Pergamon

Tetrahedron Letters, Vol. 38, No. 48, pp. 8335-8336, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)10256-8

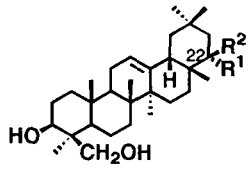
Efficient Synthesis of C(22) Homologous Derivatives of Hepatoprotective Soyasapogenol B

Kazue Sasaki, Nobuto Minowa*, Hiroyuki Kuzuhara, Shoji Nishiyama, and Shoji Omoto

Pharmaceutical Research Center, Meiji Seika Kaisha, Ltd., 760 Morooka-cho, Kohoku-ku, Yokohama 222, Japan

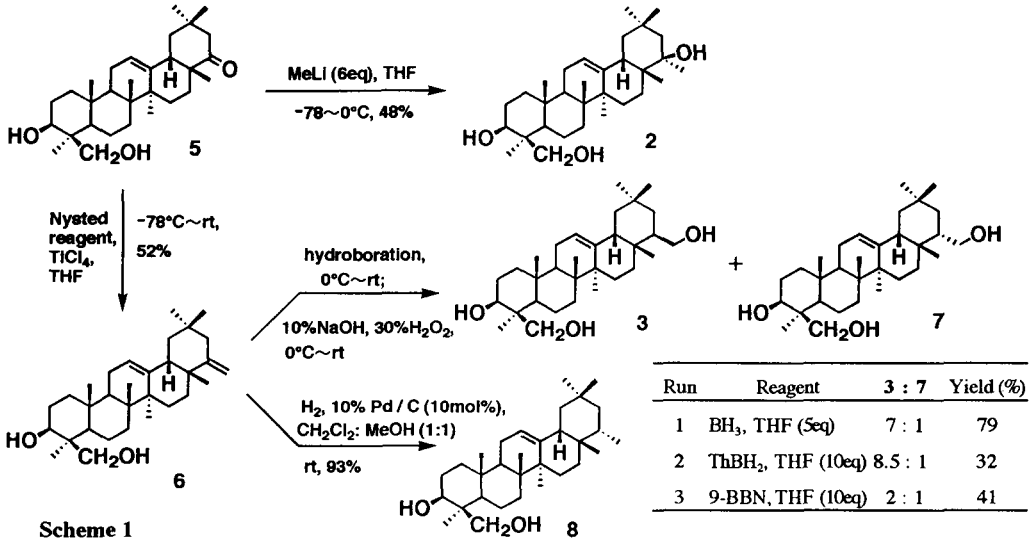
Abstract: Stereochemical behavior in the addition reactions at C(22) of ketone **5** and exomethylene **6** was studied and C(22) homologous derivatives of soyasapogenol B were efficiently synthesized.

Recently, we found that soyasapogenol B (**1**), an oleanene-type triterpene aglycon of soybeansaponins,[1,2] and its derivatives showed *in vitro* hepatoprotective effect against aflatoxin B_1-induced Hep G2 cells.[3] To shed light on the structure-activity relationships of **1** and its analogs, we undertook homologation of **1** at the C(22) position, since only few works on the chemical transformation of **1** have so far been reported.[4] In this paper, we describe the interesting stereochemical behavior observed in the addition reactions at C(22) of ketone **5** and exomethylene **6**, both being key intermediates for preparation of C(22) homologous derivatives such as **2**, **3** and **4**.



1 R^1 = H, R^2 = OH (**Soyasapogenol B**)
2 R^1 = **Me**, R^2 = OH
3 R^1 = H, R^2 = CH_2OH
4 R^1 = H, R^2 = COOH

First, stereochemistry of the addition reactions at C(22) of **5** and **6** was examined, and the results are shown in Scheme 1. The intermediary substrate **6** was readily prepared from **5**[3] with Nysted reagent[5] in the presence of $TiCl_4$, while alkylation of **5** with methyl lithium provided the desired 22β-hydroxy derivative **2** as a single stereoisomer. Similarly, hydroboration of **6**, which was envisioned as having an E-ring stereostructure similar to **5**, with diborane and thexylborane followed by oxidation gave the 22β-hydroxymethyl derivative **3** with high diastereoselectivity (runs 1 and 2). In contrast, stereoselectivity of the hydroboration reaction (run 3) was significantly decreased by using the more bulky 9-BBN. Reactivities of hydroborations with thexylborane or 9-BBN were decreased and the starting materials were recovered in each reaction (runs 2 and 3). On the other hand, hydrogenation of **6** in the presence of a 10% Pd-C catalyst gave the 22α-methyl **8** as a single stereoisomer although with opposite stereoselectivity as compared to the above alkylation and hydroboration. Additionally, when a large amount of the 10% Pd-C catalyst (45mol%) was used in this reaction, stereoselectivity did not change. [6] The structures of the thus-prepared **2**, **3** and **8** were confirmed by single-crystal X-ray analyses of the respective diacetates.[7] It has become clear that alkylation of **5** and hydroboration-oxidation of **6** take place preferentially from the sterically less hindered α face of a presumable E-ring chair conformation as shown in Fig 1. On the other hand, hydroboration of **6** with the sterically more bulky 9-BBN, which may enhance interaction with the axial methylene at C(17), resulted in



