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First Synthesis of Hunterioside, a Novel Disaccharide Carrying Monoterpenoid Indole Alkaloid, by Assembly of Three Components, Tryptamine, Secologanin, and a Newly-Developed Glucosyl Donor.

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A bstract: The novel structure of hunterioside, the first example of monoterpenoid indole alkaloids carrying a disaccharide, was confirmed by chemical synthesis starting from tryptamine, secologanin, and a newly-developed gulucosyl donor, which selectively gives α -gluco type glycosidic linkage in the reaction with a secologanin derivative. © 1999 Elsevier Science Ltd. All rights reserved.

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Over 1400 naturally occurring monoterpenoid indole alkaloids have been isolated up to this date.¹ Among them, more than thirty glycosidic indole alkaloids related to strictosidine 1 are known.² Recently we found a new type of indole alkaloids, hunterioside 2^3 and hunterioside B 3,⁴ from a Thai medicinal plant, *Hunteria zeylanica*, which were the first examples of a disaccharide-carrying monoterpenoid indole alkaloid. Very recently, new tetrahydroisoquinoline-monoterpene glycosides with disaccharide moiety were found in *Alangium* plant.⁵ The structure elucidation by spectroscopic analysis revealed that 2 is constructed by tryptamine, secologanic acid 4, and one glucose unit. To establish the structure unambiguously, we planned the synthesis of hunterioside 2 by assembly of those three units. In this paper, we describe the development of a new glucosyl donor 14, which gives an α -gluco type glycosidic linkage in the reaction with a secologanin derivative, and its utilization for the first synthesis of 2.



Figure 1

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As mentioned above, hunterioside 2 is composed of tryptamine, secologanic acid and one glucose. Initially, a secologanin derivative 9, which acts as a glycosyl acceptor, was prepared as follows (Scheme 1). The primary alcohol on the 6' position in the glucose moiety of secologanin 5 was selectively protected with *t*-butyldiphenylsilyl (TBDPS) chloride in the presence of *N*, *N*-dimethylaminopyridine (DMAP) in DMF, followed by acetylation with acetic anhydride and pyridine to give the triacetate 7. In the ¹H-NMR spectrum of 7, the signals due to H-2', -3', and -4' were observed at around δ 5.1-5.3, while those of H-6' were resonated at δ 3.75 (2H, d, *J*=3.6 Hz), revealing that the TBDPS group was actually introduced on the 6' position. Next, the C-7 aldehyde in 7 was masked as an ethylene acetal.⁶ Deprotection of the TBDPS ether in 8 with tetra *n*-butylammonium fluoride in the presence of acetic acid in THF regenerated the primary alcohol in 76% yield.

The next task was the introduction of the second glucose onto the 6'-alcohol in 9 in a stereoselective manner. We initially applied the conventional glycosidation procedure using a combination of acetobromoglucose and silver perchlorate, resulting in the formation of β -gluco type glycosidic linkage. Further attempts at the glycosidation of the secologanin derivative 9 with tetrabenzylglucose trichloroacetoimidate⁷ using many kinds of Lewis acids afforded the α and β mixture of the C1" position. This prompted us to develop a new glucosyl donor providing the α -glucosidic linkage selectively. Generally, the protecting group on the 2-hydroxyl group of a glycosyl donor is necessary to be an ether-type to obtain the desired α -gluco type glycosidic linkage.⁸ We selected the *t*-butyldimethylsilyl (TBS) group as the protecting group on the C2 hydroxyl and the trichloroimidate as the leaving group at the C1 position in glucose. Preparation of a new glycosyl donor 14° is shown in Scheme 2.





4; $R^{1}=R^{2}=R^{4}=H$, $R^{3}=O$, Secologanic acid i ζ 5; $R^{1}=R^{2}=H$, $R^{3}=O$, $R^{4}=Me$, Secologanin ii ζ 6; $R^{1}=TBDPS$, $R^{2}=H$, $R^{3}=O$, $R^{4}=Me$ iii ζ 7; $R^{1}=TBDPS$, $R^{2}=Ac$, $R^{3}=O$, $R^{4}=Me$ iii ζ 8; $R^{1}=TBDPS$, $R^{2}=Ac$, $R^{3}=OCH_{2}CH_{2}O$, $R^{4}=Me$

Reagents and Conditions: i; TBDPSCI, DMAP, DMF, rt (72%). ii; Ac₂O, Py, CH₂Cl₂ (83%). iii; ethylene glycol, Amberlite IR 120B (H⁺), Na₂SO₄, CH₃CN, 5°C (76%). iv; TBAF (5 eq), AcOH (5 eq), THF, 0°C (82%).

