Total synthesis of bidensyneosides A$_2$ and C: remarkable protecting group effects in glycosylation

Benjamin W. Gung* and Ryan M. Fox†

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

Received 12 May 2004; revised 3 August 2004; accepted 5 August 2004

Available online 8 September 2004

Abstract—Bidensyneosides are a group of five recently identified polyacetylenic glucosides from Bidens parviflora WILLD, a traditional Chinese medicinal plant that contains rich bioactive natural products. It was shown that bidensyneosides inhibited both histamine release and nitric oxide production. The synthesis of bidensyneoside A$_2$ (2) and C (4) as well as 3-deoxybidensyneoside C (5) are described. These syntheses establish a synthetic entry to the bidensyneosides and confirm the stereochemistry at C3. Furthermore, a remarkable protecting group effect on orthoester formation was observed during the glycosylation reaction.

1. Introduction

Bidensyneosides are a group of five new polyacetylenic glucosides (see Fig. 1) isolated from the traditional Chinese medicinal plant Bidens parviflora WILLD, which contains rich bioactive natural products. It was shown that bidensyneosides inhibit both histamine release and nitric oxide production. The structures of bidensyneosides have been assigned based on spectroscopic analysis, physicochemical properties and application of the Mosher ester method. Assays have been performed to identify the biological activity of bidensyneosides, but no attempt at their synthesis has been reported.

The bidensyneosides are glucosides with a 10-carbon polyacetylenic side chain. These five natural products differ from one another primarily in the oxidation degree of this side chain. In the most potent antiallergic agent, bidensyneoside C (4), the side chain contains hydroxyl groups at C3 and C10 while bidensyneosides A1, A2, and B lack a C10 hydroxyl group. Here we describe initial synthetic efforts in the polyacetylenyl glucoside area, which lead to the first total synthesis of bidensyneoside A$_2$ (2) and C (4) as well as 3-deoxybidensyneoside C (5). These syntheses establish a synthetic entry to the bidensyneosides, and furthermore, confirm the stereochemistry at C3.

Keywords: Total synthesis; Natural product; Bidensyneosides; Glycosylation; Protecting group effect.

* Corresponding author. Tel.: +1-513-529-2825; fax: +1-513-529-5715; e-mail: gungbw@muohio.edu
† Beckman predoctoral scholarship recipient.

Figure 1. Structures of bidensyneosides from Bidens parviflora WILLD.

Since the bidensyneosides differ among themselves mainly in the aglycon side chain, the development of a strategy allowing for the convergent assembly of different side chain analogs was of importance in our synthetic planning. The consideration of a mild glycosylation step, which would allow the attachment of functionalized side chain, led to the retrosynthetic intermediates 6, 7, and 8 (Scheme 1).

We chose thioglucosides as the glycosylation donors because it is known that these donors are stable, and they
couple with a variety of acceptors under mild conditions. The endiyne side chain was envisioned to arise from a copper-catalyzed coupling of intermediates 7 and 8, and the chiral acetylenic diol 7 was envisaged to arise from an enzymatic resolution of a racemate, which could be prepared from a 3-alkoxy propanal and ethynylmagnesium bromide. The enzymatic resolution of acetylenic alcohols has been studied and should provide both enantiomers, thereby allowing verification of the C3 stereochemistry.

2. Results and discussion

2.1. Preparation of 3-deoxybidensyneoside C 5

As a preliminary study, we first carried out the glycosylation reaction between glucose pentacetate and 4-pentyn-1-ol in the presence of BF3·OEt2. The desired product 10 was obtained in 30% yield (Scheme 2).

The low yield of the desired product 10 is possibly due to anhimerically-assisted deglycosylation, as reported for 4-pentenyl glucosides. For the preparation of compound 5, nevertheless, we could easily prepare enough material to continue with the synthesis. Bromo enyne 11 was prepared from commercially available (E)-2-penten-4-yn-1-ol via (1) hydroxyl protection as the t-butyldimethylsilyl (TBS) ether, and (2) bromination with NBS in the presence of AgNO3. The coupling of bromo alkyne 11 and glucoside 10 was carried out under Cadiot–Chodkiewicz conditions. The copper-promoted coupling reaction, which was carried out in a mixture of EtNH2 and MeOH, proceeded concurrently with the removal of acetate groups by EtNH2, leading to the polar glucoside 12 in 31% yield. Attempted coupling with the unprotected bromo enyne 8 resulted in loss of product during work-up due to difficulties in separating the extremely polar 5 from solvent. The problem was alleviated by using a TBS ether protecting group. Diyne 12 could be extracted from the aqueous solution and purified on a silica gel column. Removal of the TBS protecting group was achieved in THF with the HF-pyridine complex. To avoid the loss of the product, the work-up consisted of adding solid NaHCO3 and evaporating the solvent to a slurry, which was transferred to a silica gel column and eluted with a mixed solvent system (MeOH/CHCl3, 10:90) giving 51% of 5 as a white solid.

The synthetic sample gave identical 1H and 13C NMR spectra as the reported natural product. Five UV absorptions were reported for 3-deoxybidensyneoside C (328, 283, 267, 252, and 239 nm), but we observed only four (282, 266, 252, and 240 nm). Considering reported UV spectra for other endiynes and those reported for the other four bidensyneosides, we believe that the 328 nm absorption is spurious.

2.2. Synthesis of bidensyneoside C 4

The stereo center on the side chain of this substance was introduced by using a convenient enzymatic resolution approach (Scheme 3). The THP and TBS protected aldehyde 14 were prepared from 1,3-propanediol. Oxidation of 14 under the conditions of Swern and in situ addition of ethynylmagnesium bromide to the resulting aldehyde afforded the racemic propargyl alcohol 15 in 61% yield. The current preparation of 15 employs less expensive reagents and requires fewer steps than a previous reported procedure.

