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A convergent approach for the total synthesis of the α-glucosidase inhibitor (−)-panaxjapyne-C

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ABSTRACT

The stereoselective total synthesis of (−)-panaxjapyne-C was accomplished in a convergent fashion. The synthesis utilizes the readily available enantiomers L-(+)-diethyltartrate and D-(−)-diethyltartrate and involves a Cadiot–Chodkiewicz coupling reaction, and an Ohira–Bestmann reaction as the key steps.

1. Introduction

Polyacetylene compounds continue to attract significant attention because of their wide range of biological properties such as cytotoxic, anti-platelet effect, antitumor, anti-inflammatory, antimicrobial, antiviral, RNA-cleaving, sedative, and enzyme-inhibitory activities.[1] Recent investigations on the extracts from the roots of *Panax japonicus* C. A. Meyer var. major resulted in an active fraction displaying inhibitory activity against baker's yeast α-glucosidase with an IC_{50} value of 1.02 mg/mL. Further characterizations of the active fraction resulted in the isolation of three new diacetylene triol molecules; panaxjapynes A–C (Fig. 1).[2] The structures of these compounds were elucidated by chemical and spectroscopic methods in a relative fashion.[2,3] Panaxjapyne A displayed a higher inhibitory effect than panaxjapyne C and both of these compounds displayed a significant inhibitory effect in comparison with the control drug acarbose.[2] The studies also indicated that the hydroxyl moieties at C-9 and C-10 and the terminal vinylic group are responsible for decreasing the α-glucosidase inhibitory activity.

Since several diacetylene polyol molecules display a wide range of biological activities, we became interested in the synthesis of these diacetylene triol molecules to make them available for further biological screening. Our recent studies on the synthesis of the diacetylene tetrol molecules oploxynes A and B (Fig. 1) led us to revise the absolute stereochemistry of oploxyne B and showed that both (+)-oploxyne A and (−)-oploxyne-B displayed cytotoxic activity against a human neuroblastoma cell line with an IC_{50} value 7 μM and 12 μM against the reference sample doxorubicin, which displayed an IC_{50} value of 9 μM.[4] In continuation of our studies on the synthesis of diacetylene containing natural products,[4,5] we herein report the total synthesis of panaxjapyne C utilizing a convergent approach starting from both enantiomers of diethyl tartrate.

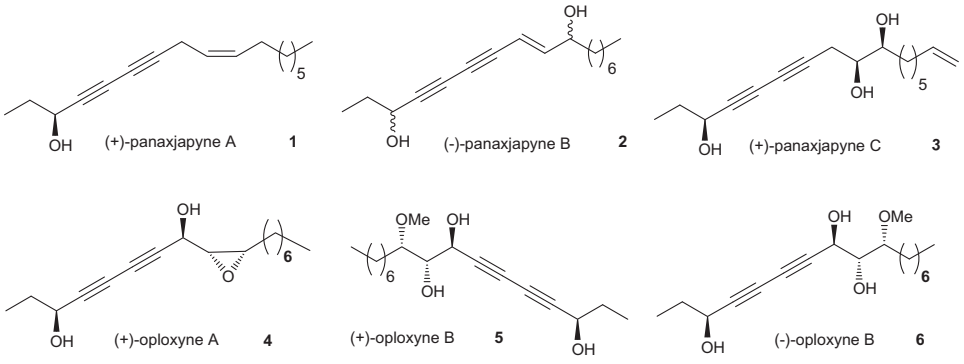

Figure 1. Examples of diacetylene polyols.

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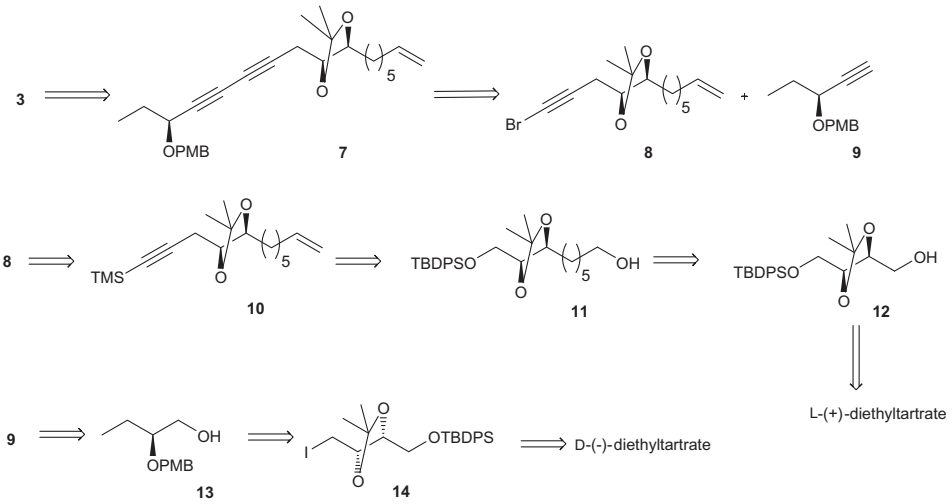
2. Results and discussion

