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First total synthesis of the brominated polyacetylenes (+)-diplyne A and D: proof of absolute configuration

Benjamin W. Gung,* Craig Gibeau and Amanda Jones

Department of Chemistry and Biochemistry, Miami University, Oxford, OH 45056, USA

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Abstract—The first total syntheses of the enantiomers of two novel brominated polyacetylenic natural products, diplynes A and D, are reported. The syntheses are based on Pd and Cu(I)-catalyzed coupling reactions. The stereocenter was derived from D-mannitol. The stereocenter in the naturally occurring (−)-diplyne A was established to have an (*R*)-configuration.

1. Introduction

Several fractions of moderate polarity from the crude extract of the Philippine sponge *Diplastrella* sp. were recently found to inhibit the activity of the HIV-1 integrase.[1] Five novel brominated polyacetylenic diols diplynes A–E **1**–**5** were isolated via the inhibitory activity guided screen. This was the first report of metabolites from the genus *Diplastrella* and the first description of naturally occurring brominated polyacetylenic diols. Each member of this group of biologically active natural products possesses one stereogenic center and diplyne A **1** was isolated as an optically active white powder.[1] However, the absolute configuration of diplyne A was not determined due to the small quantities of each isolated compound.

As part of our effort toward the total synthesis of polyacetylenic natural products,[2–4] we became interested in the synthesis of these brominated polyacetylenic diols. Herein, we report the total synthesis of diplynes A and D and the establishment of the C2 configuration in natural diplyne A as (*R*) (Fig. 1).

We envisioned a synthetic route (Fig. 2) that should rapidly provide diplyne A **1** based on our experience in the synthesis of polyacetylenes.[2–4] In this plan, the target molecule is divided into three components: the left hand piece is envisioned as arising from 1,2-dibromoethylene, the right hand piece from D-mannitol, and the center piece 1,9-decadiyne. A Sonogashira coupling reaction should link the left hand piece to 1,9-decadiyne[5] and a Cu(I) catalyzed cross coupling reaction should connect the right hand fragment to the center piece.[6] The synthesis of diplyne D **4** would follow a similar strategy with one extra acetylene unit in the left-hand side of the molecule.

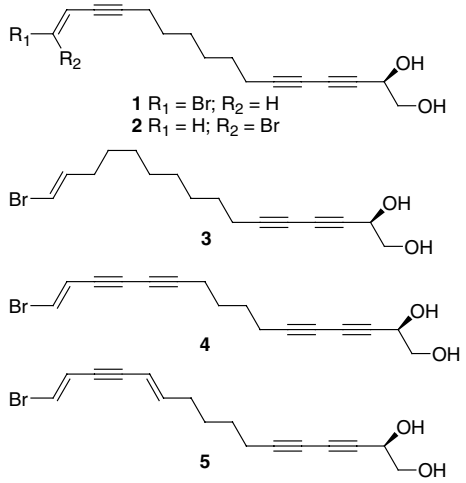

Figure 1. Polyacetylenic diols diplynes A–E **1**–**5** isolated from the Philippine sponge *Diplastrella* sp. The absolute configuration at C2 was not determined in the original report. We have established the C2 stereogenic center in the natural (−)-diplyne A **1** to be (*R*) and the stereocenter in the other members is tentatively assigned accordingly.

2. Results and discussion

The synthesis of diplyne A **1** started with the commercially available 1,9-decadiyne **6** (Scheme 1) and the

* Corresponding author. E-mail: gungbw@muohio.edu

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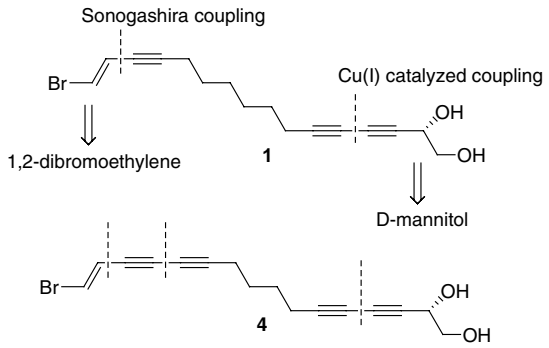


