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Total synthesis of two novel brominated acetylenic diols (+)-diplyne C and E: stereoselective construction of the (*E*)-1-bromo-1-alkene

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Abstract—The total syntheses of the enantiomers of two novel brominated polyacetylenic natural products diplynes C and E are reported. Pd and Cu(I)-catalyzed coupling reactions were employed to synthesize the diyne and enyne units. The stereochemistry of the terminal (*E*)-alkenyl bromide in diplyne C was constructed stereoselectively using Brown's hydroboration–bromination procedure. The stereochemistry of the internal (*E*)-double bond in diplyne E was established using a Takai reaction. The stereocenter was derived from D-mannitol.

1. Introduction

Many naturally occurring organobromo compounds have been reported, most of which are from marine sources.[1] The first isolation of naturally occurring brominated acetylenic diols from the genus *Diplastrella* was recently reported (Fig. 1).[2] The extract, from which these novel compounds were isolated, exhibited inhibitory activity against HIV-1 integrase.

The diplynes differ in structure in the degree of unsaturation on the left hand (vinylbromide end) of the molecules. There is an element of symmetry in both diplynes A **1** and D **4** in the center portion of the structures as a 1,*n*-diyne unit. Recently, we reported the total synthesis of diplynes A **1** and D **4** by taking advantage of the 1,*n*-diyne symmetry and by using Cadiot–Chodkiewicz and Sonogashira coupling reactions to construct the diyne and the enyne units, respectively.[3–5] While a similar strategy allows the construction of the diyne unit common to all five diplynes, the lack of symmetry in diplynes C **3** and E **5** demands a different strategy in the construction of the left-hand fragment. The presence of a terminal (*E*)-alkenyl bromide unit in diplyne C **3** and an internal (*E*)-double bond in diplyne E **5** requires additional synthetic considerations to achieve a stereoselective synthesis.

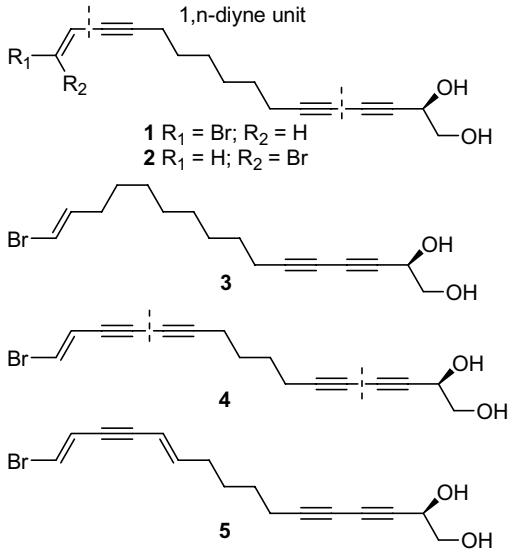

Figure 1. Acetylenic diols diplynes A–E **1**–**5** isolated from the Philippines sponge *Diplastrella* sp. The stereocenter in the natural (−)-diplyne A **1** was established to be *R* by our previous synthesis.

Initially, we chose to use the Takai reaction for the construction of the (*E*)-vinyl bromide unit in **3** because the

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procedure could produce vinyl halide directly (Fig. 2).[6] However, the reaction was not chemoselective when using a combination of $CrCl_2$ and $CHBr_3$.[6] After experimenting with a few other methods, the (*E*)-1-bromo-1-alkene unit of diplyne C **3** was introduced through a stereoselective hydroboration–bromination procedure. Based on our experience in acetylenic chemistry,[3,7,8] we anticipated the synthesis of diplyne E **5** to be brief by means of a Pd(0) and Cu(I) catalyzed coupling reactions.

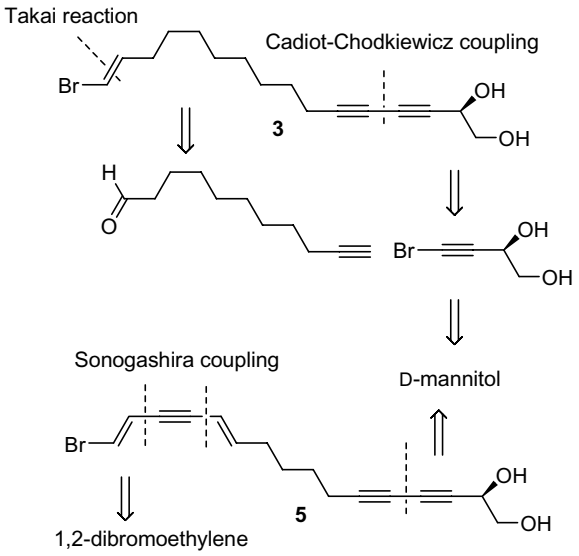


Figure 2. Retrosynthetic analysis for diplynes C **3** and E **5**.

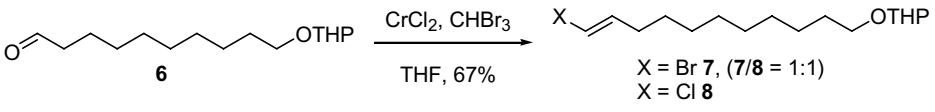
2. Results and discussion

The synthesis of diplyne C **3** started with the preparation of the (*E*)-1-bromo-1-alkene fragment. Since this double bond is connected with an Sp^3 carbon, the preferred method of Pd(0)-catalyzed coupling reactions using 1,2-dibromoethylene could not be employed. We therefore considered the most direct method of preparing an (*E*)-vinyl bromide, the Takai olefination.[6] Aldehyde **6** was treated with 6 equiv of $CrCl_2$ and 2 equiv of $CHBr_3$ in THF producing vinyl bromide **7** in 67% yield (Eq. 1). Unfortunately, the reaction gave a mixture of vinyl bromide and vinyl chloride, which could not be separated by column chromatography. Our attempts to separate the vinyl bromide from vinyl chloride in subsequent steps were not successful.

