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The First Total Synthesis of Cytopiloyne, an Anti-Diabetic, Polyacetylenic Glucoside

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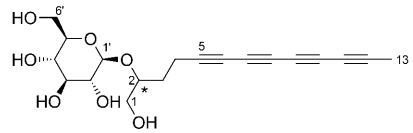
Abstract: The first total synthesis of cytopiloyne **1**, a novel bioactive polyacetylenic glucoside isolated from the extract of *Bidens pilosa*, is described. The structure of cytopiloyne was determined to be 2-β-D-glucopyranosyloxy-1-hydroxytrideca-5,7,9,11-tetrayne by using various spectroscopic methods, but the chirality of the polyyne moiety was unknown. Herein, the convergent synthesis of two diastereomers of cytopiloyne by starting from commercially available 4-(2-hydroxyethyl)-2,2-dimethyl-1,3-diozolane is described. The synthetic sequence involved two key steps: stereoselective glycosylation of the glucosyl trichloroacetimidate with 1-[(4-methoxybenzyl)oxy]hex-5-yn-2-ol to give the desired β-glycoside and the construction of the glucosyl tetrayne skeleton by using a palladium/silver-catalyzed cross-coupling reaction to form the alkyne–alkyne bond, the first such use of this reaction. Comparison between the observed and published characterization data showed the 2*R* isomer to be the natural product cytopiloyne.

Keywords: chirality · cross-coupling · glycosylation · natural products · total synthesis

Introduction

Diabetes mellitus is a metabolic disorder characterized by high blood glucose levels, which result from the deficiency or diminished effectiveness of endogenous insulin. Blood glucose levels are controlled by a complex interaction of multiple chemicals and hormones in the body, including the hormone insulin made in the β cells of the pancreas. There are two main types of diabetes mellitus, type 1 and type 2. Type 1 diabetes is an autoimmune disease resulting from the destruction of insulin-producing pancreatic β cells, leading to a deficiency of insulin.[1] Type 2 diabetes is characterized by insulin resistance and β-cell dysfunction; it is a very costly disease because of its chronic nature and its frequent association with heart disease, stroke, kidney disease, blindness and lower limb amputations.[2] To date, several oral drugs and insulin have been developed for the treatment of diabetes; however, these agents are insufficient for the great diversity of patients. Recently, the search for novel anti-diabetic drugs has focused on herbal medicines, due to efficacy in human clinical trials and minimal side effects. Some of the naturally occurring polyacetylenic extracts isolated from *Bidens pilosa* are effective in treating both type 1 and 2 diabetes,[3–7] and cytopiloyne **1**, a β-*O*-glucopyranoside that contains a glucose moiety and a tetrayne aglycone unit, is one of these extracts. Cytopiloyne has been reported to effectively control and prevent type 1 diabetes in non-obese diabetic mice and be effective in controlling type 2 diabetes in db/db mice, a leptin receptor-deficient mouse model for the study of type 2 diabetes.[7–9] This paper describes the first total synthesis of two diastereomers of cytopiloyne (**1a** and **1b**) from commercially available isomers of 4-(2-hydroxyethyl)-2-2-dimethyl-1,3-diozolane and identifies the absolute stereochemistry (C2) of the natural product.



1a: (2*S*)-Isomer
1b: (2*R*)-Isomer

Results and Discussion

Synthetic plan: Our retrosynthetic analysis of cytopiloyne **1** is shown in Scheme 1. Two approaches were designed and performed simultaneously in our laboratory to expedite the synthesis of the target molecule. The first strategy specifies an alkyne–alkyne coupling to prepare the tetra-acetylenic moiety followed by glycosylation to complete the synthesis. Coupling of the glycosyl donor **2** with the alcohol **3** was expected to furnish the β-glucosyl tetrayne skeleton with the correct stereochemistry by participation of a neighbouring acetate group. The β-glucoside could be subjected to a series of functional-group transformations to yield the target molecule **1**. The key precursor **3** would be obtained by the

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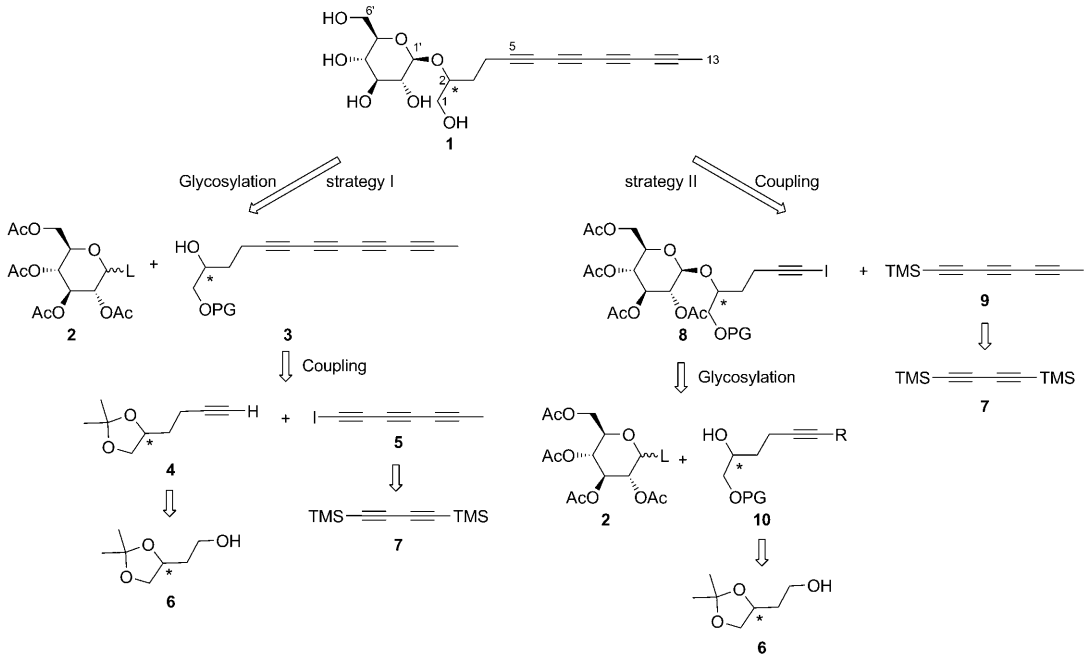


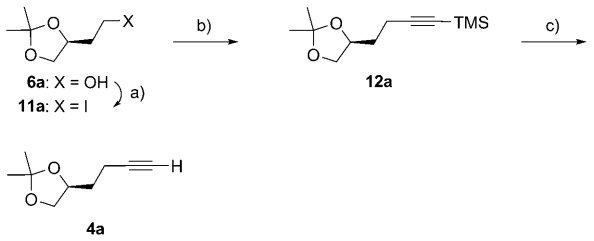
Scheme 1. Retrosynthetic analysis of cytopiloyne **1**. L = leaving group, PG = protecting group, R = TMS (trimethylsilane) or H.

hydrolysis and then selective protection of the isopropyl tetrayne, made by Sonogashira coupling of iodo-heptatriyne **5** with chiral alkyne **4**.[10] The chiral intermediate **4** would arise from the commercially available alcohol **6** through iodination followed by alkynylation, and the palladium-catalyzed cross-coupling partner **5** would be made from commercially available 1,4-bis(trimethylsilanyl)buta-1,3-diyne (**7**).

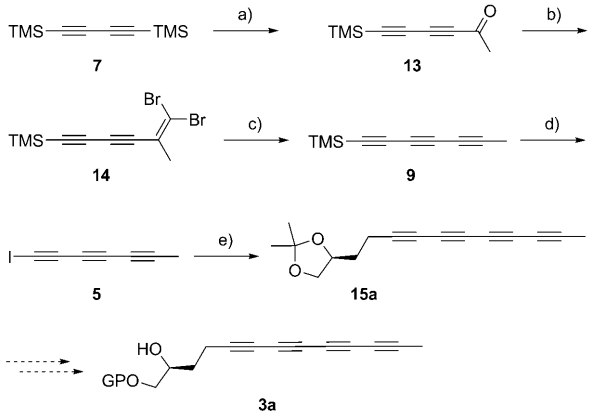
The second strategy introduces the β-glycosidic bond between glucose and the monoalkyne unit **10**, prior to completion of the glucosyl tetrayne skeleton, proposed to be formed by using a Pd/Ag-catalyzed coupling reaction[11]—the first time this reaction has been used. The β-glucosyl intermediate **8** could be prepared by the neighbouring-group-assisted glycosylation of glucosyl donor **2** with acceptor **10**. Iodination of the alcohol **6** followed by alkynylation, hydrolysis and selective protection would give the key precursor **10**. The heptatriyne **9**, the substrate of Pd/Ag-catalyzed coupling, would be obtained from commercially available **7**.

