.4 g, 85% yield) as a white solid. Recrystallization from petroleum ether (100 mL) provided a white solid **11a** (6.39 g, 68% yield, >99% ee, determined by ^{1}H NMR analysis of the ester **11a′** derived from (*R*)-(−)-MTPACl). Mp 43.0–44.0 °C; $[\alpha]_D^{20}$ = +4.7 (*c* 0.9, $CHCl_3$), lit.[19a] $[\alpha]_D^{25}$ = −4.8 (*c* 2.0, $CHCl_3$) for (2*S*,3*R*)-2,3-epoxy-1-decanol (**11b**); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.89–3.82 (m, 1H), 3.71–3.63 (m, 1H), 3.18–3.13 (m, 1H), 3.06–3.00 (m, 1H), 2.14–2.10 (m, 1H), 1.60–1.27 (m, 12H), 0.88 (t, J = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 60.9, 57.3, 56.8, 31.7, 29.3, 29.1, 27.9, 26.6, 22.6, 14.0; HRMS (ESI) calcd for $C_{10}H_{21}O_2$ $[M+H]^+$ 173.1542, found: 173.1536.

4.2.13. (*S*)-MTPA ester of 11a (11a′)

To a stirred solution of 4-(dimethy1amino)pyridine (DMAP) (18 mg, 0.15 mmol) and triethylamine (100 μL, 0.7 mmol) in CH_2Cl_2 (1 mL), was added **11a** (25.8 mg, 0.15 mmol) at 0 °C. Next, (*R*)-(−)-α-methoxy-α-(trifluoromethy1)phenylacetyl chloride (MTPACl) (60 μL, 0.3 mmol) was added immediately into the mixture. After the reaction solution turned orange, it was stirred at 0 °C until the reaction was completed as monitored by TLC. The reaction was quenched with 3-(dimethylamino)propylamine (50 μL) and concentrated under reduced pressure. The residue was purified by flash chromatography (*n*-hexane/ethyl acetate 5:1) to give the title compound **11a′** as a colorless oil. $[\alpha]_D^{20}$ = −48.1 (*c* 1.2, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55–7.52 (m, 2H), 7.43–7.39 (m, 3H), 4.45 (dd, J = 12.0, 4.6 Hz, 1H), 4.38 (dd, J = 12.0, 6.8 Hz, 1H), 3.58 (s, 3H), 3.23–3.17 (m, 1H), 3.05–3.00 (m, 1H), 1.60–1.39 (m, 12H), 0.89 (t, J = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.5, 132.0, 129.7, 128.5, 127.3, 123.2 (q, J = 286.6 Hz), 84.7 (q, J = 27.5 Hz), 64.5, 56.6, 55.5, 53.0, 31.7, 29.3, 29.1, 27.9, 26.5, 22.6, 14.0; HRMS (ESI) calcd for $C_{20}H_{27}F_3NaO_4$ $[M+Na]^+$ 411.1759, found: 411.1751.

4.2.14. (2*S*,3*R*)-2,3-Epoxy-1-decanol 11b

Similar asymmetric epoxidation as described for **11a** from (*Z*)-2-decen-l-ol **10a** (6.6 g, 42 mmol) and TBHP (15 mL, 5.6 M in decane, 84 mmol), catalyzed by (+)-diethyl tartrate (1.21 g, 5.8 mmol) and $Ti(O^iPr)_4$ (1.19 g, 4.2 mmol) afforded **11b** (6.3 g, 87% yield) as a white solid. Recrystallization from petroleum ether (30 mL) provided a white solid **11b** (4.1 g, 65% yield, >99% ee, determined by ^{1}H NMR analysis of the ester **11b′** derived from (*R*)-(−)-MTPACl). Mp 43.0–44.5 °C; $[\alpha]_D^{20}$ = −4.9 (*c* 1.3, $CHCl_3$), lit.[19a] $[\alpha]_D^{25}$ = −4.8 (*c* 2.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.90–3.82 (m, 1H), 3.71–3.63 (m, 1H), 3.18–3.13 (m, 1H), 3.06–3.00 (m, 1H), 1.94–1.90 (m, 1H), 1.60–1.27 (m, 12H), 0.89 (t, J = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 60.8, 57.2, 57.0, 31.6, 29.3, 29.1, 27.9, 26.5, 22.5, 13.9; HRMS (ESI) calcd for $C_{10}H_{21}O_2$ $[M+H]^+$ 173.1542, found: 173.1533.

