Notes

Conversion of 5-Deoxypulchelloside I to Caudatoside A[†]

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The iridoid caudatoside A (**2**) was synthesized in seven steps from the naturally occurring iridoid 5-deoxypulchelloside I (**1**) using a straightforward series of protection and deprotection procedures to introduce the requisite C-6 cinnamoyl ester.

Recently, we reported the isolation and structure elucidation of caudatosides A−F, six new iridoids from *Citharexylum caudatum* L., which are C-6 and C-7 phenylpropanoid esters of 5-deoxypulchelloside I (**1**).[1] Many phenylpropanoid esters of iridoids have shown biological activity. For example, the three arbortristosides, phenylpropanoid esters of 6β-hydroxyloganin, from *Nyctanthes arbortristis* have shown leishmanicidal activity,[2] and picroliv, a standardized extract of *Picrorhiza kurroa* containing kutkoside (the 10-cinnamoyl ester of catalpol) and picroside I, has exhibited hepatoprotective activity.[3] The three arbortristosides are nearly identical to caudatosides A−C, differing only in stereochemistry at C-8. Although the leishmanicidal activity of the caudatosides has not yet been determined, the possibility of preparing a series of natural and unnatural derivatives for future work prompted us to develop the methodology necessary to synthesize these esters, as well as other analogues, from **1**.

Synthetic work involving iridoids was recently reviewed.[4] In addition to the syntheses of iridoids themselves, iridoids have been used as chiral starting materials in the syntheses of cyclopentanoid marine diterpenoids,[5] nucleoside analogues,[6] and prostaglandin analogues.[7] Directly related to the current work, Bhaduri et al. reported the semisynthesis of esters of loganin, as well as analogues of loganin and arbortristoside A with a modified glucose moiety in the hope of finding derivatives with antihepatotoxic activity.[8] Unfortunately, the final deprotection step of the synthesized compounds was not accomplished, so the products retained the acetate moieties used as protecting groups.

To develop the methodology for the synthesis of C-6 and C-7 ester derivatives of **1** (Figure 1), we chose to focus on the conversion of **1** into caudatoside A (7-cinnamoyl-5-deoxypulchelloside I, **2**) and caudatoside B (**3**), since this would obviate the need to protect phenolic moieties present in the phenylpropanoid esters of caudatosides C−F. Selective addition of the cinnamoyl ester at C-6 or C-7 of **1** required differential protection of the hydroxyl groups in the glucose and aglucon halves of **1**. To accomplish this differential protection, we took advantage of the fact that the OH-6 and -7 groups in **1** have a *cis*-relationship. While

1 R$_1$ = H; R$_2$ = H

2 R$_1$ = ⟨cinnamoyl⟩ ; R$_2$ = H

3 R$_1$ = H; R$_2$ = ⟨cinnamoyl⟩
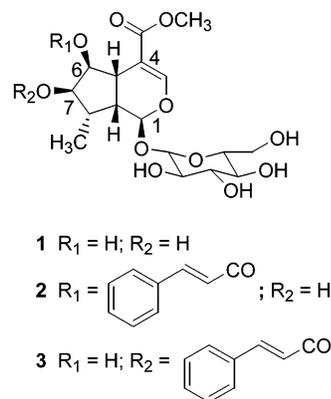
numerous protecting groups exist for protecting *cis*-diols, acetonides are probably the most common. Use of an acetonide in this case was initially of some concern since acidic conditions are used for their removal, and the glucose moieties of iridoids are somewhat susceptible to acid hydrolysis. However, an acetonide has been removed from an iridoid in a previous literature example without removing the glucose,[9] so the acetonide moiety was chosen as the *cis*-diol protecting group because of its ease of formation. When **1** was reacted with 2,2-dimethoxypropane (2,2-DMP) in the presence of acid catalyst, however, a diacetonide (**4**) was formed in 72% yield, as clearly indicated by NMR data (four methyl singlets between δ 1.23 and 1.47). This was not unexpected, since the 4′,6′-diol of the glucose is also known to readily form six-membered acetonides. Since, under the proper conditions, dioxane acetonides can be removed in the presence of dioxolane acetonides,[10] this formation of a diacetonide was not viewed as a problem. Using dilute aqueous acidic (1% HOAc) conditions[9] the glucose acetonide was easily removed to give monoacetonide **5** in 55% yield. The only byproduct formed in this reaction was **1**, and this was by choice. The reaction could be stopped prior to the point where **1** began to form, but this would have required separation by chromatography of three compounds, **1**, **4**, and **5**. By allowing the reaction to proceed until all of **4** had been consumed, the only byproduct was **1**, from which **5** could be removed by extraction with EtOAc.