Strategy I: Synthesis of alkyne **4a** commenced from commercially available (4*S*)-(+)-4-(2-hydroxyethyl)-2,2-dimethyl-1,3-dioxolane (**6a**), which was iodinated with PPh_3/I_2/imidazole in CH_3CN/Et_2O to give iodide **11a**, followed by alkynylation with trimethylsilyl acetylene in the presence of *n*BuLi (Scheme 2) to give **12a**.[12] (4*S*)-Alkyne **4a** was obtained after desilylation by using tetrabutylammonium fluoride (TBAF). The (4*S*)-isomer **6a** was chosen over its enantiomer, (4*R*)-isomer **6b**, for cost reasons.

Iodoalkyne **5** was prepared from commercially available 1,4-bis(trimethylsilanyl)-buta-1,3-diyne (**7**). Friedel–Crafts acylation of **7** in the presence of aluminium chloride ($AlCl_3$) gave ketone **13** in good yield (Scheme 3).[13] Subsequent



Scheme 2. Synthesis of (4*S*)-alkyne **4a**: a) PPh_3, I_2, imidazole, CH_3CN, Et_2O, −10 °C to RT, 17 h, 86 %; b) trimethylsilyl acetylene, *n*BuLi, THF, −78 °C to RT, 17 h, 68 %; c) TBAF, THF, 0 °C, 1.5 h, 74 %.

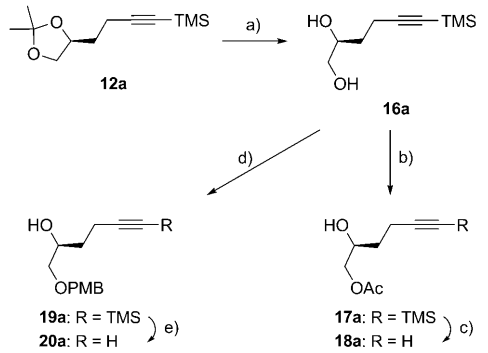


Scheme 3. Synthesis of (2*S*)-tetraalkyne **3a**: a) CH_3COCl, $AlCl_3$, CH_2Cl_2, 0 °C, 1.5 h; b) CBr_4, PPh_3, CH_2Cl_2, 45 °C, 16 h, 58 % in 2 steps; c) dry hexane, *n*BuLi, −78 to −40 °C, 1 h, 88 %; d) K_2CO_3, MeOH, acetone, 0 °C to RT, 2 h; then NIS, $AgNO_3$, RT, 16 h, 66 %; e) **4a**, $[PdCl_2(PPh_3)_2]$, CuI, THF, iPr_2NH, RT, 2 h, < 5 %.

Corey–Fuchs reaction yielded dibromoolefin **14**, which was converted into the desired trialkyne **9** by dropwise addition of *n*BuLi as a solution in hexanes.[14,15] Desilylation of **9** was carried out by using potassium carbonate (K_2CO_3) and methanol in acetone. Silver nitrate ($AgNO_3$)-catalyzed iodination by using *N*-iodosuccinimide (NIS) afforded iodoalkyne **5**.[16]

With both compounds **4a** and **5** in hand, the bis(triphenylphosphine)palladium(II) chloride [$PdCl_2(PPh_3)_2$] and copper(I) iodide (CuI)-mediated Sonogashira coupling[10] was studied. Unfortunately, tetraalkyne **15a** was obtained in poor yield (<5%) under standard conditions. Alternatively, other well-known conditions for alkyne–alkyne coupling, such as copper-catalyzed Cadiot–Chodkiewicz coupling[17] or Negishi coupling[18] were also carried out; however, no desired product was obtained. Further hydrolysis of tetrayne **15a** was performed, but the insoluble byproduct was generated. In our observation, tetrayne **15a** was decomposed easily when it was left to stand at room temperature, perhaps due to the inherently unstable nature of the longer polyynes.[19] This unsatisfactory result caused us to suspend development of this strategy.

Strategy II: Four acceptors (**17a**–**20a**) were prepared to study construction of the required glycosidic linkage. As shown in Scheme 4, hydrolysis of the isopropylidene acetal

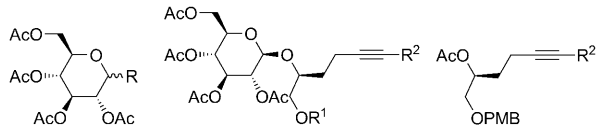


Scheme 4. Synthesis of acceptors **17a**–**20a**: a) HOAc, H_2O, RT, 16 h, 85%; b) Ac_2O, Et_3N, DMAP, CH_2Cl_2, −60°C, 16 h, 75%; c) TBAF, THF, 0°C, 1 h, 74%; d) Bu_2SnO, toluene, reflux, 2 h; then CsF, tetrabutylammonium iodide (Bu_4NI), PMBCl, DMF, reflux, 5 h, 67%; e) TBAF, THF, 0°C, 1 h, 83%.

in 80% acetic acid (HOAc) solution converted compound **12a** into diol **16a**. Two functional groups were chosen for installation at the primary alcohol position: the electron-withdrawing acetyl group, and the electron-donating *p*-methoxybenzyl group (PMB). Regioselective acetylation of compound **16a** at the primary alcohol with acetic anhydride (Ac_2O) in triethylamine furnished acceptor **17a**, which was then subjected to desilylation with TBAF to give the corresponding alkyne **18a**. The PMB group was introduced by using dibutyltin oxide (Bu_2SnO) and *p*-methoxybenzyl chloride (PMBCl) to furnish acceptor **19a**.[20] Further desilylation of **19a** yielded the acceptor **20a**.

Next, optimization of glycosylation by coupling of the well-known donors **21**–**23** with **17a**–**20a** was studied and the results are summarized in Table 1. Coupling of peracetylated

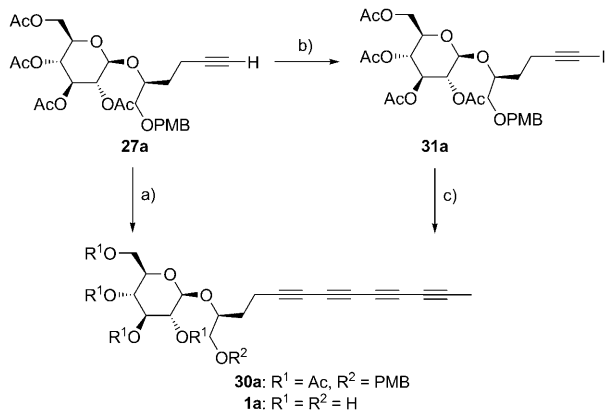
Table 1. Optimization of glycosylation conditions.



Entry	Donor	Acceptor	Activator	*T* [°C]	*t* [h]	Glycoside	Yield [%]
1	**21**	**17a**	BSP/Tf_2O	−60	0.5	–	–
2	**21**	**17a**	NIS/TfOH	−40	16	–	–
3	**22**	**17a**	Ag_2O	25	64	–	–
4	**22**	**17a**	Ag_2CO_3/I_2	25	64	**24a**	22[a]
5	**22**	**19a**	Ag_2CO_3/I_2	25	64	**26a**	5
6	**23**	**17a**	TMSOTf	−60	16	**24a**	22[b]
7	**23**	**18a**	TMSOTf	−60	16	**25a**	27
8	**23**	**19a**	TMSOTf	−60	16	**26a**	35
9	**23**	**20a**	TMSOTf	−60	16	**27a**	65

[a] The yield of the desired product **24a** and the inseparable byproduct in a 18:1 ratio determined by ^{1}H NMR spectroscopic analysis. [b] The yield of the desired product **24a** and the inseparable byproduct in a 7:1 ratio determined by ^{1}H NMR spectroscopic analysis.