4.2.15. (*S*)-MTPA ester of 11b (11b′)

A similar procedure as described for (*S*)-MTPA ester of **11a** was accomplished from **11b** (25.8 mg, 0.15 mmol) and (*R*)-(−)-MTPACl (60 μL, 0.3 mmol) to produce the title compound **11b′** as a colorless oil. $[\alpha]_D^{20}$ = −33.2 (*c* 1.2, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.56–7.52 (m, 2H), 7.44–7.39 (m, 3H), 4.51 (dd, J = 12.0, 4.6 Hz, 1H), 4.35 (dd, J = 11.8, 6.8 Hz, 1H), 3.57 (s, 3H), 3.26–3.20 (m, 1H), 3.05–3.00 (m, 1H), 1.58–1.28 (m, 12H), 0.88 (t, J = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.5, 132.0, 129.7, 128.4, 127.3, 123.2 (q, J = 286.7 Hz), 84.7 (q, J = 27.7 Hz), 64.5, 56.6, 55.5, 52.9, 31.7, 29.3, 29.1, 27.9, 26.5, 22.5, 14.0; HRMS (ESI) calcd for $C_{20}H_{27}F_3NaO_4$ $[M+Na]^+$ 411.1759, found: 411.1749.

4.2.16. (2*R*,3*R*)-2,3-Epoxy-1-decanol 11c

A similar asymmetric epoxidation as described for **11a** from (*E*)-2-decen-l-ol **10b** (6.24 g, 40 mmol) and TBHP (14.5 ml, 5.6 M in decane, 80 mmol), catalyzed by (−)-diisopropyl tartrate (0.68 g, 2.9 mmol) and $Ti(O^iPr)_4$ (0.56 g, 2 mmol) gave **11c** (6.19 g, 90% yield) as a white solid. Recrystallization from petroleum ether (40 mL) provided a white solid **11c** (4.64 g, 75% yield, >99% ee, determined by ^{1}H NMR analysis of the ester **11c′** derived from (*R*)-(+)-MTPACl). Mp 49.0–50.0 °C; $[\alpha]_D^{20}$ = +35.7 (*c* 1.4, $CHCl_3$), lit.[19c] $[\alpha]_D^{20}$ = −34.8 (*c* 1.1, $CHCl_3$) for (2*S*,3*S*)-2,3-epoxy-1-decanol **11d**; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.95–3.88 (m, 1H), 3.66–3.58 (m, 1H), 2.98–2.90 (m, 2H), 1.90–1.86 (m, 1H), 1.61–1.28 (m, 12H), 0.88 (t, J = 7.0 Hz, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 61.8, 58.6, 56.0, 31.6, 31.4, 29.2, 29.1, 25.8, 22.5, 13.9; HRMS (ESI) calcd for $C_{10}H_{21}O_2$ $[M+H]^+$ 173.1542, found: 173.1534.

4.2.17. (*S*)-MTPA ester of 11c (11c′)

A similar procedure as described for (*S*)-MTPA ester of **11a** was accomplished from **11c** (25.8 mg, 0.15 mmol) and (*R*)-(−)-MTPACl (60 μL, 0.3 mmol) to give the title compound **11c′** as a colorless oil. $[\alpha]_D^{20}$ = −40.2 (*c* 1.2, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55–7.52 (m, 2H), 7.44–7.39 (m, 3H), 4.53 (dd, J = 12.0, 3.5 Hz, 1H), 4.23 (dd, J = 12.0, 6.2 Hz, 1H), 3.57 (s, 3H), 3.00–2.97 (m, 1H), 2.85–2.81 (m, 1H), 1.58–1.26 (m, 12H), 0.88 (t, J = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.4, 132.1, 129.7, 128.5, 127.3, 123.2 (q, J = 286.7 Hz), 84.7 (q, J = 27.8 Hz), 66.3, 56.8, 55.5, 54.5, 31.7, 31.4, 29.3, 29.1, 25.8, 22.6, 14.0; HRMS (ESI) calcd for $C_{20}H_{27}F_3NaO_4$ $[M+Na]^+$ 411.1759, found: 411.1796.

