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Synthesis and Absolute Configuration of Chaboside, First Natural Gluco-camptothecin

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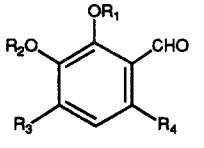
Key words: Chaboside, Gluco-camptothecin, Total synthesis, Absolute configuration, Ophiorrhiza spp., Rubiaceae

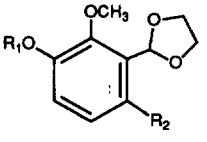
Abstract: *Chaboside, first natural glucosidic camptothecin, was synthesized enantioselectivelly to clarify the absolute configuration. The corresponding aglycone was also synthesized.*

Chaboside (**1**) was isolated in this laboratory from a Rubiaceous plant, *Ophiorrhiza pumila* Champ.[1] The structural studies by spectroscopical methods lead us to propose the structure 9-methoxy-10- O-(β-D-gucosyloxy)-camptothecin. This compound was the first glycosidic congener of camptothecin and also the first member of camptothcinoids possessing two oxygen functions on the A ring. To confirm the proposed structure and to determine the absolute configuration at the chiral center C-20 enantioselective total synthesis was undertaken.

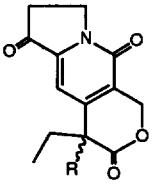
First, the aglycone of chaboside, 9-methoxy-10-hydroxycamptothecin (**2**) in racemic form was synthesized. A general synthetic plan which was initially developed by Shanghai research groups[2] and afterward brushed up by Wall *et al* .[3] was employed. A-ring part was synthesized as follows. 2,3-Dihydroxy benzaldehyde (**3**) which was derived from o-vanillin (**4**) was O-methylated specifically at 2-position by using each one molar equivalent of NaH and MeI to give **5**.[4] Nitration (c-HNO_3, toluene, -78° ~ -20°C) gave 4-



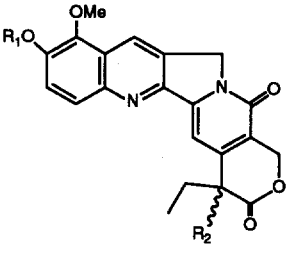
	R_1	R_2	R_3	R_4
(**3**)	H	H	H	H
(**4**)	H	CH_3	H	H
(**5**)	CH_3	H	H	H
(**6**)	CH_3	H	NO_2	H
(**7**)	CH_3	H	H	NO_2
(**9**)	CH_3	Bn	H	NO_2
(**15**)	CH_3	β-D-Glc(Ac)$_4$	H	NO_2
(**16**)	CH_3	β-D-Glc(Ac)$_4$	H	NH_2
(**17**)	CH_3	β-D-Glc	H	NH_2



	R_1	R_2
(**8**)	CH_3	NO_2
(**10**)	Bn	NO_2
(**11**)	Bn	NH_2



(**12**) R=H
(**18**) R= OH



	R_1	R_2
(**1**)	β-D-Glc	OH
(**2**)	H	OH
(**13**)	Bn	H
(**14**)	Bn	OH

nitro- (**6**) and 6-nitro (**7**) derivatives with the same yields of 36%. The fact that the latter isomer (**7**) was the objective 6-nitro derivative was proved through its conversion to 2,3-dimethoxy-6-nitrobenzaldehyde ethyleneketal (**8**), which was prepared from o-vanillin through a different sequence of reactions.[5] 4-O-Benzyl ether (**9**) was converted to **10**, which was subsequently reduced (Na_2S, EtOH, Δ) to **11**. Condensation of **11** with tricyclic ketone (**12**)[3] (TsOH, toluene, Δ, Y. 32%) followed by oxidation ($CuCl_2$, O_2, DMF, H_2O, Me_2NH, Δ) of the resultant quinoline (**13**) afforded **14** (40%). Removal of the protective group from **14** gave the expected (*dl*)-9-methoxy-10-hydroxycamptothecin.[6] This compound was identified in all respects excepting optical property with chaboside aglycone (**2**) which was obtained from **1** through hydrolysis with dilute sulfuric acid.

Then with the purpose of determining the absolute configuration of chaboside (**1**) synthesis in an enantioselective manner was carried out. The A-ring component (**16**) with O-β-D-glucosyl group at the proper position was prepared through glycosidation of the above nitrobenzaldehyde (**7**) with acetobromoglucose. Catalytic reduction of the resultant **15** in the presence of PtO_2 gave the corresponding anthranyl aldehyde (**16**), which was then deacetylated to **17**. Recently Tagawa *et al.*, Daiichi Pharmaceutical Industry, reported chiral induction by use of D-proline leading to synthesis of chiral tricyclic component (**18**) corresponding to CDE ring.[7] The same compound was synthesized and was condensed with the above A-ring component (**17**) (AcOH, MeOH, Δ, Y. 45%). The resultant material (**1**) was shown to be identical with the natural chaboside in all respects including CD spectrum. Thus the absolute configuration at C-20 of chaboside was proved to be *S*, the same configuration as camptothecin.

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6) Amorphous pale yellow powder. UV λ_{max} (EtOH) nm; 223, 271, 295, 330, and 386. ^{1}H-NMR (500MHz) δ (DMSO-d_6); 0.88 (3H,t, J=7.4 Hz, 18-H_3), 1.84 (1H, q, J= 6.8 Hz, H-19), 1.89 (1H, q, J= 7.1 Hz, H-19), 3.94 (3H, s, O-CH_3), 5.26 (2H, s, 5-H_2), 5.39 (1H, d, J=16.0 Hz, H-17), 5.43 (1H, d, J= 16.0 Hz, H-17), 6.50 (1H, s, 20-OH),7.27 (1H, s, H-14), 7.54 (1H, d, J= 9.1 Hz, H-11), 7.84 (1H, d, J= 9.1 Hz, H-12), 8.66 (1H, s, H-7), and 10.18 (1H, s, 10-OH).

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