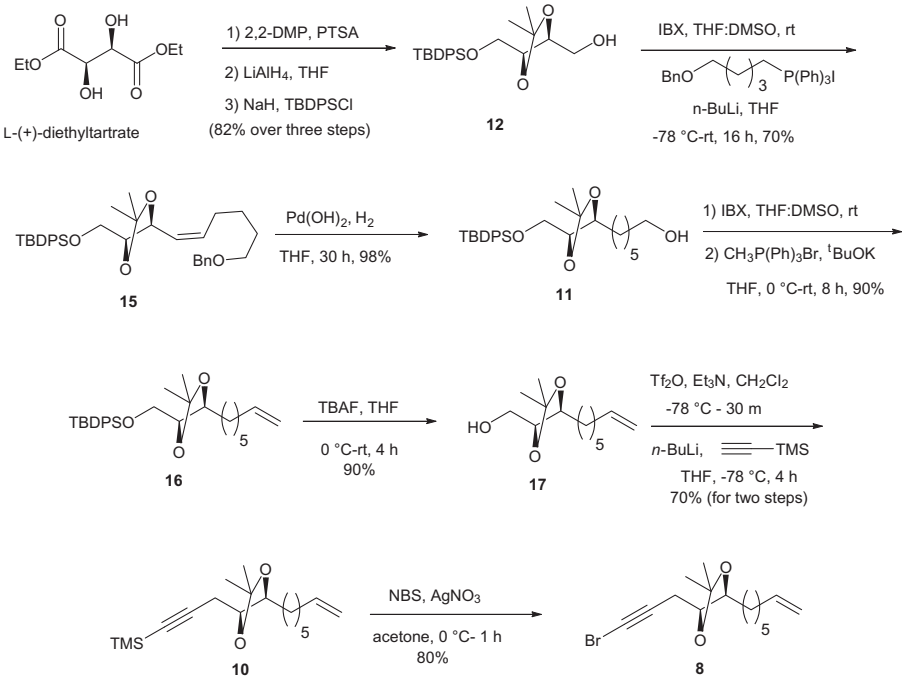
We envisioned that panaxjapyne-C could be obtained from precursor **7** by deprotection of the PMB and acetonide moieties. The precursor **7** could in turn be obtained by a coupling reaction between two key fragments, the bromoalkyne **8** and the free terminal alkyne **9** under Cadiot–Chodkiewicz conditions (Scheme 1). Compound **8** can be prepared from compound **10** via silver nitrate catalyzed bromination. Compound **10** in turn can be synthesized from L-(+)-diethyltartrate after sequential manipulations through **12** and **11**. Alkyne **9** could be prepared from compound **13** via an oxidation followed by Ohira–Bestmann homologation reaction. Compound **13** was in turn obtained from **14** in five steps; base mediated reductive elimination reaction, olefin reduction, TBDPS deprotection, acetal formation, and regioselective acetal opening to obtain the primary free alcohol. Compound **14** was easily accessed from commercially available D-(−)-diethyltartrate.

The synthesis began with the oxidation of mono silylated alcohol **12** synthesized from L-(+)-diethyltartrate in three transformations, that is, acetonide protection, $LiAlH_4$ reduction, and TBDPS protection[6] to yield the aldehyde, which upon subsequent Wittig reaction with benzyloxy-*n*-pentyltriphenyl phosphonium bromide in the presence of *n*-BuLi afforded the Wittig product **15** in good yield. Compound **15** was subjected to one-pot debenzylation and olefin reduction using $Pd(OH)_2$ to afford alcohol **11**. The IBX oxidation[7] of **11** followed by treatment with methyl triphenylphosphonium bromide in the presence of *t*-BuOK afforded olefin **16** in 90% yield. Cleavage of silyl ether **16** with TBAF provided alcohol **17**, which was converted into the triflate and then coupled to trimethylsilyl acetylene to provide **10**. The silver nitrate catalyzed bromination of compound **10** using N-bromosuccinamide produced bromoalkyne **8**, the key fragment with the desired stereochemistry (Scheme 2).

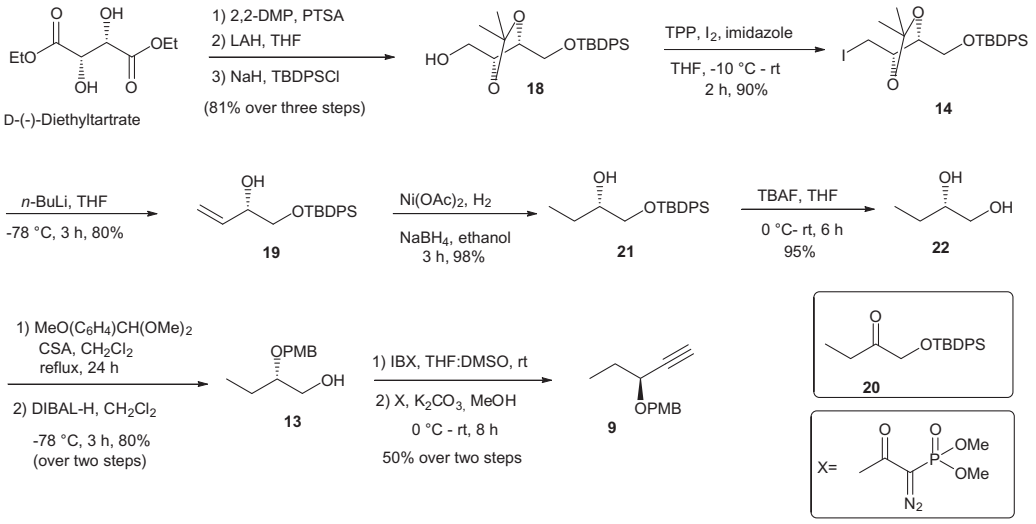
The synthesis of the other key fragment **9** is shown in Scheme 3. Accordingly, commercially available D-(−)-diethyltartrate was



Scheme 1. Retrosynthesis for panaxjapyne C.



Scheme 2. Synthesis of bromoalkyne **8**.