4.2.18. (2*S*,3*S*)-2,3-Epoxy-1-decanol 11d

A similar asymmetric epoxidation as described for **11a** from (*E*)-2-decen-l-ol **10b** (6.24 g, 40 mmol) and TBHP (14.5 ml, 5.6 M in decane, 80 mmol), catalyzed by (+)-diethyl tartrate (0.60 g, 2.9 mmol) and $Ti(O^iPr)_4$ (0.57 g, 2 mmol) furnished **11d** (6.12 g,

89% yield) as a white solid. Recrystallization from petroleum ether (40 mL) provided a white solid **11d** (4.53 g, 74% yield, >99% ee, determined by ^{1}H NMR analysis of the ester **11d′** derived from (*R*)-(−)-MTPACl). Mp 49.5–50.5 °C; $[\alpha]_D^{20} = -39.7$ (*c* 1.2, $CHCl_3$), lit.[19a] $[\alpha]_D^{25} = -36.5$ (*c* 2.8, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.95–3.88 (m, 1H), 3.66–3.58 (m, 1H), 2.98–2.90 (m, 2H), 1.93–1.89 (m, 1H), 1.61–1.28 (m, 12H), 0.88 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 61.8, 58.6, 56.0, 31.7, 31.5, 29.3, 29.1, 25.9, 22.5, 14.0; HRMS (ESI) calcd for $C_{10}H_{21}O_2$ $[M+H]^+$ 173.1542, found: 173.1535.

4.2.19. (*S*)-MTPA ester of 11d (11d′)

A similar procedure as described for (*S*)-MTPA ester of **11a** was accomplished from **11d** (25.8 mg, 0.15 mmol) and (*R*)-(−)-MTPACl (60 μL, 0.3 mmol) to give the title compound **11d′** as a colorless oil. $[\alpha]_D^{20} = -24.7$ (*c* 1.3, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55–7.52 (m, 2H), 7.44–7.40 (m, 3H), 4.58 (dd, *J* = 12.1, 3.5 Hz, 1H), 4.22 (dd, *J* = 12.1, 5.8 Hz, 1H), 3.57 (s, 3H), 3.03–3.00 (m, 1H), 2.87–2.82 (m, 1H), 1.57–1.27 (m, 12H), 0.88 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.4, 132.0, 129.7, 128.5, 127.3, 123.2 (q, *J* = 286.7 Hz), 84.7 (q, *J* = 27.3 Hz), 66.0, 56.6, 55.5, 54.5, 31.7, 31.4, 29.2, 29.1, 25.8, 22.6, 14.0; HRMS (ESI) calcd for $C_{20}H_{28}F_3O_4$ $[M+H]^+$ 389.1940, found: 389.1938.

4.2.20. (4*R*,5*S*)-4,5-Epoxy-1-trimethylsilyl-1-decyne 12a

To a stirred solution of epoxide **11a** (344 mg, 2 mmol) in anhydrous CH_2Cl_2 (8 mL) were added dropwise 2,6-lutidine (0.328 mL, 3 mmol) and trifluoromethanesulfonic anhydride (848.4 mg, 3 mmol) at −78 °C under argon. The resulting mixture was warmed slowly to −40 °C and stirred. Next, the reaction mixture was recooled to −78 °C and stirred for an additional 1 h. The reaction was quenched with saturated aqueous NH_4Cl (5 mL), and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash chromatography (petroleum ether/ethyl acetate 30:1) to afford the crude triflate of **11a** as a colorless oil, which was used in the subsequent reaction without further purification.

