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The Total Synthesis of Sarmentosin, a Potent GPT Lowering Agent

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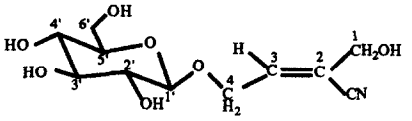
Abstract: The first total synthesis of sarmentosin (**1**), a potent GPT lowering agent was accomplished from compound **2** via a reaction sequence of 8 steps in an overall yield of 5.8%.

Sarmentosin (**1**) was isolated in 1978 by Fang et al[1] from the whole herb of Sedum sarmentosum Bunge which belongs to the family Crassulaceae. The herb is widely distributed in China and used for the treatment of hepatitis in folk medicine. Clinical trials showed that the herb had a significant effect in lowering the level of serum glutamic-pyruvic transaminase of the patients suffering from chronic virus hepatitis. Later on, sarmentosin was proved to be responsible for this effect.[1,2] It is a water soluble syrupy substance and the structure was elucidated by chemical and spectral methods, and assigned as 2-cyano-4-O-β-D-glucopyranosyl-trans-buten-2-ol (**1**), which was further confirmed by X-ray diffraction of its crystalline pentaacetate.[2]

Although the structure of **1** seems to be rather simple, there is still no report in the literature about the synthesis of sarmentosin. In this communication we report the first total synthesis of sarmentosin (**1**). Butane-1,2,4-triol-1,2-acetonide (**2**) was used as a starting material, from which the target molecule **1** was obtained through a reaction sequence of 8 steps in an overall yield of 5.8%.

Compound **2** could be prepared easily from commercially available butane-1,2,4-triol in one step.[3] Condensation of **2** with α-D- glucopyranosyl bromide tetraacetate in the presence of silver (I) oxide and molecular sieves 4Å gave the desired β-glucoside **3** (85%) and a small amount of the α-anomer (<10%). Cleavage of the acetonide **3** by MeOH/TsOH at room temperature afforded the diol **4** (65%). Selective protection of diol **4** as trityl ether (Ph_3CCl/Et_3N/DMAP/ CH_2Cl_2, reflux, 89.4%) followed by oxidation of the resulting secondary alcohol **5** with 4.5 equiv. of PCC in the presence of NaOAc gave ketone **6** (78.3%). Then **6** was treated with acetone cyanohydrin in a methanol solution of sodium bicarbonate to give cyanohydrin **7** (70.7%), which was subjected to dehydration with thionyl chloride in pyridine at room temperature for 3 days, yielding the expected E-olefin **8**[4,5] (40.2%) as the only isomer. Selective cleavage of the trityl ether of **8** with

TMSI (1.2equiv. TMSI in $CHCl_3$, N_2, r.t., 5 min.) yielded the allylic alcohol **9**[4,6] (70.9%), and subsequent deacetylation of **9** with MeOH-Et_3N-H_2O (8:1:1)[7] (74.2%) led to sarmentosin (**1**).[4,8] The UV, MS, ^1H NMR and ^{13}C NMR data[9] of the synthetic product are identical with the data of the natural sarmentosin reported in the literature.[1,2]



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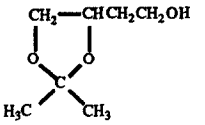

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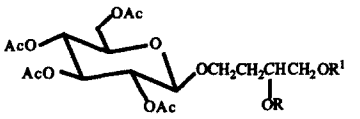
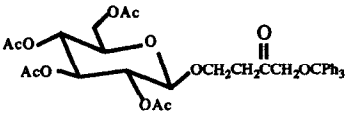


3: $R,R^1=CMe_2$
4: $R=R^1=H$
5: $R=H$, $R^1=CPh_3$



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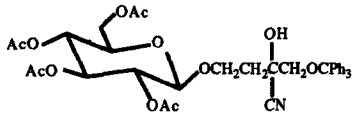

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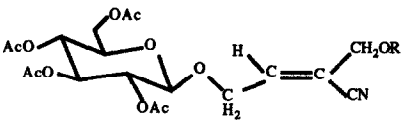

8: $R=CPh_3$
9: $R=H$

References and Notes:

1. Fang,S.D.; Yan,X.Q.; Li,J.F.; Fan,Z.Y.; Xu,X.Y.; Xu,R.S. *Kexue Tongbao* **1979**, 431.
2. Fang,S.D.; Yan,X.Q.; Li,J.F.; Fan,Z.Y.; Xu,X.Y.; Xu,R.S.*Acta Chimica Sinica* **1982**,40, 273.
3. Mori,K.; Takigawa,T.; Matsuo,T. *Tetrahedron* **1979**,35,938.
4. E-configuration of the double bond in compounds **8, 9** and **1** was assigned by NOE difference spectroscopy experiments. Irridiation at C-3 proton of **8, 9** and **1** produced 3.3%, 3.75% and 5.6% enhancement of the proton at C-1 respectively and vice versa.
5. Spectroscopic data for **8:** foam; $[\alpha]_D^{11}$-9.59°(c 0.089,$CHCl_3$); IR(KBr) ν 2950,2860,2218,1755,1608, 1490, 1448,1370,1225,1040–1090cm^{-1}; ^1H NMR(400MHz,$CDCl_3$) δ 1.99,2.01,2.04(12H,3s,1:2:1, 4xOAc), 3.70(1H,m,5'-H),3.74(2H,s,1-H),4.12(1H,dd,J=12.5,2Hz,6'-H),4.26(1H,dd,J=12.5,4.7Hz, 6'-H),4.48-4.54(3H,m,4,1'-H),4.99-5.19(3H,m,2',3',4'-H),6.50(1H,br t,J=6.4Hz,3-H),7.30-7.41 (15H,m,ar.-H)ppm; MS(m/z) 331,259,243,169,165.
6. Spectroscopic data for **9**: mp 79-81°C; $[\alpha]_D^{29}$-6.98°(c 0.153,$CHCl_3$); IR(KBr) ν 3490,2940,2880,2220, 1750,1645,1430,1375,1250,1215,1086,1045cm^{-1}; ^1H NMR(400MHz,$CDCl_3$) δ 1.70(1H, br s, OH),1.99, 2.02,2.04, 2.09(12H,4s,4xOAc),3.68(1H,m,5'-H),4.11(1H,dd,J=12.4,4.2Hz,6'-H),4.24(2H,br s,1-H), 4.34(1H,dd,J=12.4,2.3Hz,6'-H),4.51(2H,m,4-H),4.55(1H,d,J=8Hz,1'-H),4.97(1H,dd,J=9.4,8Hz, 2'-H),5.07,5.18(2H,2t,J=9.4Hz,3',4'-H),6.53(1H,br t,J=6.4Hz,3-H)ppm; MS(m/z) 443(m^+),383, 370,347,331,221,208,200,169,157,145,140; **9** gave satisfactory elemental analysis.
7. Lubineau,A.;Queneau,Y. *J.Org.Chem.* **1987**,52,1002.
8. $[\alpha]_D$ value of **1:** $[\alpha]_D^{30.5}$-17.96°(c 2.16,MeOH); Lit.[1,2]: $[\alpha]_D^{30}$-17.4°(c 0.62,H_2O).
9. IR(KBr) of synthetic sarmentosin: 3540-3240,2920,2870,2220,1640,1370,1280, 1030-1110cm^{-1}; IR of natural one[1,2]: 3540-3240,2235,1640,1110,1085,1055cm^{-1}.