Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron: Asymmetry
Tetrahedron: *Asymmetry* 17 (2006) 40–46

Total synthesis of two naturally occurring polyacetylenic glucosides (−)-bidensyneoside A1 and B, and an analogue of (−)-bidensyneoside C

Benjamin W. Gung,* Ryan M. Fox, Robert Falconer and Daniel Shissler

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

Received 26 September 2005; accepted 19 October 2005

Abstract—The total syntheses of two novel polyacetylenic natural products bidensyneoside A1 and B, as well as an analogue of bidensyneoside C are described. These syntheses are based on our recently developed strategy. A new preparation of the required starting material (*E*)-3-penten-1-yne was developed. The preparation of the analogue of (−)-bidensyneoside C further confirms the side chain configuration of the natural product as (*R*).

1. Introduction

Bidens parviflora is a plant genre that has been used in traditional Chinese medicine as an antipyretic, anti-inflammatory, and antirheumatic remedy.[1] *Bidens parviflora* contains a wide variety of bioactive compounds including sterols, monoterpenes, flavonones, flavonoids, polyacetylene glucosides, chalcones, aurones, and flavonol glycosides.[1] Over the years, several species of *Bidens* family have been investigated by chemical methods.[2–6] Polyacetylenic glucosides isolated from *Bidens parviflora*, bidensyneosides **1**–**5** (Fig. 1), have been shown to inhibit histamine release in rat mast cells and the production of nitric oxide.

Recently, we developed a strategy for the synthesis of these biologically active polyacetylenic glucosides based on sequential glycosylation and Cu(I)-catalyzed cross coupling reactions.[7] Specifically, we reported the total synthesis of (−)-bidensyneosides A2 **2** and C **4a** based on a stereoselective glycosylation and subsequent coupling of the right hand enyne fragment to the main framework (Fig. 2). The required enyne fragments for **2** and **4** were (*Z*)-3-penten-1-yne and 2-penten-4-yn-1-ol, which are commercially available. The corresponding enyne fragments for **1** and **3** are (*E*)-3-penten-1-yne and 1,3-pentadiyne, which are not available commercially.

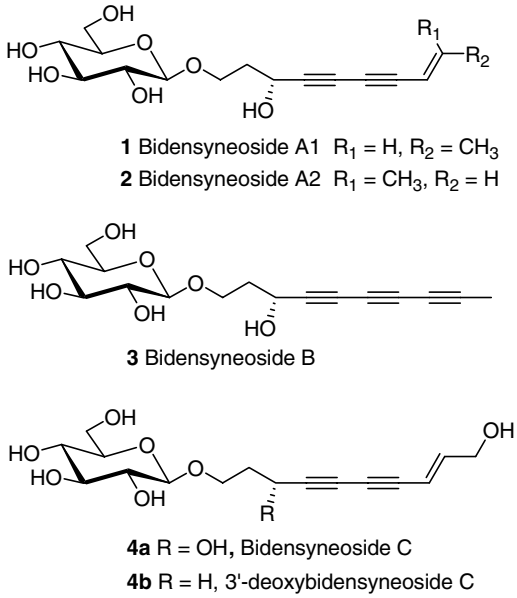


Figure 1. Structures of bidensyneosides from *Bidens parviflora* WILLD.

Bidensyneoside A_1 **1** differs from its closest relative bidensyneoside A_2 **2** simply by the configuration of the double bond in the aglycone side chain. Since we have already prepared the left hand main fragment in the synthesis of **2** and **4**,[7] to prepare (−)-bidensyneoside

* Corresponding author. Fax: +1 513 529 5715; e-mail: gungbw@muohio.edu

0957-4166/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetasy.2005.10.027

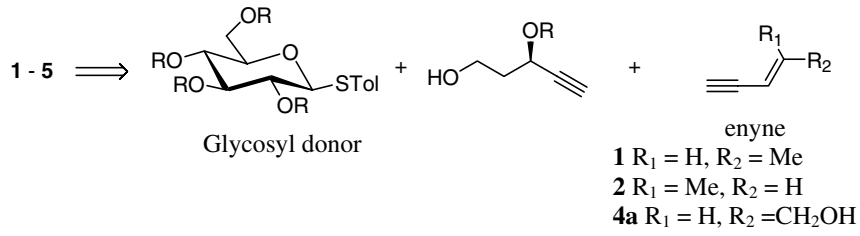


Figure 2. Retrosynthetic analysis of bidensyneosides.

A1 **1** and C **3**, the task at hand was to prepare (*E*)-3-penten-1-yne and 1,3-pentadiyne, respectively. There are several reported procedures for 1,3-pentadiyne. However, the preparation of the (*E*)-isomer of 3-penten-1-yne turned out to be more difficult than expected.