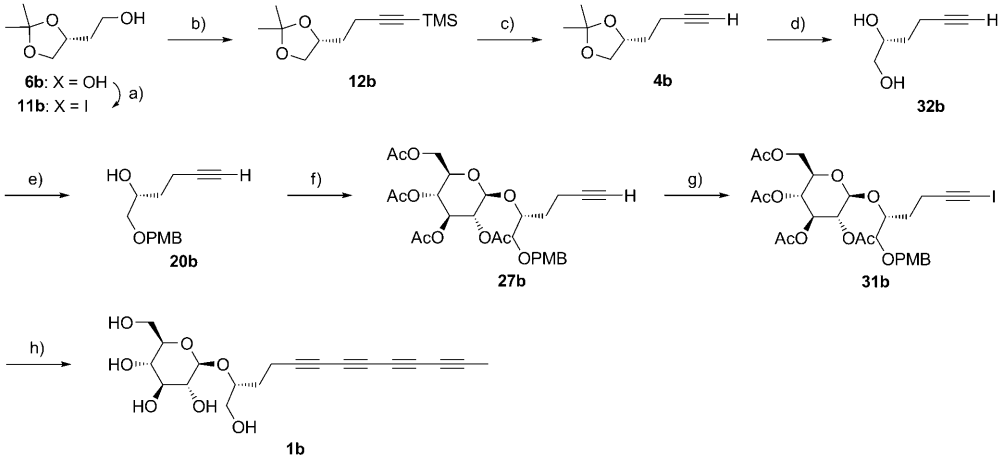
glucosyl thioglycoside **21** with acceptor **17a** activated by benzenesulfinyl piperidine/trifluoromethanesulfonic anhydride (BSP/Tf_2O)[21] or NIS/trifluoromethanesulfonic acid (TfOH)[22] failed to afford the desired β-linked glucoside (Table 1, entries 1 and 2). In entry 3, coupling of the glucosyl bromide **22** and acceptor **17a** with activation by silver oxide (Ag_2O) led to complicated mixtures.[23] When Ag_2CO_3/I_2 were used as activators, the mixture of glycoside **24a** and an inseparable byproduct was obtained in 22% yield with a ratio of 18:1 (entry 4).[24] By using donor **22** and acceptor **19a** under the same conditions, β-glycoside **26a** was produced in lower yield (entry 5). Glycosyl trichloroacetimidate **23**[25] reacted with acceptor **17a** in the presence of trimethylsilyl trifluoromethanesulfonate (TMSOTf), with the same result as described in entry 4 with a ratio of 7:1 (entry 6). The coupling of **23** with OAc-desilylated compound **18a** was also performed under the same conditions; however, insignificant improvement in the yield was observed (entry 7). In contrast, glycosylation of **23** with **19a** furnished compound **26a** in 35% yield (entry 8). Although the TMSOTf-catalyzed glycosylation provided β-glycoside **26a** in moderate yield, the acetylated product **28a** was identified as a major side product in 29% yield. Replacement of the acceptor **19a** with its desilylated compound **20a** was found to significantly decrease the acetylated product **29a** formation (8%) and give glycoside **27a** in 65% yield (entry 9).



Scheme 5. Synthesis of (2*S*)-cytopiloyne **1a**: a) **5**, $[PdCl_2(PPh_3)_2]$, CuI, THF, iPr_2NH, RT, 2 h; b) NIS, $AgNO_3$, acetone, RT, 2 h, 86%; c) i) **9**, $[Pd(PPh_3)_4]$, AgF, K_2CO_3, MeOH, DMF, RT, 16 h; ii) DDQ, CH_2Cl_2, H_2O, RT, 2 h; iii) NaOMe, MeOH, CH_2Cl_2, 0°C, 2 h, 36% over 3 steps.

With iodoalkyne **5** and β-glucosyl alkyne **27a** in hand, their Sonogashira coupling was investigated, as outlined in Scheme 5. After much experimentation, reaction of **27a** with **5** by using $[PdCl_2(PPh_3)_2]$ and CuI furnished the fully protected cytopiloyne **30a** in trace amounts. Because the Cadiot–Chodkiewicz coupling and Negishi coupling failed to give tetrayne **15a**, alternative conditions were sought and the Pd/Ag-catalyzed coupling[11] was investigated. The Pd/Ag-catalyzed cross-coupling is commonly used in the coupling of vinyl triflate or aryl iodides with either free alkynes or 1-(trialkylsilyl)alkynes to construct the functionalized enynes; no alkyne–alkyne coupling, to the best of our knowledge, has ever been reported. Iodination of glycoside **27a** by using NIS afforded iodoalkyne **31a**, which was coupled with silyl-protected triyne **9** in the presence of potassium carbonate (K_2CO_3), methanol (MeOH) and with silver fluoride (AgF) and tetrakis(triphenylphosphine)palladium $[Pd(PPh_3)_4]$ as catalysts to give the desired tetrayne.[11] Deprotection of the PMB and acetyl groups was achieved by using 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) and sodium methoxide (NaOMe), respectively, to afford (2*S*)-cytopiloyne **1a** as a colourless solid, the spectroscopic and optical rotation data for which did not match that of the natural product.

Synthesis of naturally occurring cytopiloyne 1b: The (2*R*)-cytopiloyne detailed in this account was synthesized according to the established method of (2*S*)-cytopiloyne. The synthesis of (2*R*)-cytopiloyne began with iodination of (4*R*)-4-(2-hydroxyethyl)-2,2-dimethyl-1,3-dioxolane (**6b**) with PPh_3/I_2/imidazole to give iodide **11b**, which was then alkylated with trimethylsilyl acetylene in the presence of *n*BuLi to afford monoalkynyl TMS compound **12b** as the major product and desilylated compound **4b** as the minor product (Scheme 6). Without purification, the mixture was treated with TBAF to furnish **4b** in good yield (62% in two steps), which on hydrolysis of the isopropylidene group of **4b** by using 80% HOAc gave 1,2-diol **32b**. Regioselective benzylation of the primary alcohol was performed to afford **20b** as the desired acceptor, which was coupled with the glucosyl trichloroacetimidate **23** by using TMSOTf as an activator to give the β-linked *O*-glycoside **27b** in 86% yield. Iodination of alkyne **27b** with NIS gave the important precursor alkynyl iodide **31b** for the tetralkyne skeleton development. The key step, the Pd/Ag-catalyzed cross-coupling, was then carried out to construct the alkyne–alkyne bond between **31b** and the trialkynyl silane **9**. Finally, deprotection of the fully protected β-glucosyl tetrayne was performed to furnish the target molecule **1b** as a colourless solid. The (2*R*)-cytopiloyne **1b** was finally obtained in 1.6% overall yield over 10 steps from (4*R*)-4-(2-hydroxyethyl)-2,2-dimethyl-1,3-dioxo-



Scheme 6. Synthesis of (2*R*)-cytopiloyne **1b**: a) PPh_3, I_2, imidazole, CH_3CN, Et_2O, −10°C to RT, 17 h, 91%; b) trimethylsilyl acetylene, *n*BuLi, −78°C to RT, 18 h; c) TBAF, THF, 0°C, 1 h, 62% in 2 steps; d) HOAc, H_2O, RT, 16 h, 71%; e) Bu_2SnO, toluene, reflux, 2 h; then CsF, Bu_4NI, PMBCl, DMF, reflux, 5 h, 82%; f) **23**, TMSOTf, CH_2Cl_2, MS 3 Å, −60°C, 16 h, 86%; g) NIS, $AgNO_3$, acetone, RT, 2 h, 93%; h) i) **9**, $[Pd(PPh_3)_4]$, AgF, K_2CO_3, DMF, MeOH, 0°C to RT, 16 h; ii) DDQ, CH_2Cl_2, H_2O, RT, 2 h; iii) NaOMe, MeOH, CH_2Cl_2, 0°C, 2 h, 6% over 3 steps.

lane (**6b**). The characterization data of **1b** were found to be identical in all respects to the natural product, confirming the configuration at the **1b** stereocenter to be *R*.

The low overall yield was attributed to the unexpected instability of the final product upon purification. An unidentified byproduct, insoluble in MeOH and H_2O, was generated during concentration of **1b** under reduced pressure. A water suspension of **1b** and this byproduct was filtered to remove the insoluble byproduct and the filtrate lyophilized to give **1b** in low yield. The same byproduct was quickly regenerated when **1b** was left to stand at room temperature, although samples of **1b** were found to be more stable in solution.

Conclusion

The first total synthesis of two diastereomers of cytopiloyne **1** was accomplished by starting from (4*S*)-**6a** or (4*R*)-(2-hydroxyethyl)-2,2-dimethyl-1,3-dioxolane (**6b**), confirming the absolute configuration at the C2-position of cytopiloyne. Key steps in the synthesis were formation of the β-linked glucoside by anomeric stereocontrol of glycosylation with neighbouring-group participation and the first application of Pd/Ag-catalyzed cross-coupling in the formation of the alkyne–alkyne bond. The 2*R* isomer **1b** was definitively identified as the natural product by comparison of the observed and reported characterization data. The properties of **1b** will be investigated in future studies.