Scheme 1



Scheme 2

Treatment of glucose pentaacetate 10 with piperidine gave β -piperidinoglucoside 11.¹⁰ Protection of the resulting free hydroxyl group at the C2 position with TBS chloride gave silvl ether 12. Hydrolysis of aminoacetal with acetic acid gave the corresponding hemiacetal 13 as a C1 epimeric mixture. Treatment of 13 with trichloroacetonitrile and potassium carbonate⁷ gave the trichloroacetoimidate 14 as a mixture of anomers (α : β =2:1), but, when diazabicycloundecene (DBU)¹¹ was used as a base, the α : β ratio was improved to be ca. 20:1 (α : β).

Next, glycosidation of 9 using the newly-developed donor 14 was carried out in the presence of a Lewis acid. After several attempts, we found that trityl perchlorate¹² was an efficient activator for trichloroacetoimidate 14 in the glycosidation. The desired disaccharide 15 was obtained in 82% yield when the reaction was carried out in CH_2Cl_2/Et_2O (1:1). It is noteworthy that only α -glucoside linkage was formed in this reaction, which was demonstrated by the appearance of a new anomeric proton (C1"-H) having a small J value with 3.6Hz (doublet, $\delta 4.78$ ppm). The bulkiness of the TBS group would control the stereochemical course of the reaction. Thus, it is considered that the steric hindrance of the TBS group decreases the reactivity of the oxonium intermediate, resulting in the formation of the stable α -glycosidic linkage predominantly. Deprotection of the ethylene acetal and TBS group in 15 with aqueous acetic acid, followed by hydrolysis of the acetyl and methyl ester groups with potassium carbonate gave the acetal compounds 17 in 86% yield.

Finally, the acetal compounds 17 were condensed with an excess of tryptamine in 10% aqueous acetic acid at room temperature to furnish compound 2 in 24% yield.¹³ The thus- obtained compound was completely identical with authentic natural hunterioside 2 in their FAB-mass, ¹H- and ¹³C-NMR, UV, and CD spectra. Now the complete structure of 2, including the absolute configuration has been established.





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- Spectral data of 14 (α-form); MS (FAB, NBA) m/z (%): 588 ([M+Na+2]⁺, 0.5), 586 ([M+Na]⁺, 0.5), 564 ([M+H]⁺, 0.4), 488 (15), 403 (28), 283 (100), 197 (43); HRMS (FAB, NBA+NaCl): m/z 586.0810 calcd for C₂₀H₃₂O₉NCl₃SiNa. Found; 586.0801; ¹H-NMR (400MHz, CDCl₃) δ: 8.67 (1H, s, NH), 6.38 (1H, d, J=3.6, H1), 3.99 (1H, dd, J=9.5, 3.7, H2), 5.43 (1H, dd, J=9.5, 9.5, H3), 5.09 (1H, dd, J=9.5, 9.5, H4), 4.20 (1H, ddd, J=10.5, 4.4, 2.0, H5), 4.09 (1H, d, J=12.4, 2.0, H6), 4.28 (1H, dd, J=12.4, 4.4, H6), 2.07 (3H, OAc), 2.04 (3H, OAc), 2.04 (3H, OAc), 0.82 (9H, *t*Bu), 0.09 (3H, SiMe), 0.08 (3H, SiMe); ¹³C-NMR (CDCl₃) δ: 170.58 (COCH₃), 170.04 (COCH₃), 169.75 (COCH₃), 161.26 (C=NH), 98.35 (C1), 68.54 (C2), 71.43 (C3), 75.62 (C4), 72.08 (C5), 61.75 (C6), 25.57 (*C*(CH₃)₃), 21.06 (COCH₃), 20.69 (COCH₃), 20.64 (COCH₃), 17.84 (C(CH₃)₃), -4.51 (SiCH₃), -4.51 (SiCH₃); IR (CHCl₃) v: 1750, 1230, 1040, 750 cm⁻¹.
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