The hydroxyl protecting group at C1 of rac-15 has a profound influence on the lipase-mediated kinetic resolution. The TBS ether group, unlike the THP, provides the steric bulk required for an efficient resolution and material of greater than 95% ee was obtained when this ether was treated with Amano lipase AK (from pseudomonas sp) in the presence of vinyl acetate in hexanes. The progress of the enzymatic resolution was monitored carefully by 1H NMR spectroscopy and the reaction was terminated after 50% of rac-15 was consumed. After separation of the
alcohol \( R\)-15 from the acetate 16 by column chromatography, both enantiomers were obtained in high optical purity as confirmed by the \(^1\text{H}\) NMR spectra of their \(O\)-methyl mandelic esters.\(^{15}\) No diastereomeric isomer was detectable by 500 MHz \(^1\text{H}\) NMR analysis. The final two steps in the preparation of the side chain involved the acylation of the secondary \(OH\) group in \(R\)-15 and the removal of the TBS ether with HF–pyridine complex to afford the optically pure alcohol \((R)\)-7.

The thioglucoside 6a with four acetate groups was ‘disarmed’ or inert in the presence of the promoter dimethyl(methylthio) sulfonium triflate (DMTST).\(^{16}\) Although DMTST is less active than other thiophiles, such as NIS/TfOH, it does not produce a nucleophile as a byproduct.\(^4\) We thus decided to increase the reactivity of the glucoside donor by replacing some of the acetate protecting groups with TBS ethers. Thioglucoside 6a was deacetylated with \(K_2\text{CO}_3\) in MeOH (Scheme 4) and the crude tetraol 17 was treated with either 1 or 2 equiv of TBSCI and imidazole in DMF. This led to the selective formation of either the 6-TBS ether 18a or the 3,6-di TBS ether 18b, respectively.

Bidensyneosides have the \(\beta\)-configuration at the anomeric carbon. A C2-acetate group is necessary to provide neighboring group assistance for control of stereochemistry in glycosylation.\(^{17}\) Therefore, the free hydroxyl groups of 18a and 18b were acetylated. According to a study by Wong, replacing a C6 acetate group with TBS increases the glycosyl donor reactivity by a factor of 3–5.\(^{18}\)

When thioglucoside donor 6b and \((R)\)-7 were allowed to react in the presence of DMTST for 1 h at room temperature, we were surprised to isolate the orthoester 19a in 74% yield, rather than the normal anomeric coupling product (Scheme 5). The structure of 19a was determined by a battery of NMR spectroscopy methods, including \(^1\text{H}, \^{13}\text{C}, \text{DEPT}^{13}\text{C}, \text{and 2D COSY and HMBC spectra. We expected to see four carbonyl groups in the }^{13}\text{C NMR spectrum, but saw only three and one unexpected peak at 121 ppm.}
indicating an orthoester. The normal glycosylation products have a chair conformation with large vicent coupling constants. The small coupling constants between H2 and H3 \( (J_{23} = 2.9 \text{ Hz}) \) and between H3 and H4 \( (J_{34} = 2.9 \text{ Hz}) \) is consistent with a twist boat or ‘skew’ conformation for 19a, Figure 2, due to the constraint imposed by the bicyclic structure. Previous studies of carbohydrates containing orthoesters suggested a similar conformation.19,20

The exclusive formation of the orthoester 19a was reproducible from 6b and (R)-7. When the S-enantiomer of 7 was used as the acceptor, the normal glycosylation product 20 was also isolated in addition to the orthoester, but the yield of the reaction was only 26%. The difference between R- and S-7 appears to be an effect of matching and mismatching pairs with regard to the glucoside donor 6b. Therefore, we decided to use the more reactive donor 6c to couple with alcohol 7 even though it should be possible to transform orthoester 19a to the diastereomer of 20 under acidic conditions.20

The reaction was instantaneous when glucosyl donor 6c was allowed to react with the chiral alcohol R-7 in the presence of DMTST (Scheme 6). Within 5 min at 0 °C, TLC analysis indicated no starting material remaining and the glycosylation product 21 was isolated in 68% yield with no orthoester formation. The dramatic difference in glycosylation results observed between donor 6b and 6c originates from a single protecting group at C3. Although the formation of orthoesters is quite common in glycosylation reactions, we believe this is the first time that a single hydroxyl protecting group has been shown to effectively alter the outcome of the glycosylation reaction. Currently we believe this difference is related to the relative stability of the glycosylation intermediate, the oxycarbenium ion. It appears that donor 6b with a C3 acetate group produces a less stable oxycarbenium ion and requires neighboring group stabilization and thus the formation of the orthoester. Donor 6c with a TBS ether group should yield a more stable oxycarbenium ion which then reacts directly with the acceptor. An alternative explanation is that both reactions proceed through the initial formation of the orthoester, which rearranges more rapidly in the case of 6c to the glycoside.22

The copper promoted coupling reaction (Cadiot–Chokwicz reaction) between the terminal alkyne 21 and the bromo alkyne 8 was carried out under the conditions discussed earlier (Scheme 2). This reaction furnished bidensyneoside C in its protected form. Interestingly, only the C3 acetate group was removed during the reaction; the two acetate groups on the glucose ring remained intact. Apparently the steric bulk of the TBS ethers in 21 prevents EtNH2 from attacking these esters. Removal of the protecting groups was undertaken in the sequence shown in Scheme 6. If the acetates were removed first, it was difficult to isolate the

\[
\begin{align*}
J_{12} & = 5.3 \\
J_{23} & = 2.9 \\
J_{34} & = 2.9 \\
\end{align*}
\]

\[
\begin{align*}
J_{12} & = 8.0 \\
J_{23} & = 9.0 \\
J_{34} & = 9.1 \\
\end{align*}
\]

\[^{13}C \text{ NMR (ppm):} \]

three ester carbonyl group (~175 ppm)

and one ortho ester carbon (121 ppm)

Figure 2. Comparison of the NMR data of 19a and 21.
final product after removal of the TBS ethers. The spectroscopic data of the synthetic sample are consistent with that reported for the natural product.