Experimental Section

General: All chemicals were purchased as reagent grade and used without further purification unless otherwise stated. Column chromatography was performed with silica gel (Merck Kieselgel 60, 230–400 mesh). Reactions were monitored with TLC by using Merck 60 F254 silica gel glass-backed plates and visualized under UV (254 nm) and/or by staining with either acidic ceric ammonium molybdate or basic potassium permanganate solution. ^{1}H NMR spectra were recorded on a Varian Mercury-300 (300 MHz) or Mercury-400 (400 MHz) spectrometer. Chemical shifts (in ppm) are reported relative to the internal standard signal of $CDCl_3$ ($\delta=7.24$ ppm) or CD_3OD ($\delta=3.30$ ppm). ^{13}C NMR spectra were obtained with a Varian Mercury-300 (75 MHz) or Mercury-400 (100 MHz) spectrometer and reported relative to $CDCl_3$ ($\delta=77.00$ ppm) or CD_3OD ($\delta=49.15$ ppm). Coupling constants (*J*) are reported in Hertz (Hz). Splitting patterns are described by using the following abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. LCMS data was obtained on an Agilent MSD-1100 ESI-MS/MS system. High-resolution mass spectra were measured with MAT-95XL or JEOL JMS-700 high-resolution mass spectrometers in electron impact (EI) or fast atom bombardment (FAB) ionization modes. Specific optical rotations were recorded on JASCO P-1020 digital polarimeter by using a temperature controller (PTC-102T) and sodium lamp (589 nm) as the light source.

(4*S*)-4-(2-Iodoethyl)-2,2-dimethyl-1,3-dioxolane (11a): Imidazole (1.50 g, 22.04 mmol), PPh_3 (5.25 g, 20.02 mmol) and I_2 (6.09 g, 23.99 mmol) were added to a stirred solution of (4*S*)-(+)-4-(2-hydroxyethyl)-2,2-dimethyl-1,3-dioxolane (**6a**) (1.46 g, 10.00 mmol) in CH_3CN (40 mL) and Et_2O (60 mL) at −10 °C. After being stirred at this temperature for 1 h, the mixture was warmed to room temperature gradually and stirred for another 16 h. The reaction was quenched with 10% $Na_2S_2O_3$ solution and saturated NH_4Cl solution. The resulting mixture was extracted with Et_2O. The organic phase was washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (hexanes/EtOAc 10:1) to give **11a** (2.21 g, 86%) as a colourless oil. $[\alpha]_D^{25}=-23.99$ ($c=1$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=4.19$–4.12 (m, 1H), 4.06 (dd, $J=8.0$, 6.0 Hz, 1H), 3.55 (dd, $J=8.0$, 6.8 Hz, 1H), 3.28–3.17 (m, 2H), 2.11–1.98 (m, 2H), 1.38 (s, 3H), 1.33 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=109.0$, 75.6, 68.5, 37.8, 26.9, 25.5, 1.2 ppm; the characterization data of compound **11a** were in agreement with the literature.[26]

{4-[(4*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl]but-1-yn-1-yl}(trimethyl)silane (12a): Compound **12a** was prepared according to the literature procedure.[27] To a stirred solution of trimethylsilylacetylene (786 mg, 8.00 mmol) in THF (15 mL) was added an 1.6 M solution of *n*BuLi in hexanes (5.0 mL, 8.00 mmol) dropwise at −78 °C. After stirring at −78 °C for 40 min, a solution of **11a** (1.02 g, 4.0 mmol) in hexamethylphosphoramide (HMPA) (1.5 mL) and THF (1.5 mL) was added dropwise and the resulting mixture was then allowed to warm to room temperature slowly. The reaction was quenched with 50% NH_4Cl solution after overnight stirring (ca. 16 h) and the mixture was extracted with Et_2O. The organic phase was washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (hexanes/EtOAc 10:1) to give **12a** (0.61 g, 68%) and **4a** (68 mg, 11%) as colourless oils. $[\alpha]_D^{25}=-7.8$ ($c=1$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=4.17$–4.12 (m, 1H), 4.06 (dd, $J=8.0$, 6.0 Hz, 1H), 3.56 (dd, $J=8.0$, 6.8 Hz, 1H), 2.37–2.24 (m, 2H), 1.85–1.66 (m, 2H), 1.37 (s, 3H), 1.33 (s, 3H), 0.12 ppm (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=$ 108.7, 106.2, 85.1, 74.9, 69.2, 32.7, 26.9, 25.6, 16.4, −0.1 ppm; HRMS (FAB): *m/z*: calcd for $C_{12}H_{22}O_2Si$: 226.1389 $[M]^+$; found: 226.1390.

(4*S*)-4-(But-3-yn-1-yl)-2,2-dimethyl-1,3-dioxolane (4a): A 1 M solution of TBAF in THF (2.7 mL, 2.70 mmol) was added to a stirred solution of **12a** (410 mg, 1.81 mmol) in THF (14 mL) at 0 °C. After stirring at 0 °C for 1.5 h, the reaction was quenched with saturated NH_4Cl solution. The reaction mixture was extracted with Et_2O and the organic phase was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (hexanes/EtOAc 10:1) to furnish alkyne **4a** (206 mg, 74%) as a yellowish oil. $[\alpha]_D^{25}=-8.3$ ($c=1.1$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=4.21$–4.15 (m, 1H), 4.05 (dd, $J=8.0$, 6.0 Hz, 1H), 3.55 (dd, $J=8.0$, 6.8 Hz, 1H), 2.31–2.26 (m, 2H), 1.94 (t, $J=2.8$ Hz, 1H), 1.84–1.68 (m, 2H), 1.38 (s, 3H), 1.33 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=108.7$, 83.4, 74.6, 69.0, 68.7, 32.5, 26.8, 25.5, 14.9 ppm.

6-(Trimethylsilyl)hexa-3,5-diyn-2-one (13): Acetyl chloride (0.71 mL, 9.95 mmol) and $AlCl_3$ (1.46 g, 10.95 mmol) were added to a stirred solution of 1,4-bis(trimethylsily)-1,3-butadiyne (1.94 g, 9.98 mmol) in CH_2Cl_2 (40 mL) at 0 °C. After stirring at 0 °C for 1.5 h, the reaction was quenched by the addition of iced 1 N aqueous hydrochloric acid. The aqueous phase was extracted with CH_2Cl_2 (3×50 mL) and the combined organic extracts were washed with saturated $NaHCO_3$ solution, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (hexanes/EtOAc 15:1 to 10:1) to furnish ketone **13** as a pale-yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=2.32$ (s, 3H), 0.20 ppm (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=183.1$, 97.3, 85.6, 74.6, 73.4, 32.5, −0.9 ppm; the characterization data of compound **13** were in agreement with the literature.[12]

(6,6-Dibromo-5-methylhex-5-ene-1,3-diyn-1-yl)(trimethyl)silane (14): Triphenylphosphine (10.29 g, 39.23 mmol) was added to a stirred solution of carbon tetrabromide (8.13 g, 24.52 mmol) in CH_2Cl_2 (35 mL) at 0 °C. After stirring at 0 °C for 15 min, the reaction was removed to room temperature and a solution of ketone **13** (1.61 g, 9.80 mmol) in CH_2Cl_2 (35 mL) was added. The mixture was warmed to 45 °C and stirred for another 16 h. The reaction mixture was cooled to room temperature and concentrated under reduced pressure. The residue was purified by flash column chromatography (100% hexanes) to give dibromoolefin **14** (1.84 g, 58% in 2 steps) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=$ 1.96 (s, 3H), 0.20 ppm (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=124.7$, 100.8, 94.3, 87.3, 80.7, 75.0, 23.3, −0.5 ppm; HRMS (FAB): *m/z*: calcd for $C_{10}H_{12}Br_2Si$: 317.9075 $[M]^+$; found: 317.9071.