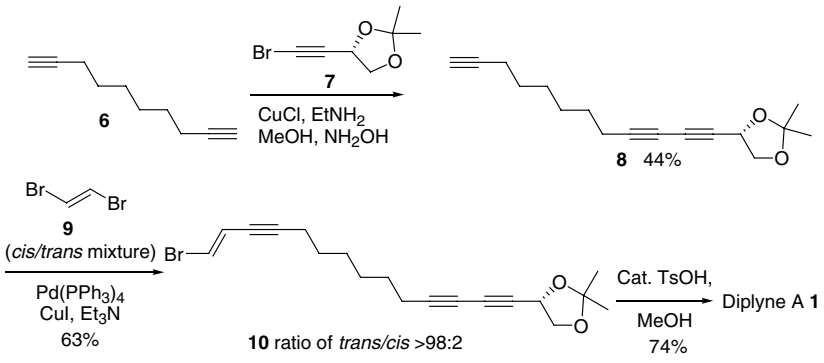
Figure 2. Retrosynthetic analysis for diplynes A **1** and D **4**.

coupling reaction proceeded smoothly with the right hand fragment **7**, which was prepared as previously reported from our laboratory.[3] Exactly 1 equiv of bromoalkyne **7** was added dropwise to a mixture of 1,9-decadiyne **6**, and the reagents in MeOH to minimize the coupling of **7** to both terminals of **6**.[6] The desired cross coupling product **8** was obtained in an unoptimized 44% yield along with a small amount of unidentified by-products. The next step was a cross-coupling reaction between the terminal alkyne **8** and 1,2-dibromoethylene **9**. A few modified Sonogashira coupling conditions were tried;[7,8] however, the reagents that gave a satisfactory yield were a combination of $Pd(PPh_3)_4$ and CuI in Et_3N. Four equivalents of a *cis*/*trans* mixture of **9** were used in the reaction, which provided 63% yield of a 98:2 ratio of the enyne **10** in favor of the *trans* coupling product. The terminal alkyne **8** reacts preferentially with the *trans* isomer of 1,2-dibromoethylene, which is consistent with a previous report that *trans*-1,2-dibromoethylene is more reactive than the corresponding *cis*-isomer in the Pd-catalyzed cross-coupling reactions.[9]

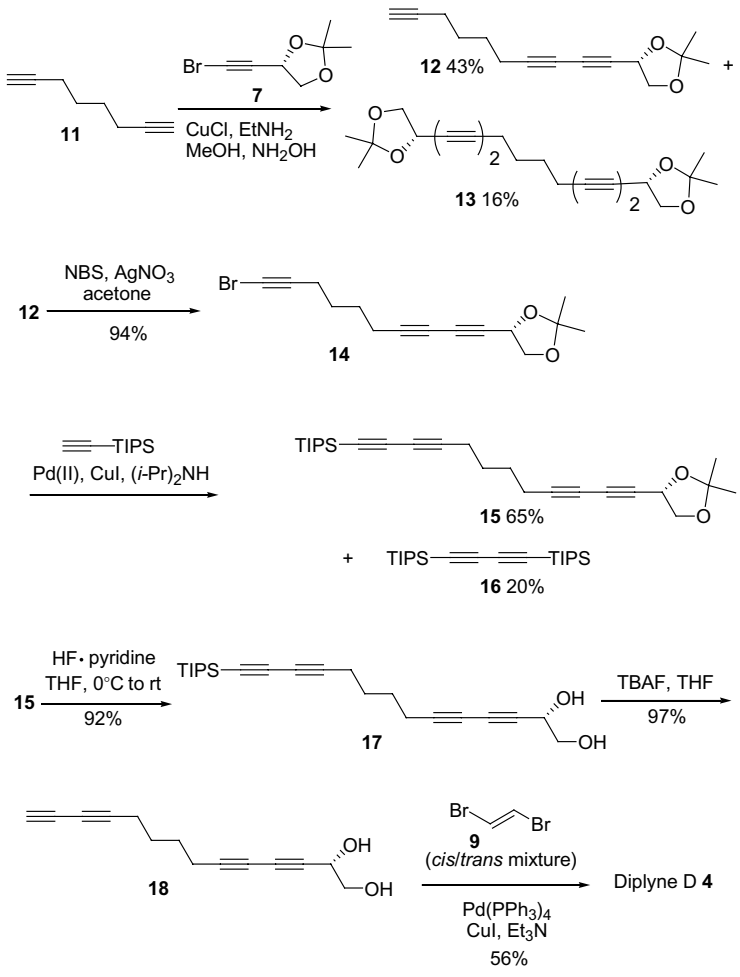
The final step in the preparation of diplyne A **1** is the removal of the acetonide protecting group, which was accomplished using a catalytic amount of *p*-toluenesulfonic acid in MeOH to afford the synthetic sample of diplyne A in 74% yield. The synthetic sample exhibits essentially identical spectroscopic data as that reported for the natural product except that the optical rotation is opposite of the natural product. The natural diplyne A was reported to have a specific rotation of $[\alpha]_D = -8.7$ in MeOH[1] while the synthetic sample showed a value of $[\alpha]_D = +9.6$ in the same solvent. The plus sign corresponds to an (*S*)-configuration since the stereocenter in the synthetic sample was derived from D-mannitol. The absolute configuration in the synthetic diplyne A is (*S*) even though D-mannitol has an (*R*)-configuration. The Cahn–Ingold–Prelog priority of the substituents has changed when D-mannitol was transformed into the acetylenic diol derivative **7**. Therefore, the naturally occurring diplyne A should have an (*R*)-configuration.