2.3. Synthesis of bidensyneoside A₂

With the key intermediate 21 in hand, we were eager to expand our synthetic route to other members of the bidensyneosides. The commercial availability of (Z)-3-penten-1-yne prompted us to prepare bidensyneoside A₂ (2) as a test for our methodology. It turns out that the more practical route for compound 2 is to prepare bromoalkyne 23 because of the volatility of (Z)-3-penten-1-yne (Scheme 7).

In the bromination reaction of the terminal alkyne 21, the preferred solvent was DMF, instead of acetone, to minimize the breakage of the glycosidic bond. The copper-catalyzed coupling of bromoalkyne 23 with (Z)-3-penten-1-yne proceeded smoothly to produce the protected bidensyneoside A₂ in 86% yield. This is consistent with our recent observation that a propargylic oxygen substitution in the bromoalkyne enhances the rate of the copper-catalyzed cross coupling reaction to produce conjugated diynes. Without a propargylic oxygen substitution, homocoupling of the bromoalkyne sometimes dominates. The removal of the TBS ether and the acetate protecting group was performed in that order affording compound 2 in 85% yield for two steps. The synthetic sample was identified by spectroscopic methods and the results are consistent with the reported natural product.

3. Conclusions

The total synthesis of bidensyneoside A₂ (2) and C (4) was achieved in 7 linear steps starting from glucose pentacetate in ~14% overall yield and 3-deoxybidensyneoside C (5) in three steps and 4.7% overall yield. These syntheses represent the first synthetic entry to the bidensyneosides and confirm the stereochemistry at C₃ of bidensyneoside C. Glycoside formation was found to be highly dependent on the nature of the protecting groups on the glucose. Exclusive formation of the normal glycosylation product or the orthoester was observed, respectively, depending on the characteristic of the protecting group at C₃ of the glucoside. The electron-withdrawing acetate group led to the formation of the orthoester while an electron-releasing TBS group led to the normal glycosylation product. Based on this study, a change of protecting groups effectively alters the outcome of the glycosylation reaction. In accord with our recent observation, a propargylic oxygen substitution in the bromoalkyne enhances the copper-catalyzed cross coupling reaction to produce conjugated diynes.

4. Experimental

4.1. General

All reactions were carried out under an atmosphere of nitrogen in oven-dried glassware with magnetic stirring. Reagents were purchased from commercial sources, and used directly without further purification. Methylene chloride was dried over P₂O₅ and freshly distilled before use. Purification of reaction products was carried out by flash chromatography using silica gel 40–63 μm (230–400 mesh), unless otherwise stated. Reactions were monitored by ¹H NMR and/or thin-layer chromatography. Visualization was accomplished with UV light, staining with 5% KMnO₄ solution followed by heating or with p-anisaldehyde (200 ml of 95% EtOH, 10 ml of H₂SO₄, and 10 ml of p-anisaldehyde). Chemical shifts are recorded in ppm (δ) using tetramethylsilane (H, C) as the internal reference. Data are reported as: (s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet; integration; coupling constant(s) in Hz). Optical rotations were measured using Autopol III. Melting points were measured with a Gallenkamp melting point apparatus. Infrared spectra were recorded on a Perkin Elmer 1600 series FTIR. High-resolution mass spectra were recorded at Ohio State University. Lipase AK from pseudomonas sp. was purchased from Amano Enzyme Inc. All new compounds were determined to be >95% pure by ¹H NMR spectroscopy.

4.1.1. 4-Pentynyl tetra-acetyl-β-D-glucopyranoside (10).

A solution of glucose penta-acetate 9 (1.95 g, 5.0 mmol) in CH₂Cl₂ (10 ml) was stirred with BF₃·Et₂O (5.5 mmol) at room temperature for 1 h. Next, 4-pentyne-1-ol (0.63 g, 7.5 mmol) was added and the mixture was stirred for 4 h. After consumption of the starting material, the mixture was cooled to 0 °C and stirred with saturated aq. NaHCO₃ for 30 min. The resulting mixture was extracted three times with diethyl ether. Then the combined extracts were washed...
with water, brine and dried over MgSO₄. The resulting solution was filtered, concentrated and purified over silica gel (50% EtOAc/hexanes) giving a yellow syrup (632 mg, 30%).

[δ]D = +10.60 (MeOH, c = 6.6). 1H NMR (200 MHz, CDCl₃): δ 1.67 (2H, m), 1.87 (1H, t, J = 2.6 Hz), 1.91–1.99 (12H, 4 s), 2.16 (2H, dt, J = 7.1, 2.6 Hz), 3.56 (2H, m), 3.87 (1H, dt, J = 9.7, 5.4 Hz), 4.00 (1H, m), 4.18 (1H, dd, J = 12.3, 4.6 Hz), 4.42 (d, 1H, J = 7.9 Hz), 4.89 (1H, t, J = 9.3 Hz), 4.99 (1H, t, J = 9.6 Hz), 5.23 (1H, t, J = 9.4 Hz). 13C NMR (50 MHz, CDCl₃): δ 51.11 (CH₂), 20.97–21.10 (CH₃), 28.53 (CH₂), 62.28 (CH₃), 68.70 (CH₃), 68.75 (CH), 69.27, 71.62 (CH), 72.10 (CH), 73.11 (CH), 83.73, 101.37 (CH), 169.74, 169.78, 170.63, 171.03. IR: ν cm⁻¹ 3402, 2930, 1740, 1654, 1077. HRMS: calcld for C₂₂H₃₀Si+Na, 463.2128, found M + Na: 463.2155.