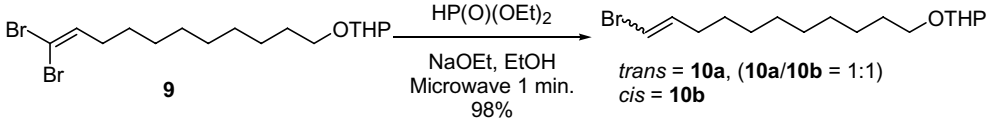
Since $CrBr_2$ was not commercially available and our attempted in situ reduction of $CrBr_3$ with $LiAlH_4$ did not lead to any desired product, we turned our attention to a potentially selective reduction of the geminal dibromoalkene **9**. A mixture of **9** with diethyl phosphite was subjected to microwave irradiation for 1 min (Eq. 2).[9] This procedure produced vinyl bromide **10** in 98% yield, but with virtually no stereoselectivity. A 1:1 mixture of the (*E*)- and (*Z*)-isomers was obtained, which again could not be separated by column chromatography in this or subsequent steps.

After encountering chemoselectivity problems with the Takai reaction and stereoselectivity problems with the reduction of dibromoalkene, we decided to use a procedure developed by Brown.[10,11] This procedure involved a stereoselective preparation of the (*E*)-vinyl bromide starting from a terminal alkyne (Scheme 1). Once this method was chosen, it became apparent that the element of symmetry involving 1,*n*-diyne also existed here. Starting from the commercially available 1,11-dodecadiyne **11**, a hydroboration reaction using catecholborane gave the desired boronic acid **13** upon workup with H_2O.[10] In order to reduce the amount of diboronic acid **14**, only 0.25 equiv of catecholborane was used, which was added slowly over 12 h using a syringe pump. The boronic acids **13** and **14** were obtained as white solids which were subjected to a mercuration reaction with $Hg(OAc)_2$. The bromination–demercuration was carried out with Br_2 in pyridine.[11] The three-step procedure afforded the desired (*E*)-1-bromo-1-alkene **15** in 60% overall yield based on the recovered starting materials and an (*E*):(*Z*) ratio of 96:4.

Vinyl bromide **15** was then coupled to bromoalkyne **17**[8] in the presence of CuCl to give diyne **18** in 45% yield. Removal of the isopropylidene protecting group using *p*-TsOH in MeOH led to the isolation of (+)-diplyne C as a white solid in 92% yield. All spectroscopic data of the synthetic sample are consistent with that reported for the natural product. The synthetic diplyne C **3** had a specific rotation of $[\alpha]_D = +13.3$ in MeOH. The positive sign corresponds to an (*S*)-configuration since the stereocenter is derived from D-mannitol. Although the



(1)



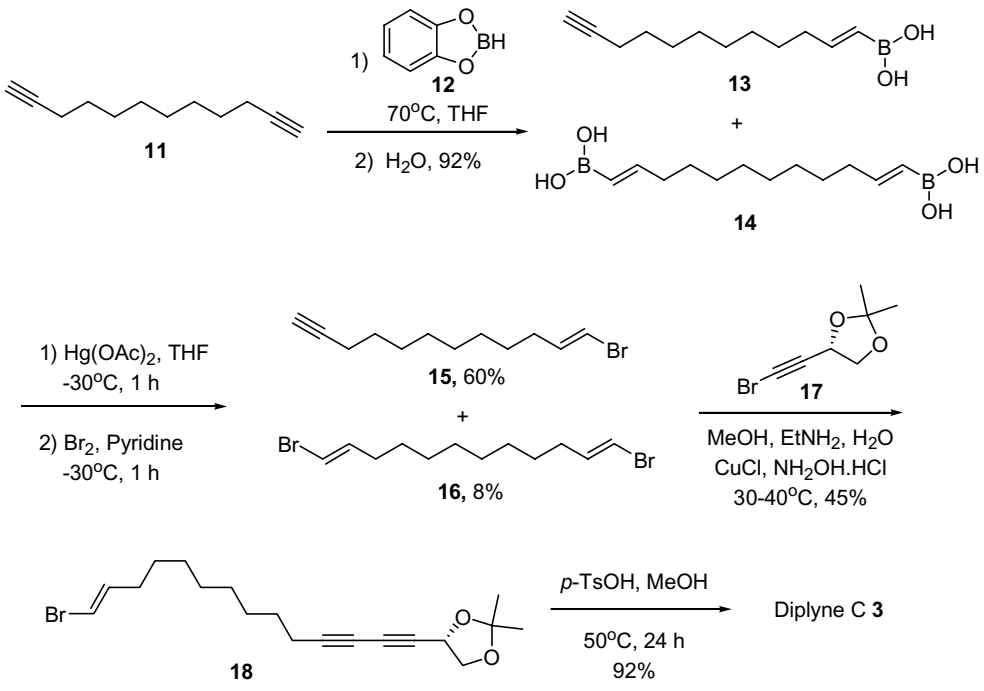
(2)

specific rotation was not available for natural diplyne C **3** due to the small quantity isolated, the natural diplyne A was reported to have a specific rotation of $[\alpha]_D = -8.7$ in MeOH.[2] From a common starting material, D-mannitol, the synthetic samples of diplynes A, C, D, and E have the same (+)-sign in specific rotation corresponding to an (*S*)-configuration. It is reasonable to assume that the natural diplyne C has an (*R*)-configuration by analogy to diplyne A because the diplynes are similar in structure and have an identical origin in nature.[2,3]

Initially, a potentially more efficient convergent route was attempted for the synthesis of diplyne E **5** (Fig. 3), which would have involved the synthesis of the bromine-containing terminal enyne **19** by a Negishi coupling reaction between trimethylsilyl (TMS) acetylene and the commercially available cis/trans mixture of 1,2-dibromoethylene.[12] The synthesis of diplyne E **5** would have followed a Pd-catalyzed coupling reaction between the intermediates **19** and **20**.

