First Synthesis of Neoalangiside, a New Tetrahydroisoquinoline-monoterpene Glucoside with Oxygen Functions at Unusual C1, C2 Positions

Osamu OHMORI, Hiromitsu TAKAYAMA, Mariko KITAJIMA, and Norio AIMI*

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

Received July 15, 1999; accepted August 29, 1999

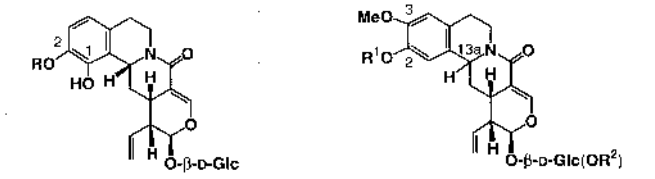
The novel structure of neoalangiside, a new tetrahydroisoquinoline-monoterpene glucoside carrying oxygen functions at the unusual C1 and C2 positions, was confirmed by chemical synthesis starting from isovanillin and secologanin.

Key words neoalangiside; synthesis; tetrahydroisoquinoline; glucoside; secologanin; *Alangium lamarckii*

Recently, Tanahashi and his co-workers reported the discovery of new types of tetrahydroisoquinoline-monoterpene glucoside, neoalangiside (**1**) and demethylneoalangiside (**2**), from *Alangium lamarckii* (Alangiaceae),[1] which has been used as a medicinal plant in Asian countries. A structural feature of these alkaloids is an unusually substituted pattern on the benzene ring of the isoquinoline moiety.[2] The usual monoterpenoid isoquinoline alkaloids,[3] represented by alangiside (**3**),[4] have a 2,3-dioxygenated isoquinoline nucleus, while **1** and **2** have oxygen functions at the unusual C1 and C2 positions. Taking the biosynthetic and chemical reaction course into account, production of both the 2,3- and 1,2-dioxygenated tetrahydroisoquinoline alkaloids by the Pictet-Spengler cyclization of dopamine and secologanin (**13**) seems to be reasonable. However, the unambiguous structure of this new type of alkaloids has not yet been determined by chemical synthesis. In this communication, we describe the first synthesis of **1** starting from isovanillin (**6**) and **13**.

We initially prepared the phenethylamine derivative (**12**) from **6** as follows. It is known that the Pictet-Spengler reaction of dopamine-type phenethylamine gives the 2,3-disubstituted tetrahydroisoquinoline derivative.[5] To prevent this reaction course, the C6 position in the dopamine derivative was masked by an appropriate substituent such as bromide. This strategy[6] has been adopted in the synthesis of the benzylisoquinoline alkaloid petaline.[7] First, direct bromination of **6** was attempted, but the undesired 2-bromoisovanillin was produced as the main product. Then, *O*-benzylisovanillin (**7**)[8] was halogenated with bromine in DMF to yield the 6-bromo derivative (**8**)[9] in 79% yield. The substituted position was confirmed by the ^{1}H-NMR spectrum (δ 7.48 and 7.06, each 1H, singlet). Debenzylation of **8** with trimethylsilyl chloride and NaI in CH_2Cl_2 gave the corresponding phenol (**9**) in 85% yield, which was then subjected to nitroaldol condensation[10] to afford the *trans*-nitrostylene derivative (**10**) (δ 8.09 and 6.73, each 1H, d, J=13.5 Hz) in 79% yield. Next, we protected the phenolic function in **10** with a trityl ether, because direct $LiAlH_4$ reduction of **10** gave the amphoteric primary amine derivative. The masked phenol derivative (**11**) was reduced with $LiAlH_4$ in THF/Et_2O to give the phenethylamine derivative (**12**).

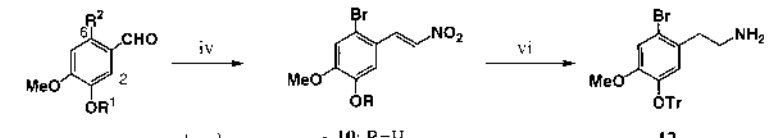
The amine thus obtained (**12**) was treated with secologanin acetate (**14**), which was prepared by acetylation of secologanin (**13**) isolated from *Lonicera morrowii*[11] in the presence of acetic acid in refluxing methanol. From the reaction mixture, the desired tetracyclic compound (**15**)[12] was isolated in 31% yield by column chromatography. The formation of **15** could be explained by Pictet-Spengler cyclization and subsequent lactam (C-ring) formation. The trityl group on the phenol in **12** was simultaneously removed during the Pictet-Spengler reaction under acidic conditions. The stereochemistry at C13a was deduced from the following spectroscopic evidence. We have reported that acetylated compounds such as methylisoalangiside tetraacetate (**5**), which has the H13a-α (C13a *S*) configuration in this class of alkaloids, showed one abnormally highly shifted acetyl signal in the ^{1}H-NMR spectrum due to the anisotropic effect of the aromatic ring.[13,5] However, compound **15** did not exhibit such an acetyl signal, indicating that the configuration at C13a should be of the *R* (H13a-β) form. Furthermore, comparison of the ^{13}C-NMR data supported the above conclusion. Thus the chemical shift at C6 and C12a in methylalangiside tetraacetate (**4**),[14] which has the H13a-β configu-