4.1.4. 3-Deoxybidensyneoside B (5). To a solution of 24 mg (0.055 mmol) 12 in 4 ml THF and at 0 °C was added 55 μl HF-pyridine. After the addition, the mixture was allowed to warm to room temperature and stirred for an additional 16 h. To the mixture was added solid NaHCO₃ and the solvent was evaporated to ~1 ml. The solution was directly purified over silica gel (30% MeOH/CHCl₃) giving a white solid (mp 158–161 °C, 9.5 mg, 51%).

[δ]D = −15.2 (MeOH, c = 0.14). 1H NMR (500 MHz, Methanol-d₄): δ 1.86 (2H, m), 2.50 (2H, J = 7.12 Hz), 3.19 (1H, dd, J = 9.1, 7.8 Hz), 3.29 (2H, m), 3.36 (1H, t, J = 8.8 Hz), 3.66(1H, dt, J = 10.0, 6.2 Hz), 3.69, (1H, dd, J = 11.8, 5.4 Hz), 3.88 (1H, dd, J = 11.8, 2.1 Hz), 3.98 (1H, dt, J = 10.0, 6.1 Hz), 4.14 (2H, dd, J = 4.8, 2.1 Hz), 4.27 (1H, d, J = 7.8 Hz), 5.78 (1H, d, J = 15.9 Hz), 6.36 (1H, dt, J = 15.9, 4.8 Hz). 13C NMR (75 MHz, Methanol-d₄): δ 16.82 (CH₂), 29.81 (CH₂), 62.69 (CH₂), 62.75 (CH₂), 66.13 (C), 69.21 (CH₂), 71.64 (CH), 74.06, 75.13 (CH), 75.24, 77.93 (CH), 78.07 (CH), 84.33, 104.45 (CH), 109.13 (CH), 147.07 (CH). IR: ν cm⁻¹ 3121, 2228, 2140, 1627, 1159, 1030, 1009, UV/Vis: λmax/nm: 282, 266, 252, 240. HRMS: Calculated C₁₆H₂₂O₂Si+Na = 349.1263, found C₁₆H₂₂O₂Si+Na = 349.1252.

4.1.5. (+)-3R-3,5-tet-butyldimethylsilyloxy-1-pentyne-3-ol (R-15). A solution of racemic 15 (2.62 g, 12.19 mmol) in 100 ml of hexanes was added 3 g of molecular sieves (4 Å) and vinyl acetate (6.29 g, 73.17 mmol). Next, lipase AK from pseudomonas sp²³ (2.62 g) was added and the mixture was stirred at room temperature. When 1H NMR analysis indicated that the ratio of acylated alcohol to free alcohol was approximately 1:1 the mixture was filtered over a pad of Celite, washed with hexanes and purified over silica gel (15% EtOAc/hexanes) giving a yellow oil (1.06 g, 40.5%, (R)-15 and a light yellow oil (1.25 g, 40.5%, (S)-16).

(R)-15: [δ]D = +14.8 (CHCl₃, c = 8.25). (S)-16: [δ]D = −51.4 (MeOH, c = 1.52). 1H NMR (200 MHz, CDCl₃): δ 0.06 (3H), 0.07 (3H), 0.88 (9H), 1.90 (2H, m), 2.44 (1H, J = 2.1 Hz), 3.55 (1H, d, J = 6.2 Hz), 3.84 (1H, m), 4.03 (1H, m), 4.60 (1H, m), 4.67 (1H, m). 13C NMR (200 MHz, CDCl₃): δ −5.14 (CH₃), 18.5, 26.25 (CH₃), 38.67 (CH₂), 61.51 (CH₂), 62.28 (CH), 73.25, 84.79. IR: ν cm⁻¹ 3437, 3033, 2111, 1654. HRMS: calcd for C₁₁H₂₂O₂Si+Na = 237.1287, found M + Na = 237.1290.

4.1.6. (+)-3R-3-Acetoxy-1-tert-butyldimethylsilyl-4-pentyn-1-ol (R)-(+-16). To a solution of R-15 (1.06 g, 4.86 mmol) in 5 ml pyridine was added DMAP (5 mg) and a solution of acetic anhydride (0.74 ml, 7.40 mmol) in 3 ml of pyridine. The mixture was heated to 60 °C and stirred for 4 h.¹⁰ After TLC analysis indicated the completion of the reaction, the solution was diluted with 2 N HCl (5 ml) and a 50:50 Et₂O/hexanes solution (5 ml). The mixture was extracted three times with a mixture of Et₂O/hexanes and the combined organic extracts were washed three times with water, and once with brine. The organic layer was dried over Na₂SO₄. The solvents were removed under reduced pressure...
and the residue was purified over silica gel (15% EtOAc/hexanes) giving a light yellow oil (1.08 g, 85%).

\[ [\alpha]_D^0 = +55.3 \quad \text{MeOH, } c = 1.25, \quad 0.1 \text{H NMR (200 MHz, CDCl}_3): \delta 0.00 \quad (6H, s), 0.84 \quad (9H, s), 1.95 \quad (2H, m), 2.03 \quad (3H, s), 2.41 \quad (1H, d, J = 2.1 Hz), 3.69 \quad (2H, m), 5.43 \quad (1H, dt, J = 2.1, 6.9 Hz), 13\text{C NMR (50 MHz, CDCl}_3): \delta -5.08 \quad (CH_3), 18.64, 21.34 \quad (CH_3), 26.26 \quad (CH_3), 37.95 \quad (CH_2), 58.93 \quad (CH_3), 61.40 \quad (CH), 73.99, 81.58, 170.13. \text{IR: } v \text{ cm}^{-1} \quad 3447, 3311, 2123, 1747, 1231. \text{HRMS: calcd for C}_{13}H_{24}O_3SiNa + Na, 279.1392, found M + Na, 279.1389.

