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# A Facile and Convergent Synthesis of Sarmentosin

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## ABSTRACT

A concise synthesis of sarmentosin (**1**) starting from butane-1,2,4-triol-1,2-acetonide is described. This convergent route can also be employed for the preparation of sarmentosin analogues for structure-activity relationship studies.

*Key Words:* Sarmentosin; Synthesis; Glycosylation.

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## INTRODUCTION

Sarmentosin (**1**) is the active principle isolated from the folk medicine, *Sedum Sarmentosum* Bunge, which is used for treatment of hepatitis in China.[1] Clinical trials showed that sarmentosin had a significant effect on lowering serum glutamate-pyruvate transaminase (SGPT) level of patients suffering from chronic virus hepatitis.[2] It was later found that sarmentosin also had immunomodulating activity.[3]

The cyano-ethylene β-glucoside structure of **1** was elucidated by spectral and chemical methods.[2] It is know that cyanogenic glycosides are readily hydrolyzed in aqueous media, so sarmentosin is chemically rather unstable. The content of sarmentosin in plant varies greatly with the growing region and the collecting season. Although the structure of sarmentosin seems rather simple, the reports on the synthesis of sarmentosin and its analogues are limited due to the instability of the aglycon. We have previously reported the first synthesis of sarmentosin.[4] The aglycon instability problem was avoided by attaching the glucose component first to the precursor of aglycon and then converting intermediate **2** to sarmentosin by functional group transformations (Fig. 1a). The overall yield of sarmentosin obtained by this method was low. In addition, we supposed that the aglycon was the pharmacophoric group of sarmentosin. Thus, it is desirable to develop a convergent synthetic approach to this target molecule, and we can also utilize it to prepare analogues for further structure-activity relationship studies. Herein, we report a new synthesis of sarmentosin, in which the protected aglycon **3** was successfully prepared, and **3** was then condensed with a glycosyl donor to give the target compound (Fig. 1b).