With diplyne A **1** in hand, we turned our attention to diplyne D **4**. Using the same cross-coupling reaction and starting with 1,7-octadiyne **11**, the desired cross-coupling product **12** was obtained in 43% yield along with 16% of a symmetrical product **13**, Scheme 2. Compound **13** is the result of coupling at both ends of 1,7-octadiyne.

The desired cross-coupling product **12** was brominated with NBS in the presence of $AgNO_3$ to yield bromoalkyne **14** in 94%.[10] The palladium-catalyzed cross-coupling reaction of **14** with triisopropylsilyl(TIPS)-protected acetylene afforded in 65% the desired tetrayne **15** and in 20% of the homocoupling product of TIPS-acetylene **16**.[11] Intended removal of the TIPS group from **15** with HF·pyridine complex resulted in the removal of the acetonide to afford diol **17** in 92% yield. There was no need to change reagents or conditions since the diol protecting group needed to be removed anyway and the remaining steps should not be affected by the open hydroxy groups. The TIPS group was then removed using tetrabutylammonium fluoride (TBAF) in THF to produce the terminal diyne **18** in 97% yield. Diol **18** is a solid with a melting point of 77–79 °C. Although it is a terminal diyne, compound **18** is remarkably stable in light of previous reports of instability for terminal diynes.[12,13] The final step is the coupling reaction between **18** and a mixture of *cis*/*trans* 1,2-dibromoethylene **9** in the presence of $Pd(PPh_3)_4$ and CuI in Et_3N. This cross-coupling reaction provided (+)-diplyne D in 56% yield with a specific rotation of $[\alpha]_D = +7.2$. No optical activity was reported for natural diplyne D. Thus from a common starting material, D-mannitol, the synthetic samples of diplynes A and D have the same (+)-sign in optical rotation. Since the structure of diplyne D is similar to diplyne A, it is reasonable to assume that the natural diplyne D also has an (*R*)-configuration.



Scheme 1.



Scheme 2.

3. Conclusion

We have completed an expedient first total synthesis of the enantiomers of two novel brominated polyacetylenic natural products (+)-diplynes A and D. The configuration of the natural product (−)-diplyne A is established to be of (*R*)-configuration since the synthetic sample, which has an (*S*)-configuration, exhibits a (+) sign in specific rotation.

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. Reactions were monitored with TLC and UV light. NMR spectra (^{1}H, ^{13}C) were recorded on Bruker 200 and 300 MHz spectrometers with $CDCl_3$ or CD_3OD as the solvents. Melting points are not corrected.

