Article

A Catalytic Asymmetric Protecting-Group-Free Total Synthesis of (4S,5S)-4,8-Dihydroxy-3,4-dihydrovernoniyne and its Enantiomer

GUJJULA V RAMAKRISHNA, and Rodney Agustinho Fernandes

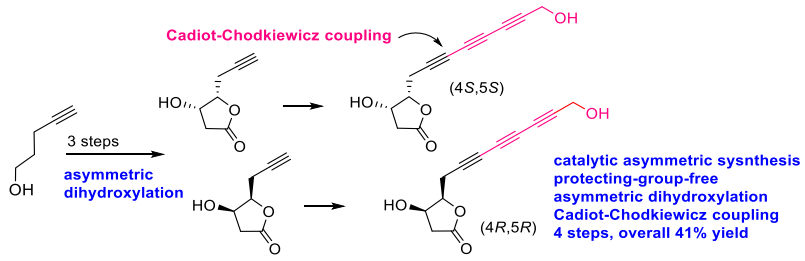
J. Org. Chem., **Just Accepted Manuscript** • DOI: 10.1021/acs.joc.9b02461 • Publication Date (Web): 18 Sep 2019

A Catalytic Asymmetric Protecting-Group-Free Total Synthesis of (4*S*,5*S*)-4,8-Dihydroxy-3,4-dihydrovernoniyne and its Enantiomer

Gujjula V. Ramakrishna and Rodney A. Fernandes*

Department of Chemistry, Indian Institute of Technology Bombay, Powai Mumbai 400076, Maharashtra, India

Supporting Information Placeholder



ABSTRACT: A catalytic asymmetric second generation synthesis of (4*S*,5*S*)-4,8-dihydroxy-3,4-dihydrovernoniyne has been completed employing the asymmetric dihydroxylation strategy. Further, a four step protecting-group-free synthesis of the natural product and its enantiomer has been achieved through modified Knoevenagel reaction, asymmetric dihydroxylation and Cadiot–Chodkiewicz coupling. The protecting-group-free synthesis is completed in 4 steps and 41% overall yield.

INTRODUCTION

Natural products containing conjugated carbon-carbon triple bonds display diverse biological activities such as antibacterial, antitumor, anti-inflammatory, antiparasitic, insecticidal, antiviral and other cytotoxic activities.[1] Polyacetylene natural products are isolated from various sources.[2] Many of these tend to decompose being reactive and relatively unstable when exposed to pH variations, light and oxidative conditions.[3] Various coupling strategies have been used toward the synthesis of polyacetylene bonds in natural products, like Glaser–Hay,[4] Sonogashira[5] and Cadiot–Chodkiewicz[6] coupling being quite popular. Catalysis in asymmetric synthesis of natural products have gained significance due to various environment and economic concerns.[7] Similarly, the protecting-group-free synthesis enables step-economy in a total synthesis. Over the past few decades, many natural products have been synthesized without relying on the use of protecting groups, displaying the potential for future course of natural product syntheses with improved economy and efficiency.[8] In this paper, we describe a catalytic asymmetric second generation synthesis of (4*S*,5*S*)-4,8-dihydroxy-3,4-dihydrovernoniyne (**1b**, Figure 1), a triyne natural product, the structure of which has been revised through total synthesis. Biavatti and coworkers[9] isolated this triyne natural product along with other related molecules from the leaves of *Vernonia scorpioides* (Asteraceae). Their structures were deduced by MS analysis and 1D and 2D NMR spectroscopy. Recently, Mohapatra *et al.*[10] accomplished the first asymmetric total synthesis of (4*S*,5*R*)-**1a** and (4*S*,5*S*)-4,8-dihydroxy-3,4-dihydrovernoniyne (**1b**) (using the chiral pool material D-mannitol) leading to the revision in the structure of the natural product, to have the (4*S*,5*S*) absolute configuration. The presence of β-hydroxy-γ-lactone moiety in this natural product caught our attention and we recently completed the total synthesis of all stereoisomers through chiral pool chemistry and confirmed the natural product to have the (4*S*,5*S*) configuration.[11] The synthesis was based on an efficient conversion of L-mannonic-γ-lactone or D-glucono-δ-lactone to either enantiomer of γ-vinyl-β-hydroxy-γ-lactone, hetero-atom directed Wacker oxidation, Seyferth–Gilbert reaction and Cadiot–Chodkiewicz coupling. Considering the C4/C5 relative configuration in the natural product to be *syn*, we envisioned the same to be derived through catalytic asymmetric dihydroxylation of a *trans*-β-γ-unsaturated ester.

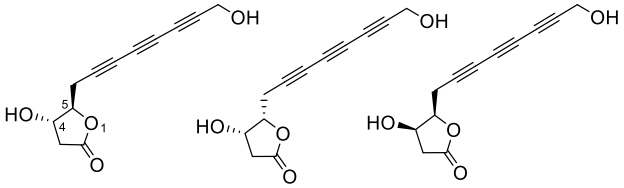
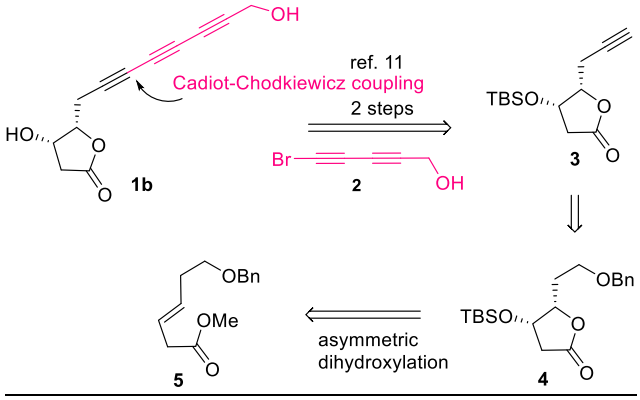


Figure 1. The triyne natural product **1a**, revised structure **1b** and its enantiomer.

The retrosynthetic analysis for **1b** based on asymmetric dihydroxylation is depicted in Scheme 1. Our initial focus was to synthesize the intermediate **3** from which the final molecule has been synthesized by us in two steps.[11] The alkyne **3** can be obtained through homologation of aldehyde

from **4** after debenzylation. The latter was planned through catalytic asymmetric dihydroxylation of *trans*-β-γ-unsaturated ester **5**, which in turn can easily be prepared through modified Knoevenagel condensation using the requisite aldehyde.

