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Catalytic asymmetric synthesis of (*S*,4*E*,15*Z*)-docosa-4,15-dien-1-yn-3-ol, an antitumor marine natural product

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ABSTRACT

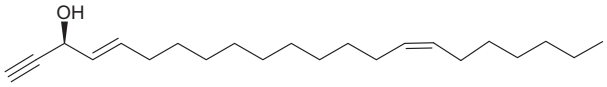
An efficient enantioselective total synthesis of an antitumor marine natural product (*S*,4*E*,15*Z*)-docosa-4,15-dien-1-yn-3-ol **1** with 96% ee and 15% overall yield has been achieved; this is the first preparation of **1** via asymmetric catalytic strategy. The key steps involve the asymmetric addition of trimethylsilylacetylene to a diolefinc aldehyde using a (*R*,*R*)-ProPhenol ligand and a zipper reaction of an alkyne.

1. Introduction

Marine natural products have received great attention due to their unique structures and biological activities over the last two decades.[1–3] (*S*,4*E*,15*Z*)-Docosa-4,15-dien-1-yn-3-ol **1** (Fig. 1) is an antitumor bioactive compound, which was first isolated from the marine sponge *Cribrochalina vasculum* collected in Belize by Gunasekera and Faircloth in 1990.[4] Thereafter, Boyd et al. have elucidated the geometry of the C-15 double bond in acetylenic alcohol **1** as *Z* based on ^{13}C NMR spectroscopic data. They have also prepared Mosher ester derivatives and assigned the absolute configuration at C-3 as (*S*).[5] Preliminary in vitro testing revealed that acetylenic alcohol **1** showed antitumor activity against the H-522 non-small cell lung line and the IGROV-1 ovarian line.[5]

The only synthesis of acetylenic alcohol **1** was achieved by Naoshima in 1996, in which the key step was converting racemic **1** into the chiral acetate catalyzed by lipase Novozym 435 with excellent enantioselectivity.[6] Despite this advance, a more efficient and convenient asymmetric synthesis of marine natural product **1** still remains highly desirable.

The key issue in the synthesis of acetylenic alcohol **1** is the construction of the stereocenter at C-3. The enantioselective addition of the terminal alkynes to aldehydes can give optically active propargyl alcohols directly.[7–9] We envisioned that the propargyl alcohol motif of **1** could be formed through this methodology. Herein, we report an efficient enantioselective synthesis of antitumor marine natural product **1** with high enantiomeric purity, which is the first synthesis of **1** via an asymmetric catalytic reaction.



(*S*,4*E*,15*Z*)-docosa-4,15-dien-1-yn-3-ol **1**

Figure 1. The structure of the marine natural product **1**.

2. Results and discussion

Our retrosynthetic analysis of the marine natural product **1** is depicted in Figure 2. The chiral acetylenic alcohol **1** can be formed via the desilylation of propargyl alcohol **11**. The enantioselective addition of trimethylsilylacetylene to diolefinc aldehyde **10** using a Trost's prophenol ligand was expected to generate chiral propargyl alcohol **11**. Our synthesis began with the preparation of diolefinc aldehyde **10**.

As outlined in Scheme 1, the preparation of diolefinc aldehyde **10** started from the coupling of propargyl alcohol **2** with 1-iodononane in the presence of *n*-BuLi, which gave dodec-2-yn-1-ol **3** in 93% yield.[10] Subsequent zipper reaction of alkyne **3** and protection of the resulting alcohol with dihydropyrane afforded the desired terminal alkyne **4** in 88% yield over two steps.[11,12] This was followed by coupling with 1-bromohexane, leading to acetylenic THP ether **5** in 91% yield.[13] Treatment of THP ether **5** with *p*-toluenesulfonic acid furnished acetylenic alcohol **6**,[14] which was oxidized to acetylenic aldehyde **7** in 91% yield with $PhI(OAc)_2$ and 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO).[15] Wittig olefination of acetylenic aldehyde **7** with triethylphosphonoacetate and