Protection of the free glucose hydroxyl groups in **5** now required a protecting group that would not be susceptible to the acidic conditions required to remove the remaining
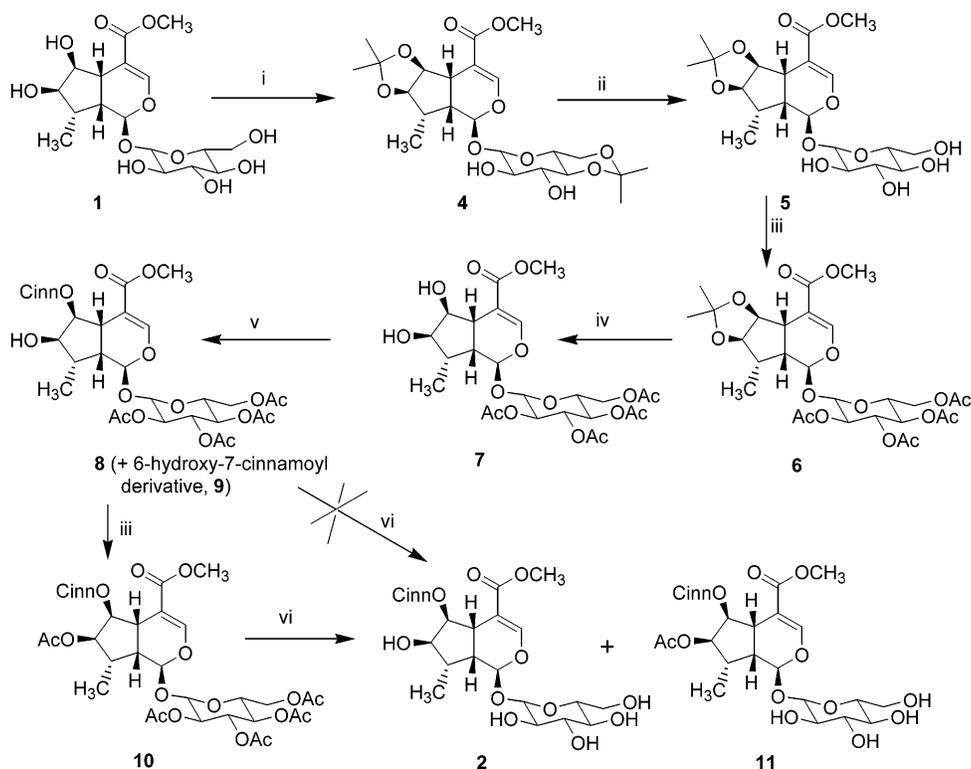

Figure 1. Conversion of 5-deoxypulchelloside I (**1**) to caudatoside A (**2**): (i) 2,2-dimethoxypropane, dry acetone, PPTS, rt, 1 h, 40 °C, 0.5 h; (ii) 1% HOAc, rt, 18 h; (iii) Ac$_2$O, rt, 24 h; (iv) 80% HOAc, rt, 38 h; (v) cinnamoyl chloride, DMAP, 80 °C, 16 h; (vi) 6% NH$_3$−MeOH, rt, 24 h.

acetonide. After consideration of a number of different protecting groups, acetate was chosen as the protecting group because of its acid stability (needed for removal of the remaining acetonide), the mild conditions required for reaction, and the generally high yield of the reactions. Accordingly, **5** was smoothly converted under standard conditions in 92% yield to monoacetonide tetraacetate **6**.

The next step was to remove the remaining acetonide of **6** to release the C-6 and C-7 hydroxyl moieties. In searching for a method that would not result in hydrolysis of the protected glucose group, the use of acidic ion-exchange resin was attempted. While the product was formed, the reaction was very slow and numerous side products were also formed. Consequently, standard acetonide removal conditions were used, treating **6** with 80% HOAc to remove the acetonide and produce **7** in 72% yield.