4.1. 1,2-Isopropylidenetetradeca-3,5,13-triyne 8

To a 50 mL round-bottom flask under an atmosphere of N_2 was added 5 mL of MeOH, 0.22 mL of an aq solution of $NH_2OH{\cdot}HCl$ (18 mg, 0.25 mmol), 5 mL 70% aq solution of $EtNH_2$, CuI (25 mg, 0.25 mmol), and diyne **6** (682 mg, 5.0 mmol) in that order. The bromoalkyne **7** (1.02 g, 5.0 mmol) was added over a period of one and a half hours to the reaction mixture via a syringe pump keeping the temperature between 30–35 °C. After an additional 30 min a solution of 1.2 g of KCN and 5 g of NH_4Cl in 16 mL of H_2O was added under vigorous stirring. The product was isolated by extraction with Et_2O (3×20 mL) and the combined organic layers were washed with saturated NH_4Cl solution and dried over $MgSO_4$. The solvents were removed under reduced pressure and the residue was purified over silica gel (5% EtOAc/Hex) to afford 569 mg (44%) of a light yellow oil.

$[\alpha]_D = +38.4$ (*c* 1.63, $CHCl_3$). UV (MeOH) 201 nm. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.36 (3H, s), 1.41 (4H, m), 1.48 (3H, s), 1.52 (4H, m), 1.94 (1H, t, $J = 2.6$ Hz), 2.17 (2H, t, $J = 13.7$ Hz), 2.28 (2H, dt, $J = 6.8$, 2.5 Hz), 3.93 (1H, dd, $J = 8.1$, 6.1 Hz), 4.14 (1H, dd, $J = 8.0$, 6.5 Hz), 4.76 (1H, dd, $J = 6.5$, 5.2). ^{13}C NMR (75 MHz, $CDCl_3$): δ 18.2, 19.1, 25.8, 26.0, 27.8, 28.0, 28.1 (2), 64.4, 65.7, 68.2, 69.6, 70.6, 72.7, 81.8, 84.3, 110.4. IR: ν cm^{-1} 3300 (sharp), 2256, 2217, 1458, 1235, 1065, 839. HRMS: calcd for $C_{17}H_{22}O_2$ + Na, 281.1518, found M + Na, 281.1517.

4.2. (15*E*)-1,2-Isopropylidene-16-bromohexadeca-15-en-3,5,13-triyne 10

To a 50 mL round-bottom flask under an atmosphere of N_2 was added 19 mL of Et_3N, triyne **8** (100 mg, 0.387 mmol), 1,2-dibromoethylene (0.127 mL, 1.54 mmol), $Pd(PPh_3)_4$ (27 mg, 0.023 mmol), and CuI (9 mg, 0.046 mmol) in that order. The resulting mixture was stirred overnight at room temperature. After 12 h the mixture was filtered through a plug of Florisil with excess hexanes. The filtrate was concentrated and the residue was purified over silica gel (5% EtOAc/Hex) to afford **10** (87.1 mg, 62%) and its *cis*-isomer (1.6 mg 1.1%) as light yellow oils.

Compound **10** $[\alpha]_D = +27.3$ ($c = 0.68$, $CHCl_3$). UV (MeOH) 238 nm. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.35 (3H, s), 1.37 (4H, m), 1.46 (3H, s), 1.51 (4H, m), 2.25 (4H, m), 3.91 (1H, dd, $J = 7.8$, 6.3 Hz), 4.12 (1H, dd, $J = 7.8$, 6.7 Hz), 4.73 (1H, dd, $J = 6.2$, 5.3 Hz), 6.15 (1H, dt, $J = 14.0$, 2.0 Hz), 6.54 (1H, d, $J = 14.0$). ^{13}C NMR (75 MHz, $CDCl_3$): δ 19.2, 19.4, 25.9, 26.1, 28.0, 28.1 (2), 28.2, 64.5, 65.9, 69.7, 70.6, 70.8, 72.9, 76.8, 81.9, 93.0, 117.0, 118.0. IR ν cm^{-1} 2256, 2216, 1458, 1235, 1064. HRMS: calcd for $C_{19}H_{23}BrO_2$ + Na, 385.0779, found M + Na, 385.0751.

cis-isomer: ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.35 (3H, s), 1.37 (4H, m), 1.46 (3H, s), 1.51 (4H, m), 2.25 (4H, m), 3.91 (1H, dd, $J = 7.8$, 6.3 Hz), 4.12 (1H, dd, $J = 7.8$, 6.7 Hz), 4.73 (1H, dd, $J = 6.2$, 5.3 Hz), 6.26 (1H, dt, $J = 6.6$, 2.1 Hz), 6.45 (1H, d, $J = 7.4$ Hz).