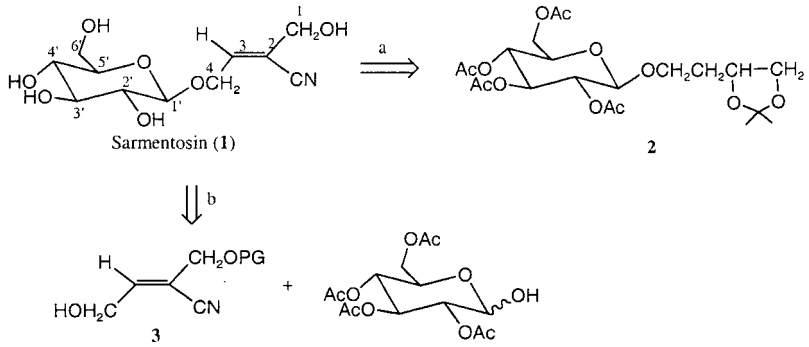



***Figure 1.*** Retrosynthetic analysis of sarmentosin.

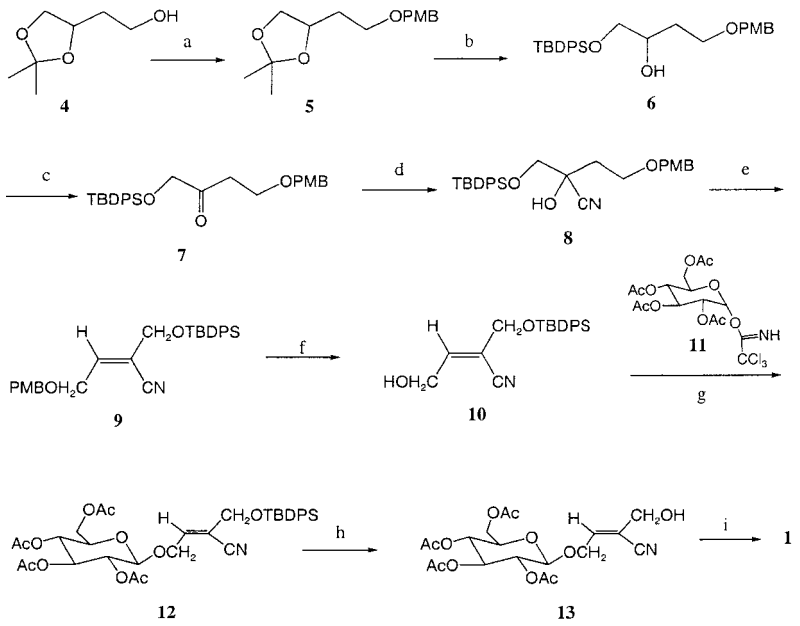
## RESULTS AND DISCUSSION

Our synthesis started from butane-1,2,4-triol-1,2-acetonide (**4**), which was easily prepared from commercially available malic acid in 2 steps.[5] Alcohol **4** was first protected as *p*-methoxy benzyl (PMB) ether **5**. Ketal hydrolysis of acetonide **5** followed by selective protection of the primary alcohol with *t*-butyldiphenylsilyl chloride (TBDPSCl) afforded **6**. The secondary alcohol in **6** was oxidized with Dess-Martin periodinane to give keone **7**. Conversion of **7** into cyanohydrin **8** by treatment with acetone cyanohydrin in the presence of $Et_3N$, followed by dehydration with thionyl chloride in pyridine yielded the desired *E*-olefin **9** as a single isomer. PMB protecting group in **9** was removed by DDQ to give the protected aglycon **10** in 90% yield. Glycosylation between **10** and the trichloroacetimidate **11**[6,7] in the presence of 1.2 equiv. of boron trifluoride etherate furnished the desired β-D-glucoside **12** stereoselectively. The TBDPS group in **12** was removed with TBAF-HOAc to afford **13** in 81% yield. Finally, deacetylation of **13** with MeOH–$Et_3N$–$H_2O$ (8:1:1) led to sarmentosin in 72% yield (Sch. 1).

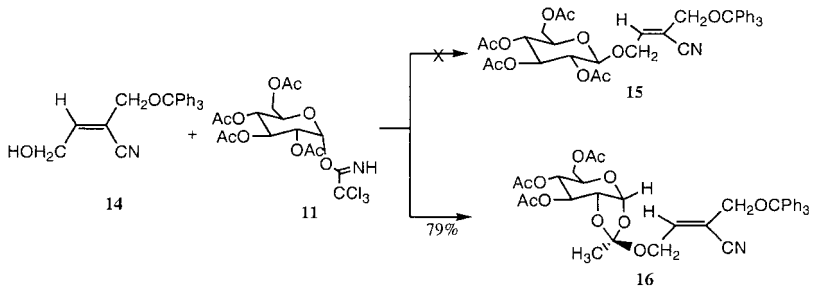
Selection of protecting groups for C1 and C4 hydroxy groups in **9** was critical to the success of this synthetic route. Initially we tried to use acetyl or TBDPS group to protect 4-hydroxy. However, all attempts to remove these protecting groups failed because of the instability of the aglycon. Considering that the aglycon is very sensitive to acids and bases, we finally chose PMB as the protecting group, which was easily removed under neutral condition by DDQ oxidation to give the key intermediate **10** in 90% yield.

For protection of 1-hydroxy group, the bulky trityl was used at the beginning for the *E*-selectivity of the dehydration step. However, glycosylation between **14** and **11** under Schmidt condition[8] afforded only the orthoester **16.** No desired product **15** was obtained (Sch. 2).

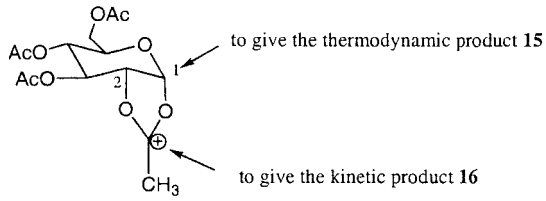
The glycosylation involved an acetoxonium intermediate **17**[9] which was formed via the C2 neighboring group participation (Fig. 2). Either the glycosyl acceptor could attack C1 to give the desired β-glucoside or attack the oxonium to give the orthoester. In the case mentioned above, the bulky aglycon **14** could only attack from the less steric hindrance face to obtain the kinetic product **16** (Fig. 2). To solve this problem, excess Lewis acid could be added to make the orthoester rearranged to the more stable thermodynamic product **15**. Therefore, 1.0 equiv. of Lewis acid was used. However, a complex mixture was obtained because the trityl group could not survive under this condition. TBDPS group was then chosen as 1-hydroxy protecting group for its stability under strong Lewis acid condition. This bulky group