However, the synthesis of **19** did not proceed as planned. Carpita and Rossi have studied the reaction shown in Scheme 2 and concluded that compound **23** is more reactive than the starting material **22** and a second coupling occurred rapidly to give **24**.[13] Since no attempt was made to improve the yield of **23** by using excess **22** in the previous study, we conducted the reaction with up to 6 equiv of **22**. The results proved disappointing. Rather than producing the desired product **23** as the major product, a mixture of **23** (13%) and the bis-coupling product **24** (57%) was obtained (Scheme 2). Therefore, we have confirmed the results of Carpita and Rossi that **23** is substantially more reactive than **22**. Due to the low yield and the volatility of **23**, the attempt at a convergent synthesis was abandoned.

Our alternative synthetic route (Scheme 3) began with the reduction of the commercially available 6-heptynoic acid **25** to alcohol **26**, which proceeded in 89% yield. The



Scheme 1.

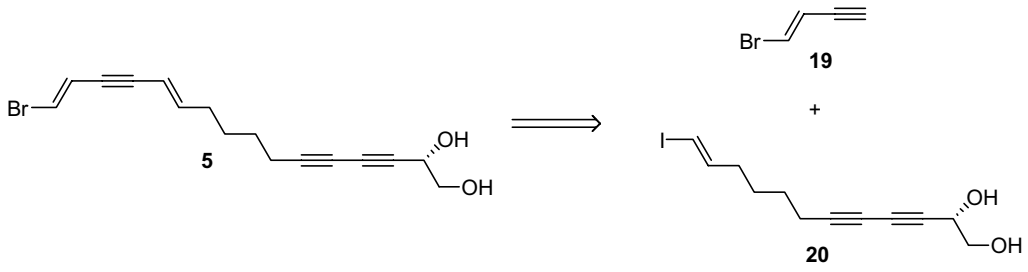
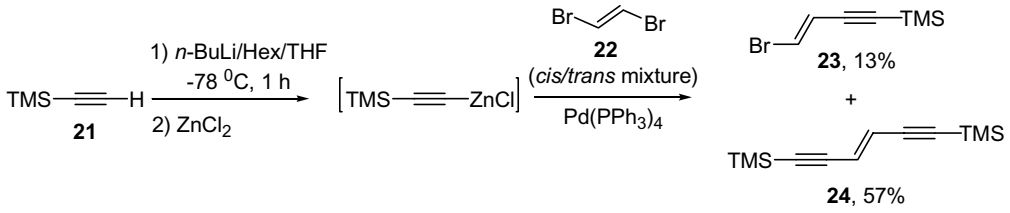
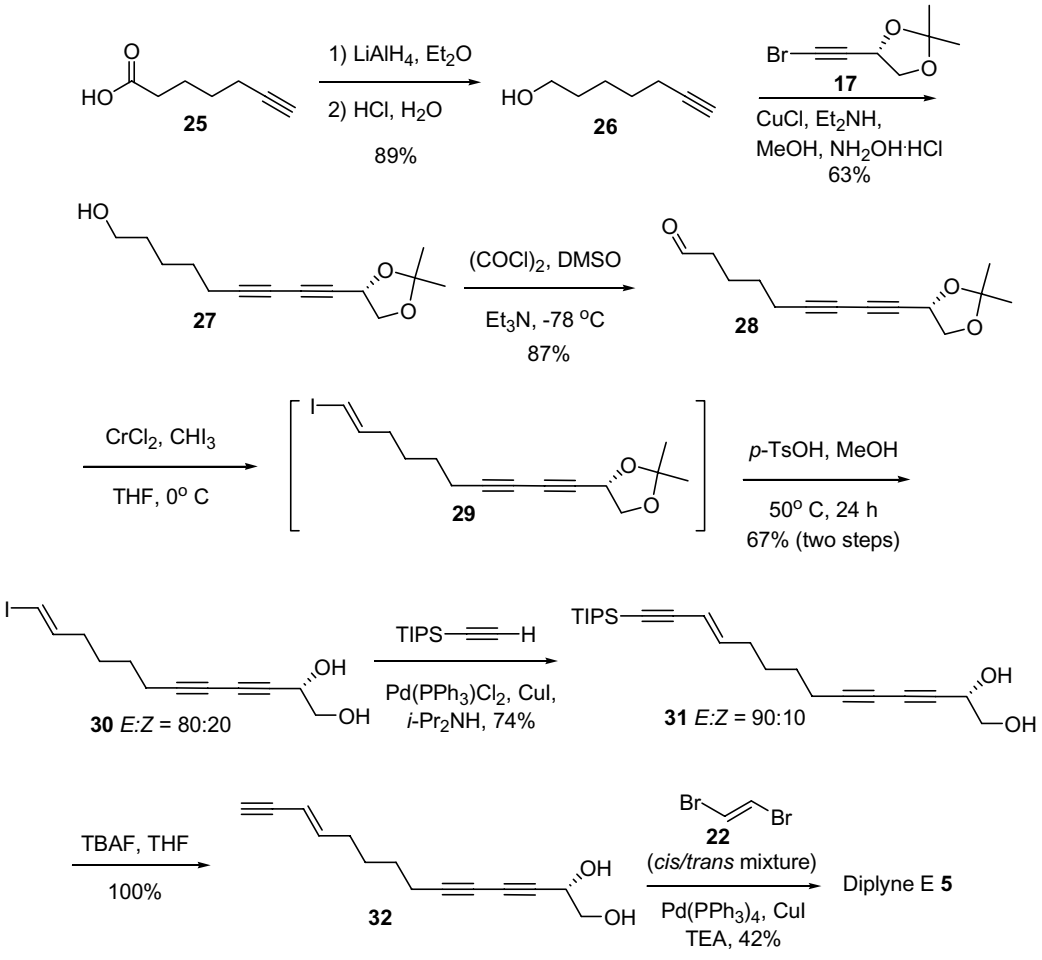