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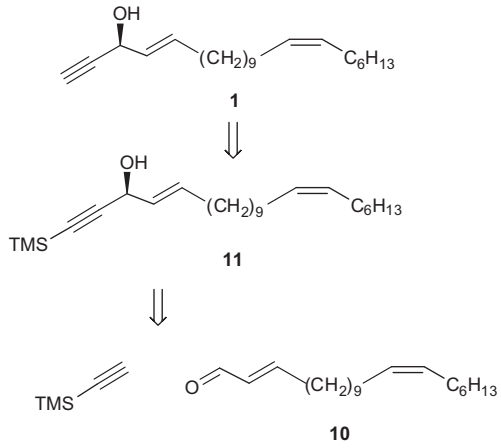


Figure 2. Retrosynthetic analysis of the marine natural product **1**.

reduction with DIBAL-H resulted in the formation of enynic alcohol **8** (77% yield for 2 steps).[16] Finally, diolefinc alcohol **9** was obtained in 89% yield via the selective reduction of **8** with a P2-Ni system,[17] followed by oxidation to give diolefinc aldehyde **10** with $PhI(OAc)_2$ and TEMPO.[15]

With diolefinc aldehyde **10** in hand, we accomplished the synthesis of the marine natural product **1** (Scheme 2). The enantioselective addition of trimethylsilylacetylene to **10** provided chiral propargyl alcohol **11** in 81% yield and with 80% ee using 20 mol % of the (*R*,*R*)-ProPhenol ligand.[18] Recrystallization of the benzoate from chiral alcohol can improve the enantiomeric purity.[19] Fortunately, recrystallization of 3,5-dinitrobenzoate **12** in *n*-hexane–ether (5:1) could significantly improve the enantiomeric purity from 81% to 96% ee. The last in situ desilylation and methanolysis of **12** with potassium carbonate and methanol afforded the target acetylenic alcohol **1** in 92% yield and with 96% ee, which were mild and did not react at chiral C-3.[20] The NMR spectrum of **1** was identical to that of the natural (*S*,4*E*,15*Z*)-docosa-4,15-dien-1-yn-3-ol **1**, furthermore, the specific rotation $\{[\alpha]_D^{20} = +18.4$ (*c* 0.10, MeOH)} measured for **1** was consistent with the literature value $\{[\alpha]_D^{20} = +21.5$ (*c* 1.1, MeOH)}.[5]

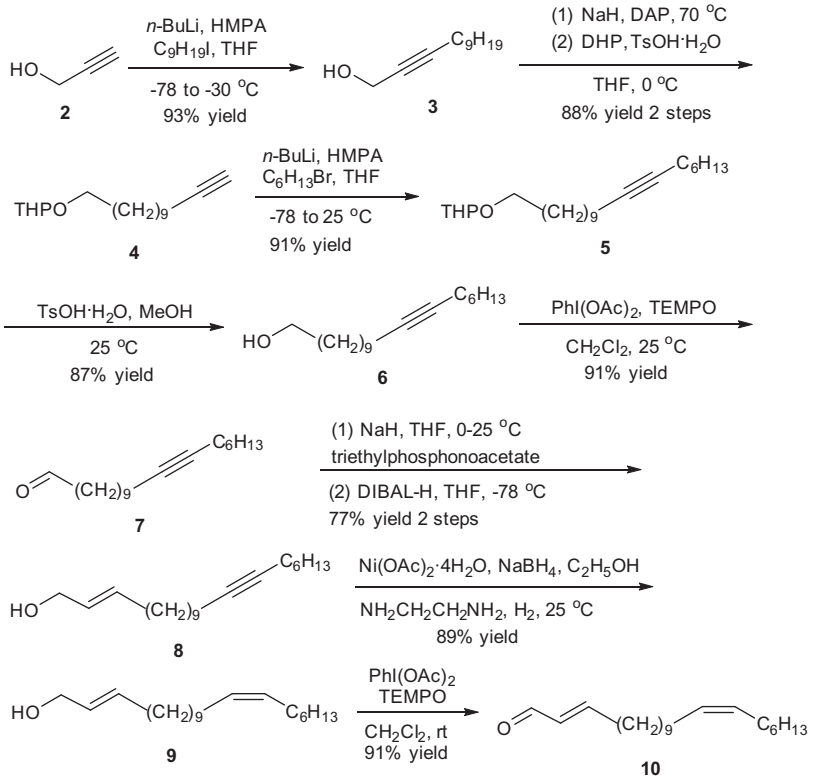
3. Conclusion

In conclusion, we have achieved an efficient enantioselective synthesis of (*S*,4*E*,15*Z*)-docosa-4,15-dien-1-yn-3-ol **1**, an antitumor marine natural product, with 96% ee and in 15% overall yield. This is the first preparation of **1** via an asymmetric catalytic reaction. The key steps involve the asymmetric addition of trimethylsilylacetylene to a diolefinc aldehyde using an (*R*,*R*)-ProPhenol ligand and a zipper reaction of an alkyne.