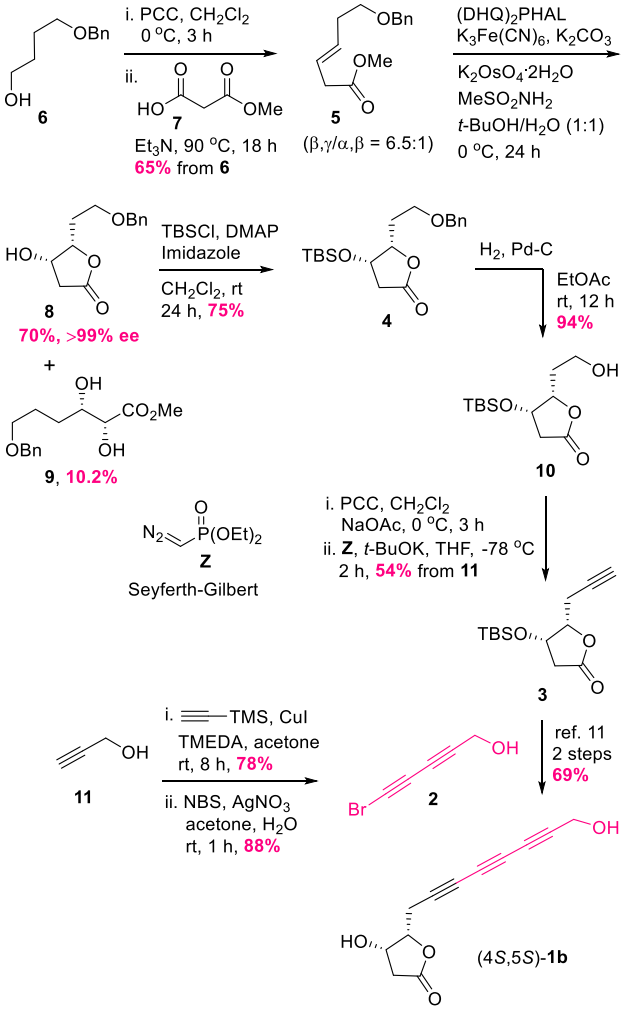
Scheme 1. Retrosynthetic Analysis for (4*S*,5*S*)-4,8-Dihydroxy-3,4-dihydrovernoniyne (1b)



RESULT AND DISCUSSION

The forward synthesis commenced from benzyl protected 1,4-diol **6** (Scheme 2). Oxidation of **6** to aldehyde and modified Knoevenagel reaction[12] with half ester of malonic acid delivered the *trans*-β,γ-unsaturated ester **5** (β,γ- v/s α,β-unsaturated = 6.5:1) in 65% yield from **6**. Further, the catalytic asymmetric dihydroxylation of **5** using the $(DHQ)_2$-PHAL ligand provided the β-hydroxy-γ-lactone **8** in 70% yield and >99% ee.[13] The latter was free from undesired α,β-dihydroxylated compound **9** isolated in 10.2% yield arising from α,β-unsaturated olefin (present in **5**) at this stage. Protection of the free hydroxyl group of **8** as TBS ether **4** in 75% yield, and further debenzylation gave **10** in 94% yield. Oxidation of alcohol **10** with PCC to the corresponding aldehyde followed by alkynylation using Seyferth–Gilbert reagent **Z**[14] proceeded optimally to give the alkyne **3** in 54% yield (over two steps from **10**). The use of Ohira–Bestmann reagent gave **3** in lower yield (43%). The required bromodiyne partner **2** was prepared in two steps from propargyl alcohol **11**, by first coupling with TMS acetylene under Glaser–Hay conditions[4] and then one-step desilylative bromination.[15] This two step sequence provided **2** in 69% overall yield. Further, coupling of alkyne **3** with bromo-alkyne **2** under Cadiot–Chodkiewicz conditions[6] (CuCl, $NH_2OH.HCl$, *n*-$BuNH_2$), and deprotection of TBS ether furnished (4*S*,5*S*)-4,8-dihydroxy-3,4-dihydrovernoniyne (**1b**) in 69% overall yield from **3**.[11] Compound **1b** had optical rotation $[\alpha]_D^{25}$ –14.8 (*c* 0.78, EtOH) in comparison to our earlier work,[11] $[\alpha]_D^{25}$ –17.6 (*c* 0.83, EtOH) and the natural isolate[9] as $[\alpha]_D^{25}$ –2.16 (*c* 0.74, EtOH). Spectral data was well in agreement with the literature data.[10] While compound **6** is prepared from 1,4-butane diol in 81% yield (see Experimental Section), the catalytic asymmetric dihydroxylation-based synthesis of **1b** was completed in 10 steps from 1,4-butanediol in overall yield of 9.7%.

Scheme 2. Catalytic Asymmetric Total Synthesis of (4*S*,5*S*)-4,8-Dihydroxy-3,4-dihydrovernoniyne (1b)

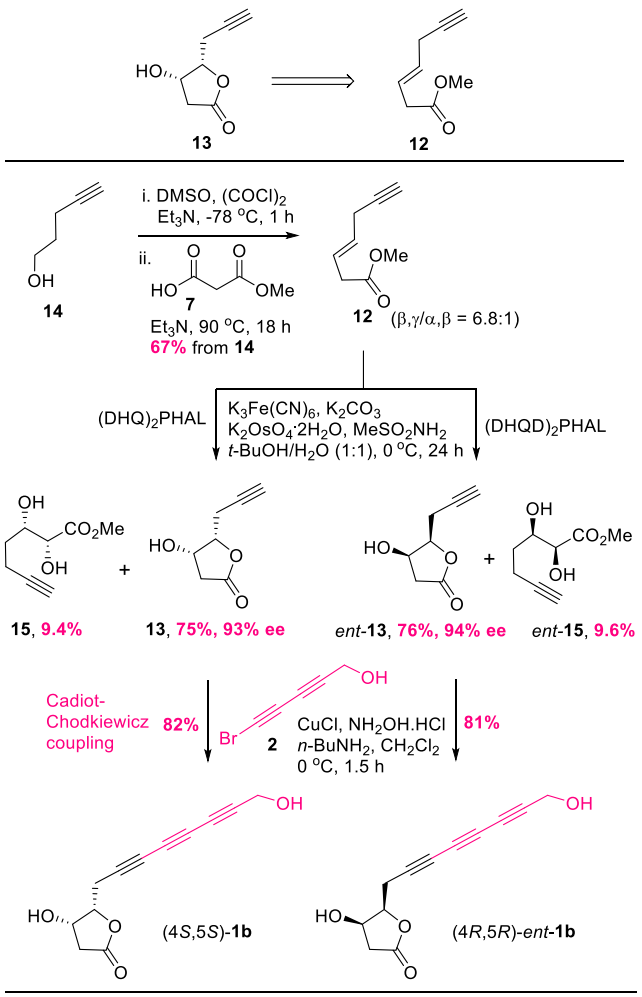


We envisioned that the oxidation of 4-pentyne-1-ol to the aldehyde, followed by modified Knoevenagel reaction would the give the *trans*-β,γ-unsaturated-ω-alkyne-ester **12**, which on catalytic asymmetric dihydroxylation would give the γ-(prop-2-yne-1-yl)-β-hydroxy-γ-lactone **13** directly (Scheme 3). This strategy appeared promising, considering a protecting-group-free approach being possible to synthesize **1b** and its enantiomer in a short four step sequence. This synthesis will be highly efficient and step-economic.

The commercially available 4-pentyne-1-ol (**14**, Sigma Aldrich, approx. $7/g) was oxidized to the aldehyde under Swern oxidation conditions and subsequent modified Knoevenagel reaction[12] using half ester of malonic acid furnished the *trans*-β,γ-unsaturated-ω-alkyne-ester **12** in 67% yield from **14** (β,γ- v/s α,β-unsaturated = 6.8:1, Scheme 3). The ensuing stereodivergent catalytic asymmetric dihydroxylation of **12** using $(DHQ)_2$-PHAL or $(DHQD)_2$-PHAL ligands provided γ-(prop-2-yne-1-yl)-β-hydroxy-γ-lactone **13** and *ent*-**13**, efficiently in 75% and 76% yields, respectively. We also isolated the minor diols **15** (9.4%) and *ent*-**15** (9.6%) arising from the dihydroxylation of the corresponding α,β-unsaturated ester compound present, in each case, respectively. Compounds **13** and *ent*-**13** were obtained in 93% ee and 94% ee, respectively.[16] Finally, the efficient

coupling of **13** or *ent*-**13**, each with bromodiyne **2**, under Cadiot–Chodkiewicz conditions[6] furnished (4*S*,5*S*)-4,8-dihydroxy-3,4-dihydrovernoniyne (**1b**, 82%) and *ent*-**1b** (81%) in a protecting-group-free synthesis. The spectral and analytical data of **1b**, $[\alpha]_D^{25}$ –14.6 (*c* 0.73, EtOH) and *ent*-**1b**, $[\alpha]_D^{25}$ +15.1 (*c* 0.75, EtOH) matched well with that reported in the literature.[10,11] The four step sequence was completed in a promising 41% overall yield for both enantiomers from **14**.

