THE STEREOSELECTIVE HYDROGENATION OF NEPETALACTOLES THE ROLE OF C1 ALKOXYL GROUPS ON THE STEREOSELECTIVITY

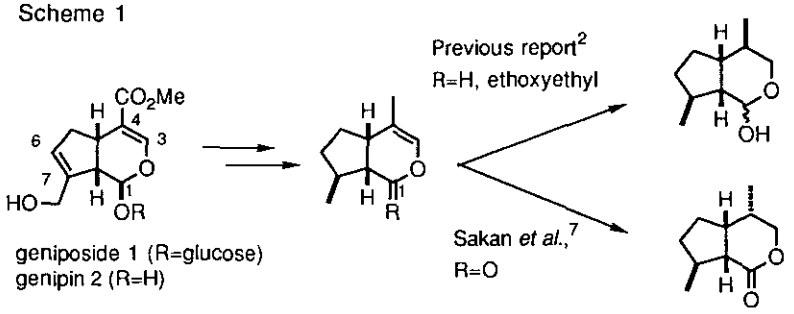
Masaharu Kigawa, Masahide Tanaka, Takao Katsuhara, Koh Sugama,
Masao Maruno, Hiroshi Mitsuhashi, and Takeshi Wakamatsu*

Tsumura Research Institute for Biology and Chemistry (*TRIBIC*)
3586 Yoshiwara, Ami-machi, Inashiki-gun, Ibaraki 300-11, Japan

Abstract - The stereoselective hydrogenation of nepetalactol and its derivatives was examined. From the stereochemical outcome and the conformational analyses of starting materials, it was concluded that, in the hydrogenation of nepetalactols, the most important factor which determined the steric course of reaction is the configuration of C1 position which carries the alkoxyl group.

Geniposide (**1**) and its aglycon genipin (**2**) isolated from *Gardenia jasminoides* have two olefinic groups at C3-C4 and C6-C7 positions, and are useful as the starting materials for the synthesis of various natural products.[1]

Scheme 1



Recently, we reported the synthesis of iridolactones utilizing the stereoselective hydrogenation of these double bonds[2]. In that paper, the observed stereoselective hydrogenation from concave face was ascribed to the steric

bulkiness of C1 alkoxyl group (ethoxyethyl group)[7] (Scheme 1). In this communication, we describe our recent results obtained by the examination of the effect of the C1 alkoxyl group on the stereoselectivity.

The hydrogenation of nepetalactol ethoxyethyl ether (**3**; R=ethoxyethyl) (atmospheric pressure of hydrogen, 10 % Pd-C / ethyl acetate) followed by hydrolysis afforded **4**[3] predominantly (>98 : 2) by the approach of hydrogen from concave face (Table 1).[2] The confirmation of its stereochemistry was achieved by the aid of nmr spectroscopic data of acetate **6**.[3,4] The inspection of NOESYPH data unambiguously demonstrated that **6** possesses axial hydroxyl group at C1 and equatorial methyl group at C4 and the bicyclic ring system is in the conformation similar to that of steroids which have A-B cis configurations. Furthermore, X-ray crystallography of **8**,[3,5] dimer of **4**, also supported this stereochemistry including its conformation (Figure 1).[6]

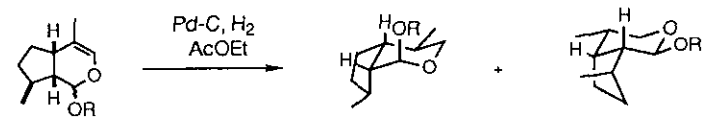
The effect of steric bulkiness was then examined by the hydrogenation of **3** with smaller alkoxyl groups at C1 position (R=H and methyl). Surprisingly, contrast to our expectation, hydrogenation of **3** (R=methyl) proceeded highly stereoselectively and after hydrolysis the mixture of **4** and **5**[3] was obtained in the ratio of 98 : 2. Moreover, nepetalactol itself (**3**; R=H. α anomer: β anomer=1 : 9) also afforded **4** as the major product (87 : 13).[7] The stereochemistry of acetate **7**[3,4] obtained from minor product (**5**) was elucidated by means of nmr spectroscopy as illustrated in Table 1, in which both substituents of C1 and C4 positions were equatorially oriented and the conformation of bicyclic system dose not correspond to that of cis A-B ring system of steroids.[6]