Figure 3. Retrosynthetic analysis for a convergent synthesis of diplyne E **5**.



Scheme 2.



Scheme 3.

cross coupling of **26** with bromoalkyne **17** in the presence of CuCl led to the desired diyne **27** in 63% yield. Next, a Swern oxidation of the primary alcohol cleanly produced aldehyde **28** in 87% yield.[14] Takai olefination was then performed using 2 equiv of CHI_3 and 6 equiv of $CrCl_2$.[6] The resulting mixture was subjected to treatment of *p*-TsOH in MeOH. This allowed the isolation of diol **30** in 67% overall yield for the two steps. Vinyl iodide **30** was isolated as an 80:20 (*E*:*Z*) mixture in favor of the (*E*)-isomer. The addition of triisopropylsilyl (TIPS) acetylene under modified Sonogashira conditions afforded the TIPS protected enyne **31** in 74% yield (unoptimized).[5,15] The (*E*):(*Z*) ratio of **31** improved to 90:10 following the cross coupling reaction to TIPS acetylene and a mixture of vinyl iodide **30** (21%) enriched with the *cis* isomer was recovered. These findings suggest that the (*E*)-isomer of vinyl iodide **30** is more reactive towards the coupling reaction and one could improve the (*E*)/(*Z*) ratio of **31** by using excess vinyl iodide **30**.

Next, removal of the TIPS group using TBAF provided terminal enyne **32**, quantitatively. A Sonogashira coupling reaction between **32** and four equivalents of the commercially available mixture of *cis*/*trans* dibromoethylene **22** in the presence of $Pd(PPh_3)_4$ and CuI gave diplyne E **5** as a pale yellow solid in 42% yield.[5,16] As we reported previously, the Pd-catalyzed coupling to an

excess mixture of *cis*/*trans* dibromoethylene **22** preferentially produces the *trans*-isomer.[3] However, the synthetic sample contained ca. 10% of the internal cis-double bond isomer originated from the Takai reaction in the preparation of **30.** Except for this contamination, the synthetic diplyne E **5** exhibited nearly identical spectroscopic data to that reported for the natural product and gave a specific rotation $[\alpha]_D = +5.9$ in MeOH. Again due to the minute amount of the natural diplyne E isolated, no optical activity data were reported.[2] As described above for diplyne C, the synthetic sample has an (*S*)-configuration while the natural diplyne E should have an (*R*)-configuration.

3. Conclusion

We have completed the first total syntheses of (+)-diplynes C and E. (+)-Diplyne C was produced in an overall yield of ca. 22% using Brown's hydroboration–bromination procedure to establish the (*E*)-vinyl bromide stereochemistry. (+)-Diplyne E was synthesized stereoselectively by means of a Takai olefination and Pd-catalyzed cross coupling reactions in an overall yield of ca. 10%.

4. Experimental

All reactions were carried out under an atmosphere of nitrogen in oven-dried glassware. Reagents were purchased from commercial sources and used without further purification. Flash column chromatographic separations were performed using silica gel 40–63 μm, unless otherwise noted. Reactions were monitored with TLC and UV light. NMR spectra (^{1}H, ^{13}C) were recorded on Bruker 200, 300, and 500 MHz spectrometers with $CDCl_3$ or CD_3OD as the solvents. Melting points are not corrected.

4.1. 2-(11-Halo-undec-10-enyloxy)-tetrahydropyran 7 and 8

A suspension of $CrCl_2$ (11.3 g, 91.7 mmol) in dry THF (38 ml) was allowed to stir at rt under an atmosphere of nitrogen. To this was added dropwise a solution of aldehyde **6** (3.9 g, 15.3 mmol) and $CHBr_3$ (2.67 ml, 30.6 mmol) in dry THF (76 ml) at 0 °C for a period of 30 min. The reaction was allowed to run an additional 2 h. Upon completion, the mixture was diluted with H_2O and extracted three times with Et_2O, and then dried over Na_2SO_4. The resulting solution was filtered, concentrated, and purified over a silica gel column to give a mixture of the bromo- and chloro-containing products **7** and **8** in a ratio of approximately 1:1 (3.4 g, 67%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.22 (8H, m), 1.29 (4H, m), 1.51 (6H, m), 1.65 (1H, m), 1.76 (1H, m), 1.97 (2H, q, $J = 7.4$ Hz), 3.32 (1H, dt, $J = 6.6$, 9.5 Hz), 3.44 (1H, m), 3.67 (1H, dt, $J = 6.8$, 9.5 Hz), 3.80 (1H, m), 4.52 (1H, t, $J = 2.7$ Hz), 5.97 (2H, m). ^{13}C NMR (75 MHz, $CDCl_3$): δ 19.5, 25.4, 26.1, 28.4, 28.7, 28.8, 29.1, 29.3, 29.4, 30.6, 32.8, 62.1, 67.5, 98.6, 103.9, 116.5, 133.9, 138.1.