Scheme 3. Catalytic Asymmetric Protecting-Group-Free Total Synthesis of (4*S*,5*S*)-4,8-Dihydroxy-3,4-dihydrovernoniyne (1b) and its Enantiomer *ent*-1b



CONCLUSION

In summary, in this paper we have accomplished the catalytic asymmetric second generation total synthesis of (4*S*,5*S*)-4,8-dihydroxy-3,4-dihydrovernoniyne **(1b)** employing modified Knoevenagel reaction, catalytic asymmetric dihydroxylation, Seyferth–Gilbert alkyne formation and Cadiot–Chodkiewicz coupling. Also, a promising protecting-group-free four step synthesis of both enantiomers of the natural product **1b** has been completed based on modified Knoevenagel reaction, asymmetric dihydroxylation and Cadiot–Chodkiewicz coupling in an overall yield of 41%.

EXPERIMENTAL SECTION

General information. Solvents were dried by using standard procedures. Thin-layer chromatography was performed on EM 250 Kieselgel 60 F254 silica gel plates. The spots were visualized by staining with $KMnO_4$ or by using a UV lamp. ^{1}H-NMR and ^{13}C-NMR were recorded with a spectrometer operating at 400 or 500 and 100 or 125 MHz for proton and carbon nuclei, respectively. The chemical shifts are based on the $CDCl_3$ peak at δ = 7.26 ppm for proton NMR and the $CDCl_3$ peak at δ = 77.00 ppm (t) for carbon NMR and acetone-d_6 peak at 29.92 (s) in carbon NMR. IR spectra were obtained on an FT-IR spectrometer by evaporating compounds dissolved in $CHCl_3$ on CsCl pellete or by preparing KBr pellets for solids. HRMS (ESI-TOF) spectra were recorded using positive electrospray ionization by the TOF method.

4-Benzyloxy-butan-1-ol ***(6)***.[13b] To a suspension of NaH (843.3 mg, 60% in mineral oil, 21.08 mmol, 1.0 equiv) in dry THF (30 mL) was added dropwise butane-1,4-diol (1.9 g, 21.08 mmol) at 0 °C. After complete addition, the mixture was stirred for 30 min and benzyl bromide (3.0 g, 17.54 mmol, 0.832 equiv) was added dropwise. Then a catalytic amount of tetra-butylammonium iodide was added and the reaction mixture was allowed to warm to room temperature and was stirred for 3 h. The reaction was quenched with sat. aq. NH_4Cl, and the solution extracted with EtOAc (2 × 20 mL). The combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated. The residue was purified by silica gel column chromatography using petroleum ether/EtOAc (4:1) as eluent to give **6** (3.08 g, 81%) as colorless oil. IR ($CHCl_3$): ν_{max} = 3419, 3030, 2937, 2871, 1638, 1496, 1454, 1364, 1204, 1087, 1072, 955, 740, 699, 608 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.35–7.26 (m, 5H), 4.52 (s, 2H), 3.62 (t, *J* = 5.9 Hz, 2H), 3.52 (t, *J* = 5.8 Hz, 2H), 2.35 (br s, 1H), 1.74–1.64 (m, 4H) ppm; ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ = 138.1, 128.4, 127.7, 127.6, 73.0, 70.3, 62.5, 30.0, 26.5 ppm.

Methyl (E)-6-(benzyloxy)hex-3-enoate ***(5)***.[13b,c] To a solution of alcohol **6** (1.0 g, 5.54 mmol) in CH_2Cl_2 (20 mL) was added PCC (1.8 g, 8.32 mmol, 1.5 equiv) at 0 °C. The resulting mixture was stirred at 0 °C for 3 h. The mixture was then filtered through a pad of Celite and silica gel and the pad washed with CH_2Cl_2. The filtrate was concentrated to give the crude aldehyde that was used for the next step.

To the above aldehyde (1.0 g) was added mono methyl malonate (654 mg, 5.54 mmol, 1.0 equiv) followed by Et_3N (0.74 mL, 5.54 mmol, 1.0 equiv). The reaction mixture was stirred at 90 °C for 18 h. It was then cooled to room temperature and concentrated. The residue was purified by silica gel column chromatography using petroleum ether/EtOAc (9:1) as eluent to give ester **5** (0.844 g, 65%, β,γ- v/s α,β-unsaturated = 6.5:1 by ^{1}H NMR) as colorless oil. IR ($CHCl_3$): ν_{max} = 3020, 2966, 2932, 1736, 1481, 1366, 1103, 1027, 968, 736, 693 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.35–7.26 (m, 5H), 5.63–5.59 (m, 2H), 4.51 (s, 2H), 3.6 (s, 3H), 3.52–3.49 (dd, *J* = 13.5, 6.7 Hz, 2H), 3.05 (d, *J* = 5.8 Hz, 2H), 2.39–2.29 (m, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CHCl_3$): δ = 172.4, 138.4, 131.0, 128.3, 127.6, 127.5, 123.6, 72.9, 69.6, 51.8, 37.9, 32.9 ppm; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ Calcd for $C_{14}H_{18}O_3Na$ 257.1148; Found 257.1145.

*(4S,5S)-5-(2-Benzyloxyethyl)-4-hydroxydihydrofuran-2(3H)-one (**8**)*[13b,c] *and Methyl (2R,3S)-6-benzyloxy-2,3-dihydroxhexanoate (**9**).* To a mixture of $K_3Fe(CN)_6$ (2.107 g, 6.40 mmol, 3.0 equiv), K_2CO_3 (884.5 mg, 6.40 mmol, 3.0 equiv), $(DHQ)_2$-PHAL (16.4 mg, 0.021 mmol, 1 mol%) in *t*-BuOH-H_2O (1:1, 40 mL) cooled at 0 °C was added $K_2OsO_4{\cdot}2H_2O$ (4.7 mg, 0.0128 mmol, 0.6 mol%) followed by methane sulfonamide (191 mg, 2.01 mmol, 1.0 equiv). After stirring for 5 min at 0 °C, the olefin **5** (500 mg, 2.134 mmol) was added in one portion. The reaction mixture was stirred at 0 °C for 24 h and then quenched with solid Na_2SO_3 (1.0 g). Stirring was continued for an additional 45 min and the solution was extracted with EtOAc (2 × 30 mL). The combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated. The residue was purified by silica gel column chromatography using petroleum ether/EtOAc (3:2) as eluent to give methyl (2*R*,3*S*)-6-benzyloxy-2,3-dihydroxhexanoate **9** (58.4 mg, 10.2 %) as colorless oil. Further elution provided the lactone **8** (353 mg, 70%) as white solid.