To a stirred solution of trimethylsilylethyne (392.8 mg, 4.0 mmol) in anhydrous diethyl ether (8 mL) was slowly added *n*-BuLi (1.44 mL, 2.5 M in *n*-hexane, 3.6 mmol) at −78 °C under argon. After the resulting mixture was stirred for 1.5 h at the same temperature, a solution of the triflate of **11a** in anhydrous diethyl ether (1.5 mL) was added at −78 °C. The reaction mixture was warmed slowly to −40 °C, continued to be warmed to −25 °C and stirred overnight. The reaction was quenched with saturated aqueous NH_4Cl (5 mL) and the aqueous layer was extracted with diethyl ether (3 × 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash column chromatography (*n*-hexane/diethyl ether 60:1) to give **12a** (367.9 mg, 73% yield) as a colorless oil. $[\alpha]_D^{20} = -33.6$ (*c* 1.4, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.17–3.11 (m, 1H), 2.99–2.93 (m, 1H), 2.64 (dd, *J* = 17.3, 5.4 Hz, 1H), 2.31 (dd, *J* = 17.3, 7.3 Hz, 1H), 1.61–1.26 (m, 12H), 0.89 (t, *J* = 6.9 Hz, 3H), 0.16 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 101.6, 86.8, 56.9, 54.9, 31.7, 29.4, 29.2, 27.6, 26,4, 22.6, 19.9, 14.0, −0.045; HRMS (ESI) calcd for $C_{15}H_{29}OSi$ $[M+H]^+$ 253.1988, found: 253.1984.

4.2.21. (4*S*,5*R*)-4,5-Epoxy-1-trimethylsilyl-1-decyne 12b

A similar procedure as described for **12a** was accomplished from **11b** (344.0 mg, 2.0 mmol), trimethylsilylethyne (392.8 mg, 4.0 mmol), and *n*-BuLi (1.44 mL, 2.5 M in *n*-hexane, 3.6 mmol) to give **12b** (362.9 mg, 72% yield) as a colorless oil. $[\alpha]_D^{20} = +38.2$ (*c* 1.2, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.17–3.11 (m, 1H), 2.99–2.93 (m, 1H), 2.64 (dd, *J* = 17.3, 5.4 Hz, 1H), 2.31 (dd, *J* = 17.3, 7.3 Hz, 1H), 1.59–1.28 (m, 12H), 0.89 (t, *J* = 7.0 Hz, 3H), 0.16 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 101.6, 86.9, 57.0, 54.9, 31.7, 29.4, 29.2, 27.6, 26.4, 22.60, 14.0, −0.026. HRMS (ESI) calcd for $C_{15}H_{29}OSi$ $[M+H]^+$ 253.1988, found: 253.1975.

4.2.22. (4*R*,5*R*)-4,5-Epoxy-1-trimethylsilyl-1-decyne 12c

A similar procedure as described for **12a** was accomplished from **11c** (344.0 mg, 2.0 mmol), trimethylsilylethyne (392.8 mg, 4.0 mmol), and *n*-BuLi (1.44 mL, 2.5 M in *n*-hexane, 3.6 mmol) to afford **12c** (373.0 mg, 74% yield) as a colorless oil. $[\alpha]_D^{20} = +0.1$ (*c* 1.2, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.87–2.80 (m, 2H), 2.63 (dd, *J* = 17.4, 4.4 Hz, 1H), 2.41 (dd, *J* = 16.5, 5.4 Hz, 1H), 1.59–1.26 (m, 12H), 0.88 (t, *J* = 7.0 Hz, 3H), 0.16 (s, 9H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 101.3, 86.9, 58.4, 56.0, 31.7, 31.6, 29.3, 29.2, 25.9, 23.5, 22.6, 14.0, −0.042; HRMS (ESI) calcd for $C_{15}H_{29}OSi$ $[M+H]^+$ 253.1988, found: 253.1992.

4.2.23. (4*S*,5*S*)-4,5-Epoxy-1-trimethylsilyl-1-decyne 12d

A similar procedure as described for **12a** was accomplished from **11d** (344.0 mg, 2.0 mmol), trimethylsilylethyne (392.8 mg, 4.0 mmol), *n*-BuLi (1.44 mL, 2.5 M in *n*-hexane, 3.6 mmol) to give **12d** (367.6 mg, 73% yield) as a colorless oil. $[\alpha]_D^{20} = -0.3$ (*c* 1.3, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.87–2.80 (m, 2H), 2.63 (dd, *J* = 17.4, 4.4 Hz, 1H), 2.41 (dd, *J* = 17.4, 5.4 Hz, 1H), 1.60–1.28 (m, 12H), 0.88 (t, *J* = 7.0 Hz, 3H), 0.16 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 101.3, 86.9, 58.4, 56.0, 31.7, 31.6, 29.3, 29.2, 25.9, 23.5, 22.6, 14.0, −0.040; HRMS (ESI) calcd for $C_{15}H_{29}OSi$ $[M+H]^+$ 253.1988, found: 253.1974.