Run	Reagent	3 : 7	Yield (%)
1	BH_3, THF (5eq)	7 : 1	79
2	$ThBH_2$, THF (10eq)	8.5 : 1	32
3	9-BBN, THF (10eq)	2 : 1	41

Scheme 1

modest stereoselectivity.[8] Stereoselectivity of hydrogenation of **6** is difficult to rationalize based solely on steric and conformational effects. Presumably, the reaction would arise through a different transition state.[9]

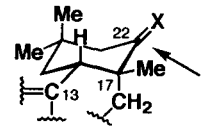
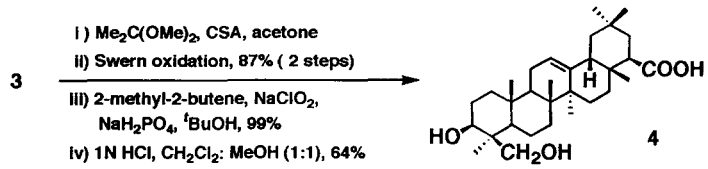


Fig. 1 X= O or CH_2

Finally, protection of **3** followed by Swern oxidation gave the 22β-formyl derivative. Oxidation of the formyl moiety with sodium chlorite[10] and subsequent deprotection gave rise to the desired C(22) carboxylic acid **4**.

Hepatoprotective effects of these C(22) homologous derivatives are currently under study.



Acknowledgment: We gratefully thank Professor Isao Kitagawa of Kinki University for helpful comments. We also thank Dr. Y. Kodama and Dr. N. Watanabe for the X-ray crystallographic data.[7]

References

1. (a) Ochiai, E.; Tsuda, K.; Kitagawa, S. *Ber.* **1937**, *70*, 2083. (b) *Idem. ibid.* **1937**, *70*, 2093. (c) Tsuda, K.; Kitagawa, S. *ibid.* **1938**, *71*, 790. (d) *Idem. ibid.* **1938**, *71*, 1604.
2. Kitagawa, I.; Yoshikawa, M.; Wang, H. K.; Saito, M.; Tosirisuk, V.; Fujiwara, T.; Tomita, K. *Chem. Pharm. Bull.* **1982**, *30*, 2294.
3. Sasaki, K.; Minowa, N.; Kuzuhara, H.; Nishiyama, S.; Omoto, S. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 85.
4. Kitagawa, I.; Wang, H. K.; Taniyama, T.; Yoshikawa, M. *Chem. Pharm. Bull.* **1988**, *36*, 153.
5. Watson, A. T.; Park, K.; Wiemer, D. F.; Scott, W. J. *J. Org. Chem.* **1995**, *60*, 5102.
6. Mitsui, S.; Gohke, K.; Saito, H.; Nanbu, A.; Senda, Y. *Tetrahedron* **1973**, *29*, 1523.
7. To be reported elsewhere in due course.
8. (a) Klein, J.; Lichtenberg, D. *J. Org. Chem.* **1970**, *35*, 2654. (b) Brown, H. C.; Liotta, R.; Brener, L. *J. Am. Chem. Soc.* **1977**, *99*, 3427.
9. (a) Cieplak, A. S.; Tait, B. D.; Johnson, C. R. *J. Am. Chem. Soc.* **1989**, *111*, 8447. (b) Harada, T.; Nakajima, H.; Ohnishi, T.; Takeuchi, M.; Oku, A. *J. Org. Chem.* **1992**, *57*, 720.
10. (a) Lindgren, B. O.; Nilsson, T. *Acta Chem. Scand.* **1973**, *27*, 888. (b) Kraus, G. A.; Taschner, M. J. *J. Org. Chem.* **1980**, *45*, 1175.

(*Received in Japan* 26 *July* 1997; *revised* 26 *September* 1997; *accepted* 29 *September* 1997)