4.3. (+)-Diplyne A 1

A solution of **10** (51 mg, 0.14 mmol) and *p*-TsOH (2.6 mg, 0.014 mmol) in MeOH (2.8 mL) was stirred for 24 h at room temperature. To the reaction mixture, solid $NaHCO_3$ (29 mg, 0.28 mmol) was added and the mixture was stirred for 15 min. The resulting solution was filtered and MeOH was evaporated. The remaining residue was purified over silica gel (50% EtOAc/Hex) to afford 32.6 mg (74%) a white solid.

$[\alpha]_D = +9.6$ (c 0.29, MeOH) (lit.[1] $[\alpha]_D = -8.7$). UV (MeOH) 238 nm. Mp 95–96 °C. ^{1}H NMR (500 MHz, MeOH): δ 1.45 (4H, m), 1.55 (4H, m), 2.31 (4H, m), 3.56 (1H, dd, $J = 11.2$, 6.8 Hz), 3.61 (1H, dd, $J = 11.2$, 5.0 Hz), 4.36 (1H, dd, $J = 6.0$, 5.6 Hz), 6.25 (1H, dt, $J = 14.0$, 2.3 Hz), 6.71 (1H, d, $J = 14.0$ Hz). ^{13}C NMR (125 MHz, MeOH): δ 19.6, 19.9, 29.2, 29.3 (2), 29.4, 64.5, 65.6,67.1, 70.7, 75.8, 78.2, 81.7, 93.7, 117.9, 119.1. IR: ν cm^{-1} 3298 (broad), 2254, 2216, 1693, 1461, 1085, 922, 728. HRMS: calcd for $C_{16}H_{19}BrO_2$ + Na, 345.0466, found M + Na, 345.0487.

4.4. 4-Deca-1,3,9-triynyl-2,2-dimethyl-[1,3]dioxolane 12

To a round bottom flask equipped with a stirring bar under an atmosphere of nitrogen was added a solution of $NH_2OH{\cdot}HCl$ (32.7 mg, 0.47 mmol) in H_2O (0.40 mL), MeOH (9.5 mL), a 70% aqueous solution of $EtNH_2$ (9.5 mL), and CuCl (46.6 mg, 0.47 mmol). Then compound **11** (1.0 g, 9.42 mmol) was added in one portion. Next, a solution of compound **7** (1.92 g, 9.42 mmol) in MeOH (2 mL) was added over the course of 0.5 h using a syringe pump. The resulting mixture was stirred for an additional 0.5 h at room temperature. A solution of KCN (1.76 g) and NH_4Cl (7.32 g) in H_2O (25 mL) was then added with vigorous stirring. The resulting mixture was extracted three times with Et_2O and the organic layers dried with $MgSO_4$. The solution was filtered and the solvent removed under reduced pressure. The crude mixture was purified over a silica gel column to afford a pale yellow oil (0.94 g, 43%) and a second fraction (0.53 g, 16%).

Compound **12**: $[\alpha]_D = +34.7$ (c 0.21, MeOH), ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.35 (3H, s), 1.46 (3H, s), 1.63 (4H, m), 1.93 (1H, t, $J = 2.5$ Hz), 2.19 (2H, m), 2.30 (2H, m), 3.91 (1H, dd, $J = 6.2$, 8.0 Hz), 4.12 (1H, dd, $J = 6.4$, 7.9 Hz), 4.73 (1H, t, $J = 6.2$ Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 18.28, 19.19, 26.31, 26.51, 27.37, 27.74, 65.14, 66.23, 69.08, 70.11, 71.09, 73.41, 81.79, 84.19, 111.00. Compound **13**: $[\alpha]_D = +47.75$ (c 0.49, MeOH), ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.35 (6H, s), 1.46 (6H, s), 1.62 (4H, m), 2.29 (4H, m), 3.92 (2H, dd, $J = 6.1$, 8.1 Hz), 4.13 (2H, dd, $J = 6.4$, 8.1 Hz), 4.73 (1H, t, $J = 6.3$ Hz). ^{13}C NMR (50 MHz, $CDCl_3$): 19.18, 26.34, 27.39, 65.30, 66.24, 70.13, 71.05, 73.51, 81.56, 111.05.