4.2.24. (4*R*,5*S*)-4,5-Epoxy-1-decyne 13a

To a solution of **12a** (320 mg, 1.3 mmol) in methanol (9 mL) was added potassium carbonate (390 mg, 2.8 mmol) at 0 °C. After stirring for 5 h at room temperature, the mixture was concentrated under reduced pressure. The residue was purified by silica gel chromatography (*n*-hexane/diethyl ether 60:1) to provide **13a** (190 mg, 81% yield) as a colorless oil. $[\alpha]_D^{20} = -42.8$ (*c* 1.5, $CHCl_3$), lit.[10] $[\alpha]_D^{25} = -53.8$ (*c* 1.1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.18–3.12 (m, 1H), 3.00–2.95 (m, 1H), 2.64–2.55 (m, 1H), 2.33–2.24 (m, 1H), 2.06 (t, *J* = 2.7 Hz, 1H), 1.55–1.28 (m, 12H) 0.89 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 79.4, 70.2, 56.9, 54.7, 31.7, 29.4, 29.1, 27.5, 26.4, 22.6, 18.4, 14.0; HRMS (ESI) calcd for $C_{12}H_{20}NaO$ $[M+Na]^+$ 203.1412, found: 203.1411.

4.2.25. (4*S*,5*R*)-4,5-Epoxy-1-decyne 13b

A similar deprotection as described for **13a** from **12b** (530 mg, 2.1 mmol) and potassium carbonate (580 mg, 4.2 mmol) gave **13b** (310 mg, 81% yield) as a colorless oil. $[\alpha]_D^{20} = +45.4$ (*c* 1.4, $CHCl_3$), lit.[7] $[\alpha]_D^{25} = 53.9$ (*c* 1.2, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.18–3.13 (m, 1H), 3.00–2.95 (m, 1H), 2.64–2.55 (m, 1H), 2.32–2.24 (m, 1H), 2.06 (t, *J* = 2.7 Hz, 1H), 1.55–1.28 (m, 12H), 0.89 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 79.4, 70.3, 57.0, 54.7, 31.7, 29.4, 29.1, 27.5, 26.4, 22.6, 18.5, 14.0. HRMS (ESI) calcd for $C_{12}H_{20}NaO$ $[M+Na]^+$ 203.1412, found: 203.1405.

4.2.26. (4*R*,5*R*)-4,5-Epoxy-1-decyne 13c

A similar deprotection as described for **13a** from **12c** (1.53 g, 6.1 mmol), potassium carbonate (1.68 g, 12.2 mmol) afforded **13c** (0.86 g, 78% yield) as a colorless oil. $[\alpha]_D^{20} = +14.6$ (*c* 1.2, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.89–2.84 (m, 2H), 2.65–2.57 (m, 1H), 2.47–2.39 (m, 1H), 2.04 (t, *J* = 2.7 Hz, 1H), 1.57–1.28 (m, 12H), 0.88 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 78.9, 70.3, 58.2, 55.6, 31.7, 31.5, 29.3, 29.1, 25.9, 22.6, 21.9, 14.0; HRMS (ESI) *m*/*z* calcd for $C_{12}H_{20}KO$ $[M+K]^+$ 219.1151, found: 219.1138.

4.2.27. (4*S*,5*S*)-4,5-Epoxy-1-decyne 13d

A similar deprotection as described for **13a** from **12d** (1.71 g, 6.8 mmol) and potassium carbonate (1.88 g, 13.6 mmol) furnished

13d (0.97 g, 79% yield) as a colorless oil. $[\alpha]_D^{20} = -14.4$ (*c* 1.3, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 2.89–2.84 (m, 2H), 2.65–2.57 (m, 1H), 2.47–2.38 (m, 1H), 2.04 (t, *J* = 2.7 Hz, 1H), 1.59–1.28 (m, 12H), 0.88 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 78.9, 70.3, 58.2, 55.6, 31.7, 31.5, 29.3, 29.1, 25.9, 22.6, 21.9, 14.0; HRMS (ESI) calcd for $C_{12}H_{20}KO$ $[M+K]^+$ 219.1151, found: 219.1146.