Neoalangiside (**1**): R=Me
Demethylneoalangiside (**2**): R=H

Alangiside (**3**): H13a (β), R¹=R²=H
4: H13a (β), R¹=Me, R²=Ac
5: H13a (α), R¹=Me, R²=Ac

Fig. 1



i Isovanillin (**6**): R¹=R²=H
ii **7**: R¹=Bn, R²=H
iii **8**: R¹=Bn, R²=Br
iii **9**: R¹=H, R²=Br

v **10**: R=H
11: R=Tr (trityl)

12

Reagents and Conditions: i: BnCl, K_2CO_3, DMF, 50°C, quant. ii: Br_2, DMF (79%). iii: TMSCl, NaI, CH_2Cl_2 (66%). iv: CH_3NO_2, CH_3NH_3Cl (7mol%), Na_2CO_3 (7mol%), (79%). v: TrCl, Et_3N, CH_2Cl_2 (94%). vi: $LiAlH_4$, THF, Et_2O (30%).

Chart 1

* To whom correspondence should be addressed.

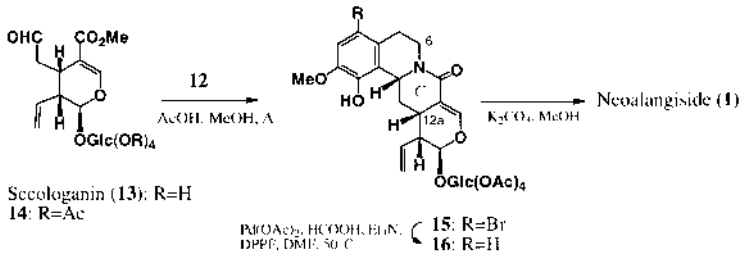


Chart 2

ration, was observed at δ 39.1 and 27.1, respectively, while in methylisoalangiside tetraacetate (**5**),[14] which has the H13a-α configuration, they resonated at δ 42.3 and 23.4, respectively. In the case of compound **15**, these signals were observed at δ 38.4 and 27.3.

Reductive debromination of **15** was achieved in 54% yield using the procedure of Cacchi (a catalytic amount of palladium acetate, formic acid, triethylamine, and DPPF [1,1-bis-diphenylphosphino-ferrocene], DMF, 50 °C).[15] The aromatic protons in **16** were observed at δ 6.73 and 6.62 (each 1H, d, J=8.3 Hz). Finally, hydrolysis of **16** with potassium carbonate in MeOH produced the deacetylated compound, which was completely identical to the natural neoalangiside (**1**) in their FAB-Mass and ^{1}H- and ^{13}C-NMR, and CD spectra. Now the complete structure of **1**, including the absolute configuration, has been established.

Acknowledgments We would like to thank Professors N. Nagakura and T. Tanahashi, Kobe Pharmaceutical University, for providing the ^{1}H-NMR spectrum of natural neoalangiside.