4.1.7. (+)-3(R)-3-Acetoxy-4-pentyn-1-ol (16). A solution of (R)-16 (689 mg, 2.68 mmol) in 40 ml THF was added at 0°C HF-pyridine complex (2.68 ml) at 0°C. The mixture was allowed to warm to room temperature and stirred for 18 h. After completion, the solution was diluted with EtOAc, and washed with NaHCO_3, brine, and dried over Na_2SO_4. The solution was concentrated and purified over silica gel (50% EtOAc/hexanes) giving a clear oil (320 mg, 84%).

\[ [\alpha]_D^0 = +103.6 \quad \text{MeOH, } c = 2.70, \quad 0.1 \text{H NMR (200 MHz, CDCl}_3): \delta 2.00 \quad (2H, m), 2.05 \quad (3H, s), 2.32 \quad (1H, s), 2.47 \quad (1H, d, J = 2.1 Hz), 3.69 \quad (2H, m), 5.49 \quad (1H, dt, J = 2.1, 6.7 Hz), 13\text{C NMR (50 MHz, CDCl}_3): \delta 21.36 \quad (CH_3), 37.86 \quad (CH_2), 58.68 \quad (CH_3), 61.70 \quad (CH), 74.56, 81.18, 170.67. \text{IR: } v \text{ cm}^{-1} \quad 3479, 3303, 2118, 1752, 1631. \text{HRMS: calcd for C}_{10}H_{19}O_3Na + Na, 165.0528, Found M + Na, 165.0536. \text{Deprotection of } (S)-(−)-16 \text{ gave } (S)-(−)-7 \text{ with } [\alpha]_D^0 = −96.6 \quad \text{MeOH, } c = 40.

4.1.8. p-Tolyl 6-O-(tert-butyldimethylsilyl)-1-thio-β-D-glucopyranoside (18a). To a dry 25 ml round bottom flask was added p-tolyl-2,3,4,6-terta-acetyl-1-thio-β-D-glucopyranoside (6a) (0.66 g, 96%).

\[ [\alpha]_D^0 = −33.6 \quad \text{CHCl}_3, \quad c = 3.62, \quad 0.1 \text{H NMR (200 MHz, CDCl}_3): \delta 0.08 \quad (3H, s), 0.12 \quad (3H, s), 0.89 \quad (18H, s), 2.31 \quad (3H, s), 3.13−3.54 \quad (4H, m), 3.85 \quad (2H, m), J = 4.5 Hz, 4.44 \quad (1H, d, J = 9.6 Hz), 7.08 \quad (2H, d, J = 7.9 Hz), 7.42 \quad (2H, d, J = 8.0 Hz), 13\text{C NMR (50 MHz, CDCl}_3): \delta −4.95 \quad (CH_3), −4.14 \quad (CH_3), −3.95 \quad (CH_3), 18.75 \quad (C), 18.80, 21.60 \quad (CH_3), 26.32 \quad (CH_3), 26.39 \quad (CH_3), 64.61 \quad (CH_2), 72.61 \quad (CH), 72.76 \quad (CH), 79.35 \quad (CH), 79.79 \quad (CH), 89.10 \quad (CH), 128.99, 130.13 \quad (CH), 133.40 \quad (CH), 138.54. \text{IR: } v \text{ cm}^{-1} \quad 3592, 3054, 1493, 1265, 1134, 1072. \text{HRMS: calcd for C}_{25}H_{38}O_8SSiNa + Na, 537.2502, Found M + Na, 537.2508.

4.1.10. p-Tolyl 2,3,4-O-tris(acetyl)-6-O-(tert-butyldimethylsilyl)-1-thio-β-D-glucopyranoside (6b). To a round bottom flask equipped with a stirring bar under an atmosphere of nitrogen was added pyridine (13 ml), compound 18a (2.17 g, 5.42 mmol), a solution of TFA (2.21 g, 21.68 mmol) in 15 ml pyridine, and 5 mg of DMAP.19 The flask was then heated to 60°C for 4 h and diluted with 2 N HCl (60 ml), and 60 ml of a 50/50 EtOAc/hexanes solution. The resulting mixture was extracted three times with EtOAc and the combined organic extracts were washed with aq. NaHCO_3, brine and dried over MgSO_4. After removing the solvents under reduced pressure, the residue was purified over silica gel (50% EtOAc/hexanes) giving a syrup (6.23 g, 85%).

\[ [\alpha]_D^0 = −4.53 \quad \text{MeOH, } c = 2.56, \quad 0.1 \text{H NMR (200 MHz, CDCl}_3): \delta 0.03 \quad (3H, s), 0.05 \quad (3H, s), 0.87 \quad (9H, s), 1.93 \quad (3H, s), 1.96 \quad (3H, s), 2.03 \quad (3H, s), 2.30 \quad (3H, s), 3.50 \quad (1H, ddd, J = 2.7, 4.2, 9.7 Hz), 3.68 \quad (2H, m), 4.64 \quad (1H, d, J = 9.9 Hz), 4.86 \quad (1H, t, J = 9.7 Hz), 4.97 \quad (1H, t, J = 9.6 Hz), 5.16 \quad (1H, t, J = 9.2 Hz), 7.05 \quad (2H, d, J = 8.0 Hz), 7.35 \quad (2H, d, J = 8.1 Hz), 13\text{C NMR (50 MHz, CDCl}_3): \delta −5.07 \quad (CH_3), 18.70, 21.07 \quad (CH_3), 21.21 \quad (CH_3), 21.60 \quad (CH_3), 26.24 \quad (CH_3), 62.73 \quad (CH_3), 68.85 \quad (CH), 70.37 \quad (CH), 74.89 \quad (CH), 79.26 \quad (CH), 86.04 \quad (CH), 128.26, 130.83 \quad (CH), 133.88 \quad (CH), 138.83, 169.64, 169.66, 170.75. \text{IR: } v \text{ cm}^{-1} \quad 2930, 2857, 1757, 1374, 837, 810, 779. \text{HRMS: calcd for C}_{25}H_{37}O_8SSiNa, 549.1954, Found M + Na: 549.1963.
slowly added. The mixture was stirred at 0 °C for 4 h and diluted with 2 N HCl (60 ml) and the combined ether extracts were washed three times with water, once with brine, and dried over Na₂SO₄. The solution was then filtered, concentrated, and purified over silica gel giving a white solid (mp 104–107 °C, 6.80 g, 87%).