Tetraacetate **7** was acylated with cinnamoyl chloride in pyridine with DMAP as an additional catalyst to give a mixture of the 6-cinnamoyl tetraacetate (**8**) and the 7-cinnamoyl tetraacetate (**9**), in an approximate ratio of 1:2. This mixture was separated by preparative TLC to give a 26% yield of **8** and a 44% yield of **9**. On a larger scale, the mixture would be carried on through the next steps and the isomers separated in the final step, which would likely increase the overall yield of this method.

Before attempting the final deprotection of the acetates of **8**, the deprotection reaction was attempted on a model compound. Caudatoside A pentaacetate (**10**), prepared from caudatoside A during the isolation and structure elucidation work,[1] was used as the model for the removal of the acetates in the presence of the cinnamoyl group. Several methods have been successfully used for the removal of acetate in the presence of benzoate,[11] but no general method for acetate removal in the presence of a cinnamoyl moiety was found. Since relatively mild conditions would be required, two separate methods, the use of dilute NH$_3$

in MeOH[12] and guanidine in MeOH,[11f] were investigated for the deprotection of **10**. In both cases, the two major products were the desired caudatoside A (**2**) and caudatoside A 7-acetate (**11**), as well as a small amount of **1**.

Since tetraacetate **8** did not contain an acetate at the 7-position, it was thought that this method would be applicable to **8**, giving only the desired **2**. However, when the reaction was carried out on **8** with dilute NH$_3$−MeOH or with guanidine, only starting material **8** and **1** were present in the reaction mixture. Presumably, the presence of the free hydroxyl group at C-7 promotes hydrolysis of the 6-cinnamoyl ester. Consequently, tetraacetate **8** was converted to pentaacetate **10** in 94% yield, and the acetate groups were removed with dilute NH$_3$−MeOH to give the mixture of **2** and **11**. Preparative TLC of this mixture gave caudatoside A (**2**) in 51% yield, 3.3% overall from **1**.

This work demonstrated that the synthesis of caudatoside A (**2**) and other C-6 or C-7 ester derivatives from 5-deoxypulchelloside I (**1**) was relatively straightforward. The only major complication with this method was that the acetate at O-7 in **10** was not as labile as the glucose acetates, likely due to steric factors. This scheme produced caudatoside A from 5-deoxypulchelloside I in seven steps, with an overall yield of 3.3%. While this yield is low, this method creates both caudatoside A and caudatoside B from the same intermediates. If the caudatoside B tetraacetate (**8**) had been carried through the last two steps, assuming similar yields for the last two steps as for caudatoside A, then caudatoside B (**3**) would have been produced in approximately 5.5% yield. The overall yield, therefore, for caudatosides A and B would be approximately 8.8%. In addition, in the removal of the glucose acetonide from **6**, the major byproduct is 5-deoxypulchelloside I, which can be recycled. This method should be directly applicable to the synthesis of the other caudatosides, as well as analogues, from **1**.

Experimental Section

General Experimental Procedures. ^{1}H NMR spectra were obtained on either a Varian Mercury 300 MHz spectrometer equipped with a Sun Microsystems Ultra 5 processor and VNMR version 5.1b software or a Varian Inova 400 MHz spectrometer with a Sun Microsystems Ultra 1 processor and VNMR version 5.1c software. Mass spectra were obtained in the positive-ion mode on a Micromass (Beverly, MA) quadrupole time-of-flight (Q-ToF2) mass spectrometer with a modified dual micro-electrospray source for internal calibration. Solvents were reagent grade and used as purchased. 5-Deoxypulchelloside I (**1**) was isolated from *C. caudatum* as previously described.[1]