***Scheme 1.*** Reagents and conditions: (a) $PMBC(=NH)CCl_3$, CSA (cat.), $CH_2Cl_2$, rt, 12 h, 91%; (b) i) TsOH, MeOH, rt, 2h; ii) TBDPSCl, imidazole, $CH_2Cl_2$, rt, 30 min, 87%; (c) Dess-Martin periodinane, pyridine, $CH_2Cl_2$, rt, 10 h, 89%; (d) acetone cyanohydrin, $Et_3N$, MeOH, rt, 2 h; (e) $SOCl_2$, pyridine, 0°C, 2 h, rt, 4 d, 32%; (f) DDQ, $CHCl_3$, $H_2O$, rt, 2 h, 90%; (g) Boron trifluoride etherate (1.2 equiv.), molecular sieve (4 Å), $CH_2Cl_2$, −20°C, 1 h, 54%; (h) TBAF, AcOH, THF, rt, 30 min, 81% (i) $Et_3N$, MeOH, $H_2O$, rt, 5 h, 72%.



***Scheme 2.*** Reagents and conditions: $Me_3SiOTf$ (0.1 equiv.), molecular sieve (4 Å), $CH_2Cl_2$, −40°C, 10 min.




**17**

***Figure 2.***

also played an important role in controlling the olefin configuration in dehydration of cyanohydrin **8**.

This convergent synthetic approach to sarmentosin has proved to be more facile for the preparation of various analogues of sarmentosin.

## EXPERIMENTAL

### General Procedures

Melting points were measured on a Büchi 510 apparatus and were uncorrected. Elemental analyses were performed on a Carlo-Erba 1106 instrument. Infrared spectra were obtained on a Nicolet Magna 750 spectrometer. NMR spectra were measured on Bruker AMX-400 or Gemini-300 MHz spectrometers for $^1$H and 100 or 75 MHz spectrometers for $^{13}$C, respectively, with tetramethylsilane as internal standard. Chemical shifts are reported in $\delta$ (ppm) and coupling constants in Hz. Specific rotations were measured on a Perkin-Elmer 241 MC. Mass spectra were determined on a Varian MAT-711 mass spectrometer.

**4-[2-(4-Methoxy-benzyloxy)ethyl]-2,2-dimethyl-[1,3]dioxolane (5).** To a stirred solution of butane-1,2,4-triol-1,2-acetonide (**4**) (4.10 g, 28.1 mmol) in $CH_2Cl_2$ (60 mL) was added *p*-methoxybenzyl trichloroacetimidate (8.60 mL, 41.2 mmol) and a catalytic amount of camphorsulfonic acid (0.37 g). After stirring for 12 h at room temperature, the reaction mixture was diluted with ether (300 mL), washed with saturated aqueous $NaHCO_3$, water and brine and dried. Concentration followed by purification of the residue by column chromatography on silica gel (petroleum ether:ether, 15:1) afforded **5** (6.83 g, 91%) as a colorless oil. IR ($\nu$, cm$^{-1}$, film): 1612, 1514, 1369, 1302, 1248, 1094. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 7.24 (2H, d, $J = 8.5$ Hz), 6.86 (2H, d, $J = 8.5$ Hz), 4.41 (2H, s), 4.19 (1H, m), 4.03 (1H, m), 3.79 (3H, s), 3.53 (3H, m), 1.88 (2H, m), 1.38 (3H, s),

1.34 (3H, s). EI-MS (*m*/*z*): 266 ($M^+$, 1), 251 (1), 199 (12), 135 (24), 121 (100). Anal. calcd. $C_{15}H_{22}O_4$: C, 67.65; H, 8.33. Found: C, 67.37; H, 8.41.