Scheme 3. Synthesis of alkyne **9**.

converted into alcohol **18** in three steps following standard literature protocols.[6] The mono protected alcohol **18** was converted into the corresponding iodide[8] **14** using triphenylphosphine, I_2, and imidazole and subjected to an elimination reaction by treatment with *n*-BuLi (2 equiv) at −78 °C to afford allylic alcohol **19** in 80% yield.[9] Our initial attempts to reduce the double bond in **19** using Pd/C or $Pd(OH)_2$ were unsuccessful and led to the formation of undesired ethyl ketone[10] **20** without the formation of the desired saturated product **21**. However, this problem was successfully overcome with $Ni(OAc)_2/NaBH_4$ to provide **21** in 98% yield.[11] Our initial attempts to protect the secondary alcohol with MPMBr ended up with a mixture of spots leading to a low yield of the desired product[12] which had to be subsequently subjected to silyl deprotection. Alternatively, compound **18** was first treated with TBAF to provide diol **22**. Diol **22** was then protected with anisaldehyde dimethyl acetal in the presence of a catalytic amount of camphor sulfonic acid and subjected to regioselective ring opening reaction with DIBAL-H[13] to furnish the free primary alcohol **13** in good yields. Compound **13** was oxidized to the aldehyde and subjected to an Ohira–Bestmann homologation reaction[14] to finish the synthesis of alkyne **9**.

With both intermediates, alkyne **9** and bromo alkyne **8** in hand, we proceeded to couple them under Cadiot–Chodkiewicz coupling conditions.[15] Compounds **9** and **8** were coupled using CuCl, *n*-$BuNH_2$ to afford precursor compound **7** in good yield. Finally, the one pot deprotection of PMB as well as the acetonide moiety in compound **7** with TFA afforded panaxjapyne-C **3** (Scheme 4).

The ^1H NMR and ^{13}C NMR spectra of the synthesized product were in full agreement with those of the reported natural product.[2] However, the specific rotation of our synthetic product was observed to be $[\alpha]_D^{25} = -16.0$ (*c* 0.1, MeOH), whereas the specific rotation for the natural product from isolation studies[2] and the earlier synthesis[3] was found to be $[\alpha]_D^{25} = +20.6$ (*c* 0.02, MeOH) and $[\alpha]_D^{25} = +17.3$ (*c* 0.2, MeOH), respectively. However, based on the outcome of our synthesis, we can herein unequivocally assign the absolute structure of natural product as **3a**, the enantiomer of our synthesized product **3**.

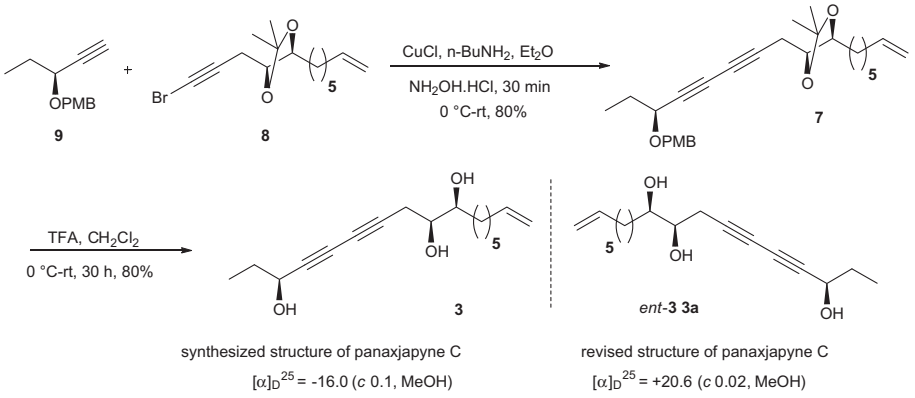
3. Conclusion

In conclusion the total synthesis of (−)-panaxjapyne-C has been achieved in a convergent fashion utilizing both enantiomers of diethyltartrate as chirons. Once again, the Cadiot–Chodkiewicz reaction has been found to be pivotal in generating diacetylene functionality. The synthesis of other members of the panaxjapynes is currently in progress in our laboratory.

4. Experimental

4.1. General

^1H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ or mixture of $CDCl_3$ and CCl_4 as solvent on 300 MHz or 500 MHz



Scheme 4. Synthesis of (−)-panaxjapyne C.

spectrometer at ambient temperature. The coupling constants *J* are given in Hz. The chemical shifts are reported in ppm on a scale downfield from TMS as the internal standard and signal patterns are indicated as follows: s = singlet, d = doublet, dd = doublet of doublet, dt = doublet of triplet, t = triplet, q = quartet, qd = quartet of doublet, m = multiplet, br = broad. FTIR spectra were recorded on KBr pellets $CHCl_3$/neat (as mentioned) and reported in wave numbers (cm^{-1}). For low (MS) and high (HRMS) resolution, *m*/*z* ratios are reported as values in atomic mass units. Mass analysis was done in ESI mode. Optical rotations were measured on Anton Paar digital polarimeter and the values given are specific rotations. All reagents were of reagent grade and used without further purification unless specified otherwise. Solvents for reactions were distilled prior to use: THF was distilled from Na and benzophenone ketyl; MeOH from Mg and I_2; CH_2Cl_2 from CaH_2. All air- or moisture-sensitive reactions were conducted under a nitrogen or argon atmosphere in flame-dried or oven-dried glassware with magnetic stirring. Reactions were monitored by thin-layer chromatography carried out on silica plates (silica gel 60 F254, Merck) using UV-light, iodine and anisaldehyde for visualization. Column chromatography was carried out using silica gel (60–120 mesh) packed in glass columns. Technical grade ethyl acetate and petroleum ether used for column chromatography were distilled prior to use.