6,7:4′,6′-Di-*O*-isopropylidene 5-Deoxypulchelloside I (4). To **1** (8.13 g, 20 mmol) in dry acetone (170 mL) were added 2,2-dimethoxypropane (50 mL, 0.4 mol) and PPTS (10.18 g, 40 mmol). Sonication at room temperature for 1 h was followed by stirring for 30 min at 40 °C, then triethylamine (9 mL, 65 mmol) was added and the reaction mixture concentrated. The oily, pale yellow residue was suspended in water (50 mL) and extracted three times with $CHCl_3$ (16 mL each). The combined $CHCl_3$ layers were extracted twice with 1 N HCl, once with 5% aqueous $NaHCO_3$, and finally once with saturated NaCl. The $CHCl_3$ layer was dried over Na_2SO_4, filtered, and evaporated to yield **2** (7.05 g, 72%) as a hygroscopic foam: ^{1}H NMR (acetone-d_6, 300 MHz) δ 7.31 (1H, d, J = 1.8 Hz, H-3), 5.51 (1H, d, J = 1.2 Hz, H-1), 4.71 (1H, d, J = 7.8 Hz, H-1′), 4.66 (1H, d, J = 5.4 Hz, H-6), 4.25 (1H, d, J = 5.4 Hz, H-7), 3.84 (1H, dd, J = 5.7, 10.8 Hz, H-6′a), 3.68 (3H, s, $-CO_2CH_3$), 3.24−3.77 (5H, glucose protons), 2.83 (1H, m, H-5), 2.80 (1H, m, H-9), 2.39 (1H, m, H-8), 1.47, 1.39, 1.32, 1.23 (12H, s, isopropylidene $-CH_3$'s), 0.96 (3H, d, J = 7.5 Hz, H-10); ESMS m/z 509 [M + Na$^+$].

6,7-*O*-Isopropylidene 5-Deoxypulchelloside I (5). To **4** (6.60 g, 13.6 mmol) was added 1% aqueous acetic acid (200 mL). The reaction mixture was stirred at room temperature for 18 h, at which time no more starting material could be detected by TLC (CH_2Cl_2−MeOH, 13:2, R_f 0.51 and 0.28 for diacetonide and monoacetonide, respectively). The reaction was halted by addition of triethylamine (5 mL). Solid NaCl was added to the mixture while stirring until the solution was saturated. The reaction mixture was then extracted four times with ethyl acetate, and the combined ethyl acetate layers were dried over Na_2SO_4, filtered, and evaporated to yield **5** as a white solid (3.32 g, 55%): ^{1}H NMR (acetone-d_6, 300 MHz) δ 7.33 (1H, d, J = 1.8 Hz, H-3), 5.64 (1H, d, J = 1.5 Hz, H-1), 4.66 (2H, m, H-6, H-1′), 4.26 (1H, d, J = 5.4 Hz, H-7), 3.86 (1H, dd, J = 11.7, 2.1 Hz, H-6′a), 3.68 (3H, s, $-CO_2CH_3$), 3.63 (1H, dd, J = 11.7, 5.7, H-6′b), 3.30−3.45 (3H, m, H-3′, H-4′, H-5′), 3.21 (1H, dd, J = 8.1, 8.1 Hz, H-2′), 2.84 (1H, m, H-5), 2.80 (1H, m, H-9), 2.38 (1H, m, H-8), 1.40, 1.24 (6H, s, isopropylidene $-CH_3$'s), 0.96 (3H, d, J = 7.8 Hz, H-10); ESMS m/z 469 [M + Na$^+$], 447 [M + H$^+$].

6,7-*O*-Isopropylidene 5-Deoxypulchelloside I Tetraacetate (6). Compound **5** (2.44 g, 5.5 mmol) was treated with Ac_2O (10 mL) and pyridine (10 mL) at room temperature for 24 h. The reaction mixture was suspended in 10 mL of H_2O and then subsequently extracted three times with $CHCl_3$ (10 mL each). The combined $CHCl_3$ layers were extracted twice with 1 N HCl (50 mL each), once with 5% $NaHCO_3$ (50 mL), and once with saturated NaCl (50 mL). The $CHCl_3$ layer was dried over Na_2SO_4, filtered, and evaporated to yield **6** as a tan solid (3.09 g, 92%): ^{1}H NMR (CDCl$_3$, 300 MHz) δ 7.23 (1H, d, J = 1.2 Hz, H-3), 5.34 (1H, d, J = <0.6 Hz, H-1), 5.13 (1H, dd, J = 9.6, 9.6 Hz, H-3′), 5.02 (1H, dd, J = 9.6, 9.6 Hz, H-4′), 4.89 (1H, dd, J = 9.6, 7.8 Hz, H-2′), 4.81 (1H, d, J = 7.8 Hz, H-1′), 4.54 (1H, dd, J = 5.4, <0.6 Hz, H-6), 4.16−4.24 (2H, m, H-7, H-6′b), 4.07 (1H, dd, J = 12.3, 2.1 Hz, H-6′a), 3.66−3.70 (4H, m, H-5′, $-CO_2CH_3$), 2.88 (1H, ddd, J = 9.0, 8.7, <0.6 Hz, H-9), 2.76 (1H, ddd, J = 9.0, 1.2, <0.6 Hz, H-5), 2.37 (1H, ddd, J = 9.3, 8.7, 7.8, H-8), 2.02, 1.95, 1.92, 1.80 (12H, s, acetate $-CH_3$'s), 1.38, 1.20 (6H, s, isopropylidene $-CH_3$'s), 0.87 (3H, d, J = 7.8 Hz, H-10); ESMS m/z 637 [M + Na$^+$].