Data for **9:** $[\alpha]_D^{25}$ –7.8 (*c* 1.0, $CHCl_3$); IR ($CHCl_3$): ν_{max}= 3505, 3284, 2955, 2928, 2854, 1740, 1647, 1449, 1363, 1285, 1219, 1127, 1093, 1019, 700, 668, 627; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.38–7.24 (m, 5H), 4.51 (s, 2H), 4.09 (d, *J* = 2.0 Hz, 1H), 3.95–3.91 (m, 1H), 3.81 (s, 3H), 3.53 (dt, *J* = 12.0, 6.1 Hz, 2H), 1.83–1.71 (m, 4H); ^{13}C{^{1}H} NMR (125 MHz, $CHCl_3$): δ = 173.9, 138.0, 128.4, 127.7, 127.67, 73.5, 73.1, 72.3, 70.1, 52.7, 31.1, 26.2 ppm; HRMS (ESI-TOF) *m/z*: [M + Na]$^+$ Calcd for $C_{14}H_{20}O_5Na$ 291.1203; Found 291.1207.

Data for **8**: M.p. 76–77 °C, $[\alpha]_D^{25}$ –41.4 (*c* 2.5, $CHCl_3$), lit.[13c] $[\alpha]_D^{22}$ –42.2 (*c* 2.68, $CHCl_3$); IR ($CHCl_3$): ν_{max} = 3403, 3037, 2961, 2941, 2892, 2862, 1763, 1453, 1346, 1318, 1295, 1233, 1201, 1177, 1128, 1067, 1002, 959, 901, 796, 751, 700, 666, 610, 531 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.38–7.28 (m, 5H), 4.57–4.49 (m, 2H), 4.46–4.41 (m, 2H), 3.74–3.69 (m, 1H), 3.57–3.52 (m, 1H), 2.75 (dd, *J* = 17.8, 5.6 Hz, 1H), 2.53 (d, *J* = 17.9 Hz, 1H), 2.30–2.26 (m, 1H), 2.24–2.12 (m, 1H) ppm; ^{13}C{^{1}H} NMR (100 MHz, $CHCl_3$): δ = 175.6, 136.9, 128.6, 128.2, 127.9, 83.7, 73.8, 68.6, 66.0, 37.9, 28.5 ppm; HRMS (ESI-TOF) *m/z*: [M + K]$^+$ Calcd for $C_{13}H_{16}O_4K$ 275.0680; Found 275.0682. The enantiomeric excess of **8** was determined by converting it into its OTBDPS ether **8′** using TBDPS-Cl and by following a similar procedure as described for compound **4**. Reaction of **8** (20 mg, 0.084 mmol) using TBDPS-Cl (34.7 mg, 0.126 mmol, 1.5 equiv) gave **8′** (29.3 mg, 76%) as colorless oil. $[\alpha]_D^{25}$ –21.8 (*c* 1.0, $CHCl_3$); IR ($CHCl_3$): ν_{max} = 2959, 2932, 2856, 1780, 1462, 1428, 1363, 1203, 1159, 1112, 1078, 1028, 936, 897, 822, 741, 702, 612, 506 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.63–7.60 (m, 4H), 7.48–7.24 (m, 11H), 4.58–4.51 (m, 2H), 4.50–4.45 (m, 2H), 3.65 (dd, *J* = 7.4, 4.6 Hz, 2H), 2.40 (dd, *J* = 17.5, 5.1 Hz, 1H), 2.37 (dd, *J* = 17.5, 2.0 Hz, 1H), 2.22–2.15 (m, 1H), 2.07–2.01 (m, 1H), 1.07 (s, 9H); ^{13}C{^{1}H} NMR (125 MHz, $CHCl_3$): δ = 175.2, 138.1, 135.8, 135.7, 133.0, 132.4, 130.2, 128.4, 128.0, 127.95, 127.8, 127.7, 81.8, 73.3, 70.9, 66.5, 39.1, 29.8, 26.9, 19.3 ppm; HRMS (ESI-TOF) *m/z*: [M + Na]$^+$ Calcd for $C_{29}H_{34}O_4SiNa$ 497.2119; Found 497.2116. HPLC: CHIRALCEL AD-H column, hexane/*i*-PrOH = 95:5, flow rate = 1.0 mL/min, t_R = 7.55 min (major) and 9.45 min (minor), >99% ee.

*(4S,5S)–5-(2-Benzyloxyethyl)-4-(tert-butyldimethylsilyloxy)dihydrofuran-2(3H)-one (**4**).* To a stirred solution of alcohol **8** (750 mg, 3.174 mmol) in CH_2Cl_2 (15 mL) at 0 °C was added imadazole (432 mg, 6.35 mmol, 2.0 equiv) and the mixture stirred for 10 min, followed by addition of *tert*-butyldimethylsilylchloride (717.5 mg, 4.76 mmol, 1.5 equiv) and 4-(*N*,*N*-dimethylamino)pyridine (77.5 mg, 0.634 mmol, 0.2 equiv). After stirring for 24 h at room temperature, the reaction was quenched by addition of sat. aq. NH_4Cl solution (50 mL) and then diluted with CH_2Cl_2 (50 mL). The layers were separated, and the aqueous layer extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated. The residue was purified by silica gel column chromatography using petroleum ether/EtOAc (4:1) as eluent to give silyl ether **4** (834 mg, 75%) as colorless oil. $[\alpha]_D^{25}$ –34.4 (*c* 1.2, $CHCl_3$); IR ($CHCl_3$): ν_{max}= 2930, 2857, 1777, 1471, 1362, 1258, 1205, 1164, 1096, 1026, 908, 838, 778, 700 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.36–7.32 (m, 5H), 4.62 (d, *J* = 9.2 Hz, 1H), 4.50 (q, *J* = 11.7 Hz, 2H), 4.38 (s, 1H), 3.65 (dd, *J* = 7.2, 4.7 Hz, 2H), 2.73 (dd, *J* = 17.2, 4.9 Hz, 1H), 2.42 (d, *J* = 17.1 Hz, 1H), 2.14–2.03 (m, 1H), 1.95–1.87 (m, 1H), 0.87 (s, 9H), 0.06 (s, 3H), 0.04 (s, 3H) ppm; ^{13}C{^{1}H} NMR (100 MHz, $CHCl_3$): δ = 175.4, 138.1, 128.4, 127.7, 127.67, 81.9, 73.2, 69.7, 66.4, 39.8, 29.5, 25.6, 17.9, –4.7, –5.2 ppm; HRMS (ESI-TOF) *m/z*: [M + Na]$^+$ Calcd for $C_{19}H_{30}O_4SiNa$ 373.1806; Found 373.1805.

*(4S,5S)-4-(tert-Butyldimethylsilyloxy)-5-(2-hydroxyethyl)dihydrofuran-2(3H)-one (**10**).* To a stirred solution of **4** (500 mg, 1.426 mmol) in EtOAc (20 mL) was added Pd-C (10%, 15 mg) and the mixture stirred at room temperature under H_2 (balloon). After stirring for 12 h at room temperature, the mixture was filtered through Celite pad and the pad washed with EtOAc. The filtrate was concentrated and the residue purified by silica gel column chromatography using petroleum ether/EtOAc (3:2) as eluent to afford **10** (349 mg, 94%) as colorless solid. M.p. 55–59 °C; $[\alpha]_D^{25}$ –36.3 (*c* 2.0, $CHCl_3$); IR ($CHCl_3$): ν_{max}= 3432, 2952, 2933, 2884, 2858, 1768, 1638, 1472, 1388, 1294, 1257, 1164, 1092, 1063, 957, 938, 878, 839, 777, 675 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.60 (dt, *J* = 9.6, 3.6 Hz, 1H), 4.42 (t, *J* = 3.8 Hz, 1H), 3.78 (dd, *J* = 6.8, 4.9 Hz, 2H), 2.74 (dd, *J* = 17.3, 5.1 Hz, 1H), 2.56 (s, 1H), 2.40 (d, *J* = 17.2 Hz, 1H), 2.07–1.98 (m, 1H), 1.84–1.76 (m, 1H), 0.85 (s, 9H), 0.04 (s, 6H) ppm; ^{13}C{^{1}H} NMR (100 MHz, $CHCl_3$): δ = 175.7, 82.2, 69.8, 58.9, 39.7, 31.8, 25.5, 17.9, –4.8, –5.2 ppm; HRMS (ESI-TOF) *m/z*: [M + Na]$^+$ Calcd for $C_{12}H_{24}O_4SiNa$ 283.1336; Found 283.1333.