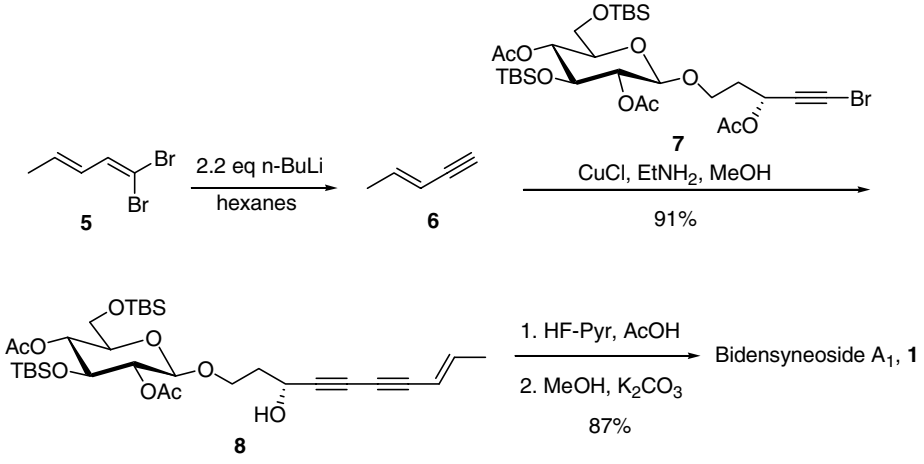
2. Results and discussion

The commercially available mixture of 3-penten-1-yne contains about 95% of the (*Z*)-isomer. Although this compound has been prepared before, the reported procedure involved a non-stereoselective elimination of toluenesulfonic acid from 4-pentyn-2-yl toluenesulfonate performed on a 5 mol scale.[8] Repeated fractional distillation was required to separate the (*E*)-(bp 52 °C)/(*Z*)-isomers (bp 45 °C) affording only 9% yield of the desired (*E*)-isomer in 95% purity.[8] This procedure was apparently not suitable for our purpose since we needed only a small amount of the (*E*)-isomer.

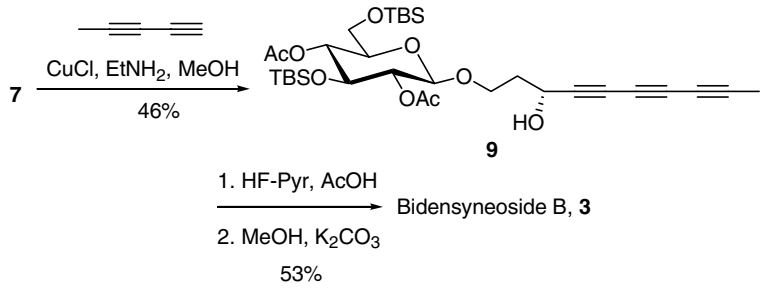
For our synthesis, the preparation of (*E*)-3-penten-1-yne started from the readily available 1,1-dibromo-1,3-pentadiene **5**,[9] which was prepared from (*E*)-crotonaldehyde using Corey–Fuchs protocol (Scheme 1).[10] A solution of **5** in hexanes was treated with 2.2 equiv of *n*-BuLi at −78 °C and quenched with saturated NH_4Cl solution after 1 h (Scheme 1). The volatility of the desired product made its isolation difficult for small scale operation, which was overcome by bubbling nitrogen through the solution of the product and the desired product was collected in MeOH solution. In the experiment, a stream of N_2 was allowed to pass through the hexanes layer and travel through two traps containing MeOH at −78 °C. The concentration of the (*E*)-3-penten-1-yne in MeOH solution was determined by integration of the relative peak heights in ^1H NMR spectrum. The MeOH solution was used directly in the cross coupling reaction.

Bromoalkyne **7**, which was available through our recent synthesis,[7] along with (*E*)-3-penten-1-yne **6** were then subjected to the copper catalyzed cross coupling reaction to give the desired enediyne functionality of the precursor to bidensyneoside A1 **8** in a remarkable 91% yield. The removal of the protecting groups of **8** was carried out by first removing the TBS groups with HF·pyridine complex in acetic acid, followed by removal of the acetate groups using a catalytic amount of K_2CO_3 in methanol. These two steps led to the isolation of (−)-bidensyneoside A_1 **1** in 87% yield (Scheme 1). All spectroscopic data of the synthetic sample are consistent with that reported for the natural product.[1]

Bidensyneoside B containing a conjugated triyne was the most intriguing target of this series of compounds due to the highest degree of unsaturation on its polyacetylenic side chain. Several different methods for preparing the needed 1,3-pentadiyne have been reported.[11,12] We chose the method reported by Brandsma, which involved a double dehydrohalogenation of 1,4-dichloro-2-butyne with sodamide in liquid ammonia followed by in situ methylation with methyl iodide.[13] Although the operation was somewhat challenging, we prepared a sufficient amount for our synthesis. With 1,3-pentadiyne and



Scheme 1.