By the fact that even hydroxyl group at C1 position prevented the hydrogenation from convex face to large extent, the effect of the orientation of alkoxyl groups at C1 position rather than that of steric bulkiness attracted our attention. The conformation analysis of **3** (R=ethoxyethyl) by molecular mechanics calculation[8] suggested that six membered ring has the *pseudo* chair conformation and C1 ethoxyethoxy group is axially oriented (Figure 2). As the conformational similarity among ethoxyethyl ether, methyl ether, and major β anomer of nepetalactol was expected from the coupling constant values between C7a and C1 hydrogens of these compounds,[3] it could be concluded reasonably that the methoxy group of **3** (R=methyl) and hydroxyl group of major β anomer of nepetalactol (**3**; R=H) were also axially oriented. Furthermore, the coincidence between population of each anomer of **3** (R=H) and stereoselectivity observed for the hydrogenation of **3** (R=H) led us to the presumption that the hydrogenation of major β anomer of **3** (R=H) with axial hydroxyl group proceeded stereoselectively giving **4** and, on the other hand, minor α anomer with equatorial hydroxyl group afforded **5**.

From these considerations, it was concluded that, in the hydrogenation of nepetalactol derivatives, axially oriented alkoxyl group at C1 position prevented the approach of the hydrogen from usually favored convex face[7]

irrespective of steric bulkiness, and consequently stereochemical outcome of the hydrogenation was inverted completely affording the product by the concave face attack.

Table 1

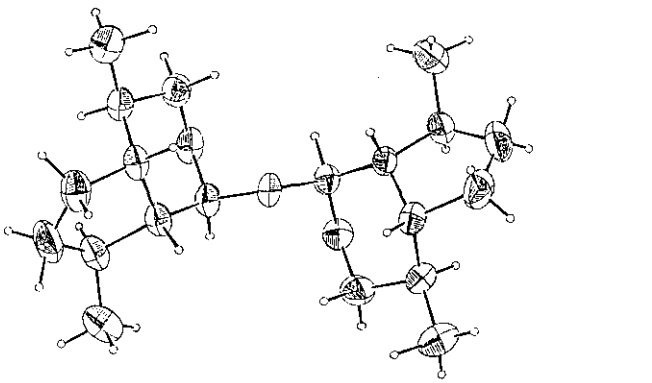


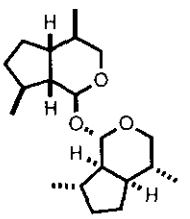
3 4: R=H 6: R=Ac 5: R=H 7: R=Ac

R	anomeric ratio of **3** (β : α)	yield (%)	ratio of products (**4** : **5**)
H	9 : 1	95	87 : 13
Me [a]	1 : 0	96	98 : 2
ethoxyethyl [a]	1 : 0	98	>98 : 2

a) Hydrolysis in 2N HCl-THF was performed after hydrogenation.

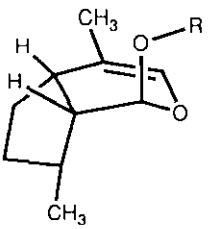
Figure 1. ORTEP Drawing of **8**





8

Figure 2. Conformation of **3** (R=ethoxyethyl)



REFERENCES AND NOTES

1. K. Inoue, Y. Tanaka, T. Tanahashi, and H. Inoue, *Chem. Pharm. Bull.*, 1981, **29**, 970; S. Isoe, S. Katsumura, T. Okada, K. Yamamoto, T. Takemoto, H. Inaba, Q. Han, and K. Nakatani, *Tetrahedron Lett.*, 1987, **28**, 5865; S. Isoe, Y. Ge, K. Yamamoto,

and S. Katsumura, *Tetrahedron Lett.*, 1988, **29**, 4591; S. Isoe, S. Katsumura, Q. Han, T. Okada, T. Takemoto, Y. Ge, *Symposium on the Chemistry of the Natural Products*, 1988, pp. 379-386, Fukuoka.