4.2.28. (3*R*,9*R*,10*S*)-Panaxydol 1a

To a stirred solution of CuCl (4.0 mg, 0.04 mmol), *n*-$BuNH_2$ (55 μL), and H_2O (125 μL) in methanol (0.7 mL) and CH_2Cl_2 (0.6 mL), were added a few crystals of $NH_2OH{\cdot}HCl$ to discharge the blue color. Epoxy alkyne **13a** (36 mg, 0.2 mmol) was then added and stirred for 5 min. Next, bromoalkyne **7a** (48.3 mg, 0.3 mmol) in CH_2Cl_2 (0.3 mL) was added slowly over 30 min at 0 °C. After stirring for 30 min, the reaction was quenched with water (3 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL), the combined organic phases were dried over Na_2SO_4, concentrated, and purified by silica gel chromatography (*n*-hexane/ethyl acetate 5:1) to give **1a** (44.3 mg, 85% yield) as a colorless oil. $[\alpha]_D^{20} = -94.8$ (*c* 1.1, $CHCl_3$); lit.[7] $[\alpha]_D = -81.8$ (*c* 1.52, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 5.95 (ddd, *J* = 17.0, 10.1, 5.3 Hz, 1H), 5.50–5.44 (m, 1H), 5.28–5.24 (m, 1H), 4.95–4.91 (m, 1H), 3.17–3.12 (m, 1H), 3.00–2.94 (m, 1H), 2.75–2.67 (m, 1H), 2.43–2.35 (m, 1H), 1.99–1.96 (m, 1H), 1.59–1.25 (m, 12H), 0.89 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.0, 117.1, 76.7, 74.9, 70.8, 66.3, 63.5, 57.0, 54.3, 31.7, 29.4, 29.1, 27.5, 26.4, 22.6, 19.4, 14.1; HRMS (ESI) calcd for $C_{17}H_{24}NaO_2$ $[M+Na]^+$ 283.1674, found: 283.1666.

4.2.29. (3*R*,9*S*,10*R*)-Panaxydol 1b

A similar Cadiot-Chodkiewicz coupling as described for **1a** from **7a** (48.3 mg, 0.3 mmol) and **13b** (36 mg, 0.2 mmol) afforded **1b** (43.2 mg, 83% yield) as a colorless oil. $[\alpha]_D^{20} = +41.2$ (*c* 1.2, $CHCl_3$), lit.[10] $[\alpha]_D^{25} = +51.2$ (*c* 1.7, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 5.95 (ddd, *J* = 17.0, 10.1, 5.3 Hz, 1H), 5.51–5.44 (m, 1H), 5.28–5.24 (m, 1H), 4.94–4.91 (m, 1H), 3.17–3.12 (m, 1H), 2.99–2.94 (m, 1H), 2.75–2.67 (m, 1H), 2.43–2.34 (m, 1H), 1.98 (d, 6.6 Hz, 1H), 1.59–1.29 (m, 12H), 0.89 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.0, 117.1, 75.0, 70.7, 66.3, 63.4, 57.0, 54.3, 31.7, 29.4, 29.1, 27.4, 26.4, 22.6, 19.4, 14.1; HRMS (ESI) calcd for $C_{17}H_{24}NaO_2$ $[M+Na]^+$ 283.1674, found: 283.1665.