[α]D = −9.27 (CHCl₃, c = 8.19). ¹H NMR (200 MHz, CDCl₃): δ 0.0–0.03 (12H, three singlet’s), 0.79 (9H, s), 0.86 (9H, s), 2.04 (3H, s), 2.10 (3H, s), 2.29 (3H, s), 3.40 (1H, ddd, J = 9.4, 5.9, 3.2 Hz), 3.61 (2H, m), 3.80 (1H, t, J = 8.9 Hz), 4.53 (1H, d, J = 10.1 Hz), 4.84 (1H, t, J = 10.0 Hz), 4.88 (1H, t, J = 10.1 Hz), 7.05 (2H, d, J = 8.0 Hz), 7.36 (2H, d, J = 8.1 Hz). ¹³C NMR (50 MHz, CDCl₃): δ −0.03 (CH3), −4.83 (CH3), −4.06 (CH3), −4.02 (CH2), 18.19, 18.78, 21.57 (CH3), 21.73 (CH3), 21.90 (CH3), 25.90 (CH3), 26.32 (CH3), 63.69 (CH2), 72.08 (CH), 73.02 (CH), 74.97 (CH), 79.90 (CH), 87.43 (CH), 130.03 (CH3), 130.45, 132.49 (CH), 138.07, 169.84. IR: ν cm⁻¹ 2926, 1736, 1222, 1132, 1051. HRMS: calcd for C₃₀H₅₀O₁₁Si₂+Na, 621.2714, Found M+Na 621.2718.

4.1.12. Orthoester (19a). To a 10 ml round bottom flask was added 4 ml dry CH₂Cl₂, compound 6b (103 mg, 0.20 mmol), compound (R)-7 (42 mg, 0.30 mmol), and 0.4 g of molecular sieves. The mixture was stirred for 20 min at room temperature. While the mixture was stirring, dimethyldisulfide (55 mg, 0.59 mmol) and MeOTf (97 mg, 0.59 mmol) were allowed to mix in a separate vial to form a solid. After the mixture had fully crystallized, it was dissolved in 1.5 ml CH₂Cl₂. The mixture of 6b and (–)-7 was then cooled to 0 °C and the DMTST solution was slowly added. The mixture was stirred at 0 °C for 30 min, then 1 h at room temperature. Next, 0.6 ml Et₃N was added to the mixture, which prompted a precipitate to form. The mixture was then filtered and diluted with CH₂Cl₂. The organic solution was washed with NaHCO₃, brine, and dried over Na₂SO₄. Finally, the mixture was filtered, and the solvents removed under reduced pressure. The residue was purified over silica gel (15% EtOAc/hexanes) giving a yellow oil (12 mg, 11%, 19b) and a clear oil (16 mg, 15%, 20).

19b: [α]D = +12.7, (MeOH, c = 0.1). ¹H NMR (300 MHz, CDCl₃): δ 0.03 (3H, s), 0.03 (3H, s), 0.87 (9H, s), 1.68 (3H, s), 2.07 (2H, m), 2.06 (3H, s), 2.08 (3H, s), 2.08 (3H, s), 2.46 (1H, d, J = 2.2 Hz), 3.60 (2H, m), 3.70 (1H, m), 3.72 (2H, m), 4.29 (1H, ddd, J = 5.2, 3.1, 0.9 Hz), 4.95 (1H, add, J = 9.0, 2.5, 0.9 Hz), 5.16 (1H, t, J = 2.8 Hz), 5.44 (1H, dt, J = 2.1, 6.9 Hz), 5.68 (1H, d, J = 5.2 Hz). ¹³C NMR: (75 MHz, CDCl₃): δ −4.96 (2 CH3), 18.73, 20.98 (CH3), 21.21 (CH3), 21.29 (2 CH3), 26.26 (CH3), 34.90 (CH3), 59.42 (CH2), 63.37 (CH2), 68.52 (CH), 70.06 (CH), 70.41 (CH), 73.49 (CH), 80.96, 97.50 (CH), 121.56, 169.66, 170.01, 170.13. IR: ν cm⁻¹ 2930, 2255, 1742, 1371, 1239, 1191, 937, 779, 732. HRMS: calcd for C₂₅H₄₀O₁₁S+Na, 567.2238, found M+Na 567.2244.

20: [α]D = −13.5, (MeOH, c = 0.15). ¹H NMR (500 MHz, CDCl₃): δ 0.02 (3H, s), 0.03 (3H, s), 0.86 (9H, s), 1.97 (3H, s), 1.99 (3H, s), 2.05 (3H, s), 2.06 (3H, s), 2.09 (2H, m), 2.44 (1H, d, J = 2.1 Hz), 3.52 (1H, ddd, J = 9.9, 5.2, 2.7 Hz), 3.63 (1H, m), 3.68 (2H, m), 3.99 (1H, dt, J = 10.0, 5.6 Hz), 4.92 (1H, ddd, J = 8.1, 9.7 Hz), 4.98 (1H, t, J = 9.7 Hz), 5.17 (1H, t, J = 9.5 Hz), 5.35 (1H, dt, J = 2.1, 6.6 Hz). ¹³C NMR (75 MHz, CDCl₃): δ −4.97 (CH3), 18.70, 21.01 (CH3), 21.04 (CH3), 21.08 (CH3), 21.24 (CH3), 26.20 (CH3), 34.76 (CH3), 61.32 (CH2), 62.84 (CH2), 65.67 (CH2), 69.39 (CH2), 71.65 (CH), 73.53 (CH), 74.39, 75.18 (CH), 101.10 (CH), 169.78, 169.90, 170.82. IR: ν cm⁻¹ 3019, 2121, 1756, 1371. HRMS: calcd for C₂₅H₃₉O₁₁Si+Na, 567.2238, found M+Na 567.2244.