4.2. 2-(11-Bromo-undec-10-enyloxy)-tetrahydro-pyran 10a and 10b

A mixture of EtONa (330 mg, 4.85 mmol), diethyl phosphite (0.62 ml), and the dibromoalkene **9** (1.0 g, 2.4 mmol) in EtOH (12 ml) was placed in an Erlenmeyer flask in a microwave oven, operated at 60% of 1500 W, and irradiated for 1 min. The reaction mixture was then cooled to rt. The solvent was removed and the product was purified over a silica gel column affording the products as a 1:1 mixture of (*E*):(*Z*) isomers (780 mg, 98%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.22 (10H, m), 1.30 (2H, m), 1.48 (6H, m), 1.62 (1H, m), 1.74 (1H, m), 1.94 (1H, q, $J = 6.8$ Hz), 2.10 (1H, q, $J = 6.8$ Hz), 3.29 (1H, dt, $J = 6.6$, 9.5 Hz), 3.41 (1H, m), 3.65 (1H, dt, $J = 6.8$, 9.5 Hz), 3.78 (1H, m), 4.50 (1H, t, $J = 4.1$ Hz), 6.01 (2H, m). ^{13}C NMR (75 MHz, $CDCl_3$): δ 19.5, 25.3, 26.0, 27.9, 28.4, 28.7, 28.9, 29.1, 29.2, 29.6, 30.6, 32.7, 62.0, 67.4, 98.6, 107.4, 103.9, 134.8, 138.0.

4.3. Dodec-1-en-11-ynyl-boranediol 13

To diyne **11** (402 mg, 2.46 mmol) was added a 1 M solution of catecholborane **12** (65 μl, 0.61 mmol) in THF (0.6 ml). This was added through the aid of a syringe pump over a period of 15 h, under an atmosphere of nitrogen in an oil bath at 70 °C. The reaction was allowed to run for a total of 24 h, yielding boronic ester. The solvent was removed and H_2O (0.6 ml) added and allowed to stir for 3 h. The solids were filtered, resulting in boronic acids **13** and **14** (117 mg, 92%) as a mixture of yellow and white solids.

Compound **13**: ^{1}H NMR (300 MHz, CD_3OD): δ 1.30 (6H, m), 1.38 (2H, m), 1.48 (4H, m), 1.92 (1H, t, $J = 2.6$ Hz), 2.15 (2H, dt, $J = 2.6$, 6.9 Hz), 2.25 (2H, q, $J = 6.8$ Hz), 5.76 (1H, d, $J = 18.0$ Hz), 7.02 (3H, m), 7.17 (2H, m). ^{13}C NMR (75 MHz, CD_3OD): δ 18.2, 25.4, 28.0, 28.3, 28.5, 28.6, 28.9, 29.0, 29.2, 35.9, 68.0, 84.5, 112.1 (2), 122.4 (2), 148.2, 157.8.

Compound **14**: ^{1}H NMR (300 MHz, CD_3OD): δ 1.30 (8H, m), 1.40 (4H, m), 1.48 (2H, m) 2.14 (5H, m), 5.55 (1H, d, $J = 17.6$), 6.52 (1H, dt, $J = 6.5$, 17.7 Hz). ^{13}C NMR (75 MHz, CD_3OD): δ 19.0, 29.6, 30.1, 30.2, 30.2, 30.4, 36.9, 69.3, 85.0, 116.3, 120.9, 153.9.

4.4. (*E*)-1-Bromo-dodec-1-en-11-yne 15

To a solution of boronic acids **13** and **14** (99 mg, 0.50 mmol) in THF (0.50 ml) at −30 °C was added $Hg(OAc)_2$ (152 mg, 0.50 mmol). This was allowed to stir for 1 h at −30 °C. Next, a solution of Br_2 (30 μl, 0.50 mmol) in pyridine (0.50 ml) was added at −30 °C. This was allowed to stir for 1 h. The solution was warmed to rt and slowly poured into an ice cold mixture of *n*-pentane and 6 M HCl. The layers were separated and the aqueous layer extracted twice with *n*-pentane. The combined organic layers were then washed with 6 N HCl, saturated aqueous $Na_2S_2O_3$, then dried over $MgSO_4$. The resulting solution was filtered, concentrated and purified over silica gel column affording compounds **15** (80 mg, 60%) and **16** (9 mg, 8%) as yellow

oils. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.26 (4H, m), 1.35 (4H, m), 1.48 (4H, m), 1.91 (1H, t, $J = 2.6$ Hz), 2.01 (2H, q, $J = 6.5$ Hz), 2.15 (2H, dt, $J = 2.8$, 6.9 Hz), 5.97 (1H, d, $J = 13.5$ Hz), 6.12 (1H, dt, $J = 7.0$, 14.0 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 18.3, 28.3, 28.5, 28.6, 28.8, 28.9, 29.1, 32.8, 68.0, 84.6, 104.0, 138.1. IR: υ cm^{-1} 3307, 3064, 2929, 2856, 2117, 1620, 1463, 1434, 1231, 940.