**1-(*tert*-Butyldiphenylsilyloxy)-4-(4-methoxy-benzyloxy)-butan-2-ol (6).** To a solution of acetonide **5** (1.00 g, 3.76 mmol) in methanol (15 mL) was added *p*-toluenesulfonic acid monohydrate (0.075 g, 0.40 mmol). The mixture was stirred at room temperature for 2 h, before $NaHCO_3$ (0.04 g) was added. The solution was concentrated and ethyl acetate was added to the residue. The mixture was filtered and the filtrate concentrated. The crude diol thus obtained was dissolved in $CH_2Cl_2$ (25 mL). To the solution was added imidazole (0.56 g, 8.4 mmol) and *tert*-butylchlorodiphenylsilane (1.10 mL, 4.26 mmol) at 0°C. The mixture was stirred at 0°C for 30 min and then diluted with ether (75 mL), washed with water (10 mL) and dried. After concentration, the residue was purified by flash chromatography on silica gel (petroleum ether:-ethyl acetate, 12:1) to give **6** (1.51 g, 87% for two steps) as a colorless oil. IR ($\nu$, $cm^{-1}$, film): 3481, 1612, 1587, 1514, 1427, 1248, 1113. $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 7.3–7.7 (10H, m), 7.20 (2H, d, $J = 8.5$ Hz), 6.84 (2H, d, $J = 8.5$ Hz), 4.41 (2H, s), 3.89 (1H, m), 3.78 (3H, s), 3.58 (4H, m), 1.74 (2H, m), 1.04 (9H, s). EI-MS (*m*/*z*): 199 (50), 149 (60), 121 (100). Anal. calcd. $C_{28}H_{36}O_4Si$: C, 72.38; H, 7.81. Found: C, 72.14; H, 7.94.

**1-(*tert*-Butyldiphenylsilyloxy)-4-(4-methoxy-benzyloxy)-butan-2-one (7).** To a stirred solution of alcohol **6** (1.41 g, 3.04 mmol) in $CH_2Cl_2$ (30 mL) was added pyridine (1.9 mL) and Dess-Martin periodinane (1.65 g, 3.89 mmol). After stirring at room temperature for 10 h, ether (150 mL), saturated aqueous $NaHCO_3$ solution (30 mL) and saturated aqueous $Na_2S_2O_3$ solution was added successively to the reaction mixture. The organic layer was separated. The aqueous phase was extracted with ether. The combined organic layers were washed with brine, dried and concentrated. The residue was purified by column chromatography on silica gel (petroleum ether:ethyl acetate, 12:1) to give **7** (1.25 g, 89%) as a colorless oil. IR ($\nu$, $cm^{-1}$, film): 1736, 1612, 1514, 1427, 1248, 1113, 1036. $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 7.3–7.7 (10H, m), 7.22 (2H, d, $J = 8.5$ Hz), 6.84 (2H, d, $J = 8.5$ Hz), 4.39 (2H, s), 4.18 (2H, s), 3.78 (3H, s), 3.69 (3H, t, $J = 6.3$ Hz), 2.78 (3H, t, $J = 6.3$ Hz), 1.07 (9H, s). EI-MS (*m*/*z*): 405 ($M^+ - 57$, 3), 327 (3), 199 (17), 121 (100). Anal. calcd. $C_{28}H_{34}O_4Si$: C, 72.69; H, 7.41. Found: C, 72.37; H, 7.53.