*(4S,5S)-4-(tert-Butyldimethylsilyloxy)-5-(prop-2-yn-1-yl)dihydrofuran-2(3H)-one (**3**).* To a solution of alcohol **10** (100 mg, 0.384 mmol) in dry CH_2Cl_2 (10 mL) was added PCC (124 mg, 0.576 mmol, 1.5 equiv) and NaOAc (63 mg, 0.768 mmol, 2.0 equiv) at 0 °C. The reaction mixture was stirred at 0 °C for 3 h and then filtered through a pad of Celite and silica gel and the pad washed with CH_2Cl_2. The filtrate was concentrated to give the aldehyde (90 mg) which was used for next step without purification.

To a solution of diethyl (diazomethyl)phosphonate **Z** (136.8 mg, 0.768 mmol, 2.0 equiv) in THF (3 mL), cooled to –78 °C under N_2 was added *t*-BuOK (86.2 mg, 0.768 mmol, 2.0 equiv). The reaction mixture was stirred for 15 min and then a solution of above aldehyde (90 mg) in THF (2 mL) was added dropwise at –78 °C. The mixture was stirred at –78 °C for 2 h and then quenched with sat. aq. NH_4Cl solution. The solution was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated. The residue was purified by

silica gel column chromatography using petroleum ether/EtOAc (4:1) as eluent to give the alkyne **3** (52.8 mg, 54%) as yellow solid, M.p. 55–58 °C, $[\alpha]_D^{25}$ +4.1 (*c* 1.0, $CHCl_3$); IR ($CHCl_3$): ν_{max}= 3302, 2930, 2253, 1781, 1620, 1416, 1350, 1193, 1159, 1031, 987, 911, 736, 649 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 4.55 (dt, *J* = 8.6, 4.8 Hz, 1H), 4.50–4.46 (m, 1H), 2.75–2.68 (m, 3H), 2.47 (dd, *J* = 17.3, 1.0 Hz, 1H), 2.0 (t, *J* = 2.6 Hz, 1H), 0.89 (s, 9H), 0.12 (s, 3H), 0.10 (s, 3H) ppm; $^{13}C\{^1H\}$ NMR (125 MHz, $CHCl_3$): δ = 174.7, 82.4, 78.9, 70.7, 68.6, 39.6, 25.6, 18.6, 17.9, –4.7 –5.2 ppm; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ Calcd for $C_{13}H_{22}O_3Si$ Na 277.1230; Found 277.1231.

*5-Bromopenta-2,4-diyn-1-ol (**2**).* The titled compound **2** was prepared from propargyl alcohol **11** in a two-step sequence following our earlier report.[11] ^1H NMR (400 MHz, $CDCl_3$): δ = 4.32 (s, 2H), 1.86 (br s, 1H, *OH*) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 73.1, 70.7, 64.7, 51.3, 41.8 ppm.

*(4S,5S)-4,8-Dihydroxy-3,4-dihydrovernoniyne (**1b**)*. The titled compound was prepared from **3** and **2** following our earlier report[11] in overall 69% yield over two steps as a pale yellow solid, M.p. 107–108 °C; $[\alpha]_D^{25}$ –14.8 (*c* 0.78, EtOH), lit.[11] M.p. 106–109 °C; $[\alpha]_D^{25}$ –17.6 (*c* 0.83, EtOH), lit.[10] M.p. 108–110 °C; $[\alpha]_D^{25}$ –61.5 (*c* 0.94, EtOH). Spectral data is same as reported earlier.[11]

*Methyl (E)-hept-3-en-6-ynoate (**12**)*. To a solution of DMSO (1.3 mL, 17.83 mmol, 3.0 equiv) in CH_2Cl_2 (40 mL) at –78 °C under argon was added oxalyl chloride (0.76 mL, 8.91 mmol, 1.5 equiv) dropwise. The resulting solution was stirred at –78 °C for 20 min and then a solution of alcohol **14** (0.5 g, 5.94 mmol) in CH_2Cl_2 (5 mL) was added slowly, and the reaction mixture was stirred at –78 °C for 1 h. Et_3N (3.7 mL, 26.8 mmol) was then added, and the reaction mixture was maintained at –78 °C for 10 min before being warmed to room temperature and stirred for 30 min. The reaction was then quenched with water (100 mL), and the phases were separated. The organic layer was washed sequentially with 1 N HCl (20 mL), sat. aq. $NaHCO_3$ (20 mL), brine (20 mL), and then dried (Na_2SO_4) and concentrated to give the crude aldehyde (0.5 g), which was used for next step without purification. To the aldehyde (0.5 g) was added mono methyl malonate **7** (0.701 g, 5.94 mmol, 1.0 equiv) followed by Et_3N (0.83 mL, 5.94 mmol, 1.0 equiv). The reaction mixture was refluxed for 18 h. It was then cooled and concentrated. The residue was purified by silica gel column chromatography using petroleum ether/EtOAc (9:1) as eluent to give ester **12** (0.55 g, 67%, β,γ- v/s α,β-unsaturated = 6.8:1) as colorless oil. IR ($CHCl_3$): ν_{max}= 3308, 3018, 2955, 2926, 2897, 2849, 2401, 2121, 1735, 1661, 1523, 1437, 1422, 1391, 1361, 1220, 1168, 1078, 1043, 971, 929, 878, 849, 760, 667, 644, 525 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 5.87–5.80 (m, 1H), 5.59–5.52 (m, 1H), 3.68 (s, 3H), 3.07 (dd, *J* = 7.1, 1.4 Hz, 2H), 2.96–2.94 (m, 2H), 2.10 (t, *J* = 2.4 Hz, 1H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CHCl_3$): δ = 172.0, 127.7, 123.9, 81.1, 70.4, 50.8, 37.4, 21.6 ppm. Since it is a mixture, HRMS is not recorded.