4.5. 4-(10-Bromo-deca-1,3,9-triynyl)-2,2-dimethyl-[1,3]dioxolane 14

To a suspension of NBS (812 mg, 4.56 mmol) and compound **12** (897 mg, 3.89 mmol) in acetone (39 mL) at room temperature was added $AgNO_3$ (66.1 mg, 0.39 mmol). The mixture was stirred at room temperature for 1 h and was then diluted with H_2O (75 mL). The aqueous layer was extracted three times with Et_2O and the combined organic layers were dried over $MgSO_4$, filtered, and the solvent removed under reduced pressure. The crude mixture was purified over a silica gel column to afford the desired product as a yellow oil (1.08 g, 94%). $[\alpha]_D = +27.6$ (c 2.98, MeOH), ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.35 (3H, s), 1.46 (3H, s), 1.61 (4H, m), 2.21 (2H, m), 2.28 (2H, m), 3.92 (1H, dd, $J = 6.2$, 7.3 Hz), 4.13 (1H, dd, $J = 6.7$, 7.8 Hz), 4.73 (1H, t, $J = 6.1$ Hz), ^{13}C NMR (75 MHz, $CDCl_3$): 19.19, 19.56, 26.31, 26.51, 27.40, 27.59, 38.67, 65.20, 66.23, 70.12, 71.07, 73.46, 79.97, 81.71, 111.02. HRMS: Calcd for $C_{15}H_{17}BrO_2$ + Na, 331.0310, found M + Na: 331.0309.

4.6. [12-(2,2-Dimethyl-[1,3]dioxolan-4-yl)-dodeca-1,3,9,11-tetraynyl]-triisopropyl-silane 15

To a solution of compound **14** (1.08 g, 3.49 mmol), TIPS–acetylene (0.96 g, 5.24 mmol), $Pd(PPh_3)_2Cl_2$ (0.25 g, 0.35 mmol), and CuI (67 mg, 0.35 mmol) in THF (21 mL) at room temperature was added diisopropylamine (1.0 mL, 7.15 mmol) with stirring. The reaction was allowed to proceed for 2 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 the major product as an orange oil (936 mg, 65%), and a second fraction as a yellow solid (mp 64–66 °C, 249 mg, 20%).

Compound **15**: $[\alpha]_D$ = +31.8 (*c* 0.19, $CHCl_3$), ^1H NMR (300 MHz, $CDCl_3$): δ 1.06 (21H, m), 1.35 (3H, s), 1.47 (3H, s), 1.63 (4H, m), 2.29 (4H, m), 3.92 (1H, dd, J = 6.1, 8.1 Hz), 4.13 (1H, dd, J = 6.4, 8.0 Hz), 4.73 (1H, t, 6.2 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 11.68, 18.94, 19.18 (2), 26.31, 26.50, 27.46 (2), 65.27, 66.23, 66.74, 70.11, 71.05, 73.50, 77.60, 78.24, 80.81, 81.58, 111.02. HRMS: Calcd for $C_{26}H_{38}O_2Si$ + Na, 433.2539, found M + Na: 433.2545. Compound **16**: ^1H NMR (500 MHz, $CDCl_3$): δ 1.07 (42H, m). ^{13}C NMR (125 MHz, $CDCl_3$): δ 11.32, 18.56, 81.59, 90.20.

4.7. 14-Triisopropylsilanyl-tetradeca-3,5,11,13-tetrayne-1,2-diol 17

To a solution of compound **15** (0.94 g, 2.28 mmol) in THF (23 mL) at 0 °C was added HF·pyridine complex (2.51 mL). The resulting solution was warmed to room temperature and stirred for an additional 18 h. Then, the mixture was diluted with Et_2O and washed one time with saturated $NaHCO_3$ solution and one time with saturated NaCl solution. The organic layer was then dried over $MgSO_4$, filtered, and the solvent removed under reduced pressure. The crude mixture was purified over a silica gel column giving a yellow oil (777 mg, 92%).