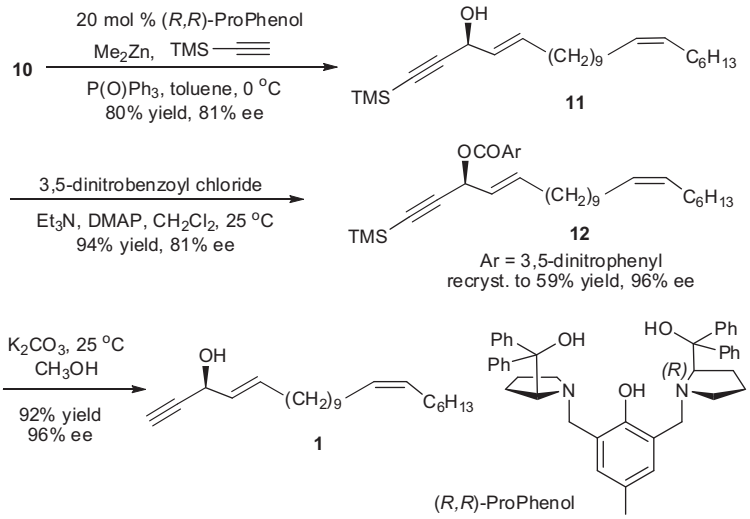
4. Experimental

4.1. General

All reactions were performed under an argon atmosphere in oven-dried glassware unless otherwise indicated. Solvents were dried according to standard procedures and distilled before use. All other reagents including (*R*,*R*)-ProPhenol ligand were purchased from Sigma–Aldrich, Acros or Alfa Aesar and used without further purification unless specified otherwise. ^1H and ^{13}C NMR spectra were recorded on a Bruker DP-X300 MHz spectrometer, and tetramethylsilane was used as the internal standard. High-resolution mass spectra were obtained on an Agilent instrument using the TOF MS technique. Optical rotations were measured with Perkin–Elmer 341 polarimeter. Enantiomeric excesses (ee) were



Scheme 1. Synthesis of diolefinc aldehyde **10**.



Scheme 2. Synthesis of the marine natural product **1**.

determined on an Agilent 1200 HPLC system with Daicel Chiralcel OD-H column or R&C OD column.

4.2. Synthesis of (*S*,4*E*,15*Z*)-docosa-4,15-dien-1-yn-3-ol 1

4.2.1. Dodec-2-yn-1-ol 3

To a stirred solution of HMPA (42 mL) in THF (50 mL) was added propargyl alcohol **2** (3.36 g, 60 mmol) at 25 °C. The resulting mixture was cooled to −78 °C, and *n*-butyllithium (48 mL, 2.5 M in *n*-hexane, 120 mmol) was added slowly under argon. Next, the mixture was warmed to −30 °C and stirred for 1.5 h, after which 1-iodononane (16.8 g, 66 mmol) was added dropwise via syringe at the same temperature. The reaction mixture was maintained for 12 h at room temperature and then quenched with water (5 mL). The aqueous phase was extracted with ethyl acetate (3 × 40 mL). The combined organic phases were dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (*n*-hexane/ethyl acetate 5:1–10:1) to afford **3** (10.2 g, 93% yield) as a white solid. Mp 32–33 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.25 (dt, J = 6.0, 2.1 Hz, 2H), 2.24–2.18 (m, 2H), 1.95 (t, J = 6.0 Hz, 1H), 1.55–1.46 (m, 2H), 1.38–1.27 (m, 12H), 0.88 (t, J = 6.5 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 86.5, 78.2, 51.2, 31.8, 29.4, 29.2, 29.1, 28.8, 28.6, 22.6, 18.7, 14.0. HRMS (APCI-TOF) calcd for $[M+H]^+$ $C_{12}H_{23}O$ 183.1749, found: 183.1756.