Hepta-1,3,5-triyn-1-yl(trimethyl)silane (9): *n*BuLi (7.2 mL, 11.50 mmol, 1.6 M in hexanes) was added dropwise to a stirred solution of dibromoole-

fin **14** (1.84 g, 5.75 mmol) in dry hexanes (30 mL) at −78 °C under argon over 10 min. The mixture was warmed to −40 °C gradually and then quenched with saturated NH_4Cl solution. Et_2O was added (5 mL) and the organic layer was separated, washed with saturated NH_4Cl solution, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (100% hexanes) to give **9** as a yellow oil (0.81 g, 88%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.95 (s, 3H), 0.17 ppm (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 88.3, 85.2, 76.6, 64.7, 62.5, 59.3, 4.5, −0.5 ppm; the characterization data of compound **9** were in agreement with the literature.[28]

1-Iodohepta-1,3,5-triyne (5): K_2CO_3 (95 mg, 0.69 mmol) was added to a stirred solution of **9** (50 mg, 0.31 mmol) in acetone (2 mL) and methanol (30 μL) at 0 °C. The reaction was warmed up to room temperature and stirred for 2 h. The mixture was filtered and then NIS (77 mg, 0.34 mmol) and $AgNO_3$ (5.3 mg, 0.03 mmol) were added to the filtrate. After overnight stirring, the reaction mixture was filtered through a pad of Celite. The filtrate was concentrated under reduced pressure and the residue was purified by flash column chromatography (100% hexanes) to give **5** as a yellow solid (44 mg, 66%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.97 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 79.1, 75.9, 64.2, 60.1, 59.6, 4.5 ppm.

(2*S*)-6-(Trimethylsilyl)hex-5-yne-1,2-diol (16a): A solution of **12a** (498 mg, 2.20 mmol) in HOAc (15 mL) and H_2O (8 mL) was stirred at room temperature overnight (ca. 16 h). The solvent was then removed by coevaporation with toluene under reduced pressure and the residue was purified by flash column chromatography (hexanes/EtOAc 1:1) to give **16a** (348 mg, 85%) as a colourless solid. $[\alpha]_D^{25}$ = −15.4 (c = 1 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.85–3.80 (m, 1H), 3.64 (dd, J = 11.2, 3.2 Hz, 1H), 3.46 (dd, J = 11.2, 7.2 Hz, 1H), 2.35 (t, J = 6.8 Hz, 2H), 1.62 (q, J = 6.8 Hz, 2H), 0.12 ppm (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 106.6, 85.5, 71.3, 66.4, 31.6, 16.3, 0.0 ppm; HRMS (FAB): m/z: calcd for $C_9H_{18}O_2SiNa$: 209.0974 $[M+Na]^+$; found: 209.0980.

(2*S*)-2-Hydroxy-6-(trimethylsilyl)hex-5-yn-1-yl acetate (17a): Ac_2O (145 μL, 1.54 mmol) was added to a stirred solution of diol **16a** (261 mg, 1.40 mmol) and Et_3N (215 μL, 1.54 mmol) in anhydrous CH_2Cl_2 (20 mL) under argon at −60 °C in the presence of a catalytic amount of 4-dimethylaminopyridine (DMAP) (17 mg, 0.14 mmol). The reaction was quenched with 1 N HCl solution (10 mL) after stirring at −60 °C for 16 h and the resulting mixture was extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (hexanes/EtOAc 5:1) to afford **17a** (239 mg, 75%) as a colourless oil. $[\alpha]_D^{25}$ = −3.7 (c = 1 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.14–4.11 (m, 1H), 4.01–3.97 (m, 2H), 2.38 (t, J = 7.2 Hz, 2H), 2.32 (br s, 1H), 2.08 (s, 3H), 1.69–1.64 (m, 2H), 0.12 ppm (s, 9H); ^{13}C NMR (400 MHz, $CDCl_3$): δ = 171.1, 106.2, 85.7, 69.0, 68.3, 31.9, 20.9, 16.2, 0.0 ppm; HRMS (FAB): m/z: calcd for $C_{11}H_{20}O_3SiNa$: 251.1080 $[M+Na]^+$; found: 251.1079.

(2*S*)-2-Hydroxyhex-5-yn-1-yl acetate (18a): A 1 M solution of TBAF in THF (0.6 mL, 0.60 mmol) was added to a stirred solution of **17a** (114 mg, 0.50 mmol) in THF (5 mL) at 0 °C under nitrogen. After stirring at 0 °C for 1 h, the reaction was quenched with saturated NH_4Cl solution. The reaction mixture was extracted with EtOAc and the organic phase was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (hexanes/EtOAc 2:1) to furnish alkyne **18a** (58 mg, 74%) as a colourless oil. $[\alpha]_D^{25}$ = −10.7 (c = 1 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.14–4.12 (m, 1H), 4.01–3.96 (m, 2H), 2.35 (td, J = 7.2, 2.4 Hz, 2H), 2.23 (d, J = 4.4 Hz, 1H), 2.08 (s, 3H), 1.96 (t, J = 2.4 Hz, 1H), 1.70–1.63 ppm (m, 2H); ^{13}C NMR (400 MHz, $CDCl_3$): δ = 171.2, 83.4, 69.0, 68.3, 68.2, 31.7, 20.7, 14.5 ppm; HRMS (FAB): m/z: calcd for $C_8H_{12}O_3Na$: 179.0684 $[M+Na]^+$; found: 179.0684.

(2*S*)-1-[(4-Methoxybenzyl)oxy]-6-(trimethylsilyl)hex-5-yn-2-ol (19a): A stirred solution of diol **16a** (224 mg, 1.20 mmol) and Bu_2SnO (448 mg, 1.80 mmol) in toluene (5 mL) was refluxed for 2 h in a flask equipped with a Dean–Stark separator. The solvent was evaporated under reduced pressure to leave the crude dibutylstannylene, which was combined with CsF (365 mg, 2.40 mmol) and dried in vacuum for 2 h. The reaction flask was charged with DMF (5 mL) and stirred at room temperature for 10 min. The solution was then treated with PMBCl (169 μL, 1.25 mmol) and TBAI (111 mg, 0.30 mmol) and the resulting mixture was refluxed for 5 h. The solvent was removed under reduced pressure and the residue was purified by column chromatography (hexanes/EtOAc 5:1) to yield **19a** (248 mg, 67%) as a colourless oil. $[\alpha]_D^{25}$ = −3.8 (c = 0.5 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.24 (d, J = 8.4 Hz, 2H), 6.87 (d, J = 8.4 Hz, 2H), 4.47 (s, 2H), 3.92–3.89 (m, 1H), 3.79 (s, 3H), 3.48 (dd, J = 9.6, 3.6 Hz, 1H), 3.32 (dd, J = 9.6, 7.6 Hz, 1H), 2.39 (d, J = 3.6 Hz, 1H), 2.35 (t, J = 7.2 Hz, 2H), 1.66–1.61 (m, 2H), 0.12 ppm (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.3, 130.0, 129.4, 113.9, 106.8, 85.0, 73.9, 73.0, 69.4, 55.3, 32.0, 16.2, 0.1 ppm; HRMS (FAB): m/z: calcd for $C_{17}H_{26}O_3SiNa$: 329.1549 $[M+Na]^+$; found: 329.1547.

(2*S*)-1-[(4-Methoxybenzyl)oxy]hex-5-yn-2-ol (20a): A 1 M solution of TBAF in THF (0.6 mL, 0.60 mmol) was added to a stirred solution of **19a** (153 mg, 0.50 mmol) in THF (5 mL) at 0 °C under nitrogen. The reaction was stirred at 0 °C for 1 h and quenched with saturated NH_4Cl solution. The resulting mixture was diluted with EtOAc and the organic phase was separated. The aqueous was extracted with EtOAc and the combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (hexanes/EtOAc 2:1) to give alkyne **20a** (97 mg, 83%) as a colourless oil. $[\alpha]_D^{25}$ = −4.9 (c = 1 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.24 (d, J = 8.8 Hz, 2H), 6.87 (d, J = 8.8 Hz, 2H), 4.47 (s, 2H), 3.94–3.91 (m, 1H), 3.79 (s, 3H), 3.48 (dd, J = 9.6, 3.2 Hz, 1H), 3.31 (dd, J = 9.6, 7.6 Hz, 1H), 2.38 (d, J = 3.2 Hz, 1H), 2.34–2.30 (m, 2H), 1.93 (t, J = 2.8 Hz, 1H), 1.66–1.61 ppm (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.3, 129.9, 129.4, 113.8, 83.9, 73.9, 73.0, 69.1, 68.6, 55.3, 31.8, 14.7 ppm; HRMS (FAB): m/z: calcd for $C_{14}H_{18}O_3$: 234.1256 $[M]^+$; found: 234.1257.