4.1.1. (((4*S*,5*S*)-5-((*Z*)-6-(Benzyloxy)hex-1-en-1-yl)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)(*tert*-butyl)diphenylsilane 15

Compound **12** (10.0 g, 25 mmol) was dissolved in a solvent mixture of THF (60 mL) and DMSO (60 mL). To this IBX was (10.5 g, 37.5 mmol) added in one portion and stirred for 2 h at room temperature. The reaction mixture was diluted with ice cold water and extracted with CH_2Cl_2 (5 × 40 mL). The combined organic layers were washed with saturated $NaHCO_3$ (150 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to yield the crude aldehyde, which was directly used for next step without further purification. Benzyloxy-*n*-pentyltriphenyl phosphonium bromide (20.27 g, 37.6 mmol) was dissolved in dry THF (150 mL) and cooled to −78 °C. To this *n*-BuLi (20.41 mL, 32.66 mmol) was added dropwise and stirred for 3 h at −78 °C. During this time, the reaction color changed from colorless to brick red. To this, the crude aldehyde obtained above (dissolved in 30 mL dry THF) was added dropwise and stirred overnight. After the addition of aldehyde the reaction color changed from brick red to colorless. The reaction mixture was quenched with aq saturated ammonium chloride solution (20 mL) at 0 °C. The reaction mixture was extracted with ethyl acetate (5 × 30 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The resulting crude was purified through column chromatography to afford compound **15** (9.81 g, 17.58 mmol, 70%) as a colorless oil. $[\alpha]_D^{25} = +12.67$ (*c* 0.6, $CHCl_3$). IR [NEAT]: 3068, 2931, 2858, 1656, 1056, 1428, 1217, 1109, 1070, 822, 702, 606, 504 cm^{-1}. ^1H NMR, (300 MHz, $CDCl_3$): δ 7.73–7.65 (m, 4H), 7.44–7.35 (m, 11H), 5.68–5.60 (m, 1H), 5.42–5.35 (m, 1H), 4.86 (t, *J* = 8.7 Hz, 1H), 4.47 (s, 2H), 3.83 (dd, *J* = 11.1, 3.0 Hz, 1H), 3.74–3.63 (m, 2H), 3.42 (t, *J* = 6.4 Hz, 2H), 2.29–2.17 (m, 1H), 2.11–1.97 (m, 1H), 1.68–1.50 (m, 3H),1.45 (s, 3H), 1.44 (s, 3H), 1.50–1.36 (m, 1H), 1.07 (s, 4H), 1.05 (s, 5H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 138.5, 135.7, 135.6, 135.5, 135.2, 134.8, 133.3, 133.1, 129.7, 129.6, 129.5, 128.3, 127.6, 127.4, 126.7, 108.8, 81.7, 72.8, 70.1, 62.3, 29.6, 27.6, 27.3, 27.0, 26.8, 26.5, 26.2, 19.2, 19.0 ppm. MS(ESI): *m*/*z* 581 $[M+Na]^+$. HRMS(ESI) *m*/*z* calculated for $C_{35}H_{46}O_4NaSi$ 581.30576, found: 581.30521.

4.1.2. 6-((4*S*,5*S*)-5-(((*tert*-Butyldiphenylsilyl)oxy)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)hexan-1-ol 11

To compound **15** (5.0 g, 8.96 mmol) dissolved in anhydrous THF (30 mL) was added $Pd(OH)_2$ (100 mg) and the reaction mixture was stirred under an H_2 atmosphere for 24 h. The reaction mixture was filtered over Celite and concentrated under reduced pressure. The resulting crude product was purified through column chromatography to afford compound **11** (4.12 g, 8.76 mmol, 98%) as a colorless oil. $[\alpha]_D^{25} = -4.2$ (*c* 1.0, $CHCl_3$). IR [NEAT]: 3451, 2930, 2858, 1633, 1374, 1107, 701, 610, 502 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.69–7.64 (m, 4H), 7.45–7.34 (m, 6H), 3.98–3.92 (m, 1H), 3.78–3.68 (m, 3H), 3.63 (t, *J* = 6.4 Hz, 2H), 1.67–1.45 (m, 5H), 1.43–1.18 (m, 5H), 1.40 (s, 3H), 1.37 (s, 3H), 1.05 (s, 9H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 135.6, 133.2, 133.1, 129.7, 129.6, 127.6, 108.4, 81.1, 78.4, 64.1, 62.8, 33.2, 32.6, 29.4, 27.4, 26.9, 26.8, 26.0, 25.5, 19.2 ppm. MS(ESI): *m*/*z* 493 $[M+Na]^+$. HRMS(ESI) *m*/*z* calculated for $C_{28}H_{42}O_4NaSi$ 493.27446, found: 493.27328.