4.2.30. (3*R*,9*R*,10*R*)-Panaxydol 1c

A similar Cadiot-Chodkiewicz coupling as described for **1a** from **7a** (48.3 mg, 0.3 mmol) and **13c** (36 mg, 0.2 mmol) gave **1c** (42.6 mg, 82% yield) as a colorless oil. $[\alpha]_D^{20} = -35.6$ (*c* 0.7, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 5.95 (ddd, *J* = 17.0, 10.1, 5.3 Hz, 1H), 5.50–5.44 (m, 1H), 5.28–5.24 (m, 1H), 4.94–4.90 (m, 1H), 2.89–2.82 (m, 2H), 2.75–2.68 (m, 1H), 2.56–2.49 (m,1H), 1.94–1.91 (m, 1H), 1.59–1.28 (m, 12H), 0.89 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.0, 117.1, 76.4, 74.8, 70.9, 66.3, 63.5, 58.4, 55.3, 31.7, 31.5, 29.3, 29.2, 25.8, 22.9, 22.6, 14.0; HRMS (ESI) calcd for $C_{17}H_{24}NaO_2$ $[M+Na]^+$ 283.1674, found: 283.1667.

4.2.31. (3*R*,9*S*,10*S*)-Panaxydol 1d

A similar Cadiot-Chodkiewicz coupling as described for **1a** from **7a** (48.3 mg, 0.3 mmol) and **13d** (36 mg, 0.2 mmol) provided **1d** (44.7 mg, 86% yield) as a colorless oil. $[\alpha]_D^{20} = -43.0$ (*c* 1.4, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 5.95 (ddd, *J* = 17.0, 10.2, 5.3 Hz, 1H), 5.50–5.44 (m, 1H), 5.27–5.23 (m, 1H), 4.93–4.90 (m, 1H), 2.89–2.82 (m, 2H), 2.75–2.68 (m, 1H), 2.56–2.49 (m,1H), 2.15 (br s, 1H), 1.58–1.28 (m, 12H), 0.89 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.0, 116.9, 76.2, 74.9, 70.7, 66.3, 63.3, 58.4, 55.3, 31.7, 31.4, 29.2, 29.1, 25.8, 22.8, 22.5, 14.0; HRMS (ESI) calcd for $C_{17}H_{24}NaO_2$ $[M+Na]^+$ 283.1674, found: 283.1662.

4.2.32. (3*S*,9*R*,10*S*)-Panaxydol 1e

A similar Cadiot-Chodkiewicz coupling as described for **1a** from **7b** (48.3 mg, 0.3 mmol) and **13a** (36 mg, 0.2 mmol) gave **1e** (42.1 mg, 81% yield) as a colorless oil. $[\alpha]_D^{20} = -43.4$ (*c* 0.6, $CHCl_3$), lit.[10] $[\alpha]_D^{25} = -57.7$ (*c* 1.6, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 5.95 (ddd, *J* = 17.0, 10.1, 5.3 Hz, 1H), 5.51–5.44 (m, 1H), 5.28–5.24 (m, 1H), 4.95–4.91 (m, 1H), 3.18–3.12 (m, 1H), 2.98–2.96 (m, 1H), 2.75–2.67 (m, 1H), 2.43–2.35 (m, 1H), 1.95 (d, 6.7 Hz, 1H), 1.54–1.29 (m, 12H), 0.89 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.0, 117.1, 76.7, 74.9, 70.8, 66.2, 63.4, 57.0, 54.3, 31.7, 29.4, 29.1, 27.5, 26.4, 22.6, 19.5, 14.1; HRMS (ESI) calcd for $C_{17}H_{24}NaO_2$ $[M+Na]^+$ 283.1674, found: 283.1663.

4.2.33. (3*S*,9*S*,10*R*)-Panaxydol 1f

A similar Cadiot-Chodkiewicz coupling as described for **1a** from **7b** (48.3 mg, 0.3 mmol) and **13b** (36 mg, 0.2 mmol) gave **1f** (43.7 mg, 84% yield) as a colorless oil. $[\alpha]_D^{20} = +90.0$ (*c* 0.5, $CHCl_3$), lit.[10] $[\alpha]_D^{25} = +103$ (*c* 3.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 5.95 (ddd, *J* = 17.0, 10.1, 5.3 Hz, 1H), 5.51–5.44 (m, 1H), 5.28–5.24 (m, 1H), 4.95–4.91 (m, 1H), 3.18–3.12 (m, 1H), 2.98–2.96 (m, 1H), 2.75–2.67 (m, 1H), 2.43–2.35 (m, 1H), 1.99–1.96 (m, 1H) 1.60–1.25 (m, 12H), 0.89 (t, *J* = 6.9 Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.0, 117.1, 76.7, 74.5, 70.8, 66.2, 63.4, 57.0, 54.3, 31.7, 29.4, 29.1, 27.5, 26.4, 22.6, 19.4, 14.1; HRMS (ESI) calcd for $C_{17}H_{24}NaO_2$ $[M+Na]^+$ 283.1674, found: 283.1670.