5-Deoxypulchelloside I Tetraacetate (7). Compound **6** (2.98 g, 4.85 mmol) was treated with 70 mL of 80% AcOH in water for 38 h, at which time no more starting material could be detected by TLC. The reaction mixture was neutralized by addition of concentrated NH_4OH. The aqueous mixture was extracted three times with EtOAc (40 mL each). The combined EtOAc layers were washed with 1 N HCl (three times, 30 mL each), 5% $NaHCO_3$ (once, 30 mL), and saturated NaCl (once, 30 mL). The EtOAc layer was dried over Na_2SO_4, filtered, and evaporated to yield **7** as a tan solid (2.01 g, 72%): ^{1}H NMR (CDCl$_3$, 400 MHz) δ 7.34 (1H, d, J = <0.6 Hz, H-3), 5.28 (1H, d, J = 2.4 Hz, H-1), 5.21 (1H, dd, J = 9.6, 9.6 Hz, H-3′), 5.10 (1H, dd, J = 9.6, 9.6 Hz, H-4′), 4.96 (1H, dd, J = 9.6, 8.0 Hz, H-2′), 4.84 (1H, d, J = 8.0 Hz, H-1′), 4.26 (1H, dd, J = 12.4, 4.0 Hz, H-6′b), 4.15 (1H, dd, J = 12.4, 2.0 Hz, H-6′a), 3.93 (1H, dd, J = 4.0, 4.0 Hz, H-6), 3.83 (1H, dd, J = 4.0, 2.8 Hz, H-7), 3.75 (3H, s, $-CO_2CH_3$), 3.71 (1H, ddd, J = 9.6, 4.0, 3.2 Hz, H-5′), 3.00 (1H, ddd, J = 10.8, 7.6, 2.4 Hz, H-9), 2.72 (1H, ddd, J = 10.8, 4.8, <0.6 Hz, H-5), 2.36 (1H, qdd, J = 7.6, 7.6, 2.8 Hz, H-8), 2.09, 2.02, 2.00, 1.92 (12H, s, acetate $-CH_3$'s), 0.93 (3H, d, J = 7.6 Hz, H-10); ESMS m/z 597 [M + Na$^+$].