2. M. Kigawa, M. Tanaka, H. Mitsuhashi, and T. Wakamatsu, *Heterocycles*, 1992, **33**, 117.

3. **3** (R=ethoxyethyl): ^{1}H-Nmr ($CDCl_3$) δ: 1.07 (3H, d, J=6 Hz, C7-Me), 1.20 (3H, t, J=7 Hz, OCH_2Me), 1.35 (3H, d, J=6 Hz, OCHMeO), 1.61 (3H, t, J=1 Hz, C4-Me), 1.35-2.26 (7H, m, C4, 4a, 5, 6, 7, 7a-H,), 3.46-3.80 (2H, m, OCH_2Me), 4.70 (0.5H, d, J=8 Hz, OCH(Me)O), 4.80 (0.5H, d, J=7 Hz, OCH(Me)O), 4.88 (0.5H, d, J=5 Hz, C1-H), 4.98 (0.5H, d, J=5 Hz, C1-H), 5.96 (1H, t, J=1 Hz, C3-H). **3** (R=methyl): ^{1}H-Nmr ($CDCl_3$) δ: 1.05 (3H, d, J=6 Hz, C7-Me), 1.53 (3H, t, J=1 Hz, C4-Me), 1.08-2.00 (6H, m, C5, 6, 7, 7a-H), 2.36-2.50 (1H, m, C4a-H), 3.46 (3H, s, OMe), 4.48 (1H, d, J=4 Hz, C1-H), 5.97 (1H, t, J=1 Hz, C3-H). **3** (R=hydrogen, major anomer): ^{1}H-Nmr ($CDCl_3$) δ: 1.09 (3H, d, J=7 Hz, C7-Me), 1.35-2.26 (7H, C4, 5, 6, 7, 7a-H), 1.57 (3H, t, J=1 Hz, C4-Me), 1.08-2.04 (6H, m, C5, 6, 7, 7a-H), 2.36-2.50 (1H, m, C4a-H), 2.92 (1H, brs, OH), 4.85 (1H, d, J=4 Hz, C1-H), 6.02 (1H, t, J=1 Hz, C3-H). **4**: ^{1}H-Nmr ($CDCl_3$) δ: 0.79 (3H, d, J=7 Hz, C4-Me), 1.01 (3H, d, J=6 Hz, C7-Me), 1.14-2.05 (8H, m, C4, 4a, 5, 6, 7, 7a-H), 3.41 (1H, dd, J=5, 11 Hz, C3α-H), 3.58 (1H, t, J=11 Hz, C3β-H), 5.13 (1H, brs, C1-H). **5**: ^{1}H-Nmr ($CDCl_3$) δ: 0.86 (3H, d, J=8 Hz, C4-Me), 1.06 (3H, d, J=7 Hz, C7-Me), 1.10-2.28 (8H, m, C4, 4a, 5, 6, 7, 7a-H), 2.97 (1H, d, J=2 Hz, OH), 3.31 (1H, t, J=11 Hz, C3α-H), 3.70 (1H, dd, J=4, 11 Hz), 4.44 (1H, dd, J=2, 10 Hz, C1-H). **6**: ^{1}H-Nmr ($CDCl_3$) δ: 0.79 (3H, d, J=7 Hz, C4-Me), 1.04 (3H, d, J=6 Hz, C7-Me), 1.17-1.95 (8H, m, C4, 4a, 5, 6, 7, 7a-H), 2.07 (3H, s, OCOMe), 3.39 (1H, t, J=11 Hz, C3α-H), 3.52 (1H, dd, J=5, 11 Hz, C3β-H), 6.05 (1H, brs, C1-H). **7**: ^{1}H-Nmr ($CDCl_3$) δ: 0.86 (3H, d, J=7 Hz, C4-Me), 1.05 (3H, d, J=6 Hz, C7-Me), 1.21-1.97 (8H, m, C4, 4a, 5, 6, 7, 7a-H), 2.08 (3H, s, OCOMe), 3.30 (1H, dd, J=5, 11 Hz, C3α-H), 3.65 (1H, t, J=11 Hz, C3β-H), 6.08 (1H, d, J=10 Hz, C1-H). **8**: ^{1}H-Nmr ($CDCl_3$) δ: 0.75 (6H, d, J=7 Hz, C4-Me), 1.00 (6H, d, J=6 Hz, C7-Me), 1.17-1.99 (16H, m, C4, 4a, 5, 6, 7, 7a-H), 3.28 (2H, t, J=11 Hz, C3β-H), 3.34 (2H, dd, J=5, 11 Hz, C3α-H), 4.99 (2H, brs, C1-H).

4. **6** and **7** were prepared by the acetylation (Ac_2O, pyridine, DMAP) of **4** and **5**, respectively.

5. **8** was prepared as follows. After the reaction with 3, 5-dinitrobenzoyl chloride, recrystallization of crude dinitrobenzoate of **4** from ether afforded **8** as a crystalline solid.

6. H. G. Grant, C. A. Russell-Maynard, and M. D. Sutherland, *Aust. J. Chem.*, 1985, **38**, 325.

7. T. Sakan, S. Isoe, S. B. Hyeon, R. Katsumura, T. Maeda, J. Wolinsky, D. Dickerson, M. Slabaugh, and D. Nelson, *Tetrahedron Lett.*, 1965, 4097.

8. Molecular mechanics calculation was carried out with CHARMm/QUANTA (version 3.32, Polygen Corporation) software package implemented on graphics workstation IRIS 4D/220 (Silicon Graphics).

Received, 30th November, 1992