4.2.2. 2-(Dodec-11-yn-1-yloxy)tetrahydro-2*H*-pyran 4

To NaH (4.6 g, 60% in mineral oil, 115 mmol) was added 1,3-diaminopropane (150 mL). The resulting mixture was warmed to 70 °C and stirred for 1 h. After being cooled to room temperature, alkynol **3** (5.0 g, 27.5 mmol) was added. The reaction mixture was warmed to 55 °C and stirred overnight. The reaction solution was quenched with water (3 mL), and the aqueous phase was extracted with ethyl acetate (3 × 50 mL). The combined organic phases were dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to obtain the crude dodec-11-yn-1-ol as a colorless oil.

To a solution of crude dodec-11-yn-1-ol (1.1 g, 6 mmol) and dihydropyrane (0.6 g, 7.2 mmol) in THF (30 mL) was added $TsOH{\cdot}H_2O$ (62 mg, 0.3 mmol) at 25 °C. The reaction mixture was cooled to 0 °C and stirred for 12 h. The reaction solution was quenched with saturated aqueous Na_2CO_3 solution (30 mL), and the aqueous phase was extracted with Et_2O (3 × 50 mL). The combined organic layers were dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (*n*-hexane/ethyl acetate 20:1) to furnish **4** (1.4 g, 88% yield for 2 steps) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.59–4.56 (m, 1H), 3.87–3.84 (m, 1H), 3.77–3.69 (m, 1H), 3.52–3.48 (m, 1H), 3.42–3.34 (m, 1H), 2.18 (dt, J = 4.3, 2.6 Hz, 2H), 1.94 (t, J = 2.6 Hz, 1H), 1.84–1.82 (m, 1H), 1.72–1.70 (m, 1H), 1.62–1.48 (m, 8H), 1.41–1.28 (m, 12H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 98.8, 84.7, 68.0, 67.6, 62.2, 30.7, 29.7, 29.4, 29.3, 29.0, 28.7, 28.4, 26.2, 25.5, 19.6, 18.3. HRMS (APCI-TOF) calcd for $[M+H]^+$ $C_{17}H_{31}O_2$ 267.2324, found: 267.2336.

4.2.3. 2-(Octadec-11-yn-1-yloxy)tetrahydro-2*H*-pyran 5

To a stirred solution of HMPA (3.5 mL) in THF (30 mL) was added terminal alkyne **4** (1.3 g, 5 mmol) at 25 °C. The resulting mixture was cooled to −78 °C, after which *n*-butyllithium (13.5 mL, 2.3 M in *n*-hexane, 31 mmol) was added slowly under argon. After stirring for 1.5 h at −30 °C, 1-bromohexane (0.9 g, 5.5 mmol) was added dropwise via syringe at the same temperature. The reaction mixture was maintained at room temperature for 12 h and then quenched with water (1 mL). The aqueous phase was extracted with ethyl acetate (3 × 40 mL). The combined organic phases were dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (*n*-hexanes/ethyl acetate 20:1) to furnish **5** (1.6 g, 91% yield) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.58 (t, J = 4.5 Hz, 1H), 3.90–3.83 (m, 1H), 3.77–3.69 (m, 1H), 3.53–3.48 (m, 1H), 3.42–3.34 (m, 1H), 2.13 (t, J = 6.8 Hz, 4H), 1.86–1.68 (m, 2H), 1.61–1.28 (m, 28H), 0.88 (t, J = 6.8 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 98.7, 80.05, 80.04, 67.5, 62.1, 31.3, 30.7, 29.7, 29.5, 29.4, 29.3, 29.1, 29.06, 29.05, 28.7, 28.4, 26.2, 25.5, 22.5, 19.6, 18.7, 13.9. (One resonance was not observed due to overlapping.) HRMS (APCI-TOF) calcd for $C_{23}H_{43}O_2$ $[M+H]^+$ 351.3263, found 351.3274.

4.2.4. Octadec-11-yn-1-ol 6

To a stirred solution of THP ether **5** (1.75 g, 5 mol) in MeOH (20 mL) was added $TsOH{\cdot}H_2O$ (103 mg, 0.54 mmol). The reaction mixture was stirred at 25 °C until the complete consumption of **5** was observed by TLC. The reaction solution was quenched with water (2 mL) and extracted with ethyl acetate (3 × 10 mL). The combined organic phases were dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified

by silica gel chromatography (*n*-hexane/ethyl acetate 2:1) to give **6** (1.16 g, 87% yield) as a white solid. Mp 28–29 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.64 (q, J = 6.5 Hz, 2H), 2.16–2.11 (m, 4H), 1.59–1.28 (m, 25H), 0.89 (t, J = 6.8 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 80.23, 80.19, 63.0, 32.8, 31.4, 29.53, 29.45, 29.4, 29.15, 29.13, 28.8, 28.5, 25.7, 22.6, 18.8, 18.7, 14.0. (One resonance was not observed due to overlapping.) HRMS (APCI-TOF) calcd for $[M+H]^+$ $C_{18}H_{35}O$ 267.2688, found: 267.2700.