4.5. (13*E*)-4-(14-Bromo-tetradec-13-ene-1,3-diynyl)-2,2-dimethyl-[1,3]dioxolane 18

To a round bottom flask equipped with a stirring bar and under nitrogen was added MeOH (0.16 ml), a solution of $NH_2OH{\cdot}HCl$ (16 mg, 0.23 mmol) in 58 μl of water, 70% aqueous solution of $EtNH_2$ (0.13 ml), and CuCl (2 mg, 0.025 mmol). Acetylene **15** (80 mg, 0.32 mmol) was added in one portion. Next, bromoalkyne **17** (67 mg, 0.32 mmol) was added over a period of 1 h keeping the temperature between 30 and 35 °C. The reaction was allowed to run for an additional 1.5 h at 40 °C, then a solution of KCN (0.6 g) and NH_4Cl (2.5 g) in H_2O (8 ml) was added with vigorous stirring. The product was extracted twice with Et_2O and the combined organic layers washed with saturated aqueous NH_4Cl and then dried over $MgSO_4$. The resulting solution was filtered, concentrated, and purified over a silica gel column, affording compound **18** as a pale yellow oil (54 mg, 45%) as well as the homocoupling product of compound **17** (21 mg, 17%). $[\alpha]_D = +28.6$ (MeOH). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.25 (8H, m), 1.34 (3H, s), 1.34 (2H, m), 1.46 (3H, s), 1.48 (2H, m), 2.00 (2H, q, $J = 6.7$ Hz), 2.24 (2H, t, $J = 7.0$ Hz), 3.91 (1H, dd, $J = 1.9$, 6.1 Hz), 4.12 (1H, dd, $J = 1.6$, 6.4 Hz), 4.73 (1H, t, $J = 6.3$ Hz), 5.98 (1H, d, $J = 13.4$), 6.14 (1H, dt, $J = 7.2$, 13.4 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ 19.2, 25.8, 26.0, 28.0, 28.5, 28.7, 28.8, 28.9, 29.1, 32.8, 64.0, 65.8, 69.7, 70.8, 72.7, 82.0, 104.0, 110.5, 138.1. IR: υ cm^{-1} 3064, 2927, 2855, 2256, 1620, 1458, 1323, 1235, 1065, 939. HRMS: Calcd for $C_{19}H_{27}BrO_2$+Na: 389.1092, found M+Na: 389.1109, M+2+Na: 391.1082.

4.6. (+)-Diplyne C 3

To a round bottom flask equipped with a stirring bar under nitrogen was loaded a solution of the protected diol **18** (30 mg, 0.08 mmol) in MeOH (1.6 ml). PTSA (2 mg, 8 μmol) was added at 50 °C. The reaction was allowed to run for 24 h at 50 °C. Then, $NaHCO_3$ (17 mg, 0.16 mmol) was added while stirring for 15 min. The solids were removed by filtration and the product purified over a silica gel column, affording diplyne C as a white solid (mp 61–63 °C, 24 mg, 92%). $[\alpha]_D = +13.3$ (MeOH). ^{1}H NMR (500 MHz, CD_3OD): δ 1.24 (6H, m), 1.32 (4H, m), 1.44 (2H, m), 1.98 (2H, q, $J = 7.0$ Hz), 2.20 (2H, m), 3.46 (1H, dd, $J = 5.6$, 11.0 Hz), 3.51 (1H, dd, $J = 6.0$, 11.0 Hz), 4.27 (1H, dd, $J = 5.7$, 6.0 Hz), 6.05 (1H, d, $J = 14.0$ Hz), 6.10 (1H, dt, $J = 7.0$, 14.0 Hz). ^{13}C NMR (125 MHz, CD_3OD): δ 19.6, 29.2, 29.7, 29.8, 29.9, 30.0, 30.2, 33.7, 64.5, 65.5, 67.0, 70.7, 75.7, 81.7, 105.0, 139.4. IR: υ cm^{-1} 3377 (broad), 3054, 2931, 2856, 2254, 1620, 1422, 941, 739. HRMS: Calcd for $C_{16}H_{23}BrO_2$+Na, 349.0779: found M+Na: 349.0779, M+2+Na: 351.0748.

4.7. 6-Heptyn-1-ol 27

To a round bottom flask equipped with a stirring bar under nitrogen was added $LiAlH_4$ (903 mg, 23.8 mmol) and anhydrous Et_2O (75 ml) at 0 °C. Then, a solution of 6-heptynoic acid **25** (1.5 g, 11.9 mmol) in dry Et_2O (15 ml) was added dropwise with vigorous stirring. The mixture was then allowed to warm to rt and stirred for an additional hour. Next, 1 M HCl (40 ml) was added dropwise and the reaction mixture stirred for an additional 0.5 h before being diluted with Et_2O. The layers were separated and the aqueous layer extracted three times with Et_2O. The organic layers were combined, dried over $MgSO_4$ and then filtered. The solvent was emoved under reduced pressure and the crude purified using a silica gel column to afford the product as a clear oil (1.18 g, 89%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.52 (6H, m), 1.91 (1H, t, $J = 2.7$ Hz), 2.15 (2H, dt, $J = 2.5$, 6.6 Hz), 3.59 (1H, t, $J = 6.4$ Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 18.74, 25.28, 28.59, 32.54, 63.03, 68.72, 84.83.