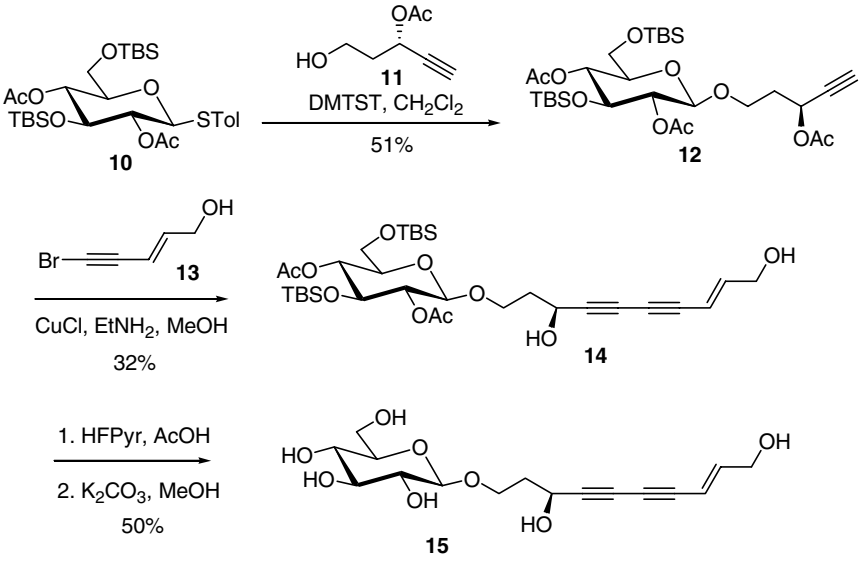


Scheme 2.

the advanced intermediate **7** in hand, a cross coupling reaction under Cadiot-Chodkiewicz conditions (Scheme 2) led to the desired triyne **9**.[14]

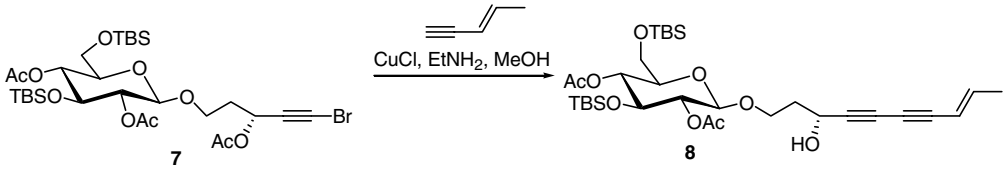
Although a propargylic oxygen substitution on bromoalkynes typically increases the coupling yield,[15] for example, the case with bidensyneoside A_1, the triyne moiety in **9** appears to suffer from decomposition. The relatively low yield was due to loss of product during purification. The removal of the protecting groups on **9** was carried out analogously by first removing the TBS groups and then the acetate groups, which led to bidensyneoside B **3** in 53% yield. All spectroscopic data of the synthetic sample are consistent with that reported for the natural product.[1] During the purification of the final product, a surprisingly polar property was observed for bidensyneoside B **3**. Although bidensyneoside B **3** lacks the primary OH group that is part of the side chain of bidensyneoside C **4a**, **3** is considerably more polar than **4a**. In fact, **3** is so polar that the mobile phase for thin layer and column chromatograph has to contain 5% H_2O in a mixed solvent system (H_2O/MeOH/$CHCl_3$ = 5:35:60) in order to elute **3** successfully. This unusual polarity cannot be attributed to the usual polar functional groups, such as OH, because the structures of **3** and **4a** are identical except for the polyacetylenic side chains. It is not entirely clear why **3** is more polar than **4a** at this time. However, one possibility is that the three conjugated triple bonds are so electronegative that the terminal methyl group becomes acidic and forms CH–O hydrogen bonds with silica gel. Even though a CH–O bond is much weaker than an OH–O bond, the three CH–O bonds in the side chain of **3** might have a greater affinity for silica gel than a single OH–O interaction. We are currently designing experiments to test this hypothesis.

In our recently reported synthesis of bidensyneoside C **4a**, all of the spectroscopic data for the synthetic sample were nearly identical with that reported for the natural product, except for the specific rotation, which was reported to be $[\alpha]_D = -71.6$, compared to our observed $[\alpha]_D = -50.8$. The only stereocenter that might be questionable was the stereogenic center on the side chain. We considered the possibility that the natural product might have an (*S*)-stereocenter on the side chain and we prepared the bidensyneoside C with an (*R*)-stereocenter on the side chain, which led to the lower specific rotation. This uncertainty can only be resolved by synthesizing the other isomer, that is, the analogue of (−)-bidensyneoside C **4a** with a side chain that has an (*S*)-stereocenter **15** (Scheme 3). To synthesize **15**, the (*S*)-enantiomer of **11** was used in the glycosylation with **10**,[7] which led to a 51% yield of **12**.



Scheme 3.

The subsequent copper catalyzed coupling with bromoalkyne **13** afforded the precursor **14** in a low yield of 32%. The removal of the protecting groups follows the usual protocol. The NMR data for **15** are almost identical to that of its natural occurring counterpart, but the optical rotation has an opposite sign {**15**: $[\alpha]_D = +13.0$ (*c* 0.2, MeOH), **4a**: $[\alpha]_D = -71.6$ (*c* 0.5, MeOH)}. This firmly proves that the stereocenter on the side chain of the natural bidensyneoside C **4a** has an (*R*)-configuration. The difference in the specific rotation values between the reported natural bidensyneoside C and our synthetic sample could be due to errors in the measurements or insufficient enantiomeric excess of (*R*)-**11** in our synthesis of **4a**.