4.1.3. *tert*-Butyl(((4*S*,5*S*)-5-(hept-6-en-1-yl)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy) diphenylsilane 16

Compound **11** (4.0 g, 8.51 mmol) was dissolved in a solvent mixture of THF (30 mL) and DMSO (30 mL). To this, IBX was (3.57 g, 12.76 mmol) added in one portion and the reaction mixture was stirred for 5 h at room temperature. The reaction mixture was diluted with ice cold water (30 mL) and extracted with CH_2Cl_2 (5 × 30 mL). The combined organic layers were washed with saturated $NaHCO_3$ (100 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to yield the crude aldehyde, which was directly used for the next step without further purification. Dry THF (50 mL) was added to a mixture of methyl triphenyl phosphonium bromide (7.62 g, 21.36 mmol) and *t*-BuOK (2.2 g, 19.65 mmol) at 0 °C for 20 min and then stirred for 1 h at room temperature. During this time, the reaction color changed from colorless to yellow. Again the reaction was cooled to 0 °C and to this was added dropwise the aldehyde obtained above and then allowed to stir for 12 h at room temperature. The reaction mixture was quenched with aq saturated ammonium chloride solution (10 mL) at 0 °C. The reaction mixture was extracted with ethyl acetate (4 × 30 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The resulting crude was purified through column chromatography to afford compound **16** (3.56 g, 7.63 mmol, 90%) as a colorless oil. $[\alpha]_D^{25} = -9.85$ (*c* 5.0, $CHCl_3$). IR [NEAT]: 3071, 2931, 2859, 1639, 1465, 1372, 1109, 1082, 822, 703, 608, 505 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.70–7.65 (m, 4H), 7.45–7.35 (m, 6H), 5.87–5.74 (m, 1H), 5.03–4.91 (m, 2H), 3.99–3.92 (m, 1H), 3.76–3.68 (m, 3H), 2.08–2.01 (m, 2H), 1.60–1.46 (m, 3H), 1.44–1.25 (m, 5H), 1.40 (s, 3H), 1.37 (s, 3H), 1.06 (s, 9H) ppm. ^{13}C NMR, (75 MHz, $CDCl_3$): δ 138.9, 135.6, 133.2, 133.1, 129.7, 129.6, 127.7, 114.2, 108.3, 81.1, 78.4, 64.1, 33.7, 33.3, 29.1, 28.7, 27.4, 27.0, 26.8, 25.9, 19.2 ppm. MS(ESI): *m*/*z* 489 $[M+Na]^+$. HRMS(ESI) *m*/*z* calculated for $C_{29}H_{42}O_3NaSi$ 489.27954, found: 489.27781.

4.1.4. ((4*S*,5*S*)-5-(Hept-6-en-1-yl)-2,2-dimethyl-1,3-dioxolan-4-yl)methanol 17

Compound **16** (3.5 g, 7.51 mmol) was dissolved in anhydrous THF (30 mL) and cooled to 0 °C. To this tetra *n*-butyl ammonium fluoride (12.76 mmol, 12.76 mL, 1 M solution in THF) was added dropwise and stirred for 3 h. The reaction was quenched with aq. saturated ammonium chloride solution (20 mL) at 0 °C and extracted with ethyl acetate (3 × 30 mL). The organic layer was separated and dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The resulting crude product was purified through column chromatography to afford compound **17** (1.71 g, 7.5 mmol, 90%) as a colorless oil. $[\alpha]_D^{25} = -22.0$ (*c* 2.7, $CHCl_3$). IR [NEAT]: 3450, 3075, 2930, 2859, 1640, 1457, 1374, 1102, 910, 759, 516 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 5.87–5.73 (m, 1H), 5.03–4.89 (m, 2H), 3.91–3.70 (m, 3H), 3.66–3.57 (m, 1H), 2.08–2.01 (m, 2H), 1.75 (br s, 1H), 1.62–1.45 (m, 3H), 1.42–1.23 (m, 5H), 1.41 (s, 3H), 1.40 (s, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.9, 114.3, 108.5, 81.5, 76.8, 62.0, 33.6, 33.0, 29.1, 28.7, 27.3,

27.0, 25.8 ppm. MS(ESI): *m*/*z* 229 $[M+H]^+$. HRMS(ESI) *m*/*z* calculated for $C_{13}H_{25}O_3$ 229.17982, found: 229.17982.

4.1.5. (3-((4*S*,5*S*)-5-(Hept-6-en-1-yl)-2,2-dimethyl-1,3-dioxolan-4-yl)prop-1-yn-1-yl) trimethylsilane 10

To alcohol **17** (0.5 g, 2.19 mmol) dissolved in dry CH_2Cl_2 (15 mL) was added triethylamine (0.66 g, 6.57 mmol) at room temperature and stirred for 5 min. The reaction mixture was cooled to −78 °C and trifluoromethane sulfonic anhydride (0.74 g, 2.63 mmol) was added and stirred for an additional 30 min. The reaction mixture was quenched with aq saturated ammonium chloride solution (4 ml) at 0 °C, and extracted with CH_2Cl_2 (4 × 5 mL). The organic layer was separated, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude triflate was purified through short pad of silica gel and used without further characterization.

Next, *n*-BuLi (1.37 mL, 1.6 M, 2.19 mmol) was added to a solution of trimethylsilyl acetylene (0.21 g, 2.19 mmol) in dry THF (7 mL) at 0 °C. The reaction mixture was stirred for 3 h at 0 °C and cooled to −78 °C. To this, HMPA (2.35 g, 13.15 mmol) and triflate in dry THF (5 mL) were added and stirred for 3–4 h at −78 °C. The reaction mixture was quenched with aq saturated ammonium chloride (5 mL) at 0 °C, and extracted with ethyl acetate (4 × 5 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The resulting crude product was purified through column chromatography to afford compound **10** (0.47 g, 1.52 mmol, 70%) as a colorless oil. $[\alpha]_D^{25} = -1.9$ (*c* 1.5, $CHCl_3$). IR [NEAT]: 2923, 2854, 1633, 1436, 1116, 542 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 5.87–5.74 (m, 1H), 5.02–4.91(m, 2H), 3.92–3.59 (m, 2H), 2.64–2.47 (m, 2H), 2.08–2.02 (m, 2H), 1.74–1.45 (m, 3H), 1.44–1.25 (m, 5H), 1.39 (s, 6H), 0.15 (s, 9H) ppm. ^{13}C NMR, (75 MHz, $CDCl_3$): δ 139.0, 114.2, 108.2, 80.6, 80.3, 79.4, 78.1, 33.7, 33.1, 29.2, 28.8, 27.5, 27.0, 25.9, 24.0, 0.03 ppm. MS(ESI): *m*/*z* 331 $[M+Na]^+$.