**(*E*)-1-(*tert*-Butyldiphenylsilyloxymethyl)-4-(4-methoxy-benzyloxy)-2-butenenitrile (9).** To a solution of ketone **7** (1.17 g, 2.53 mmol) in methanol (35 mL) was added triethyl amine (0.49 mL, 3.55 mmol) and acetone cyanohydrin (1.7 mL, 18 mmol). The reaction mixture was stirred at

room temperature for 2 h and then concentrated in vacuo. The crude cyanohydrin **8** was dissolved in pyridine (15 mL). Thionyl chloride (0.41 mL, 5.6 mmol) was added to this solution at 0°C. The reaction mixture was stirred at 0°C for 2 h and then at room temperature for 4 days. The mixture was diluted with ethyl acetate and washed with water, saturated aqueous $CuSO_4$ solution, water and brine successively. The organic layer was dried and concentrated. The residue was purified by column chromatography on silica gel (petroleum ether:ethyl acetate, 20:1 to 15:1) to give the olefin **9** (0.38 g, 32% for two steps) as a colorless oil. IR ($\nu$, $cm^{-1}$, film): 2222, 1612, 1514, 1427, 1250, 1113. $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 7.3–7.7 (10H, m), 7.24 (2H, d, $J = 8.5$ Hz), 6.88 (2H, d, $J = 8.5$ Hz), 6.55 (1H, t, $J = 6.3$ Hz), 4.45 (2H, s), 4.28 (2H, d, $J = 6.3$ Hz), 4.22 (2H, d, $J = 1.6$ Hz), 3.78 (3H, s), 1.08 (9H, s). Anal. calcd. $C_{29}H_{33}NO_3Si$: C, 73.85; H, 7.05; N, 2.97. Found: C, 73.38; H, 7.09; N, 2.49.

**(*E*)-1-(*tert*-Butyldiphenylsilyloxymethyl)-4-hydroxy-2-butenenitrile (10).** To a solution of PMB ether **9** (0.220 g, 0.467 mmol) in $CHCl_3$ (20 mL) and water (1 mL) was added DDQ (0.310 g, 1.37 mmol). After stirred at room temperature for 2 h, the reaction mixture was diluted with ethyl acetate (120 mL) and washed with water, 0.5% aqueous $NaHCO_3$ solution, water and brine successively. The organic layer was dried and concentrated. The residue was purified by column chromatography on silica gel (petroleum ether:ethyl acetate, 8:1) to give **10** (0.148 g, 90%) as a colorless oil. The aglycon **10** was not stable and was carried forward to the next step immediately. $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 7.3–7.7 (10H, m), 6.53 (1H, t, $J = 6.3$ Hz), 4.43 (2H, d, $J = 6.3$ Hz), 4.23 (2H, d, $J = 1.5$ Hz), 1.08 (9H, s).

**(*E*)-1-(*tert*-Butyldiphenylsilyloxy)-2-cyano-4-β-D-tetraacetylglucopyranosyloxy-2-butene (12).** A suspension of the aglycon **10** (141 mg, 0.40 mmol), the glycosyl donor trichloroacetimidate **11** (390 mg, 0.79 mmol) and 4 Å molecular sieve (1.2 g) in $CH_2Cl_2$ (3 mL) was stirred at room temperature for 30 min. The reaction mixture was cooled to −20°C, and boron trifluoride etherate (0.060 mL, 0.48 mmol) was added dropwise. After stirred at −20°C for 1 h, the reaction was quenched by triethyl amine (2 drops). The reaction mixture was filtered, and the filtrate was concentrated in vacuo. The residue was purified by column chromatography on silica gel (petroleum ether:ethyl acetate, 4:1) to give **12** (147 mg, 54%) as a colorless oil. $[\alpha]_D^{20}$ −4.2 (c 0.59, $CHCl_3$). IR ($\nu$, $cm^{-1}$, film): 2234, 1757, 1429, 1367, 1223, 1051. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 7.3–7.7 (10H, m), 6.50 (1H, t, $J = 6.3$ Hz), 5.17 (1H, t, $J = 9.5$ Hz), 5.07 (1H, t, $J = 9.8$ Hz), 5.00 (1H, dd, $J = 9.1$, 8.0 Hz), 4.45–4.55 (3H, m), 4.20–4.30 (3H, m), 4.13 (1H, dd, $J = 12.4$, 1.5 Hz), 3.70 (1H, m), 2.06

(3H, s), 2.01 (3H, s), 2.00 (3H, s), 1.99 (3H, s), 1.06 (9H, s). FAB-MS (*m*/*z*): 681 ($M^+$+1, 78), 656 (6), 625 (8), 604 (11), 185 (100), 133 (54).