3. Conclusions

The total syntheses of bidensyneoside A1 **1** and B **3**, as well as an analogue of bidensyneoside C have been achieved. The observed specific rotation of the analogue **15** firmly establishes that the stereocenter on the side chain of the natural bidensyneoside C has an (*R*) configuration. An improved small scale preparation of configurationally pure (*E*)-3-penten-1-yne has been developed. Finally, an unexpected strongly polar property was observed for bidensyneoside B. It was suggested that this unusual polarity might be due to CH–O hydrogen bonding of the terminal methyl group activated by the three conjugated triple bonds. Theoretical and experimental investigations of this proposal are currently underway in our laboratories.

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 P_2O_5 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 ^{1}H NMR and/or thin-layer chromatography. Visualization was accomplished with UV light, staining with 5% $KMnO_4$ solution followed by heating or with *p*-anisaldehyde in EtOH solution. Chemical shifts were 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 hertz. 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 for liquids and on a Perkin Elmer Spectrum 2000 FTIR for solids. High-resolution mass spectra were recorded at the Ohio State University.

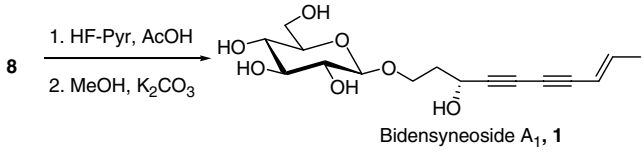
4.1.1. (8′*E*)-(3′*R*)-3′-Hydroxy-8′-decen-4′,6′-diyn-1-yl 3,6-*O*-di(*tert*-butyldimethylsilyl)-2,4-*O*-di(acetyl)-β-D-glucopyranoside 8

To a solution of 1,1-dibromo-1,3-pentadiene (5.3 g, 23.6 mmol) in 135 mL of hexanes at −78 °C under N_2 was added *n*-BuLi (29 mL of 1.6 M in hexanes) over 15 min. After 1 h at −78 °C, the reaction was quenched with 20 mL of NH_4Cl. The aqueous and the organic layers were separated and the organic layer was dried over $MgSO_4$. After filtration, the organic layer was loaded into a distillation apparatus, which was connected to two traps half-filled with MeOH and cooled by dry ice-acetone bath. A stream of N_2 was allowed to bubble through the solution and the traps. Some hexanes were also collected in the first trap, which was separated in a separatory funnel. The concentration of the desired (*E*)-3-penten-1-yne was determined by ^{1}H NMR and the methanol solution was used for the following reaction.

To a mixture of MeOH (5 mL), $EtNH_2$ (2 mL), solution of (*E*)-3-penten-1-yne in MeOH (0.5 mL, ~0.18 mM), and $NH_2OH{\cdot}HCl$ (0.9 mg, 0.015 mmol) at 0 °C under nitrogen was added CuCl (0.6 mg, 6 μmol) followed by slow addition of 1.0 mL solution of **7** (42 mg, 0.061 mmol) in MeOH. After 2.5 h at rt, TLC analysis indicated the complete disappearance of **7**. The mixture was then cooled to 0 °C and diluted with 8 mL EtOAc and 5 mL of a saturated KCN/NH_4Cl solution. The aqueous layer was extracted with EtOAc (3 × 8 mL), and the combined extracts were washed with $NaHCO_3$ solution and brine. The resulting solution was dried over $MgSO_4$ and purified by flash column chromatography (20% EtOAc/Hex) to give 36 mg (91%) of **8** as a clear oil. $[\alpha]_D = -28.6$ (*c* 0.4, MeOH), ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.0 (3H, s), 0.01 (3H, s), 0.02 (6H, s), 0.78 (9H, s), 0.85 (9H, s), 1.79 (3H, dd, $J = 6.86$, 1.59 Hz), 1.85 (1H, m), 2.04 (3H, s), 2.09 (1H, m), 2.10 (3H, s), 3.38 (1H, ddd, $J = 9.61$, 5.72, 3.68 Hz), 3.61 (2H, m), 3.79 (1H, dt, $J = 9.62$, 3.62 Hz), 3.80 (1H, t, $J = 8.93$ Hz), 4.02 (1H, m), 4.32 (1H, d, $J = 8.04$ Hz), 4.59 (1H, m), 4.80 (1H, dd, $J = 9.87$, 9.14 Hz), 4.83 (1H, dd, $J = 9.14$, 8.30 Hz), 5.49 (1H, dd, $J = 15.84$, 1.64 Hz), 6.30 (1H, dq, $J = 15.83$, 6.87 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ −4.97, −4.88, −4.15, −4.07,

18.17, 18.73, 19.31, 21.68 ($2\times CH_3$), 25.86 ($3\times CH_3$), 26.22 ($3\times CH_3$), 36.82, 61.57, 63.60, 66.70, 70.20, 72.09, 72.40, 73.41, 74.34, 75.67, 77.98, 81.94, 101.24, 109.98, 144.41, 169.83, 170.43. IR: ν cm^{-1} 2930, 2345, 1751, 1654, 1220. HRMS: calcd for $C_{32}H_{54}O_9Si_2$+Na, 661.3204, found M+Na, 661.3252.