Caudatoside A Tetraacetate (8) and Caudatoside B Tetraacetate (9). To **7** (22 mg, 38 μmol) in 250 μL of pyridine and 175 μL of CH_2Cl_2 were added cinnamoyl chloride (41 mg, 0.25 mmol) and a catalytic amount of DMAP. The reaction was heated in a tightly capped reaction vial to 80 °C for 16 h with stirring. After cooling to room temperature, the reaction mixture was suspended in 5 mL of water and extracted three times with $CHCl_3$ (5 mL each). The combined $CHCl_3$ layers were washed twice with 1 N HCl (5 mL each), once with 5% $NaHCO_3$ (5 mL), and once with saturated NaCl (5 mL). The $CHCl_3$ layer was dried over Na_2SO_4 and the solvent concentrated to ∼100 μL. The product mixture was then applied to a silica gel preparative TLC plate and developed with 97:3 CH_2Cl_2−MeOH. The bands were scraped from the plate and desorbed twice with 4:1 CH_2Cl_2−MeOH to yield **8** (low R_f band, 7 mg, 26%) and **9** (high R_f band, 12 mg, 44%): ^{1}H NMR (CDCl$_3$, 400 MHz): **8**: δ 7.73 (1H, d, J = 16.0 Hz, H-β), 7.54−7.56 (2H, m, H-2′′, H-6′′), 7.40−7.41 (3H, m, H-3′′, H-4′′, H-5′′), 6.48 (1H, d, J = 16.0 Hz, H-α), 5.41 (1H, m, H-6), 5.40 (1H, d, J = 1.6 Hz, H-1), 5.21 (1H, dd, J = 9.6, 9.6 Hz, H-3′), 5.10 (1H, dd, J = 9.6, 9.6 Hz, H-4′), 4.97 (1H, dd, J = 9.6, 8.0 Hz, H-2′), 4.83 (1H, d, J = 8.0 Hz, H-1′), 4.29 (1H, dd, J = 12.4, 4.4 Hz, H-6′b), 4.17 (1H, dd, J = 12.4, 2.0 Hz, H-6′a), 3.84 (1H, dd, J = 8.0, 4.4 Hz, H-7), 3.71−3.75 (4H, m, H-5′, $-CO_2CH_3$), 3.06 (1H, dd, J = 9.6, <0.4 Hz, H-5), 2.98 (1H, ddd, J = 9.6, 9.6, 1.6 Hz, H-9), 2.35 (1H, ddd, J = 9.6, 8.0, 7.2 Hz, H-8), 2.11, 2.03, 2.00, 1.90 (12H, s, acetate $-CH_3$'s), 1.12 (3H, d, J = 7.2 Hz, H-10); ESMS m/z 727 [M + Na$^+$], 705 [M + H$^+$]; **9**: δ 7.72 (1H, d, J = 16.0 Hz, H-β), 7.53−7.55 (2H, m, H-2′′, H-6′′), 7.38−7.40 (3H, m, H-3′′, H-4′′, H-5′′), 6.50 (1H, d, J = 16.0 Hz, H-α), 5.32 (1H, d, J = 2.4 Hz, H-1), 5.22 (1H, dd, J = 9.6, 9.6 Hz, H-3′), 5.11 (1H, dd, J = 9.6, 9.6 Hz, H-4′), 5.02−4.97 (2H, m, H-7, H-2′), 4.86 (1H, d, J = 8.0 Hz, H-1′), 4.24−4.31 (2H, m, H-6, H-6′b), 4.15 (1H, dd, J = 12.4, 2.0 Hz, H-6′a), 3.68−3.75 (4H, m, H-5′, $-CO_2CH_3$), 2.88−2.99 (2H, m, H-5, H-9), 2.59 (1H, m, H-8), 2.09, 2.03, 2.01, 1.94 (12H, s, acetate $-CH_3$'s), 1.07 (3H, d, J = 7.2 Hz, H-10).

Caudatoside A Pentaacetate (10). To **8** (4 mg, 5.6 μmol) were added 0.5 mL of pyridine and 0.5 mL of acetic anhydride. The reaction mixture was stirred at room temperature for 24 h. The reaction mixture was then suspended in 10 mL of H_2O and subsequently extracted three times with $CHCl_3$ (10 mL each). The combined $CHCl_3$ layers were extracted twice with 1 N HCl (10 mL each), once with 5% $NaHCO_3$ (10 mL), and finally once with saturated NaCl (10 mL). Each $CHCl_3$ layer was dried over Na_2SO_4, filtered, and evaporated to yield **10** (4 mg, 94%). ^{1}H NMR data for **10** were identical to data previously reported.[1]

Caudatoside A (2). To **10** (11 mg, 0.015 mmol) was added 0.5 mL of dry methanol with stirring at room temperature. Then, 30 μL of concentrated NH_4OH was added to the mixture and was allowed to stir for 24 h. The reaction mixture was neutralized with acetic acid and separated by silica gel preparative TLC (9:1 CH_2Cl_2−MeOH). The band corresponding

to R_f 0.14 was scraped and desorbed with 4:1 CH_2Cl_2−MeOH to yield **2** (4 mg, 51%). ^{1}H NMR data were identical to data previously obtained for **2**.[1]

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