(2*S*)-2-[(2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl)oxy]-6-(trimethylsilyl)-hex-5-yn-1-yl acetate (24a): A mixture of **17a** (50 mg, 0.22 mmol), 50% Ag_2CO_3 in Celite (165 mg, 0.30 mmol), I_2 (17 mg, 0.07 mmol) and freshly activated powdered molecular sieves 3 Å (160 mg) in anhydrous CH_2Cl_2 (1 mL) was stirred at room temperature under argon for 30 min. A solution of glycosyl donor **22** (82 mg, 0.20 mmol) in anhydrous CH_2Cl_2 (1 mL) was added to the mixture dropwise and stirred for 3 d. The mixture was filtered through a pad of Celite and the filtrate was washed with aqueous $Na_2S_2O_3$ solution. The solvent was removed under reduced pressure and the residue was purified by column chromatography (hexanes/EtOAc 2:1) to afford **24a** and an inseparable byproduct in a 18:1 ratio (24 mg, 22%) as a colourless solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.17 (t, J = 10.0 Hz, 1H), 5.05 (t, J = 10.0 Hz, 1H), 4.93 (dd, J = 10.0, 8.0 Hz, 1H), 4.58 (d, J = 8.0 Hz, 1H), 4.23 (dd, J = 12.4, 4.4 Hz, 1H), 4.13 (dd, J = 12.4, 2.4 Hz, 1H), 4.10–3.99 (m, 2H),

, 3.90–3.87 (m, 1H), 3.67–3.63 (m, 1H), 2.37–2.31 (m, 2H), 2.07 (s, 3H), 2.06 (s, 3H), 2.01 (s, 1H), 2.00 (s, 3H), 1.98 (s, 3H), 1.78–1.67 (m, 2H), 0.11 ppm (s, 9H); ^{13}C NMR (400 MHz, $CDCl_3$): δ = 170.64, 170.56, 170.3, 169.4, 169.3, 106.6, 100.5, 84.9, 76.9, 72.8, 71.7, 71.3, 68.4, 66.1, 61.9, 31.0, 20.8, 20.7, 20.60, 20.58, 20.5, 16.0, 0.1 ppm; HRMS (FAB): m/z: calcd for $C_{25}H_{38}O_{12}SiNa$: 581.2031 $[M+Na]^+$; found: 581.2026.

(2*S*)-2-[(2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl)oxy]hex-5-yn-1-yl acetate (25a): A mixture of alcohol **18a** (47 mg, 0.30 mmol), glucosyl trichloroacetimidate **23** (246 mg, 0.50 mmol) and freshly activated powdered molecular sieves AW-300 (500 mg) in anhydrous CH_2Cl_2 (20 mL) was stirred at room temperature under argon for 10 min. The reaction mixture was cooled to −60 °C and TMSOTf (5 μL, 0.03 mmol) was added. After stirring at −60 °C overnight (ca. 16 h), the reaction mixture was quenched with Et_3N (10 μL) and filtered through a pad of Celite. The filtrate was concentrated under reduced pressure and the residue was purified by column chromatography (hexanes/EtOAc 2:1) to give β-glucoside **25a** (40 mg, 27%) as a colourless solid. $[\alpha]_D^{25}$ = −33.6 (c = 0.8 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.15 (t, J = 9.6 Hz, 1H), 5.03 (t, J = 9.6 Hz, 1H), 4.92 (dd, J = 9.6, 8.0 Hz, 1H), 4.58 (d, J = 8.0 Hz, 1H), 4.19 (dd, J = 12.4, 4.4 Hz, 1H), 4.12 (dd, J = 12.4, 2.8 Hz, 1H), 4.08–3.97 (m, 2H), 3.95–3.93 (m, 1H), 3.67–3.62 (m, 1H), 2.31–2.27 (m, 2H), 2.04 (s, 6H), 1.982 (s, 3H), 1.977 (s, 3H), 1.96 (s, 3H), 1.88 (t, J = 2.8 Hz, 1H), 1.71–1.64 ppm (m, 2H); ^{13}C NMR (400 MHz, $CDCl_3$): δ = 170.6, 170.5, 170.2, 169.3, 169.2, 100.4, 83.8, 76.4, 72.7, 71.6, 71.3, 68.6, 68.4, 66.1, 61.9,

30.7, 20.8, 20.7, 20.54, 20.53, 20.48, 14.4 ppm; HRMS (FAB): *m/z*: calcd for $C_{22}H_{30}O_{12}Na$: 509.1635 $[M+Na]^+$; found: 509.1641.

(2*S*)-1-[(4-Methoxybenzyl)oxy]-6-(trimethylsilyl)hex-5-yn-2-yl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside (26a): A mixture of alcohol **19a** (116 mg, 0.38 mmol), glucosyl trichloroacetimidate **23** (278 mg, 0.56 mmol) and molecular sieves AW-300 (100 mg) in anhydrous CH_2Cl_2 (20 mL) was stirred at room temperature for 10 min. The reaction mixture was cooled to −60 °C and TMSOTf (6 μL, 0.04 mmol) was added. After stirring at −60 °C overnight (ca. 16 h), the reaction was quenched by the addition of Et_3N (12 μL) and the resulting mixture was filtered through a pad of Celite. The filtrate was concentrated under reduced pressure and the residue was purified by column chromatography (hexanes/EtOAc 3:1) to give β-glucoside **26a** (85 mg, 35 %) as a colourless solid. $[\alpha]_D^{25}=-25.0$ ($c=1.4$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=$ 7.23 (d, $J=8.4$ Hz, 2H), 6.87 (d, $J=8.4$ Hz, 2H), 5.16 (t, $J=9.6$ Hz, 1H), 5.03 (t, $J=9.6$ Hz, 1H), 4.92 (dd, $J=9.6$, 8.0 Hz, 1H), 4.69 (d, $J=8.0$ Hz, 1H), 4.42, 4.38 (ABq, $J=11.2$ Hz, 1H), 4.20 (dd, $J=12.0$, 4.8 Hz, 1H), 4.09 (dd, $J=12.0$, 2.4 Hz, 1H), 3.88–3.85 (m, 1H), 3.78 (s, 3H), 3.62–3.58 (m, 1H), 3.41–3.40 (m, 2H), 2.33–2.28 (m, 2H), 2.05 (s, 3H), 1.99 (s, 3H), 1.97 (s, 3H), 1.94 (s, 3H), 1.70–1.65 (m, 2H), 0.10 ppm (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=$170.6, 170.2, 169.4, 169.3, 159.2, 129.9, 129.1, 113.8, 107.1, 100.4, 84.4, 77.9, 73.1, 72.9, 72.8, 71.5, 71.4, 68.5, 62.0, 55.2, 31.2, 20.7, 20.6, 20.5, 16.0, 0.1 ppm; HRMS (FAB): *m/z*: calcd for $C_{31}H_{44}O_{12}Si$: 636.2602 $[M]^+$; found: 636.2594.

(2*S*)-1-[(4-Methoxybenzyl)oxy]hex-5-yn-2-yl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside (27a): A mixture of alcohol **20a** (457 mg, 1.95 mmol), glucosyl trichloroacetimidate **23** (1.92 g, 3.90 mmol) and molecular sieves AW-300 (1 g) in anhydrous CH_2Cl_2 (40 mL) was stirred at room temperature for 10 min. The reaction mixture was cooled to −60 °C and TMSOTf (35 μL, 0.20 mmol) was added. After stirring at −60 °C overnight (ca. 16 h), the reaction was quenched by the addition of Et_3N (70 μL) and the resulting mixture was filtered through a pad of Celite. The filtrate was concentrated under reduced pressure and the residue was purified by column chromatography (hexanes/EtOAc 2:1) to give β-glucoside **27a** (713 mg, 65 %) as a colourless solid. $[\alpha]_D^{25}=-27.4$ ($c=2.06$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=$7.24 (d, $J=8.4$ Hz, 2H), 6.88 (d, $J=$ 8.4 Hz, 2H), 5.18 (t, $J=9.6$ Hz, 1H), 5.04 (t, $J=9.6$ Hz, 1H), 4.94 (dd, $J=$ 9.6, 8.0 Hz, 1H), 4.70 (d, $J=8.0$ Hz, 1H), 4.43, 4.39 (ABq, $J=11.6$ Hz, 2H), 4.19 (dd, $J=12.0$, 4.8 Hz, 1H), 4.12 (dd, $J=12.0$, 2.4 Hz, 1H), 3.94–3.91 (m, 1H), 3.79 (s, 3H), 3.64–3.60 (m, 1H), 3.40 (d, $J=5.2$ Hz, 2H), 2.30–2.26 (m, 2H), 2.06 (s, 3H), 2.00 (s, 3H), 1.98 (s, 3H), 1.95 (s, 3H), 1.87 (t, $J=2.4$ Hz, 1H), 1.69–1.64 ppm (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=$170.7, 170.3, 169.5, 169.4, 159.3, 129.9, 129.2, 113.9, 100.4, 84.2, 77.6, 73.2, 72.9, 71.54, 71.52, 68.6, 68.3, 62.1, 55.3, 31.0, 20.7, 20.64, 20.61, 14.5 ppm; HRMS (FAB): *m/z*: calcd for $C_{28}H_{36}O_{12}Na$: 587.2105 $[M+Na]^+$; found: 587.2093.