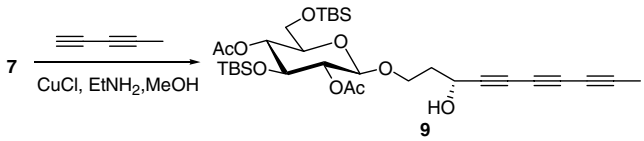
4.1.2. Bidensyneoside A_1



Bidensyneoside A_1, **1**

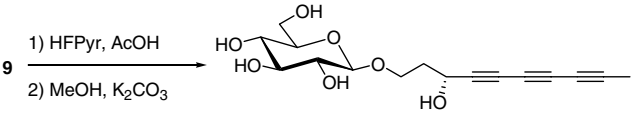
To a solution of **8** (35.5 mg, 0.056 mmol) in 5 mL of THF under nitrogen was slowly added HF·pyridine (0.66 mL) at 0 °C followed by acetic acid (0.52 mL). The mixture was allowed to warm to room temperature, and stirring was continued for 16 h in the absence of light. The mixture was diluted with EtOAc (10 mL) and satd $NaHCO_3$ solution (8 mL). The aqueous layer was saturated with NaCl and extracted with EtOAc (5×10 mL). The combined EtOAc extracts were then subjected to rotary evaporation and then high vacuum to remove all traces of solvents. The residue was dissolved in MeOH (2 mL) and transferred back into a 10 mL round bottom flask in the absence of light and stirring resumed. Next, K_2CO_3 (0.7 mg, 7 μmol) was added, and the solution was allowed to stir at room temperature for 4 h. Careful TLC analysis with solvent systems consisting of 2.5–5% H_2O indicated a single spot. Approximately half of the MeOH was removed under reduced pressure, and the resulting solution was purified over silica gel with a mixed solvent system, MeOH/$CHCl_3$ (40/60) to give 15.8 mg (87%) of a light brown oil. $[\alpha]_D = -47.0$ (c 0.21, MeOH), ^{1}H NMR (500 MHz, methanol-d_4): δ 1.80 (3H, dd, $J = 6.86$, 1.75 Hz), 1.96 (2H, m), 3.16 (1H, dd, $J = 8.14$, 8.68 Hz), 3.27 (2H, m), 3.34 (1H, t, $J = 8.76$ Hz), 3.67 (1H, dd, $J = 11.89$, 5.14 Hz), 3.73 (1H, dt, $J = 10.10$, 6.44 Hz), 3.85 (1H, dd, $J = 11.95$, 1.99 Hz), 3.99 (1H, dt, $J = 10.13$, 5.77 Hz), 4.26 (1H, d, $J = 7.76$ Hz), 4.63 (1H, t, $J = 6.68$ Hz), 5.57 (1H, dd $J = 19.90$, 1.65 Hz), 6.32 (1H, dq, $J =$ 15.77, 6.91 Hz). ^{13}C NMR (125 MHz, methanol-d_4): δ 18.82, 38.97, 60.21, 62.71, 66.83, 69.71, 71.61, 72.41, 75.10, 77.93, 78.05, 78.13, 83.67, 104.57, 110.53, 145.09. IR: ν cm^{-1} 3332, 2916, 2231, 2140, 1626, 1161, 1074, 949. UV/vis: $\lambda_{(max)}$ nm: 283, 267, 253, 240. HRMS: calculated $C_{16}H_{22}O_7$+Na = 349.1263, found M+Na 349.1269.

4.1.3. (3′*R*)-3′-Hydroxy-4′,6′,8′-decatriyn-1-yl 3,6-*O*-di(*tert*-butyldimethylsilyl)-2,4-*O*-di(acetyl)-β-D-glucopyranoside 9