4.2.5. Octadec-11-ynal 7

To a stirred solution of alkynol **6** (4.3 g, 16 mmol) in CH_2Cl_2 (50 mL) was added iodobenzene diacetate (5.7 g, 17.6 mmol) at 25 °C. The resulting mixture was cooled to 0 °C, and the solution of 2,2,6,6-tetramethyl-1-piperidinyloxy (276 mg, 1.76 mmol) in CH_2Cl_2 (2 mL) was added slowly. The reaction mixture was stirred at 25 °C until the complete consumption of **6** was observed by TLC. The reaction solution was quenched with saturated aqueous $Na_2S_2O_3$ solution (20 mL), and the aqueous phase was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic phases were washed with water (30 mL) and brine (30 mL) successively, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was purified by silica gel chromatography (*n*-hexane/ethyl acetate 20:1) to afford **7** (3.84 g, 91% yield) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.76 (t, J = 1.7 Hz, 1H), 2.45–2.39 (m, 2H), 2.16–2.11 (m, 4H), 1.65–1.58 (m, 2H), 1.47–1.30 (m, 20H), 0.89 (t, J = 6.7 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 202.7, 80.2, 80.1, 43.8, 31.3, 29.3, 29.1, 29.0, 28.7, 28.5, 22.5, 22.0, 18.7, 18.6, 14.0. (Three resonances were not observed due to overlapping.) HRMS (APCI-TOF) calcd for $[M+H]^+$ $C_{18}H_{33}O$ 265.2531, found: 265.2501.

4.2.6. (*E*)-Icos-2-en-13-yn-1-ol 8

To a stirred mixture of NaH (0.240 g, 60% in mineral oil, 6 mmol) in THF (5 mL) was slowly added triethylphosphonoacetate (1.2 mL, 6 mmol) at 0 °C. After stirring for 30 min, acetylenic aldehyde **7** (1.58 g, 6 mmol) was added. The reaction was maintained for 30 min at the same temperature, warmed to room temperature slowly and stirred for 16 h. The reaction solution was diluted with Et_2O (10 mL) and washed with saturated aqueous Na_2CO_3 solution (10 mL). The combined organic phases were dried over anhydrous $MgSO_4$, and concentrated under reduced pressure to obtain the crude (*E*)-ethyl icos-2-en-13-ynoate as a colorless oil.

To a stirred solution of the crude (*E*)-ethyl icos-2-en-13-ynoate in THF (10 mL) was added dropwise DIBAL-H (12.0 mL, 1.0 M in *n*-hexane, 12.0 mmol) at −78 °C. The reaction mixture was stirred for 2 h at the same temperature and then warmed to room temperature slowly. The reaction solution was quenched with saturated aqueous NH_4Cl solution (3 mL). The aqueous phase was extracted with CH_2Cl_2 (15 mL) dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (*n*-hexane/ethyl acetate 2:1) to furnish **8** (1.35 g, 77% yield for 2 steps) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.74–5.58 (m, 2H), 4.08 (s, 2H), 2.14 (t, J = 6.8 Hz, 4H), 2.02 (dd, J = 13.0, 6.4 Hz, 2H), 1.47–1.28 (m, 23H), 0.89 (t, J = 6.8 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 133.4, 128.8, 80.2, 80.1, 63.8, 32.2, 31.3, 29.44, 29.40, 29.13, 29.11, 28.8, 28.5, 22.5, 18.73, 18.72, 14.0. (Three resonances were not observed due to overlapping.) HRMS (APCI-TOF) calcd for $[M+H]^+$ $C_{20}H_{37}O$: 293.2844, found: 293.2845.