4.1.14. (3R)-3-Acetoxy-4-pentynyl 2',3',4'-O-bis(acetyl)-3',6'-O-(butylidimethylsilyl)-β-D-glucopyranoside (21). To a 25 ml round bottom flask was added 8 ml dry CH₂Cl₂, compound 6c (289 mg, 0.48 mmol), compound (+)-7 (103 mg, 0.72 mmol) and 0.8 g of molecular sieves. The mixture was stirred for 20 min at room temperature. While the mixture was stirring, dimethyldisulfide (136 mg, 1.44 mmol) and MeOTf (236 mg, 1.44 mmol) were allowed to mix in a separate vial to form a solid. After the mixture had fully crystallized, it was dissolved in 2.5 ml CH₂Cl₂. The mixture was then cooled to 0 °C and the DMTST solution was slowly added. The mixture was stirred at 0 °C
for 30 min, then allowed to warm to room temperature. TLC analysis indicated the disappearance of 6c. Next, 0.6 ml Et$_3$N was added to the mixture, which led to a precipitate. The mixture was filtered and diluted with CH$_2$Cl$_2$. The organic solution was then washed with aq. NaHCO$_3$, brine and dried over Na$_2$SO$_4$. The mixture was filtered, and the solvents removed under reduced pressure. The residue was purified over silica gel (15% EtOAc/hexanes) giving a yellow oil (189 mg, 64%).

$[\alpha]_D = +19.4$ (MeOH, c = 2.3). $^1$H NMR (200 MHz, CDCl$_3$): $\delta$ 0.00 (6H, s), 0.02 (6H, s), 0.78 (9H, s), 0.85 (9H, s), 1.99 (2H, m), 2.04 (3H), 2.07 (3H), 2.08 (3H), 2.42 (1H, d, $J$ = 2.1 Hz), 3.37 (1H, m), 3.46 (1H, m), 3.59 (2H, m), 3.80 (1H, t, $J$ = 9.1 Hz), 3.94 (1H, dt, $J$ = 9.9, 6.5 Hz), 4.28 (1H, d, $J$ = 8.0 Hz), 4.79 (1H, t, $J$ = 9.2 Hz), 4.84 (1H, t, $J$ = 9.0 Hz), 5.36 (1H, dt, $J$ = 2.0, 6.6 Hz), 2.16 (1H, m), 3.19 (1H, t, $J$ = 12.1 Hz), 4.02 (1H, d, $J$ = 15.9, 4.5 Hz), $^1$C NMR (50 MHz, CDCl$_3$): $\delta$ -4.94 (CH$_3$), -4.83 (CH$_3$), -4.14 (CH$_3$), -4.03 (CH$_3$), 18.17, 18.75, 21.33 (CH$_3$), 21.61 (CH$_3$), 21.74 (CH$_3$), 25.88 (CH$_3$), 26.25 (CH$_3$), 35.17 (CH$_3$), 61.08 (CH$_3$), 63.65 (CH$_3$), 64.94 (CH$_3$), 72.45 (CH), 73.47 (CH), 74.05, 74.48 (CH), 75.66 (CH), 81.11 (CH), 101.10 (CH), 169.82, 169.90, 170.16. IR: $\nu$ cm$^{-1}$ 3342, 2126, 1752. HRMS: calcd for C$_{25}$H$_{52}$O$_{10}$Si$_2$Na, 639.2953, found M + Na, 639.2953.

4.1.15. 5-Bromo-2-penten-4-yn-1-ol (8). To a suspension of 2-penten-4-yn-1-ol (0.50 g, 6.09 mmol) and NBS (1.27 g, 7.00 mmol) in 8 ml DMF, compound (acetyl) bidensyneoside C (22). A 10 ml round bottom flask was added compound 22 (270 mg, 0.41 mmol), HF-pyridine complex (5 ml), AcOH (4 ml) and THF (35 ml). The mixture was stirred overnight and was diluted with EtOAc and aq. NaHCO$_3$. The mixture was then saturated with NaCl and extracted 5 times with EtOAc. The solvents were removed under reduced pressure and the residue purified over silica gel (10% MeOH/CHCl$_3$) yielding a yellow/brown syrup (102 mg, 58%), which was used in the next step without further identification. To a solution of the syrup in 12 ml MeOH was added K$_2$CO$_3$ (1.6 mg). The mixture was stirred for 4 h. The reaction was monitored by TLC and the appearance of a single polar spot indicated the completion of the reaction. Then, about half of the solvent was removed under vacuum and the residue was purified over silica gel (35% MeOH/CHCl$_3$) giving a light brown oil (76 mg, 94%).