4.1.6. (4*S*,5*S*)-4-(3-Bromoprop-2-yn-1-yl)-5-(hept-6-en-1-yl)-2,2-dimethyl-1,3-dioxolane 8

Compound **10** (0.2 g, 0.64 mmol) was dissolved in dry acetone (10 mL) and cooled to 0 °C. To this N-bromosuccinamide (0.14 g, 0.77 mmol) and a catalytic amount of silver nitrate were added successively and stirred for 1 h at 0 °C. The solvent was evaporated under reduced pressure and the resulting residue was diluted with ethyl acetate and washed with brine solution. The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The resulting crude was purified through column chromatography to afford compound **8** (0.16 g, 0.5 mmol, 80%) as a yellow oil. $[\alpha]_D^{25} = -9.1$ (*c* 1.0, $CHCl_3$). IR [NEAT]: 3075, 2986, 2858, 1730, 1640, 1613, 1459, 1244, 1060, 911, 748, 514 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 5.88–5.74 (m, 1H), 5.03–4.91 (m, 2H), 3.92–3.59 (m, 2H), 2.52 (d, *J* = 5.3 Hz, 2H), 2.08–2.02 (m, 2H), 1.68–1.46 (m, 3H), 1.45–1.25 (m, 5H), 1.40 (s, 6H) ppm. ^{13}C NMR, (75 MHz, $CDCl_3$): δ 139.0, 114.3, 108.6, 80.4, 79.3, 78.2, 75.9, 33.7, 33.0, 29.7, 28.7, 27.4, 27.0, 25.8, 23.8 ppm.

4.1.7. (4*S*,5*S*)-4-(Hept-6-en-1-yl)-5-((*S*)-6-((4-methoxybenzyl)oxy)-octa-2,4-diyn-1-yl)-2,2-dimethyl-1,3-dioxolane 7

At first, CuCl (1 mg) was added to 30% *n*-butylamine solution (3 mL). After blue coloration occurs, few crystals of hydroxylamine hydrochloride were added until the blue color disappeared. Next, alkyne **9** (0.05 g, 0.24 mmol) dissolved in diethyl ether (5 mL) was added in one portion and immediately cooled to 0 °C. The bromo alkyne **8** (0.06 g, 0.19 mmol) in diethyl ether (5 mL) was added in one portion and stirred for 30 min. The reaction mixture was extracted with diethyl ether (5 × 20 mL) and the combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The resulting crude product was purified through column chromatography to afford compound **7** (0.085 g, 0.18 mmol, 80%) as a colorless oil. $[\alpha]_D^{25} = -154.5$ (*c* 1.5, $CHCl_3$). IR [NEAT]: 2932, 2970, 2859, 1612, 1460, 1513, 1247, 1064, 821, 766, 517 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.31–7.28 (m, 2H), 6.90–6.85 (m, 2H), 5.87–5.73 (m, 1H), 5.03–4.91 (m, 2H), 4.76–4.69 (m, 1H), 4.46–4.39 (m, 1H), 4.08–4.00 (m, 1H), 3.85–3.71 (m, 2H), 3.81 (s, 3H), 2.61 (d, *J* = 5.3 Hz, 2H), 2.08–2.01 (m, 2H), 1.82–1.69 (m, 2H), 1.65–1.47 (m, 3H), 1.45–1.32 (m, 5H), 1.41 (s, 6H), 1.03–0.95 (m, 3H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 159.2, 138.9, 129.7, 129.6, 114.2, 113.7, 108.7, 80.4, 78.4, 78.1, 75.8, 70.4, 70.3, 69.8, 66.8, 55.2, 33.6, 32.8, 29.1, 28.7 (2C), 27.4, 27.0, 25.7, 23.5, 9.6 ppm. MS(ESI): *m*/*z* 461 $[M+Na]^+$. HRMS(ESI) *m*/*z* calculated for $C_{28}H_{38}O_4Na$ 461.26623, found: 461.26483.

4.1.8. Panaxjapyne-C 3

Compound **7** (0.04 g, 0.09 mmol) was dissolved in 8 mL of dry CH_2Cl_2 and cooled to 0 °C. To this, trifluoroacetic acid (0.1 mL) was added and stirred for 30 h at room temperature. The solvent was evaporated under reduced pressure and the resulting crude was purified through column chromatography to afford compound **3** (20 mg, 0.07 mmol, 80%) as colorless oil. $[\alpha]_D^{25} = -16.0$ (*c* 0.1, MeOH). Lit.[3] $[\alpha]_D^{25} = -20.6$ (*c* 0.02, MeOH) IR [NEAT]: 3350, 2931, 2856, 1780, 1639, 1611, 1506, 13336, 1247, 1035, 969, 811, 756, 665 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 5.87–5.74 (m, 1H), 5.03–4.92 (m, 2H), 4.35 (t, *J* = 6.4 Hz, 1H), 3.78–3.58 (m, 2H), 2.56 (d, *J* = 5.5 Hz, 2H), 2.31 (br s, 2H), 2.08–2.02 (m, 2H), 1.78–1.69 (m, 2H), 1.58–1.20 (m, 8H), 1.01 (t, *J* = 7.4 Hz, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.9, 114.3, 77.3, 77.2, 73.1, 72.1, 69.5, 66.7, 64.0, 33.7, 33.5, 30.7, 29.0, 28.8, 25.4, 25.0, 9.3 ppm. MS(ESI): *m*/*z* 301 $[M+Na]^+$. HRMS(ESI) *m*/*z* calculated for $C_{17}H_{26}O_3Na$ 301.17742, found: 301.17783.