*(4S,5S)-4-Hydroxy-5-(prop-2-yn-1-yl)dihydrofuran-2(3H)-one (**13**)[16] and Methyl (2R,3S)-2,3-dihydroxyhept-6-ynoate (**15**).* To a mixture of $K_3Fe(CN)_6$ (1.43 g, 4.34 mmol, 3.0 equiv), K_2CO_3 (600 mg, 4.34 mmol, 3.0 equiv), $(DHQ)_2$-PHAL (11.2 mg, 0.0144 mmol, 1.0 mol%) in *t*-BuOH-H_2O (1:1, 20 mL) cooled at 0 °C was added $K_2OsO_4{\cdot}2H_2O$ (3.3 mg, 0.00893 mmol, 0.6 mol%) followed by methane sulfonamide (137.7 mg, 1.448 mmol, 1.0 equiv). After stirring for 5 min at 0 °C, the olefin **12** (0.2 g, 1.448 mmol) was added in one portion. The reaction mixture was stirred at 0 °C for 24 h and then quenched with solid Na_2SO_3 (1.0 g) with stirring continued for an additional 45 min. The solution was extracted with EtOAc (2 × 30 mL). The combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated. The residue was purified by silica gel column chromatography using petroleum ether/EtOAc (3:2) as eluent to give methyl (2*R*,3*S*)-2,3-dihydroxyhept-6-ynoate **15** (23.4 mg, 9.4%) as colorless oil. Further elution provided the lactone **13** (152.2 mg, 75%) as colorless oil.

Data for **15**: $[\alpha]_D^{25}$ –8.8 (*c* 1.0, $CHCl_3$); IR ($CHCl_3$): ν_{max} = 3488, 3308, 3016, 2955, 2935, 2861, 2332, 2115, 1741, 1439, 1395, 1283, 1246, 1120, 1061, 988, 926, 810, 671, 638 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): 4.12 (d, *J* = 2.0 Hz, 1H), 4.10–4.06 (m, 1H), 3.84 (s, 3H), 2.37 (td, *J* = 7.4, 2.6 Hz, 2H), 1.99 (t, *J* = 2.6 Hz, 1H), 1.92–1.71 (m, 2H); $^{13}C\{^1H\}$ NMR(100 MHz, $CHCl_3$): δ =173.7, 83.4, 73.2, 71.1, 69.1, 52.9, 32.2, 14.9 ppm; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ Calcd for $C_8H_{12}O_4Na$ 195.0628; Found 195.0623

Data for **13**: $[\alpha]_D^{25}$ –10.5 (*c* 1.0, $CHCl_3$); IR ($CHCl_3$): ν_{max}= 3433, 3303, 2929, 2253, 2123, 1783, 1626, 1416, 1350, 1293, 1200, 1158, 1097, 1074, 1031, 987, 958, 911, 816, 736, 649, 557 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 4.65 (t, *J* = 4.3 Hz, 1H), 4.53 (dt, *J* = 6.0, 3.8 Hz, 1H), 2.83–2.76 (m, 2H), 2.75–2.71 (m, 1H), 2.64 (s, 1H), 2.60 (d, *J* = 17.8 Hz, 1H), 2.08 (t, *J* = 2.6 Hz, 1H) ppm; $^{13}C\{^1H\}$ NMR (125 MHz, $CHCl_3$): δ = 175.3, 81.7, 78.4, 71.3, 68.0, 38.6, 18.6 ppm; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ Calcd for $C_7H_8O_3Na$ 163.0366; Found 163.0361. The enantiomeric excess of **13** was determined by converting it into its OTBDPS ether **13′** using TBDPS-Cl and by following a similar procedure as described for compound **4**. Reaction of **13** (20 mg, 0.142 mmol) using TBDPS-Cl (58.9 mg, 0.214 mmol, 1.5 equiv) gave **13′** (40 mg, 74%) as colorless oil. $[\alpha]_D^{25}$ –5.2 (*c* 1.0, $CHCl_3$); IR ($CHCl_3$): ν_{max}= 3292, 3073, 2958, 2857, 2253, 2123, 1788, 1643, 1472, 1427, 1345, 1297, 1200, 1151, 1112, 1079, 1038, 978, 934, 886, 822, 742, 703, 613, 506 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 7.69–7.60 (m, 4H), 7.51–7.35 (m, 6H), 4.60 (dd, *J* = 6.8, 4.9 Hz, 1H), 4.44 (dd, *J* = 10.8, 6.5 Hz, 1H), 2.82 (dt, *J* = 5.3, 2.6 Hz, 2H), 2.42 (dd, *J* = 17.6, 4.2 Hz, 1H), 2.35 (dd, *J* = 17.2, 5.5 Hz, 1H), 2.05 (t, *J* = 2.5 Hz, 1H), 1.09 (s, 9H); $^{13}C\{^1H\}$ NMR(125 MHz, $CHCl_3$): δ = 174.4, 135.8, 135.7, 132.9, 132.0, 130.3, 130.2, 128.0, 127.9, 82.0, 79.1, 71.0, 69.8, 38.5, 26.8, 19.2 ppm; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ Calcd for $C_{23}H_{26}O_3SiNa$ 401.1543; Found 401.1540. HPLC **13′**: CHIRALCEL AD-H column, hexane/*i*-PrOH = 98:2, flow rate = 0.8 mL/min, t_R = 13.21 min (major) and 15.24 min (minor), 93% ee.

*(4R,5R)-4-Hydroxy-5-(prop-2-yn-1-yl)dihydrofuran-2(3H)-one (ent-**13**)[16] and Methyl (2S,3R)-2,3-dihydroxyhept-6-ynoate (ent-**15**).* The titled compounds were obtained from **12** (0.150 g, 1.09 mmol) using $(DHQD)_2$-PHAL ligand and following a similar procedure as described for **13**, to give methyl (2*S*,3*R*)-2,3-dihydroxyhept-6-ynoate *ent*-**15** (18 mg, 9.6%) and the alkyne lactone *ent*-**13** (116 mg, 76%) as colorless oils, respectively.

Data for *ent*-**15**: $[\alpha]_D^{25}$ +9.3 (*c* 1.0, $CHCl_3$). Other spectral data is same as **15**.

Data for *ent*-**13**: $[\alpha]_D^{25}$ +12.4 (*c* 1.0, $CHCl_3$). Other spectral data is same as **13**. The enantiomeric excess of *ent*-**13** was determined by converting it into its OTBDPS ether *ent*-**13′** using TBDPS-Cl and by following a similar procedure as described for compound **4**. Reaction of *ent*-**13** (25 mg, 0.178 mmol) using TBDPS-Cl (73.5 mg, 0.267 mmol, 1.5 equiv) gave *ent*-**13′** (49.5 mg, 75%) as colorless oil. $[\alpha]_D^{25}$ +5.8 (*c* 1.0, $CHCl_3$). Other spectral data is same as **13′**. HPLC *ent*-**13′**: CHIRALCEL AD-H column, hexane/*i*-PrOH = 98:2, flow rate = 0.8 mL/min, t_R = 12.99 min (minor) and 15.14 min (major), 94% ee.