4.8. 9-(2,2-Dimethyl-[1,3]dioxolan-4-yl)-nona-6,8-diyne-1-ol 27

To a round bottom flask equipped with a stirring bar under an atmosphere of nitrogen was added a solution of $NH_2OH{\cdot}HCl$ (7.8 mg, 0.11 mmol) in H_2O (0.10 ml), MeOH (2.25 ml), a 70% aqueous solution of $EtNH_2$ (2.25 ml), and CuCl (11.1 mg, 0.11 mmol). Then, alkyne **26** (251 mg, 2.24 mmol) was added in one portion. Next, a solution of bromoalkyne **17** (505 mg, 2.47 mmol) in MeOH (1 ml) was added over the course of 0.5 h using a syringe pump. The resulting mixture was stirred for an additional 1 h at rt. A solution of KCN (0.43 g) and NH_4Cl (1.79 g) in H_2O (6 ml) was then added with vigorous stirring. The resulting mixture was extracted three times with Et_2O and the organic layers dried over $MgSO_4$. The solution was filtered and the solvent removed under reduced pressure. The crude mixture was purified over a silica gel column to afford a yellow oil (335 mg, 63%). $[\alpha]_D = +42.9$ (*c* 1.1, MeOH), ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.35 (3H, s), 1.46 (3H, s), 1.52 (6H, m), 2.78 (2H, t, $J = 6.5$ Hz), 3.62 (2H, t, $J = 6.2$ Hz), 3.91 (1H, dd, $J = 6.2$, 8.0 Hz), 4.12 (1H, dd, $J = 6.4$, 8.0 Hz), 4.73 (1H, t, $J = 6.2$ Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 19.64, 25.40, 26.31, 26.51, 28.26, 32.56, 63.11, 64.96, 66.25, 70.12, 71.16, 73.30, 82.18, 111.00. HRMS: Calcd for $C_{14}H_{20}O_3$+Na: 259.1310, found M+Na: 259.1305.

4.9. 9-(2,2-Dimethyl-[1,3]dioxolan-4-yl)-nona-6,8-diynal 28

To a three-necked round bottom flask equipped with a stirring bar under nitrogen was added $(COCl)_2$ (0.87 ml, 1.73 mmol) in freshly distilled CH_2Cl_2 (7 ml). This solution was cooled to −78 °C and DMSO (0.13 ml, 1.88 mmol) added dropwise over a period of

5 min. After stirring for 10 min, a solution of **27** (371 mg, 1.57 mmol) in anhydrous CH_2Cl_2 (3 ml) was added dropwise. After an additional 15 min. at −78 °C, TEA (1.37 ml, 9.73 mmol) was added dropwise and the reaction mixture was warmed to −10 °C. Then, 1 M HCl (5 ml) was added and the aqueous layer extracted twice with Et_2O. The organic layers were combined and washed once with H_2O before being dried over $MgSO_4$ and filtered. The solvent was removed under reduced pressure and the crude mixture purified over a silica gel column to afford an orange oil (319 mg, 87%). $[\alpha]_D = +33.7$ (*c* 0.5, MeOH), ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.35 (3H, s), 1.46 (3H, s), 1.56 (2H, m), 1.70 (2H, m), 2.27 (2H, t, $J = 6.8$ Hz), 2.44 (1H, dt, $J = 1.6$, 7.1 Hz), 3.91 (1H, dd, $J = 6.1$, 8.1 Hz), 4.12 (1H, dd, $J = 6.4$, 8.1 Hz), 4.73 (1H, t, $J = 6.2$ Hz), 9.72 (1H, d, $J = 1.5$ Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 19.49, 21.55, 26.29, 26.51, 27.82, 43.62, 65.34, 66.22, 70.10, 71.01, 73.55, 81.47, 111.02, 202.31. HRMS: Calcd for $C_{14}H_{18}O_3$+Na: 257.1154, found M+Na: 257.1157.

4.10. 12-Iodo-dodec-11-ene-3,5-diyne-1,2-diol 30

To a round bottom flask equipped with a stirring bar under an atmosphere of nitrogen was added $CrCl_2$ (4.4 g, 35.9 mmol) and THF (60 ml) at 0 °C. Next, a solution of aldehyde **28** (1.4 g, 5.98 mmol) and CHI_3 (4.7 g, 11.9 mmol) in anhydrous THF (30 ml) was added dropwise. The reaction mixture was stirred at 0 °C for 4 h before being diluted with H_2O (150 ml). The layers were separated and the aqueous layer extracted four times with Et_2O. The combined organic layers were dried over Na_2SO_4 and then filtered. The solvent was removed under reduced pressure and the crude mixture purified over a silica gel plug to remove any metal to afford a mixture of the protected vinyl iodide **29** and excess iodoform (2.48 g). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.24 (3H, s), 1.46 (3H, s), 1.51 (4H, m), 2.04 (2H, m), 2.27 (2H, m), 3.92 (1H, dd, $J = 6.1$, 8.1 Hz), 4.13 (1H, dd, $J = 6.4$, 8.1 Hz), 5.99 (1H, dt, $J = 1.4$, 14.4 Hz), 6.47 (1H, dt, $J = 7.1$, 14.4 Hz).

The crude mixture containing the protected vinyl iodide **29** and CHI_3 was dissolved in MeOH (120 ml). Next, *p*-TsOH (114 mg, 0.59 mmol) was added and the mixture heated to 50 °C while stirring under an atmosphere of nitrogen. After 24 h, $NaHCO_3$ (1.27 g, 11.9 mmol) was added, the reaction mixture was cooled to rt, and the solids were filtered. The solvent was removed under reduced pressure and the crude mixture was purified over a silica gel column to afford a pale yellow solid (mp 56–57 °C, 1.29 g, 67% for two steps, (*E*):(*Z*) = 80:20). $[\alpha]_D = +8.9$ (*c* 0.6, MeOH), ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.50 (4H, m), 2.05 (2H, m), 2.27 (2H, t, $J = 6.5$ Hz), 2.59 (1H, s), 2.92 (1H, s), 3.65 (1H, dd, $J = 6.5$, 11.5 Hz), 3.73 (1H, dd, $J = 3.4$, 11.6 Hz), 4.46 (1H, t, $J = 3.9$ Hz), 5.99 (1H, dt, $J = 1.4$, 14.4 Hz), 6.46 (1H, dt, $J = 7.1$, 14.4 Hz). ^{13}C NMR (75 MHz, CDCl3): δ 19.44, 27.64, 27.80, 35.82, 64.01, 64.95, 66.70, 71.51, 73.66, 75.44, 81.99, 146.27. HRMS: Calcd for $C_{12}H_{15}IO_2$+Na: 341.0015, found M+Na: 341.0016.