4.1.9. *tert*-Butyl (((4*S*,5*R*)-5-(iodomethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)diphenylsilane 14

Into a 250 mL round bottom flask, compound **18** (10.0 g, 25 mmol), triphenylphosphine (13.1 g, 50 mmol), and imidazole (5.1 g, 75 mmol) were added. To this, dry THF (120 mL) was added and cooled to −10 °C. Next, I_2 (14.0 g, 55 mmol) was added in portion wise and then the ice bath was removed and the reaction was stirred for 2 h at room temperature. The solvent was removed through rotavapour and the resulting crude was purified by column chromatography to afford compound **14** (11.47 g, 22.49 mmol, 90%) as a colorless oil. $[\alpha]_D^{25} = +6.2$ (*c* 5.0, $CHCl_3$). IR [NEAT]: 3069, 2932, 2858, 1428, 1238, 1110, 1080, 939, 824, 703, 609, 505 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.72–7.66 (m, 4H), 7.46–7.33 (m, 6H), 3.99–3.93 (m, 1H), 3.89–3.74 (m, 3H), 3.41–3.36 (m, 1H), 3.31–3.26 (m, 1H), 1.46 (s, 3H), 1.39 (s, 3H), 1.06 (s, 9H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 135.6, 135.5, 133.0, 132.8, 129.8, 129.7, 109.5, 81.1, 77.5, 64.1, 27.4, 27.3, 26.8, 19.2, 6.8 ppm. MS(ESI): *m*/*z* 533 $[M+Na]^+$. HRMS(ESI) *m*/*z* calculated for $C_{23}H_{31}O_3INaSi$ 533.09794, found: 533.09827.

4.1.10. (*S*)-1-((*tert*-Butyldiphenylsilyl)oxy)but-3-en-2-ol 19

Compound **14** (5.0 g, 9.8 mmol) was dissolved in 50 mL dry THF and cooled to −78 °C. To this *n*-BuLi (12.25 mL, 1.6 M, 19.6 mmol) was added and stirred for 3 h. The reaction was quenched with aq saturated ammonium chloride solution (25 mL) and extracted with ethyl acetate (5 × 30 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The resulting crude material was purified by column chromatography to afford compound **19** (2.55 g, 7.8 mmol, 80%) as a colorless oil. $[\alpha]_D^{25} = -4.6$ (*c* 3.2, $CHCl_3$). IR [NEAT]: 3447, 3071, 2931, 2858, 1643, 1468, 1427, 1110, 927, 703, 613, 505 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 7.67–7.66 (m, 4H), 7.45–7.38 (m, 6H), 5.83–5.76 (m, 1H), 5.33–5.15 (m, 2H), 4.27–4.22 (m, 1H), 3.71–3.69 (m, 1H), 3.57–3.54 (m, 1H), 2.58 (br s, 1H), 1.07 (s, 9H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 136.6, 135.5, 133.1, 133.0, 129.8, 127.7,

116.4, 73.0, 67.7, 26.8, 19.2 ppm. MS(ESI): m/z 349 $[M+Na]^+$. HRMS(ESI) m/z calculated for $C_{20}H_{26}O_2NaSi$ 349.15943, found: 349.15832.

4.1.11. (*S*)-1-((*tert*-Butyldiphenylsilyl)oxy)butan-2-ol 21

Into a 50 mL double neck round bottom flask $Ni(OAc)_2$ (0.4 g, 66 mg per mmol) in 10 mL of ethanol was added and an H_2 balloon was fixed. To this, 1 M $NaBH_4$ (1.5 mL) was added and stirred for 10 min. To this, compound **19** (2.0 g, 6.13 mmol) was added and stirred for 3 h. The reaction mixture was filtered through a sintered funnel and the solvent was evaporated under reduced pressure. The resulting crude product was purified by column chromatography to afford compound **21** (1.96 g, 6.0 mmol, 98%) as a colorless oil. $[\alpha]_D^{25} = +4.2$ (c 2.2, $CHCl_3$). IR [NEAT]: 3447, 3070, 2932, 2859, 1466, 1110, 772, 703, 611, 505 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.67–7.65 (m, 4H), 7.44–7.36 (m, 6H), 3.68 (m, 2H), 3.52–3.45 (m, 1H), 2.51 (br s, 1H), 1.49–1.41 (m, 1H), 1.32–1.25 (m, 1H), 1.06 (s, 9H), 0,90 (t, J = 7.5 Hz, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 135.5, 133.2, 133.1, 129.8, 127.7, 73.3, 67.7, 26.8, 25.7, 19.2, 9.9 ppm. MS(ESI): m/z 351 $[M+Na]^+$. HRMS(ESI) m/z calculated for $C_{20}H_{28}O_2NaSi$ 351.17508, found: 351.17379.