$[\alpha]_D$ = +7.3 (*c* 0.36, MeOH), UV (MeOH): 217, 240, 253, 268 nm. ^1H NMR (300 MHz, $CDCl_3$): δ 1.05 (21H, m), 1.63 (4H, m), 2.28 (4H, m), 3.65 (1H, dd, J = 6.5, 11.5 Hz), 3.73 (1H, dd, J = 3.6, 11.5 Hz), 4.46 (1H, dd, 3.8, 6.4 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 11.67, 18.94, 19.16 (2), 27.45, 27.47, 63.98, 65.09, 66.68, 66.74, 71.42, 73.77, 78.24, 80.83, 81.67, 90.28. HRMS: Calcd for $C_{23}H_{34}O_2Si$ + Na: 393.2226, found M + Na: 393.2223.

4.8. Tetradeca-3,5,11,13-tetrayne-1,2-diol 18

To a solution of compound **17** (150 mg, 0.38 mmol) in THF (5 mL) was added TBAF (1 M, 0.58 mL, 0.58 mmol) and the resulting mixture was stirred for 1.5 h at room temperature. Next, ice water (20 mL) followed by 1 M HCl (2 mL) was added and the aqueous layer was extracted two times with Et_2O. The combined organic layers were then washed once with H_2O, dried over $MgSO_4$, filtered, and the solvent removed under reduced pressure. The crude mixture was purified over a silica gel column to afford a pale brown solid (mp 77–79 °C, 79 mg, 97%).

$[\alpha]_D$ = +21.0 (*c* 0.20, $CHCl_3$), IR ν cm^{-1}: 3276, 2937, 2871, 2299, 2223, 1454, 1279, 1082. ^1H NMR (300 MHz, $CDCl_3$): δ 1.64 (4H, m), 1.96 (1H, t, J = 1.1 Hz), 2.29 (4H, m), 3.67 (1H, dd, J = 6.1, 11.4 Hz), 3.74 (1H, dd, J = 4.0, 11.4 Hz), 4.48 (1H, dd, J = 4.0, 6.1 Hz). ^{13}C NMR (50 MHz, MeOH): δ 18.06, 18.29, 27.31, 27.40, 63.51, 64.91, 65.08, 65.67, 66.05, 68.03, 69.66, 75.03, 76.99, 80.22. HRMS: Calcd for $C_{14}H_{14}O_2$ + Na, 237.0891, found M + Na: 237.0885.

4.9. (+)-Diplyne D 4

To a round bottom flask equipped with a stirring bar under nitrogen was added triethylamine (3 mL), $Pd(PPh_3)_4$ (6.8 mg, 0.006 mmol), CuI (2.2 mg, 0.012 mmol), a mixture of *cis* and *trans* dibromoethylene (73 mg, 0.39 mmol), and compound **18** (21 mg). The resulting solution was stirred at room temperature for 6.5 h. The mixture was then diluted with $CHCl_3$ (5 mL) and filtered through a pad of Florisil using $CHCl_3$. The solvents were removed under reduced pressure and the crude mixture purified over a silica gel column to afford the product as a pale yellow solid (mp 103–105 °C, 16.7 mg, 56%). $[\alpha]_D$ = +7.2 (*c* 0.10, MeOH), UV (MeOH): 290, 273, 258, 221 nm. IR ν cm^{-1} : 3055, 2987, 2927, 2341, 1266, 896, 739. ^1H NMR (300 MHz, MeOH-d_4): δ 1.62 (4H, m), 2.34 (4H, m), 3.53 (1H, dd, J = 6.6, 11.1 Hz), 3.57 (1H, dd, J = 5.1, 11.1 Hz), 4.33 (1H, dd, J = 5.3, 6.4 Hz), 6.32 (1H, dt, J = 1.0, 14.0 Hz), 7.00 (1H, d, J = 14.6 Hz). ^{13}C NMR (125 MHz, MeOH-d_4): 19.22, 19.57, 28.27, 28.38, 64.51, 65.89, 65.99, 67.06, 70.59, 72.12, 76.07, 77.13, 81.11, 86.24, 117.74, 123.03. HRMS: Calcd for $C_{16}H_{15}BrO_2$ + Na, 341.0153, found M + Na: 341.0178.

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