To a mixture of 4 mL MeOH, 4 mL $EtNH_2$, 1,3-pentadiyne (28 mg, 0.44 mmol), CuCl (1.5 mg, 0.015 mmol), and NH_2OH·HCl (3 mg, 0.37 mmol) at 0 °C under nitrogen was added a solution of **7** (15 mg, 0.022 mmol) in 0.5 mL MeOH. After 1 h at rt, TLC analysis indicated the completion of the reaction. The mixture was then cooled to 0 °C and diluted with 8 mL EtOAc and 10 mL of a KCN/NH_4Cl solution. The aqueous layer was extracted with EtOAc (3×5 mL), and the combined extracts were washed with satd $NaHCO_3$ solution and brine. The resulting solution was dried over $MgSO_4$ and purified over silica gel column chromatography (20% EtOAc/Hex) to give 43 mg (46%) of **9** as a light yellow oil. $[\alpha]_D = -13.8$ (c 0.6, MeOH), ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.01 (3H, s), 0.02 (3H, s), 0.03 (6H, s), 0.79 (9H, s), 0.86 (9H, s), 1.82 (1H, m), 1.95 (3H, s), 2.05 (3H, s), 2.10 (3H, s), 2.12 (1H, m), 2.86 (1H, d, $J = 8.10$ Hz), 3.38 (1H, ddd, $J = 9.57$, 6.13, 3.39 Hz), 3.58 (1H, dd, $J = 11.40$, 3.65 Hz), 3.63 (1H, dd, $J = 11.45$, 5.81 Hz), 3.78 (1H, dt, $J = 9.84$, 3.60 Hz), 3.81 (1H, t, $J = 9.10$ Hz), 4.04 (1H, dt, $J = 9.56$, 4.47 Hz), 4.33 (1H, d, $J = 8.10$ Hz), 4.56 (1H, m), 4.80 (1H, dd, $J = 8.84$, 8.02 Hz), 4.83 (1H, dd, $J = 9.21$, 8.04 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ −4.96, −4.87 (CH_3), −4.15, −4.05, 4.92, 16.87, 18.18, 18.73, 21.69, 25.86, 26.22, 36.61, 58.91, 61.60, 63.57, 64.56, 65.05, 66.65, 70.53, 72.36, 73.89, 74.35, 75.69, 77.18, 77.23, 101.21, 169.82, 170.52. IR: ν cm^{-1}, 3438, 3055, 2306, 1735, 1422, 1217. MS (ESI): calcd for $C_{32}H_{52}O_9Si_2$+Na, 659.3, found M+Na, 659.5.

4.1.4. Bidensyneoside B

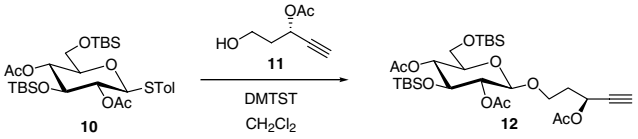


Bidensyneoside B, **3**

To a solution of **9** (38 mg, 0.06 mmol) in 4 mL of THF at 0 °C was added HF·pyridine (0.6 mL) followed by acetic acid (0.45 mL). The mixture was allowed to warm to room temperature, and stirring was continued for 18 h in the absence of light. The mixture was diluted with EtOAc (15 mL) and saturated $NaHCO_3$ (8 mL). The aqueous layer was saturated with NaCl and extracted with EtOAc (5×5 mL). The combined EtOAc extracts were then subjected to rotary evaporation and then high vacuum to remove all traces of solvents. The residue was dissolved in MeOH (2 mL) and transferred into a 5 mL round bottom flask in the absence of light, and stirring was resumed. Next, K_2CO_3 (1 mg, 6 μmol) was added, and the solution was allowed to stir at room temperature for 4 h. Careful TLC analysis with solvent systems consisting of 2.5–5% H_2O indicated a single spot. Approximately half of the MeOH was removed under reduced pressure, and the resulting solution was purified over silica gel (35/5/60) MeOH/H_2O/$CHCl_3$ to give 10.3 mg (53%) of a light brown oil. $[\alpha]_D = -60.2$ (c 0.07, MeOH), ^{1}H NMR (500 MHz, methanol-d_4): δ 1.95 (2H, m), 1.96 (3H, s), 3.15 (1H, dd, $J = 7.88$,

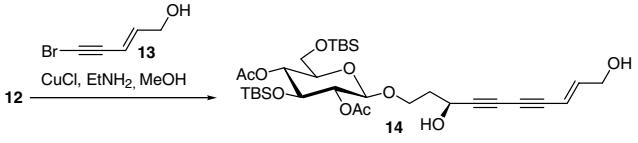
8.97 Hz), 3.25 (1H, m), 3.33 (2H, m), 3.66 (1H, dd, $J = 11.88$, 5.19 Hz), 3.71 (1H, ddd, $J = 10.20$, 6.99, 6.02 Hz), 3.85 (1H, dd, $J = 11.78$, 2.10 Hz), 3.98 (1H, dt, $J = 10.19$, 5.79 Hz), 7.25 (1H, d, $J = 7.80$ Hz), 4.61 (1H, t, $J = 6.96$ Hz). ^{13}C NMR (75 MHz, methanol-d_4): δ 3.75, 38.86, 59.08, 60.01, 62.71, 64.52, 64.87, 66.66, 69.64, 71.60, 75.10, 77.94, 77.99, 78.05, 79.37, 104.59. IR: ν cm^{-1} 3305, 2918, 2218, 2112, 2028, 1641, 1158, 1074. UV/vis: $\lambda_{(max)}$ nm: 308, 288, 270, 255, 241, HRMS: calculated $C_{16}H_{22}O_7$+Na = 347.1107, found 347.1130.