2(*S*)-1-[(4-Methoxybenzyl)oxy]-6-(trimethylsilyl)hex-5-yn-2-yl acetate (28a): ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=$7.24 (d, $J=8.4$ Hz, 2H), 6.87 (d, $J=8.4$ Hz, 2H), 5.10–5.07 (m, 1H), 4.49, 4.42 (ABq, $J=11.6$ Hz, 2H), 3.79 (s, 3H), 3.50 (d, $J=5.2$ Hz, 2H), 2.25 (t, $J=7.2$ Hz, 2H), 2.05 (s, 3H), 1.85 (q, $J=7.2$ Hz, 2H), 0.12 ppm (s, 9H); LCMS (ESI): *m/z*: 349.1 $[M+H]^+$, 371.1 $[M+Na]^+$.

2(*S*)-1-[(4-Methoxybenzyl)oxy]hex-5-yn-2-yl acetate (29a): ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=$7.24 (d, $J=8.8$ Hz, 2H), 6.88 (d, $J=8.8$ Hz, 2H), 5.16–5.10 (m, 1H), 4.51, 4.43 (ABq, $J=11.6$ Hz, 2H), 3.80 (s, 3H), 3.51 (d, $J=4.8$ Hz, 2H), 2.25–2.20 (m, 2H), 2.08 (s, 3H), 1.95 (t, $J=2.8$ Hz, 1H), 1.90–1.84 ppm (m, 2H); LCMS (ESI): *m/z*: 299.1 $[M+Na]^+$.

(2*S*)-6-Iodo-1-[(4-methoxybenzyl)oxy]hex-5-yn-2-yl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside (31a): NIS (96 mg, 0.43 mmol) and $AgNO_3$ (5 mg, 0.03 mmol) were added to a stirred solution of alkyne **27a** (161 mg, 0.29 mmol) in acetone (10 mL) in the dark at room temperature. After stirring at same temperature for 2 h, the reaction mixture was filtered through a pad of Celite and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography (hexanes/EtOAc 2:1) to furnish iodoalkyne **31a** (169 mg, 86 %) as a colourless solid. $[\alpha]_D^{25}-27.4$ ($c=1.1$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=$7.24 (d, $J=8.4$ Hz, 2H), 6.89 (d, $J=8.4$ Hz, 2H), 5.18 (t, $J=9.6$ Hz, 1H), 5.04 (t, $J=9.6$ Hz, 1H), 4.93 (dd, $J=9.6$, 7.8 Hz, 1H), 4.69 (d, $J=$ 7.8 Hz, 1H), 4.43, 4.39 (ABq, $J=14.8$ Hz, 2H), 4.21 (dd, $J=12.0$, 4.8 Hz, 1H), 4.10 (dd, $J=12.0$, 2.4 Hz, 1H), 3.92–3.87 (m, 1H), 3.79 (s, 3H), 3.64–3.59 (m, 1H), 3.40 (d, $J=5.7$ Hz, 1H), 2.50–2.44 (m, 2H), 2.07 (s, 3H), 2.01 (s, 3H), 1.98 (s, 3H), 1.95 (s, 3H), 1.70–1.62 ppm (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=$170.7, 170.3, 169.5, 169.4, 159.3, 129.9, 129.2, 113.9, 100.4, 94.2, 77.5, 77.2, 73.2, 72.9, 71.6, 71.5, 68.5, 62.0, 55.3, 31.0, 20.8, 20.7, 20.6, 16.9 ppm; HRMS (FAB): *m/z*: calcd for $C_{28}H_{35}O_{12}NaI$: 713.1071 $[M+Na]^+$; found: 713.1069.

Cytopiloyne 1a: A mixture of **31a** (169 mg, 0.24 mmol), **9** (118 mg, 0.74 mmol), $[Pd(PPh_3)_4]$ (14 mg, 12.12 μmol), AgF (6 mg, 47.2 μmol) and K_2CO_3 (271 mg, 1.96 mmol) in DMF (5 mL) was stirred at room temperature under nitrogen for 10 min. MeOH (79 μL, 1.98 mmol) was added and the mixture was stirred at room temperature for 16 h. The reaction was diluted with Et_2O and quenched by the addition of H_2O. The resulting mixture was filtered through a pad of Celite. The organic phase was separated and the aqueous phase was extracted with Et_2O. The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (hexanes/EtOAc 2:1) to give the desired tetrayne and the inseparable byproduct as a colourless solid (137 mg).

DDQ (72 mg, 0.32 mmol) was added to a stirred solution of the desired tetrayne and the byproduct (137 mg) in CH_2Cl_2/H_2O (20:1, 10.5 mL) at room temperature. The resulting mixture was stirred for 2 h and the mixture was poured into saturated $NaHCO_3$ solution. The mixture was diluted with CH_2Cl_2 and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (hexanes/EtOAc 2:1 to 1:2) to give the fully protected (2*S*)-cytopiloyne and the inseparable byproduct as a colourless solid (114 mg).

A 30 % solution of NaOMe in MeOH (46 μL) was added to a stirred solution of the above residue (114 mg) in MeOH/CH_2Cl_2 (2:1, 6.0 mL) at 0 °C under argon. After stirring at 0 °C for 2 h, the reaction was diluted with MeOH and neutralized with acidic resin. The mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography (CH_2Cl_2/MeOH 20:1 to 10:1) to furnish the desired (2*S*)-cytopiloyne **1a** (32 mg, 36 % over 3 steps) as a white solid. $[\alpha]_D^{22}=-81.6$ ($c=0.32$ in MeOH); ^{1}H NMR (400 MHz, CD_3OD): $\delta=$4.37 (d, $J=7.6$ Hz, 1H), 3.85 (dd, $J=12.0$, 2.4 Hz, 1H), 3.78 (quint, $J=5.6$ Hz, 1H), 3.69 (dd, $J=12.0$, 5.2 Hz, 1H), 3.63 (dd, $J=12.0$, 4.0 Hz, 1H), 3.53 (dd, $J=12.0$, 5.6 Hz, 1H), 3.38–3.32 (m, 2H), 3.26–3.22 (m, 1H), 3.20–3.16 (m, 1H), 2.57–2.53 (m, 2H), 1.98 (s, 3H), 1.75 ppm (q, $J=6.8$ Hz, 2H); ^{13}C NMR (100 MHz, CD_3OD): $\delta=$104.2, 82.2, 80.7, 78.2, 78.0, 77.97, 75.5, 71.6, 66.0, 65.12, 65.11, 62.8, 62.4, 62.0, 60.9, 60.2, 31.5, 16.6, 4.0 ppm; HRMS (FAB): *m/z*: calcd for $C_{19}H_{22}O_7$: 362.1366 $[M]^+$; found: 362.1365.

(4*R*)-4-(2-Iodoethyl)-2,2-dimethyl-1,3-dioxolane (11b): The title compound was obtained from (4*R*)-(+)-4-(2-hydroxyethyl)-2,2-dimethyl-1,3-dioxolane (**6b**) (2.09 g, 14.30 mmol) as a colourless oil in 91 % yield by following the procedure described for **11a**. $[\alpha]_D^{25}=+23.46$ ($c=1$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=$4.17–4.11 (m, 1H), 4.05 (dd, $J=8.0$, 6.4 Hz, 1H), 3.54 (dd, $J=8.0$, 6.4 Hz, 1H), 3.27–3.16 (m, 2H), 2.11–1.96 (m, 2H), 1.38 (s, 3H), 1.33 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=$109.1, 75.6, 68.6, 37.8, 26.9, 25.5, 1.2 ppm; HRMS (FAB): *m/z*: calcd for $C_7H_{13}IO_2$: 255.9960 $[M]^+$; found: 255.9963.