4.2.7. (2*E*,13*Z*)-Icosa-2,13-dien-1-ol 9

To a stirred mixture of $Ni(OAc)_2{\cdot}4H_2O$ (0.99 g, 4 mmol) in EtOH (10 mL) was added $NaBH_4$ (0.15 g, 4 mmol) portionwise at 25 °C. After being stirred for 30 min, ethylenediamine (0.97 g, 16 mmol) and enynic alcohol **8** (1.18 g, 4 mmol) were added sequentially. The reaction mixture was stirred for 4 h under hydrogen monitored by TLC at the same temperature, and filtered through a Celite pad. The filtrate was concentrated under reduced pressure and purified by silica gel chromatography (*n*-hexane/ethyl acetate 2:1) to afford **9** (1.05 g, 89% yield) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.72–5.58 (m, 2H), 5.36 (t, J = 4.5 Hz, 2H), 4.07 (d, J = 4.1 Hz, 2H), 2.07–1.98 (m, 6H), 1.51–1.27 (m, 23H), 0.88 (t, J = 6.8 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 133.5, 129.9, 129.8, 128.8, 63.8, 32.2, 31.8, 29.73, 29.71, 29.55, 29.51, 29.46, 29.3, 29.2, 29.1, 29.0, 27.18, 27.17, 22.6, 14.1. HRMS (ESI-TOF) calcd for $C_{20}H_{39}O$ $[M+H]^+$: 295.3001, found: 295.2995.

4.2.8. (2*E*,13*Z*)-Icosa-2,13-dienal 10

According to the similar procedure described above for acetylenic aldehyde **7**, diolefinc alcohol **9** (4.70 g, 16 mmol) was converted into **10** (4.25 g, 91% yield) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.51 (d, J = 7.9 Hz, 1H), 6.85 (dt, J = 15.6, 6.8 Hz, 1H), 6.16–6.07 (m, 1H), 5.35 (t, J = 5.4 Hz, 2H), 2.37–2.30 (m, 2H), 2.09–1.98 (m, 4H), 1.53–1.25 (m, 22H), 0.88 (t, J = 6.8 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 194.0, 158.9, 132.9, 129.9, 129.7, 32.7, 31.7, 29.7, 29.43, 29.42, 29.3, 29.2, 29.1, 28.9, 27.9, 27.2, 27.1, 22.6, 14.0. (One resonance was not observed due to overlapping.) HRMS (APCI-TOF) calcd for $[M+H]^+$ $C_{20}H_{37}O$: 293.2844, found: 293.2857.

4.2.9. (*S*,4*E*,15*Z*)-1-(Trimethylsilyl)docosa-4,15-dien-1-yn-3-ol 11

To a solution of the (*R*,*R*)-ProPhenol ligand (25.6 mg, 0.04 mmol, 0.20 equiv) and $P(O)Ph_3$ (22.3 mg, 0.08 mmol, 0.40 equiv) in toluene (2 mL) was added trimethylsilylacetylene (59.0 mg, 0.60 mmol, 3 equiv) at 0 °C under argon. A solution of Me_2Zn (0.5 mL, 1.2 M in toluene, 0.60 mmol, 3 equiv) was then added slowly at the same temperature. The resulting mixture was warmed to 25 °C and stirred for 90 min, then cooled to 0 °C. After diolefinc aldehyde **10** (58.5 mg, 0.20 mmol, 1 equiv) was added, the reaction was maintained for 48 h at 0 °C. The reaction solution was quenched with a saturated aqueous NH_4Cl solution (5 mL), and the aqueous phase was extracted with Et_2O (3 × 10 mL). The organic layers were dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (*n*-hexane/ethyl acetate 10:1) to give **11** (62.4 mg, 80% yield, 81% ee) as a colorless oil. Enantiomeric excess was determined by HPLC with a Daicel Chiralcel OD-H column (2% 2-propanol in *n*-hexane, 0.8 mL/min, 254 nm); minor (*R*)-enantiomer t_r = 5.52 min, major (*S*)-enantiomer t_r = 6.38 min. $[\alpha]_D^{20}$ = +11.0 (*c* 0.5, MeOH). ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.87 (dt, J = 15.2, 6.8 Hz, 1H), 5.58 (dd, J = 15.2, 6.1 Hz, 1H), 5.35 (t, J = 4.7 Hz, 2H), 4.82 (t, J = 5.8 Hz, 1H), 2.09–1.98 (m, 6H), 1.86 (d, J = 5.9 Hz, 1H), 1.27–1.20 (m, 22H), 0.88 (t, J = 6.7 Hz, 3H), 0.18 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 134.3, 129.91, 129.86, 128.7, 105.0, 90.6, 63.4, 31.9, 31.8, 29.8, 29.7, 29.6, 29.53, 29.46, 29.3, 29.2, 29.0, 28.9, 27.2, 22.6, 14.1, −0.2. (One resonance was not observed due to overlapping.) HRMS (ESI-TOF) calcd for $[M+NH_4]^+$ $C_{25}H_{50}NOSi$ 408.3662, found 408.3657.