4.11. 14-Triisopropylsilanyl-tetradec-11-ene-3,5,13-triyne-1,2-diol 31

To a round bottom flask equipped with a stirrer bar under nitrogen was added a solution of compound **30** (75 mg, 0.21 mmol) in THF (2 ml). To this solution was added TIPS acetylene (0.07 ml, 0.31 mmol), CuI (0.4 mg, 0.002 mmol), and $Pd(PPh_3)_2Cl_2$ (1.5 mg, 0.002 mmol). Next, *i*-Pr_2NH (0.06 ml, 0.43 mmol) was added dropwise. The reaction was allowed to proceed for 3 h before quenching with saturated NH_4Cl solution and diluting with Et_2O. The organic layer was washed one time with saturated NaCl, dried over $MgSO_4$, and filtered. The solvent was removed under reduced pressure and the crude mixture purified over a silica gel column to afford an orange oil (64 mg, 74%). $[\alpha]_D = +8.2$, (*c* 0.4, MeOH), ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.05 (21H, m), 1.51 (4H, m), 2.08 (2H, m), 2.27 (2H, m), 3.65 (1H, dd, $J = 6.5$, 11.3 Hz), 3.72 (1H, dd, $J = 2.6$, 11.1 Hz), 4.47 (1H, t, $J = 5.6$ Hz), 5.51 Hz (1H, dt, $J = 1.4$, 15.9 Hz), 6.14 (1H, dt, $J = 7.0$, 15.9 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 11.70, 19.03, 19.47, 27.85, 28.10, 32.80, 64.01, 64.87, 66.71, 71.52, 73.61, 82.07, 89.46, 106.14, 110.90, 145.14. HRMS: Calcd for $C_{23}H_{36}O_2Si$+Na: 395.2383, found M+Na: 395.2374.

4.12. Tetradec-11-ene-3,5,13,triyne-1,2-diol 32

To a round bottom flask equipped with a stirrer bar under nitrogen was added a solution of compound **31** (62 mg, 0.17 mmol) in THF (2 ml). TBAF (0.25 ml, 0.25 mmol) was added and the resulting mixture stirred for 2 h at rt. Next, ice water (10 ml) followed by 1 M HCl (1 ml) was added and the aqueous layer extracted two times with Et_2O. The combined organic layers were washed once with H_2O, dried over $MgSO_4$, then filtered. The solvent was removed under reduced pressure and the crude mixture purified over a silica gel column to afford a pale yellow solid (mp 46–48 °C, 36 mg, 100%). $[\alpha]_D = +6.1$ (*c* 0.1, MeOH), ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.51 (4H, m), 2.10 (2H, m), 2.27 (2H, m), 2.77 (1H, d, $J = 2.2$ Hz), 3.66 (1H, dd, $J = 6.3$, 11.4 Hz), 3.74 (1H, dd, $J = 3.9$, 11.5 Hz), 4.48 (1H, dd, $J = 4.0$, 6.0 Hz), 5.45 (1H, dq, $J = 1.9$, 15.9 Hz), 6.20 (1H, dt, $J = 7.0$, 15.9 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 19.44, 27.77, 27.99, 32.75, 64.04, 64.90, 66.73, 71.57, 73.63, 76.31, 82.03, 82.73, 109.50, 146.29. HRMS: Calcd for $C_{14}H_{16}O_2$+Na, 239.1048: found M+Na: 239.1046.

4.13. (+)-Diplyne E 5

To a round bottom flask equipped with a stirring bar under nitrogen was added a solution of compound **32** (120 mg, 0.56 mmol), dibromoethylene **22** (413 mg, 2.22 mmol), $Pd(PPh_3)_4$ (39 mg, 0.034 mmol), and CuI (13 mg, 0.067 mmol) in TEA (9.3 ml). The resulting mixture was stirred at rt for 16 h, before being diluted with Et_2O and filtered over a pad of florisil using excess Et_2O. The solvent was removed under reduced pressure and the crude mixture purified over a silica gel column to afford a pale yellow solid (mp 80–82 °C, 74 mg, 42%). $[\alpha]_D = +5.9$ (*c* 0.15, MeOH), UV (MeOH): 287, 272, 214 nm. ^{1}H NMR (500 MHz, CD_3OD): δ 1.53 (4H,

m), 2.16 (2H, m), 2.31 (2H, m), 3.54 (1H, dd, $J = 6.8$, 11.2 Hz), 3.58 (1H, dd, $J = 5$, 11.2 Hz), 4.36 (1H, t, $J = 6.2$ Hz), 5.61 (1H, dq, $J = 2.0$, 15.9 Hz), 6.16 (1H, dt, $J = 7.1$, 15.8 Hz), 6.37 (1H, dd, $J = 2.1$, 14 Hz), 6.78 (1H, d, $J = 14$ Hz). ^{13}C NMR (125 MHz, CD_3OD): δ 19.56, 28.76, 28.90, 33.57, 64.58, 65.79, 67.14, 70.71, 76.00, 81.51, 85.42, 91.43, 110.79, 118.65, 118.97, 146.42. HRMS: Calcd for $C_{16}H_{17}BrO_2$+Na, 343.0310: found M+Na: 343.0318, M+2+Na: 345.0272.

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