(4*R*)-4-(But-3-yn-1-yl)-2,2-dimethyl-1,3-dioxolane (4b): A 1.6 M solution of *n*BuLi in hexanes (7.8 mL, 12.50 mmol) was added dropwise to a stirred solution of trimethylsilylacetylene (1.28 g, 13.03 mmol) in THF (20 mL) at −78 °C. After stirring at −78 °C for 40 min, a solution of **11b** (1.28 g, 5.00 mmol) in HMPA (2 mL) and THF (2 mL) was added dropwise and the resulting mixture was then allowed to warm to room temperature slowly. The reaction was quenched with 50 % NH_4Cl solution after overnight stirring (ca. 16 h) and the mixture was extracted with Et_2O. The organic phase was washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was used for the next step without further purification. A 1 M solution of TBAF in THF (6.0 mL, 6.0 mmol) was added to a stirred solution of crude **12b** (1.13 g) in THF (40 mL) at 0 °C. After stirring at 0 °C for 1.5 h, the reac-

tion was quenched with saturated NH_4Cl solution. The reaction mixture was extracted with Et_2O and the organic phase was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (hexanes/EtOAc 10:1) to furnish alkyne **4b** (478 mg, 62% in 2 steps) as a yellowish oil. $[\alpha]_D^{24} = +8.04$ ($c = 1$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 4.20$–4.15 (m, 1H), 4.05 (dd, $J = 8.0$, 6.0 Hz, 1H), 3.55 (dd, $J = 8.0$, 6.8 Hz, 1H), 2.31–2.26 (m, 2H), 1.94 (t, $J = 2.8$ Hz, 1H), 1.83–1.70 (m, 2H), 1.38 (s, 3H), 1.33 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 108.8$, 83.5, 74.7, 69.1, 68.7, 32.6, 26.9, 25.6, 15.0 ppm; HRMS (FAB): m/z: calcd for $C_9H_{15}O_2$: 155.1067 $[M+H]^+$; found: 155.1073; the characterization data of compound **4b** were in agreement with the literature.[29]

(2*R*)-Hex-5-yne-1,2-diol (32b): The title compound was obtained from **4b** (478 mg, 3.10 mmol) as a colourless solid in 71% yield by following the procedure described for **16a**. $[\alpha]_D^{25} = +43.39$ ($c = 1$ in MeOH); ^{1}H NMR (400 MHz, CD_3OD): $\delta = 3.74$–3.68 (m, 1H), 3.50–3.42 (m, 2H), 2.33–2.25 (m, 2H), 2.21 (t, $J = 2.8$ Hz, 1H), 1.76–1.68 (m, 1H), 1.60–1.52 ppm (m, 1H); ^{13}C NMR (100 MHz, CD_3OD): $\delta = 84.9$, 71.9, 69.8, 67.2, 33.5, 15.6 ppm; HRMS (FAB): m/z: calcd for $C_6H_{10}O_2Na$: 137.0578 $[M+Na]^+$; found: 137.0576.

(2*R*)-1-[(4-Methoxybenzyl)oxy]hex-5-yn-2-ol (20b): The title compound was obtained from **32b** (298 mg, 2.07 mmol) as a colourless oil in 82% yield by following the procedure described for **19a**. $[\alpha]_D^{25} = +3.1$ ($c = 1$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.23$ (d, $J = 8.8$ Hz, 2H), 6.86 (d, $J = 8.8$ Hz, 2H), 4.46 (s, 2H), 3.93–3.90 (m, 1H), 3.78 (s, 3H), 3.47 (dd, $J = 9.6$, 3.2 Hz, 1H), 3.30 (dd, $J = 9.6$, 7.6 Hz, 1H), 2.38 (d, $J = 3.6$ Hz, 1H), 2.33–2.29 (m, 2H), 1.92 (t, $J = 2.8$ Hz, 1H), 1.66–1.60 ppm (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 159.1$, 129.8, 129.3, 113.7, 83.9, 73.8, 72.8, 68.9, 68.5, 55.1, 31.7, 14.6 ppm; HRMS (FAB): m/z: calcd for $C_{14}H_{18}O_3$: 234.1256 $[M]^+$; found: 234.1255.

(2*R*)-1-[(4-Methoxybenzyl)oxy]hex-5-yn-2-yl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside (27b): The title compound was obtained from **20b** (703 mg, 3.00 mmol) and glucosyl trichloroacetimidate **23** (2.76 g, 5.60 mmol) as a white solid in 86% yield by following the procedure described for **27a**. $[\alpha]_D^{25} = +17.00$ ($c = 1$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.24$ (d, $J = 8.8$ Hz, 2H), 6.87 (d, $J = 8.8$ Hz, 2H), 5.19 (t, $J = 9.6$ Hz, 1H), 5.05 (t, $J = 9.6$ Hz, 1H), 4.99 (dd, $J = 9.6$, 8.0 Hz, 1H), 4.66 (d, $J = 8.0$ Hz, 1H), 4.48 (s, 2H), 4.20 (dd, $J = 12.4$, 5.2 Hz, 1H), 4.09 (dd, $J = 12.4$, 2.4 Hz, 1H), 3.93–3.90 (m, 1H), 3.80 (s, 3H), 3.67–3.62 (m, 2H), 3.47 (dd, $J = 10.0$, 5.6 Hz, 1H), 2.26–2.21 (m, 2H), 2.07 (s, 3H), 2.06 (s, 3H), 2.02 (s, 3H), 2.00 (s, 3H), 1.97 (t, $J = 2.8$ Hz, 1H), 1.81–1.74 ppm (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 170.4$, 170.1, 169.3, 159.1, 130.0, 129.1, 113.6, 101.2, 83.4, 78.8, 72.84, 72.76, 72.0, 71.5, 71.4, 69.0, 68.2, 61.9, 55.1, 30.7, 20.6, 20.52, 20.46, 14.0 ppm; HRMS (FAB): m/z: calcd for $C_{28}H_{36}O_{12}Na$: 587.2105 $[M+Na]^+$; found: 587.2100.

(2*R*)-6-Iodo-1-[(4-methoxybenzyl)oxy]hex-5-yn-2-yl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside (31b): The title compound was obtained from **27b** (425 mg, 0.75 mmol) as a yellowish solid in 93% by following the procedure described for **31a**. $[\alpha]_D^{20} = +17.05$ ($c = 1$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.22$ (d, $J = 8.8$ Hz, 2H), 6.85 (d, $J = 8.8$ Hz, 2H), 5.17 (t, $J = 9.6$ Hz, 1H), 5.04 (t, $J = 9.6$ Hz, 1H), 4.96 (dd, $J = 9.6$, 8.0 Hz, 1H), 4.61 (d, $J = 8.0$ Hz, 1H), 4.43 (s, 2H), 4.18 (dd, $J = 12.4$, 4.8 Hz, 1H), 4.07 (dd, $J = 12.0$, 2.4 Hz, 1H), 3.87–3.84 (m, 1H), 3.78 (s, 3H), 3.64–3.59 (m, 2H), 3.43 (dd, $J = 10.0$, 5.6 Hz, 1H), 2.40–2.37 (m, 2H), 2.040 (s, 3H), 2.037 (s, 3H), 2.00 (s, 3H), 1.98 (s, 3H), 1.75–1.70 ppm (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 170.6$, 170.3, 169.4, 159.2, 130.0, 129.2, 113.7, 101.2, 93.5, 78.8, 73.0, 72.9, 72.1, 71.6, 71.5, 68.3, 61.9, 55.2, 30.8, 20.70, 20.65, 20.56, 16.4 ppm; HRMS (FAB): m/z: calcd for $C_{28}H_{35}O_{12}NaI$: 713.1071 $[M+Na]^+$; found: 713.1059.

Cytopiloyne 1b: The title compound was obtained from **31b** (450 mg, 0.65 mmol) and **9** (313 mg, 1.95 mmol) as a white solid in 6% yield over 3 steps by following the procedure described for **1a**. $[\alpha]_D^{22} = +52.1$ ($c = 0.286$ in MeOH); ^{1}H NMR (400 MHz, CD_3OD): $\delta = 4.31$ (d, $J = 8.0$ Hz, 1H), 3.85 (dd, $J = 12.0$, 1.6 Hz, 1H), 3.77–3.72 (m, 1H), 3.67–3.55 (m, 3H), 3.37–3.27 (m, 3H), 3.19 (dd, $J = 9.2$, 8.0 Hz, 1H), 2.58 (t, $J = 6.8$ Hz, 2H), 1.98 (s, 3H), 1.78 ppm (q, $J = 6.8$ Hz, 2H); ^{13}C NMR (100 MHz, CD_3OD): $\delta = 104.9$, 81.8, 81.7, 78.1, 78.0, 75.3, 71.6, 66.4, 65.9, 65.1, 62.7, 62.5, 61.9, 61.1, 60.2, 31.5, 16.2, 4.0 ppm; HRMS (FAB): m/z: calcd for $C_{19}H_{22}O_7$: 362.1366 $[M]^+$; found: 362.1351.

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