(4S,5S)-4,8-Dihydroxy-3,4-dihydrovernoniyne ***(1b)***. To the flask containing CuCl (3.5 mg, 0.0356 mmol, 10 mol%) was added a 30% aq. solution of *n*-$BuNH_2$ (1.2 mL) at room temperature under nitrogen to form a blue color solution. A few crystals of hydroxylamine hydrochloride were added to discharge the blue color. To this solution, was added alkyne **13** (50 mg, 0.356 mmol) in CH_2Cl_2 (1 mL) at 0 °C to result in the formation of a yellow acetylide suspension that was immediately cooled with an ice-water mixture. To this reaction mixture, bromodiyne **2** (85 mg, 0.534 mmol, 1.5 equiv) was added at once. More crystals of hydroxylamine hydrochloride were added throughout the reaction as necessary to prevent the solution from turning blue or green. The reaction mixture was stirred at 0 °C for 1.5 h and then extracted with CH_2Cl_2 (4 × 20 mL). The combined organic layers were dried (Na_2SO_4) and concentrated. The crude product was purified by silica gel column chromatography using petroleum ether/EtOAc (1:1) as eluent to afford **1b** (63.7 mg, 82%) as a pale yellow solid, M.p. 107–109 °C; $[\alpha]_D^{25}$ −14.6 (*c* 0.73, EtOH), lit.[11] M.p. 106–109 °C; $[\alpha]_D^{25}$ −17.6 (*c* 0.83, EtOH); lit.[10] M.p. 108–110 °C; $[\alpha]_D^{25}$ −61.5 (*c* 0.94, EtOH); IR ($CHCl_3$): ν_{max}= 3416, 3024, 2928, 2858, 2220, 1774, 1453, 1407, 1350, 1152, 1104, 1021, 924, 901, 809, 667 cm^{-1}; ^1H NMR (500 MHz, Acetone–d_6): δ = 4.85 (d, *J* = 4.4 Hz, 1H), 4.64 (ddd, *J* = 7.6, 6.0, 3.8 Hz, 1H), 4.61–4.59 (m, 1H), 4.54 (t, *J* = 6.1 Hz, 1H), 4.31 (d, *J* = 6.0 Hz, 2H), 2.93 (dd, *J* = 17.4, 5.3 Hz, 1H), 2.89–2.81 (m, 2H), 2.42 (dd, *J* = 17.4, 1.1 Hz, 1H) ppm; $^{13}C\{^1H\}$ NMR (125 MHz, Acetone–d_6): δ = 175.5, 82.2, 78.9, 78.0, 69.2, 68.6, 66.8, 63.5, 60.5, 51.0, 39.8, 20.4 ppm; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{12}H_{11}O_4$ 219.0652; Found 219.0659.

*(4R,5R)-4,8-Dihydroxy-3,4-dihydrovernoniyne (ent-**1b**).* The titled compound was prepared from *ent*-**13** (40 mg, 0.285 mmol) by a similar procedure as described for **1b**, to give *ent*-**1b** (50.4 mg, 81%) as pale yellow solid, M.p. 105–107 °C, $[\alpha]_D^{25}$ +15.1 (*c* 0.75, EtOH). Other spectral data is same as its enantiomer **1b**.

ASSOCIATED CONTENT

Supporting Information.

The Supporting Information is available free of charge on the ACS Publications website at DOI:

NMR spectra (PDF)

AUTHOR INFORMATION

Corresponding Author

E-mail: rfernand@chem.iitb.ac.in

ORCID

Rodney A. Fernandes: 0000-0001-8888-0927

Notes

The authors declare no competing financial interests.

ACKNOWLEDGMENT

We thank SERB New Delhi, Grant No. EMR/2017/000499 for financial support. G.V.R. thanks CSIR New Delhi for senior research fellowship.

REFERENCES

1. (a) Ladika, M.; Fisk, T. E.; Wu, W. W.; Jons, S. D. High-Stability Liposomes from Macrocyclic Diyne Phospholipids. *J. Am. Chem. Soc.* **1994**, *116*, 12093–12094. (b) de Jesus, R. P.; Faulkner, D. J. Chlorinated Acetylenes from the San Diego Sponge *Haliclona lunisimilis*. *J. Nat. Prod*. **2003**, *66*, 671–674. (c) Lerch, M. L.; Harper, M. K.; Faulkner, D. J. Brominated Polyacetylenes from the Philippines Sponge *Diplastrella* sp. *J. Nat. Prod.* **2003**, *66*, 667–670. (d) Stavri, M.; Mathew, K. T.; Gibson, T.; Williamson, R. T.; Gibbons, S. New Constituents of *Artemisia monosperma*. *J. Nat. Prod.* **2004**, *67*, 892–894. (e) Nakai, Y.; Sakakibara, I.; Hirakura, K.; Terabayashi, S.; Takeda, S. A New Acetylenic Compound from the Rhizomes of *Atractylodes chinensis* and Its Absolute Configuration. *Chem. Pharm. Bull.* **2005**, *53*, 1580–1581. (f) Kanokmedhakul, S.; Kanokmedhakul, K.; Kantikeaw, I.; Phonkerd, N. 2-Substituted Furans from the Roots of *Polyalthia eviecta*. *J. Nat. Prod.* **2006**, *69*, 68–72. (g) Nakayama, S.; Uto, Y.; Tanimoto, K.; Okuno, Y.; Sasaki, Y.; Nagasawa, H.; Nakata, E.; Arai, K.; Momose, K.; Fujita, T.; Hashimoto, T.; Okamoto, Y.; Asakawa, Y.; Goto, S.; Hori, H. TX-2152: A Conformationally Rigid and Electron-rich Diyne analogue of FTY720 with in vivo Antiangiogenic Activity. *Bioorg. Med. Chem.* **2008**, *16*, 7705–7714. (h) Pan, Y.; Lowary, T.; Tykwinski, R. Naturally Occurring and Synthetic Polyyne Glycosides. *Can. J. Chem*. **2009**, *87*, 1565–1582. (i) Lee, Y. M.; Lim, C.; Lee, H. S.; Shin, Y. K.; Shin, K.-O; Lee, Y.-M.; Kim, S. Synthesis and Biological Evaluation of a Polyyne-Containing Sphingoid Base Probe as a Chemical Tool. *Bioconjugate Chem*. **2013**, *24*, 1324–1331.
2. (a) Ross, C.; Scherlach, K.; Kloss, F.; Hertweck, C. The Molecular Basis of Conjugated Polyyne Biosynthesis in Phytopathogenic Bacteria. *Angew. Chem., Int. Ed.* **2014**, *53*, 7794–7798. (b) Zhou, Z.-F.; Menna, M.; Cai, Y.-S.; Guo, Y.-W. Polyacetylenes of Marine Origin: Chemistry and Bioactivity. *Chem. Rev.* **2015**, *115*, 1543–1596.
3. *Thin Layer Chromatography in Phytochemistry*; Waksmundzka-Hajnos, M.; Sherma, J.; Kowalska, T., Eds.; CRC Press: Boca Raton, FL, 2008.
4. (a) Glaser, C. Beiträge zur Kenntniss des Acetenylbenzols. *Ber. Dtsch. Chem. Ges.* **1869**, *2*, 422–424. (b) Glaser, C. Untersuchungen über einige Derivate der Zimmtsäure. *Ann. Chem. Pharm.* **1870**, *154*, 137–171. (c) Hay, A. S. Oxidative Coupling of Acetylenes. *J. Org. Chem.* **1960**, *25*, 1275–1276. (d) Hay, A. S. Oxidative Coupling of Acetylenes II. *J. Org. Chem*. **1962**, *27*, 3320–3321. (e) Siemsen, P.; Livingston, R. C.; Diederich, F. Acetylenic Coupling: A Powerful Tool in Molecular Construction. *Angew. Chem., Int. Ed*. **2000**, *39*, 2632–2657.
5. (a) Sonogashira, K.; Tohda, Y.; Hagihara, N. A Convenient Synthesis of Acetylenes: Catalytic Substitutions of Acetylenic Hydrogen with Bromoalkenes, Iodoarenes, and Bromopyridines. *Tetrahedron Lett.* **1975**, *16*,

4467–4470. (b) Sonogashira, K. Coupling Reactions Between sp Carbon Centers. In Comprehensive Organic Synthesis; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, UK, **1990**; Vol. 3, p 521. (c) Sonogashira, K. In Handbook of Organopalladium Chemistry for Organic Synthesis; Negishi, E.-I., Ed.; Wiley-Interscience: New York, **2002**; p 493. (d) Negishi, E.; Anastasia, L. Palladium-Catalyzed Alkynylation. *Chem. Rev*. **2003**, *103*, 1979–2018.

