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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.

Osamu Ohmori, Hiromitsu Takayama, and Norio Aimi*

Research Center of Medicinal Resources, Faculty of Pharmaceutical Sciences, Chiba University, 1-33, Yayoi-cho, Inage-ku, Chiba 263-8522, Japan.

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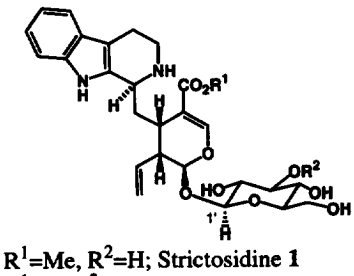
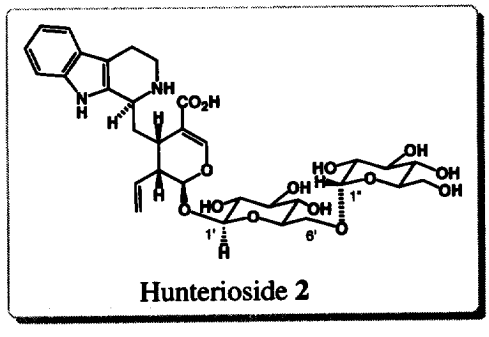
Abstract: The novel structure of hunterioside, the first example of monoterpenoid indole alkaloids carrying a disaccharide, was confirmed by chemical synthesis starting from tryptamine, secologanin, and a newly-developed gulucosyl donor, which selectively gives α-gluco type glycosidic linkage in the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

Keywords: alkaloids; indole; glycoside; glycosidation.

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**.



R^1=Me, R^2=H; Strictosidine **1**
R^1=H, R^2=α-D-Glc; Hunterioside B **3**



Hunterioside **2**

Figure 1

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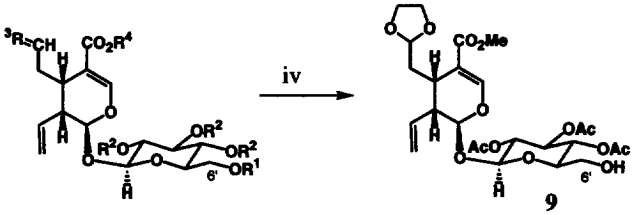
As mentioned above, hunterioside **2** is composed of tryptamine, secologanic acid and one glucose. Initially, a secologanin derivative **9**, which acts as a glycosyl acceptor, was prepared as follows (Scheme 1). The primary alcohol on the 6' position in the glucose moiety of secologanin **5** was selectively 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 ^{1}H-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.

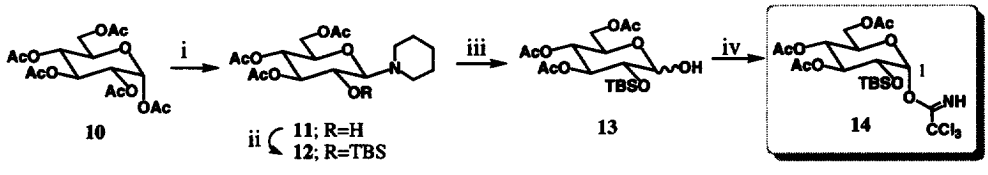
The next task was the introduction of the second glucose onto the 6'-alcohol in **9** in a stereoselective manner. We initially applied the conventional glycosidation procedure using a combination of acetobromoglucose and silver perchlorate, resulting in the formation of β-gluco type glycosidic linkage. Further attempts at the glycosidation of the secologanin derivative **9** with tetrabenzylglucose trichloroacetoimidate[7] 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**[9] is shown in Scheme 2.



4; R^1=R^2=R^4=H, R^3=O, Secologanic acid
i (**5**; R^1=R^2=H, R^3=O, R^4=Me, Secologanin
ii (**6**; R^1=TBDPS, R^2=H, R^3=O, R^4=Me
iii (**7**; R^1=TBDPS, R^2=Ac, R^3=O, R^4=Me
8; R^1=TBDPS, R^2=Ac, R^3=OCH_2CH_2O, R^4=Me

Reagents and Conditions: i; TBDPSCl, DMAP, DMF, rt (72%). ii; Ac_2O, Py, CH_2Cl_2 (83%). iii; ethylene glycol, Amberlite IR 120B (H^+), Na_2SO_4, CH_3CN, 5°C (76%). iv; TBAF (5 eq), AcOH (5 eq), THF, 0°C (82%).

Scheme 1



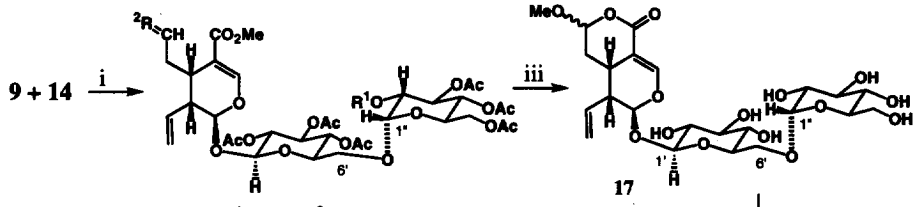
Reagents and Conditions: i; piperidine (3 eq), Et_2O (25%). ii; TBSCl, imidazole, DMF, rt (97%). iii; AcOH, H_2O, acetone, Δ (85%). iv; CCl_3CN, DBU, CH_2Cl_2 (84%).

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 silyl 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 carbonate[7] 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 perchlorate[12] 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, δ 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 ^{13}C-NMR, UV, and CD spectra. Now the complete structure of **2**, including the absolute configuration has been established.



Reagents and Conditions: i; $TrClO_4$ (20mol%), CH_2Cl_2/Et_2O (1:1) (82%). ii; $AcOH/H_2O$ (2:1), Δ (81%). iii; K_2CO_3, MeOH (86%). iv; tryptamine, $AcOH/H_2O$ (9:1) (24%).

Scheme 3

Acknowledgment

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9 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 $C_{20}H_{32}O_9NCl_3SiNa$. Found; 586.0801; ^{1}H-NMR (400MHz, $CDCl_3$) δ: 8.67 (1H, s, N*H*), 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, Si*Me*), 0.08 (3H, Si*Me*); ^{13}C-NMR ($CDCl_3$) δ: 170.58 (*C*OCH_3), 170.04 (*C*OCH_3), 169.75 (*C*OCH_3), 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*$(CH_3)_3$), 21.06 ($COCH_3$), 20.69 ($COCH_3$), 20.64 ($COCH_3$), 17.84 (C(*C*$H_3)_3$), -4.51 (Si*C*H_3), -4.51 (Si*C*H_3); IR ($CHCl_3$) ν: 1750, 1230, 1040, 750 cm^{-1}.

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13 The C-3 epimer of **2** could not be obtained owing to the difficulty of the purification of the H3-β isomer from the mixture including the unreacted tryptamine.