4.2.10. (*S*,4*E*,15*Z*)-1-(Trimethylsilyl)docosa-4,15-dien-1-yn-3-yl 3,5-dinitrobenzoate 12

To a stirred solution of **11** (0.078 g, 0.20 mmol), DMAP (2.5 mg, 0.02 mmol) and triethylamine (0.04 mL, 0.30 mmol) in dry CH_2Cl_2 (5 mL) was added 3,5-dinitrobenzoyl chloride (0.055 g, 0.24 mmol). The reaction mixture was stirred at 25 °C until the complete loss of **11** was observed by TLC. The reaction solution was quenched with water (5 mL), and the aqueous phase was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic phases were washed with saturated brine solution (50 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (*n*-hexane/ethyl acetate 20:1) to afford **12** (0.110 g, 94% yield, 81% ee)

as a white solid. Slow recrystallization of **12** from *n*-hexane–ether (5:1) improved enantiomeric purity and gave **12** (0.069 g, 59% yield, 96% ee) as white crystals. Mp 53–54 °C. Enantiomeric excess was determined by HPLC with a R&C OD column (5% 2-propanol in *n*-hexane, 1.0 mL/min, 254 nm); minor (*R*)-enantiomer t_r = 7.40 min, major (*S*)-enantiomer t_r = 8.63 min. $[\alpha]_D^{20}$ = +16.0 (*c* 0.5, MeOH). ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.24–9.14 (m, 3H), 6.19–6.10 (m, 2H), 5.71–5.64 (m, 1H), 5.39–5.28 (m, 2H), 2.17–2.10 (m, 2H), 2.02–1.99 (m, 4H), 1.44–1.28 (m, 22H), 0.88 (t, *J* = Hz, 3H), 0.22 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 161.3, 148.7, 138.8, 133.9, 129.9, 129.8, 129.6, 123.8, 122.4, 99.6, 93.6, 67.5, 32.0, 31.7, 29.7, 29.53, 29.49, 29.4, 29.25, 29.1, 28.9, 28.5, 27.2, 27.1, 22.6, 14.1, −0.3. HRMS (APCI-TOF) calcd for $[M]^-$ $C_{32}H_{48}N_2O_6Si$ 584.3282, found 584.3269.

4.2.11. (*S*,4*E*,15*Z*)-Docosa-4,15-dien-1-yn-3-ol 1

To a stirred solution of **12** (0.059 g, 0.1 mmol) in MeOH (7 mL) was added K_2CO_3 (0.027 g, 0.2 mmol). After the resulting mixture was stirred at 25 °C until complete loss of **12** was observed by TLC, the reaction mixture was extracted with Et_2O (3 × 10 mL). The combined organic phases were washed with brine (30 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (*n*-hexane/ethyl acetate 2:1) to furnish **1** (0.0293 g, 92% yield) as a colorless oil. $[\alpha]_D^{20}$ = +18.4 (*c* 0.10, MeOH). Lit[5] $[\alpha]_D$ = +21.5 (*c* 1.1, MeOH). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.94–5.87 (m, 1H), 5.65–5.57 (m, 1H), 5.35 (t, *J* = 4.7 Hz, 2H), 4.85–4.81 (m, 1H), 2.56 (d, *J* = 2.2 Hz, 1H), 2.10–1.98 (m, 6H), 1.93–1.28 (s, 23H), 0.88 (t, *J* = 6.7 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 134.5, 129.9, 129.8, 128.4, 83.4, 73.9, 62.8, 31.9, 31.8, 29.74, 29.71, 29.52, 29.50, 29.4, 29.3, 29.2, 29.0, 28.8, 27.20, 27.18, 22.6, 14.1. HRMS (APCI-TOF) calcd for $[M+H]^+$ $C_{22}H_{39}O$ 319.3001, found 319.3013.

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