References and Notes

1) Itoh A., Tanahashi T., Nagakura N., *J. Nat. Prod.*, **58**, 1228—1239 (1995).
2) *a*) Itoh A., Tanahashi T., Nagakura N., *Chem. Pharm. Bull.*, **37**, 1137—1139 (1989); *b*) *Idem*, *Phytochem.*, **30**, 3117—3123 (1991).
3) Bentley K. W. (ed.), *The Isoquinoline Alkaloids*. Harwood Academics, Amsterdam, 1998.
4) Shoeb A., Raj K., Kapil R. S., Popli S. P., *J. Chem. Soc.*, *Perkin Trans. 1*, **1975**, 1245—1248.
5) Hoefle G., Nagakura N., Zenk M. H., *Chem. Ber.*, **113**, 566—576 (1980).
6) Battersby A. R., Southgate R., Stannton J., Hirst H., *J. Chem. Soc.* (*C*), **1966**, 1052—1057.
7) Kametani T., Kobari T., Fukumoto K., Fujihara M., *J. Chem. Soc.* (*C*), **1971**, 1796—1800.
8) Speath E., Orechoff A., Kuffner F., *Ber.*, **1934**, 1214—1217.
9) Kametani T., Terui T., Ogino T., Fukumoto K., *J. Chem. Soc.* (*C*), **1969**, 874—878.
10) Ramirez F. A., Burger A., *J. Am. Chem. Soc.*, **72**, 2781—2782 (1950).
11) *a*) Ohmori O., Kumazawa K., Hoshino H., Suzuki T., Morishima Y., Kohno H., Kitajima M., Sakai S., Takayama H., Aimi N., *Tetrahedron Lett.*, **39**, 7737—7740 (1998); *b*) Ohmori O., Takayama H., Aimi N., *Tetrahedron Lett.*, **40**, 5039—5042 (1999), and references cited therein.
12) Selected data of compound **15**: HR-FAB-MS (NBA): Found *m/z* 754.1536 (Calcd 754.1554 for $C_{33}H_{39}O_{14}NBr$); $[\alpha]_D^{14}$ −32.2° (c=0.26, $CHCl_3$); UV_{MeOH} λ_{max} nm (log ε): 295 (3.64, sh), 231 (4.30), 204 (4.53); CD (MeOH, 21 °C) $\Delta\varepsilon$: 307 (0), 288.2 (+1.7), 274.6 (0), 246.2 (−8.6), 231.8 (−5.4), 218.2 (0), 204.6 (+15); ^{1}H-NMR ($CDCl_3$): 7.46 (d, J=2.4 Hz, 1H, H-9), 6.99 (s, 1H, H-3), 5.81 (s, 1H, 1-OH), 5.45 (ddd, J=17.1, 9.7, 9.7 Hz, 1H, H-14), 5.27 (d, J=1.7 Hz, 1H, H-11), 5.25 (dd, J=9.5, 9.5 Hz, H-3′), 5.22 (d, J=17.6 Hz, 1H, H-15), 5.12 (d, J=9.7 Hz, 1H, H-15), 5.08 (dd, J=9.5, 9.5 Hz, 1H, H-4′), 5.05 (m, H-6α), 5.03 (dd, J=9.5, 8.3 Hz, H-2′), 4.95 (m, H-13a), 4.94 (d, J=8.3 Hz, 1H, H-1′), 4.29 (dd, J=12.5, 4.7 Hz, 1H, H-6′), 4.15 (dd, J=12.5, 2.4 Hz, 1H, H-6′), 3.88 (s, 3H, 2-OCH_3), 3.75 (ddd, J=7.8, 4.4, 2.2 Hz, 1H, H-5′), 2.95 (m, H-12a), 2.70 (m, H-12), 2.65 (m, H-13β), 2.62 (m, H-5), 2.55 (m, H-5), 1.14 (m, H-13α), 2.10 (OAc), 2.04 (OAc), 2.01 (OAc), 1.99 (OAc); ^{13}C-NMR ($CDCl_3$): 141.72 (C-1), 145.14 (C-2), 113.13 (C-3), 113.64 (C-4), 128.58 (C-4a), 30.02 (C-5), 38.44 (C-6), 162.97 (C-8), 108.86 (C-8a), 146.56 (C-9), 96.06 (C-11), 42.65 (C-12), 27.32 (C-12a), 31.07 (C-13), 53.62 (C-13a), 120.18 (C-14), 131.97 (C-15), 56.37 (2-OMe), 96.49 (C-1′), 70.47 (C-2′), 72.37 (C-3′), 68.22 (C-4′), 72.22 (C-5′), 61.74 (C-6′), 20.57 ($OCOCH_3$), 20.72 ($OCOCH_3$), 169.44 ($OCOCH_3$), 169.54 ($OCOCH_3$), 170.03 ($OCOCH_3$), 170.59 ($OCOCH_3$).
13) Takayama H., Ohmori O., Subhadhirasakul S., Kitajima M., Aimi N., *Chem. Pharm. Bull.*, **45**, 1231—1233 (1997).
14) Nagakura N., Hoefle G., Coggiola D., Zenk M. H., *J. Chem. Soc.*, *Chem. Commun.*, **1978**, 896—897.
15) Cacchi S., Ciattini P. G., Morera E., Ortar G., *Tetrahedron Lett.*, **45**, 5541—5544 (1986).