**(*E*)-2-cyano-4-β-D-tetraacetylglucopyranosyloxy-2-buten-1-ol (13).** To a solution of TBDPS ether **12** (95 mg, 0.14 mmol) in THF (3 mL) was added acetic acid (0.040 mL) and *tert*-butyl ammonium fluoride (90 mg, 0.28 mmol). The reaction mixture was stirred at room temperature for 30 min. Saturated aqueous $NH_4Cl$ solution (10 mL) was added. The reaction mixture was extracted with ether. The combined organic layers were washed with brine, dried, and concentrated. The residue was purified by column chromatography on silica gel (petroleum ether:ether 1:10) to give **13** (50 mg, 81%) as a white solid. M.p. 90–92$^+$C; $[\alpha]_D^{20}$ −4.8 (c 0.74, $CHCl_3$); IR ($\nu$, $cm^{-1}$, KBr): 3500, 2220, 1763, 1379, 1252, 1213, 1045. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 6.54 (1H, t, $J$ = 6.3 Hz), 5.20 (1H, t, $J$ = 9.5 Hz), 5.08 (1H, t, $J$ = 9.5 Hz), 4.98 (1H, dd, $J$ = 9.4, 8.0 Hz), 4.57 (1H, $d$ = 7.8 Hz), 4.52 (2H, $d$ = 6.5 Hz), 4.32 (1H, dd, $J$ = 12.4, 2.3 Hz), 4.24 (2H, s), 4.14 (1H, dd, $J$ = 12.4, 4.1 Hz), 3.69 (1H, m), 2.10 (3H, s), 2.05 (3H, s), 2.02 (3H, s), 2.00 (3H, s). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 171.0, 170.2, 169.4 × 2, 142.6, 116.8, 115.3, 100.8, 72.7, 72.2, 71.1, 68.2, 67.6, 62.5, 61.4, 20.8, 20.7, 20.5 × 2. EI-MS (*m*/*z*): 443 ($M^+$), 383 (4), 346 (7), 323 (6), 243 (23), 200 (37), 169 (38), 157 (78), 145 (55), 140 (45), 115 (100), 98 (83). Anal. calcd. $C_{19}H_{25}NO_{11}$: C, 51.46; H, 5.68; N, 3.16. Found: C, 51.30; H, 5.66; N, 3.14.

## Sarmentosin (1)

A solution of compound **13** (40 mg, 0.09 mmol) in a mixture of MeOH-$Et_3N$-$H_2O$ (8:1:1, 5 mL) was stirred at room temperature for 5 h. After evaporation of the solvent in vacuo, toluene was added to the residue and removed again in vacuo. This process was repeated several times to remove water. The residue was purified by column chromatography on silica gel ($CHCl_3$:MeOH, 8:3) to give sarmentosin (**1**) (18 mg, 72%) as a syrup. $[\alpha]_D^{20}$ −18.3 (c 0.91, MeOH). IR ($\nu$, $cm^{-1}$, film): 3540–3240, 2227, 1643, 1100, 1076, 1050. $^1$H NMR (400 MHz, $D_2O$): $\delta$ 6.70 (1H, t, $J$ = 6.4 Hz), 4.5–4.7 (2H, m), 4.49 (1H, t, $J$ = 7.9 Hz), 4.24 (2H, s), 3.90 (1H, dd, $J$ = 12.4, 1.9 Hz), 3.71 (1H, dd, $J$ = 12.4, 5.4 Hz), 3.25–3.52 (4H, m). $^{13}$C NMR (100 MHz, $D_2O$): $\delta$ 145.3, 118.0, 117.6, 103.2, 77.4, 77.1, 74.4, 70.9, 68.6, 63.0, 62.0. FAB-MS (*m*/*z*): 276 ($M^+$+1, 10), 207 (17), 185 (62), 93 (100). The above data are consistent with those of the authentic natural sample reported in the literature.[1,2,4]

## ACKNOWLEDGMENTS

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