4.2.34. (3*S*,9*R*,10*R*)-Panaxydol 1g

A similar Cadiot-Chodkiewicz coupling as described for **1a** from **7b** (48.3 mg, 0.3 mmol) and **13c** (36 mg, 0.2 mmol) afforded **1g** (44.2 mg, 85% yield) as a colorless oil. $[\alpha]_D^{20} = +45.6$ (*c* 1.2, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 5.95 (ddd, *J* = 17.0, 10.1, 5.3 Hz, 1H), 5.50–5.44 (m, 1H), 5.28–5.24 (m, 1H), 4.94–4.90 (m, 1H), 2.89–2.82 (m, 2H), 2.76–2.68 (m, 1H), 2.57–2.49 (m,1H), 1.99–1.97 (m, 1H), 1.61–1.25 (m, 12H), 0.89 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.0, 117.2, 76.4, 74.8, 70.9, 66.3, 63.5, 58.4, 55.3, 31.7, 31.5, 29.3, 29.2, 25.8, 22.9, 22.6, 14.1; HRMS (ESI) calcd for $C_{17}H_{24}NaO_2$ $[M+Na]^+$ 283.1674, found: 283.1661.

4.2.35. (3*S*,9*S*,10*S*)-Panaxydol 1h

A similar Cadiot-Chodkiewicz coupling as described for **1a** from **7b** (48.3 mg, 0.3 mmol) and **13d** (36 mg, 0.2 mmol) gave **1h** (42.6 mg, 82% yield) as a colorless oil. $[\alpha]_D^{20} = +37.0$ (*c* 1.2, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 5.95 (ddd, *J* = 17.0, 10.1, 5.3 Hz, 1H), 5.50–5.44 (m, 1H), 5.28–5.24 (m, 1H), 4.94–4.90 (m, 1H), 2.88–2.82 (m, 2H), 2.76–2.68 (m, 1H), 2.57–2.49 (m, 1H), 1.94 (d, 6.6 Hz, 1H), 1.59–1.22 (m, 12H), 0.89 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.0, 117.2, 76.3, 74.8, 70.9, 66.3, 63.5, 58.4, 55.3, 31.7, 31.5, 29.3, 29.2, 25.8, 22.9, 22.6, 14.1; HRMS (ESI) calcd for $C_{17}H_{24}NaO_2$ $[M+Na]^+$ 283.1674, found: 283.1669.

4.3. Antitumor activity investigations

The HCT-116 (human colon cancer), NCI-H1650 (human lung cancer), and A2780 (human ovarian cancer) cell lines were obtained from American Type Culture Collection (ATCC, Manassas, VA) or Cell Culture Center at the Institute of Basic Medical Sciences, Chinese Academy of Medical Sciences. These cells were incubated in DMEM (Dulbecco's modified Eagle medium) containing 10% fetal bovine serum (FBS), streptomycin (100 μg/mL), and penicillin (100 U/mL), at 37 °C and a 5% CO_2 humidified air. The cells were seeded at 2.0×10^3/well into 96-well plate and incubated for 24 h. After the cells were treated with different concentrations of tested compounds for 96 h, 20 μL MTT (5 mg/mL) solution was added to each cell and incubated for 4 h at 37 °C to form formazan crystals. Then, the medium was carefully removed, and dimethyl sulfoxide (DMSO) was added to each well to dissolve the formazan

crystals. The plates were read immediately at 570 nm on a microplate reader (Biotek Instruments, Inc. USA). The IC_{50} value is the drug concentration for which vitality is 50%, and the results are summarized in Table 1. For all tests, taxol was used as positive control.

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Supplementary data

Supplementary data (NMR and HPLC data) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetasy.2015.12.001.

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