6. (a) Chodkiewicz, W.; Cadiot, P. New Synthesis of Symmmetrical and Asymmetrical Conjugated Polyacetylenes. *C. R. Acad. Sci.* **1955**, *241*, 1055–1057. (b) Montierth, J. M.; DeMario, D. R.; Kurth, M. J.; Schore, N. E. The Polymer-Supported Cadiot–Chodkiewicz Coupling of Acetylenes to Produce Unsymmetrical Diynes. *Tetrahedron* **1998**, *54*, 11741–11748. (c) Gung, B. W.; Dickson, H. Total Synthesis of (−)-Minquartynoic Acid: An Anti-Cancer, Anti-HIV Natural Product. *Org. Lett*. **2002**, *4*, 2517–2519. (d) Marino, J. P.; Nguyen, H. N. Bulky Trialkylsilyl Acetylenes in the Cadiot–Chodkiewicz Cross-Coupling Reaction. *J. Org. Chem*. **2002**, *67*, 6841–6844. (e) López, S.; Fernández-Trillo, F.; Midón, P.; Castedo, L.; Saá, C. Synthesis of Marine Polyacetylenes Callyberynes A–C by Transition-Metal-Catalyzed Cross-Coupling Reactions to sp Centers. *J. Org. Chem*. **2006**, *71*, 2802–2810. (f) Jiang, H.-F.; Wang, A.-Z. Copper-Catalyzed Cross-Coupling Reactions of Bromoalkynols with Terminal Alkynes in Supercritical Carbon Dioxide. *Synthesis* **2007**, 1649–1654.
7. (a) Mohr, J. T.; Krout, M. R.; Soltz, B. M. Natural Products as Inspiration for the Development of Asymmetric Catalysis. *Nature*, **2008**, *455*, 323-332. (b) Taylor, M. S.; Jacobsen, E. N. Asymmetric Catalysis in Complex Target Synthesis. *Proc. Natl. Acad. Sci. USA* **2004**, 101, 5368–5373.
8. (a) Trost, B. M. The Atom Economy – A Search for Synthetic Efficiency. *Science* **1991,** 254, 1471–1477. (b) Young, I. S.; Baran, P. S. Protecting-Group-Free Synthesis as an Opportunity for Invention. *Nat. Chem.* **2009***, 1***,** 194–205. (c) Hoffmann, R. W. Protecting-Group-Free Synthesis. *Synthesis* **2006**, 3531–3541. (d) Protecting-Group-Free Organic Synthesis: Improving Economy and Efficiency, Fernandes, R. A. Ed. John-Wiley & Sons, 2018.
9. Pollo, L. A. E.; Bosi, C. F.; Leite, A. S.; Rigotto, C.; Kratz, J.; Simões, C. M. O.; Fonseca, D. E. P.; Coimbra, D.; Caramori, G.; Nepel, A.; Campos, F. R.; Barison, A.; Biavatti, M. W. Polyacetylenes from the Leaves of *Vernonia scorpioides* (Asteraceae) and their Antiproliferative and Antiherpetic Activities. *Phytochemistry* **2013**, *95*, 375–383.
10. Kanikarapu, S.; Marumudi, K.; Kunwar, A. C.; Yadav, J. S.; Mohapatra, D. K. Total Synthesis and Stereochemical Revision of 4,8-Dihydroxy-3,4-dihydrovernoniyne. *Org. Lett*. **2017**, *19*, 4167–4170.
11. Ramakrishna, G. V.; Fernandes, R. A. Total Synthesis of the Sensitive Triyne Natural Product (4*S*,5*S*)-4,8-Dihydroxy-3,4-dihydrovernoniyne and All of Its Stereoisomers. *Org. Lett.* **2019**, *21*, 5827.
12. (a) Yamanaka, H.; Yokoyama, M.; Sakamoto, T.; Shiraishi, T.; Sagi, M.; Mizugaki, M. Influence of Heteroaromatic Amines to Knoevenagel Condensation. *Heterocycles* **1983**, *20*, 1541–1544. (b) Ragoussis, N. Modified Knovenagel Condensations. Synthesis of (E)-3-Alkenoic acids. *Tetrahedron Lett*. **1987**, *28*, 93–96. (c) Halle, M. B.; Fernandes, R. A. A Relay Ring-opening/Double Ring-closing Metathesis Strategy for the Bicyclic Macrolide-Butenolide Core Structures. *RSC Advances* **2014**, *4*, 63342–63348.
13. (a) Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. Catalytic Asymmetric Dihydroxylation. *Chem. Rev*. **1994**, *94*, 2483. (b) García, C.; Martín, T.; Martín, V. S. β-Hydroxy-γ-lactones as Chiral Building Blocks for the Enantioselective Synthesis of Marine Natural Products. *J. Org. Chem*. **2001**, *66*, 1420–1428. (c) Paterson, I.; Anderson, E. A.; Dalby, S. M.; Loiseleur, O. Toward the Synthesis of Spirastrellolide A: Construction of a Tetracyclic C26–C40 Subunit Containing the DEF-Bis-Spiroacetal. *Org. Lett.* **2005,** *7*, 4121–4124. (d) Brimble, M. A.; Finch, O. C.; Heapy, A. M.; Fraser, J. D.; Furkert, D. P.; O'Connor, P. D. A Convergent Synthesis of the [4.4]-Spiroacetal-γ-lactones Cephalosporolides E and F. *Tetrahedron* **2011**, *67*, 995–1001. (e) The enantiomeric excess of compound **8** was determined by HPLC by converting it into its corresponding OTBDPS ether **8′**. For HPLC traces see Supporting Information.
14. (a) Seyferth, D.; Marmor, R. S.; Hilbert, P. Reactions of Dimethylphosphono-Substituted Diazoalkanes. $(MeO)_2P(O)CR$ Transfer to Olefins and 1,3-Dipolar Additions of $(MeO)_2P(O)C(N_2)R$. *J. Org. Chem*. **1971**, *36*, 1379–1386. (b) Gilbert, J. C.; Weerasooriya, U. Diazoethenes: Their Attempted Synthesis from Aldehydes and Aromatic Ketones by Way of the Horner–Emmons Modification of the Wittig Reaction. A Facile Synthesis of Alkynes. *J. Org. Chem*. **1982**, *47*, 1837–1845. (c) Evans, M. A.; Morken, J. P. Asymmetric Synthesis of (−)-Dihydroxanthatin by the Stereoselective Oshima–Utimoto Reaction. *Org. Lett*. **2005**, *7*, 3371–3373.
15. Gulia, N.; Pigulski, B.; Szafert, S. Reactivity of 3-Halopropynols: X-Ray Crystallographic Analysis of 1,1-Dihalocumulenes and 2+2 Cycloaddition Products. *Arkivoc* **2017**, *iii*, 191–204.
16. (a) Harcken, C.; Brückner, R. A Four-Step Route from Aldehydes to C2-Elongated Enantiomerically Pure α,β-Unsaturated-γ-Hydroxy Esters. *Synlett* **2001**, 718–721. (b) The enantiomeric excess of compounds **13** and *ent*-**13** were determined by HPLC by converting them into the corresponding OTBDPS ethers **13′** and *ent*-**13′**, respectively. See Supporting Information for HPLC traces.