4.1.5. (3′*S*)-3′-Acetoxy-4′-pentyn-1-yl 2,4-*O*-di(acetyl)-3,6-*O*-di(*tert*-butyldimethylsilyl)-β-D-glucopyranoside 12



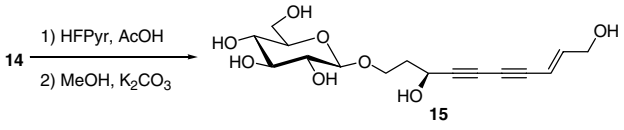
A mixture of **10** (600 mg, 1.0 mmol), (−)-**11** (213 mg, 1.5 mmol), and 2 g of molecular sieves in 15 mL CH_2Cl_2 (distilled over P_2O_5) was allowed to stir for 20 min at room temperature. While the mixture was stirring, dimethyldisulfide (283 mg, 3.0 mmol) and MeOTf (492 mg, 3.0 mmol) were allowed to mix in a separate vial to form a solid. After the solid had fully crystallized, it was dissolved in 3 mL CH_2Cl_2. The mixture of **10** and **11** was cooled to 0 °C, and the DMTST solution was slowly added. The mixture was stirred at 0 °C for 30 min and then allowed to warm to room temperature. TLC analysis indicated the disappearance of **10**. Next, 1.0 mL Et_3N was added to the mixture, which led to a precipitate. The mixture was filtered and diluted with CH_2Cl_2. The organic solution was then washed with satd $NaHCO_3$ solution, brine, and dried over Na_2SO_4. The mixture was filtered, and the solvents removed under reduced pressure. The residue was purified over silica gel (15% EtOAc/Hex) to give 370 mg (61%) a yellow oil. $[\alpha]_D = -26.2$ (c 1.4, MeOH), ^{1}H NMR (300 MHz, CD_3OD): δ 0.03 (3H, s), 0.04 (3H, s), 0.05 (3H, s), 0.06 (3H, s), 0.82 (9H, s), 0.88 (9H, s), 2.08 (3H, s), 2.09 (2H, m), 2.13 (3H, s), 2.47 (1H, d, $J = 2.03$ Hz), 3.40 (1H, ddd, $J = 9.78$, 5.75, 3.73), 3.60 (3H, m), 3.82 (1H, d, $J = 9.08$ Hz), 4.00 (1H, dt, $J = 10.15$, 5.50), 4.33 (1H, d, $J = 8.04$ Hz), 4.83 (1H, dd, $J = 9.84$, 8.90 Hz), 4.87 (1H, dd, $J = 9.22$, 8.09 Hz), 5.35 (1H, dt, $J = 6.27$, 2.12 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ −4.97, −4.86, −4.18, −4.07, 18.16, 18.71, 21.24, 21.53, 21.68, 25.86, 26.09, 34.75, 61.47, 63.64, 65.17, 72.44, 73.49, 74.00, 74.31, 75.72, 81.10, 101.25, 169.76, 169.82.

4.1.6. (3′*S*)-3,6-*O*-Di(*tert*-butyldimethylsilyl)-2,4-*O*-di(acetyl) bidensyneoside C 14



To a mixture of **12** (150 mg, 0.24 mmol), 1 mL of an aqueous $EtNH_2$ solution, 2 mL MeOH, and NH_2OH·HCl (4 mg, 0.06 mmol) at 0 °C was added CuCl (2.4 mg, 0.024 mmol) followed by slow addition of **13** (78 mg, 0.48 mmol). The mixture was allowed to stir until **12** disappeared. Next, the mixture was diluted with a KCN/NH_4Cl solution. The resulting mixture was extracted three times with Et_2O, and the combined extracts were washed with a solution of $NaHCO_3$, brine, and dried over $MgSO_4$. The solvents were removed under reduced pressure, and the residue was purified over silica gel (50% EtOAc/Hex) to give a yellow oil (14 mg, 56%). $[\alpha]_D = +18.0$ (c 1.7, MeOH), ^{1}H NMR (500 MHz, CD_3OD): δ 0.05 (3H, s), 0.06 (3H, s), 0.08 (3H, s), 0.09 (3H, s), 0.83 (3H, s), 0.91 (3H, s), 1.97 (2H, m), 2.09 (3H, s), 2.12 (3H, s), 3.42 (1H, ddd, $J = 9.79$, 6.79, 2.85 Hz), 3.63 (1H, dd, $J = 11.38$, 2.78 Hz), 3.68 (1H, dd, $J = 11.37$, 6.81 Hz), 3.73 (1H, m), 3.84 (1H, t, $J = 9.08$ Hz), 4.04 (1H, ddd, $J = 10.23$, 7.81, 4.26 Hz), 4.26 (2H, dd, $J = 4.68$, 1.74 Hz), 4.35 (1H, d, $J = 8.07$ Hz), 4.69 (1H, t, $J = 6.35$ Hz), 4.83 (1H, dd, $J = 9.58$, 9.36 Hz), 4.88 (1H, dd, $J = 8.90$, 8.38 Hz), 5.83 (1H, d, $J = 15.97$ Hz), 6.43 (1H, dt, $J = 15.91$, 4.81 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ −5.37, −5.30, 4.53, −4.46, 17.18, 18.41, 21.25, 25.46, 25.89, 37.27, 60.02, 62.68, 63.31, 66.27, 69.25, 71.99, 73.05, 73.84, 74.06, 75.33, 76.77, 82.91, 101.09, 108.73, 145.59, 169.46, 169.51. IR: ν cm^{-1} 3504, 3054, 2126, 1752, 1265, 1066. MS (ESI): calculated for $C_{32}H_{54}O_9Si_2$+Na = 677.3, found $C_{32}H_{54}O_9Si_2$+Na = 677.4.