$[\alpha]_D = -50.84$ (MeOH, c = 0.83). $^1$H NMR (500 MHz, CD$_2$OD): $\delta$ 1.99 (2H, m), 3.19 (1H, t, $J$ = 8.5 Hz), 3.20 (2H, m), 3.37 (1H, m), 3.69 (1H, dd, $J$ = 5.1, 11.7 Hz), 3.76 (1H, dt, $J$ = 10.0, 6.5 Hz), 3.88 (2H, dd, $J$ = 1.2, 12.1 Hz), 4.02 (1H, dt, $J$ = 10.1, 5.7 Hz), 4.29 (1H, d, $J$ = 4.8 Hz), 4.68 (1H, t, $J$ = 6.6 Hz), 5.83 (1H, d, $J$ = 15.9 Hz), 6.42 (1H, dt, $J$ = 15.9, 4.5 Hz), $^1$C NMR (125 MHz, Methanol-d$_4$): $\delta$ 38.88 (CH$_2$), 60.15 (CH), 62.60 (CH$_3$), 62.65 (CH$_2$), 66.76 (CH$_3$), 69.52, 71.51 (CH), 74.14, 75.03 (CH), 77.56, 77.84 (CH), 77.97 (CH), 84.31, 104.49 (CH), 108.54 (CH), 148.09 (CH). IR: $\nu$ cm$^{-1}$ 3302, 2885, 2233, 1629, 1438, 1368, 1161, 1071, UV/Vis: $\lambda_{\text{max}}$ (nm): 283, 267, 253, 240. HRMS: Calculated for C$_{16}$H$_{22}$O$_8$Na, 365.1212, found C$_{16}$H$_{22}$O$_8$Na, 365.1219.
(3H, s), 0.84 (9H, s), 0.94 (9H, s), 2.07 (2H, m), 2.09 (3H, s), 2.11 (3H, s), 2.13 (3H, s), 3.41 (1H, ddd, J = 9.7, 6.1, 3.6 Hz), 3.52 (1H, dt, J = 10.1, 6.7 Hz), 3.64, (1H, dd, J = 11.6, 3.4 Hz), 3.68 (1H, dd, J = 11.4, 6.2 Hz), 3.83 (1H, t, J = 9.1 Hz), 3.96 (1H, dt, J = 10.1, 5.7 Hz), 4.32 (1H, d, J = 8.0 Hz), 4.85 (1H, t, J = 9.1 Hz), 4.88 (1H, t, J = 8.4 Hz), 5.42 (1H, t, J = 6.6 Hz), 7.14 (9414). HRMS: calcd for C_{29}H_{51}BrO_{10}Si_{2} (CH), 63.66 (CH2), 64.91 (CH2), 72.46 (CH), 73.47 (CH), 74.05 (CH), 75.69 (CH), 77.55, 101.14 (CH), 169.74, 169.84, 170.05. IR: v cm⁻¹ 2930, 2250, 2219, 1751, 1735, 1220, 1063. HRMS: calcd for C_{28}H_{51}BrO_{10}Si_{2} + Na, 717.2102, Found M + Na, 717.2089.

4.1.19. (8Z)-(3'R)-3'-Hydroxy-8'-decen-4',6'-diynyl 3,6-O-bis(tert-butyldimethylsilyl)-2,4-O-bis(acetyl)-β-D-glucopyranoside (24). In the absence of light, a 5 ml round bottom flask equipped with a stir bar under an atmosphere of nitrogen was added MeOH (0.5 ml), EtNH₂ (0.5 ml), Z-3-pentene-1-yne (3 mg, 0.044 mmol) and NH₂OH–HCl (0.5 mg 0.007 mmol) at 0°C in an ice bath. Next CuCl₂ (0.2 mg, 2.2 m), Na, 661.3218. IR: v cm⁻¹ 3330, 2918, 2231, 1611, 1161, 1071, UV/Vis: λ_{max, nm}: 282, 266, 252, 240. HRMS: Calculated for C_{16}H_{22}O_{7} + Na 349.1263, found 349.1267.

[α]D = −152.5 (MeOH, c = 0.02), 1H NMR (500 MHz, Methanol-d₄): δ 1.88 (3H, dd, J = 7.02, 1.63 Hz), 1.97 (2H, m), 3.16 (1H, dd, J = 7.9, 8.9 Hz), 3.26 (2H, m), 3.34 (1H, m), 3.67 (1H, dd, J = 11.7, 5.0 Hz), 3.73 (1H, dt, J = 10.0, 6.6 Hz), 3.85 (1H, dd, J = 11.7, 1.9 Hz), 4.00 (1H, d, J = 10.1, 5.9 Hz), 7.26 (1H, d, J = 7.8 Hz), 4.66 (1H, t, J = 6.6 Hz), 5.53 (1H, dm, J = 10.9 Hz), 6.20 (1H, dq, J = 10.8, 6.9 Hz), 13C NMR (75 MHz, Methanol-d₄): δ 16.42 (CH₃), 38.97 (CH₃), 60.22 (CH₂), 62.73 (CH₂), 66.80 (CH₂), 69.45, 71.61 (CH), 75.11 (CH), 75.96, 77.96 (CH), 78.07 (CH), 78.46, 85.15, 104.59 (CH), 109.70 (CH), 144.00 (CH). IR: v cm⁻¹ 3330, 2918, 2231, 1611, 1161, 1071, UV/Vis: λ_{max, nm}: 282, 266, 252, 240. HRMS: Calculated for C_{16}H_{22}O_{7} + Na 349.1263, found 349.1267.

Acknowledgements

This research is supported in part by a grant from the National Institutes of Health (GM60263) and the Beckman Foundation. Acknowledgment is also made to the donors of the Petroleum Research Fund (PRF#36841-AC4) administered by the American Chemical Society. We thank Robert Falconer and Amanda Jones for preparing some of the starting materials.

References and notes

22. One reviewer has given another reasonable explanation regarding the outcome of glycosylation versus orthoester formation: ‘The C2-acetate stabilized oxycarbenium ion may be attacked by the incoming nucleophile at either the acetate carbonyl carbon, thus leading to the orthoester product, or at the anomeric carbon, leading to the desired glycosylation. The observed differences (between observed products with C3-Otbs versus C3-OAc protected donors) may simply reflect subtle differences in the kinetics of the attacks at these two centers: the more sterically congested Otbs protected substrate (which also yields a more stable oxycarbenium ion that ‘demands less’ in terms of stabilization by the C2-acetate relative to the C3-OAc protected donor) may not favor orthoester formation, as this would require developing unfavorable interactions (between the methyl group of the C2 acetate and the Tbs group) in the transition state. Similar unfavorable interactions may deter the Tbs-protected system from adopting a ring conformation that is favorable to orthoester formation.’