4.1.12. (*S*)-Butane-1,2-diol 22

Compound **21** (1.5 g, 4.5 mmol) was dissolved in 20 mL of dry THF and cooled to 0 °C. To this, tetra *n*-butylammonium fluoride (7.7 mL, 7.7 mmol, 1 M solution THF) was added and stirred for 4–6 h at room temperature. The reaction mixture was quenched with saturated ammonium chloride solution (10 mL) and extracted with ethyl acetate (4 × 20 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The resulting crude was purified through column chromatography to afford compound **22** (0.26 g, 4.3 mmol, 95%) as a colorless oil. $[\alpha]_D^{25} = +2.5$ (c 1.0, $CHCl_3$). IR [NEAT]: 3410, 2966, 2880, 1401, 1059, 989, 768, 540 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 3.67–3.58 (m, 2H), 3.46–3.40 (m, 1H), 3.12 (br s, 2H), 1.51–1.40 (m, 2H), 1.00 (t, J = 7.5 Hz, 3H) ppm. ^{13}C NMR, 75 MHz, $CDCl_3$: δ 73.7, 66.5, 26.0, 9.9 ppm.

4.1.13. (*S*)-2-((4-Methoxybenzyl)oxy)butan-1-ol 13

Into a 50 mL round bottom flask, diol **22** (0.2 g, 3.3 mmol), CSA (catalytic amount), anisaldehyde dimethyl acetal (0.91 g, 5.0 mmol) and CH_2Cl_2 (12 mL) were added and refluxed for 20 h. The reaction mixture was quenched with triethylamine (2 mL). The solvent was removed with a rotary evaporator and the resulting crude acetal was directly utilized for the next reaction without further purification. The crude acetal (0.5 g) was dissolved in 15 mL of dry CH_2Cl_2 and cooled to −78 °C. To this, diisobutyaluminium hydride (2.6 mL, 3.6 mmol, and 1.4 M solution in toluene) was added and stirred for 2 h at −30 °C. The reaction mixture was quenched with saturated sodium potassium tartrate solution and stirred for 6 h at room temperature. The reaction mixture was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The resulting crude was purified by column chromatography to afford compound **13** (0.38 g, 1.8 mmol, 80%) as a colorless oil. $[\alpha]_D^{25} = 6.4$ (c 1.5, $CHCl_3$). IR [NEAT]: 3426, 2926, 2875, 1612, 1586, 1513, 1247, 1034, 820, 516 cm^{-1}. ^1H NMR, (300 MHz, $CDCl_3$): δ 7.30–7.26 (m, 2H), 6.90–6.87 (m, 2H), 4.56 (d, J = 11.2 Hz, 1H), 4.46 (d, J = 11.2 Hz, 1H), 3.80 (s, 3H), 3.80–3.72 (m, 1H), 3.70–3.65 (m, 1H), 3.55–3.39 (m, 1H), 1.97 (br s, 1H), 1.72–1.39 (m, 2H), 0.92 (t, J = 7.5 Hz, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.2, 129.3, 128.6, 113.9, 80.7, 71.1, 64.9, 55.2, 23.5, 9.6 ppm. MS(ESI): m/z 233 $[M+Na]^+$. HRMS(ESI) m/z calculated for $C_{12}H_{18}O_3Na$ 233.11482, found: 233.11446.

4.1.14. (*S*)-1-Methoxy-4-((pent-1-yn-3-yloxy)methyl)benzene 9

Compound **13** (0.2 g, 1.0 mmol) was dissolved in a solvent mixture of dry THF/dry DMSO (16 mL, 1:1). To this IBX (0.4 g, 1.4 mmol) was added in one portion and stirred for 2 h at room temperature. The reaction mixture was diluted with ice cold water (50 mL) and extracted with CH_2Cl_2 (5 × 10 mL). The combined organic layers were washed with saturated $NaHCO_3$ solution (30 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to yield the crude aldehyde which was used directly for the alkyne formation.

The aldehyde obtained above was dissolved in dry methanol (5 mL). To this Ohira–Bestmann (0.28 g, 1.4 mmol) reagent in 5 mL dry methanol was added and cooled to 0 °C. K_2CO_3 (0.26 g, 2.0 mmol) was added and the reaction mixture was stirred for 12 h at room temperature. The reaction mixture was filtered and the filtrate was concentrated. The resulting crude was purified by silica gel column chromatography to afford compound **9** (0.1 g, 0.5 mmol, 50%) as colorless oil. $[\alpha]_D^{25} = -108.3$ (c 1.2, $CHCl_3$). Lit.[1] $[\alpha]_D^{25} = -112.2$ (c 2.0, $CHCl_3$). IR [NEAT]: 3291, 2967, 2869, 1612, 1513, 1248, 1068, 821, 644, 517 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.30–7.25 (m, 2H), 6.90–6.85 (m, 2H), 4.73 (d, J = 11.3 Hz, 1H), 4.44 (d, J = 11.3 Hz, 1H), 3.99 (td, J = 6.4, 1.9 Hz, 1H), 3.80 (s, 3H), 2.45 (d, J = 2.1 Hz, 1H), 1.81–1.71 (m, 2H), 1.00 (t, J = 7.3 Hz, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.0, 129.7, 129.3, 113.5, 82.6, 73.7, 69.8, 69.0, 54.8, 28.5, 9.3 ppm. HRMS(ESI) m/z calculated for $C_{13}H_{16}O_2Na$ 227.10425, found: 227.10399.

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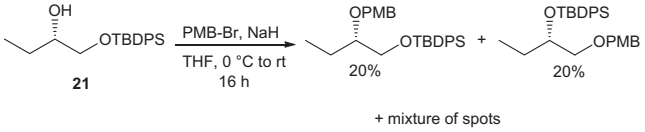

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