4.1.7. Bidensyneoside C with an inverted chiral center on the side chain 15



A mixture of **14** (270 mg, 0.41 mmol), 5.0 mL HF·pyridine, 4 mL of AcOH, and 35 mL of THF was allowed to stir overnight and was diluted with EtOAc and $NaHCO_3$. The mixture was then saturated with NaCl and extracted five times with EtOAc. The solvents were removed under reduced pressure and the residue purified over silica gel (10% MeOH/$CHCl_3$) yielding 102 mg (58%) of a yellow/brown syrup, which was used in the next step without further identification. To a solution of the residue in 12 mL MeOH was added 1.6 mg of K_2CO_3. The mixture was allowed to stir for 4 h. 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%). $[\alpha]_D = +13$ (c 0.2, MeOH), ^{1}H NMR (500 MHz, methanol-d_4): δ 1.99 (2H, m), 3.19 (1H, dt, $J = 7.80$, 9.10 Hz), 2.39 (2H, m), 3.37 (1H, t, $J = 9.15$ Hz), 3.68 (1H, ddd, $J = 1.38$, 4.17, 11.88 Hz), 3.73 (1H, dt, $J = 5.8$, 10.25 Hz), 3.89 (2H, dd, $J = 1.40$, 11.90 Hz), 4.06 (1H, dt, $J = 6.30$, 10.23 Hz), 4.16 (2H, dd, $J = 2.06$, 4.67 Hz), 4.28 (1H,

d, $J = 7.82$ Hz), 4.68 (1H, t, $J = 4.68$ Hz), 5.83 (1H, dd, $J = 1.92$, 15.97 Hz), 6.42 (1H, dt, $J = 4.68$, 15.97 Hz). ^{13}C NMR (125 MHz, methanol-d_4): δ 38.02, 60.26, 62.63, 62.75, 66.85, 69.57, 71.70, 74.15, 75.10, 77.55, 77.92, 78.06, 84.29, 104.46, 108.58, 148.12. IR: ν cm^{-1} 3490, 3955, 2122, 1373, 1225, 1063; UV/vis: $\lambda_{(max)}$ nm: 282, 265, 254, 241, HRMS: calculated for $C_{16}H_{22}O_8$+Na = 365.1212, found $C_{16}H_{22}O_8$+Na = 365.1211.

Acknowledgments

The authors acknowledge the donors of the Petroleum Research Fund (PRF#40361-AC1) administered by the American Chemical Society. D.S. wishes to thank the NSF-REU program for a summer internship. We also thank Miami University for support in the form of a Shoupp Award.

References

1. Wang, N. L.; Yao, X. S.; Ishii, R.; Kitanaka, S. *Chem. Pharm. Bull.* **2001**, *49*, 938–942.
2. Brandao, M. G. L.; Krettli, A. U.; Soares, L. S. R.; Nery, C. G. C.; Marinuzzi, H. C. *J. Ethnopharm.* **1997**, *57*, 131–138.
3. Christensen, L. P.; Lam, J.; Thomasen, T. *Phytochemistry* **1990**, *29*, 3155–3156.
4. Redl, K.; Breu, W.; Davis, B.; Bauer, R. *Planta Med.* **1994**, *60*, 58–62.
5. Redl, K.; Davis, B.; Bauer, R. *Phytochemistry* **1992**, *32*, 218–220.
6. Bauer, R.; Redl, K.; Davis, B. *Phytochemistry* **1992**, *31*, 2035–2037.
7. Gung, B. W.; Fox, R. M. *Tetrahedron* **2004**, *60*, 9405–9415.
8. Marvell, E. N.; Caple, G.; Schatz, B.; Pippin, W. *Tetrahedron* **1973**, *29*, 3781–3789.
9. Siegel, K.; Bruckner, R. *Synlett* **1999**, 1227–1230.
10. Corey, E. J.; Fuchs, P. L. *Tetrahedron Lett.* **1972**, 3769–3772.
11. Pfueller, U.; Schulze, K.; Muehlstaedt, M. *Z. Chem.* **1978**, *18*, 59–60.
12. Cook, C. L.; Jones, E. R. H.; Whiting, M. C. *J. Chem. Soc., Abstr.* **1952**, 2883–2891.
13. Verkruijsse, H. D.; Brandsma, L. *Synth. Commun.* **1991**, *21*, 141–144.
14. Brandsma, L. *Preparative Acetylenic Chemistry*, 2nd ed.; Elsevier: New York, 1988.
15. Gung, B. W.; Kumi, G. *J. Org. Chem.* **2003**, *68*, 5956–5960.