Central Research Laboratories,
Sankyo Co., Ltd.
Hiromachi, Shinagawa-ku, Tokyo

AKIRA YOSHIDA
SADAO OIDA
EIJI OHKI

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Modification of α-Santonin. I. An Abnormal Chlorination of 3-Hydroxy-4,5-epoxy-6,11βH-eudesm-1-en-6,12-olide with Methanesulfonyl Chloride

An abnormal, stereospecific chlorination of 3-hydroxy-4,5-epoxy-6,11βH-eudesm-1-en-6,12-olide (**5**, **6**, **7** and **8**) with methanesulfonyl chloride (or *p*-toluenesulfonyl chloride)–pyridine is described.

The stereochemistry of the chlorides (**9**, **10**, **11** and **12**) were confirmed by their nuclear magnetic resonance spectra and chemical reactions.

It is well known that mesylation (or tosylation) of an allylic alcohol (I) with methanesulfonyl chloride (or *p*-toluenesulfonyl chloride)–pyridine produce a mixture of the corresponding mesylate (or tosylate (II) and the rearranged isomer (III), but there are few reports on stereospecific chlorination under these conditions.

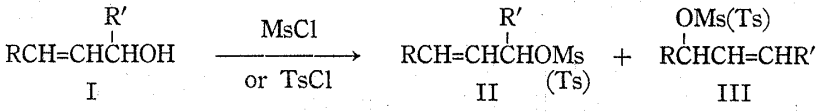

Chart 1

In this communication, we wish to report an abnormal stereospecific chlorination of 3-hydroxy-4,5-epoxy-6,11βH-eudesm-1-en-6,12-olide (**5**, **6**, **7**, **8**) by the action of methanesulfonyl chloride (or *p*-toluenesulfonyl chloride)–pyridine.

α-Santonin (**1**) was treated with *m*-chloroperbenzoic acid in the presence of 4,4′-thiobis-(6-*t*-butyl-3-methylphenol) as a radical inhibitor[1] to give the α-epoxide (**2**)[2a-c] (yield 38.6%), β-epoxide (**3**)[2a,c] (yield 43.2%) and diepoxide (**4**)[2c] (yield 1.8%). Selective reduction of the carbonyl group of **2** with $LiAlH_4$ (tetrahydrofuran, −78°) afforded a mixture of the β-alcohol (**5**) (yield 16.7%, mp 200—202°, NMR ($CDCl_3$) δ: 4.27 (1H, d, J=5.0 Hz; C_3–H), 5.37 (1H, d, J=10.0 Hz; C_1–H), 5.65 (1H, dd, J=10.0, 5.0 Hz; C_2–H) and α-alcohol (**6**) (yield 65.6%, mp 196—197°, NMR ($CDCl_3$) δ: 4.18 (1H, dq, J=11.0, 2.0, 2.0 Hz; C_3–H), 5.26 (1H, dd, J=10.0, 2.0 Hz; C_1–H), 5.46 (1H, dd, J=10.0, 2.0 Hz; C_2–H), while reduction of **2** with $NaBH_4$ gave a mixture of **5**, **6** and corresponding dihydro derivatives (**13**, **14**).

Similar reduction of **3** with $LiAlH_4$ gave a mixture of the β-alcohol (**7**) (yield 65.9%, mp 106—107°, NMR ($CDCl_3$) δ: 4.12 (1H, m, C_3–H), 5.22 (1H, dd, J=10.5, 2.0 Hz; C_1–H), 5.43 (1H, dd, J=10.5, 2.0 Hz; C_2–H) and α-alcohol (**8**) (yield 15.6%, mp 158—160°, NMR ($CDCl_3$) δ: 4.20 (1H, d, J=5.0 Hz; C_3–H), 5.27 (1H, d, J=10.5 Hz; C_1–H), 5.57 (1H, dd, J=10.5, 5.0 Hz; C_2–H).

1) Y. Kishi, M. Aratani, H. Tanino, T. Fukuyama, T. Goto, S. Inoue, S. Sugiura, and H. Kakoi, *J. C. S. Chem. Comm.*, **1972**, 64.
2) *a*) E. Wedekind and K. Tettweiler, *Ber.*, **64**, 1796 (1931); *b*) J.B. Hendrickson and T.L. Bogard, *J. Chem. Soc.*, **1962**, 1678; *c*) M. Yanagita, T. Hirose, and T. Okura, The 91th Annual Meeting of Pharmaceutical Society of Japan, Fukuoka, Apr. 1971.

The configurations of C_3–H of the alcohols were assigned to those shown on the structures (**5**, **6**, **7** and **8**) respectively from the coupling patterns[3] of C_3–H, C_2–H and C_1–H on their NMR spectra. Treatment of **5** with methanesulfonyl chloride (or *p*-toluenesulfonyl chloride)–pyridine (0°, 3 hr) did not afford the corresponding mesylate (or tosylate), but gave an unexpected chlorinated compound (**9**) (yield 92.3%, mp 189—191°, NMR ($CDCl_3$) δ: 4.51 (1H, m, C_3–H), 5.32 (1H, dd, J=10.0, 2.0 Hz; C_1–H), 5.49 (1H, dd, J=10.0, 2.0 Hz; C_2–H). For the structure of the chlorinated compound, possibility of the rearranged isomer (**17**) was excluded by the following experiments.

The alcohol **5** and **6** was hydrogenated with H_2/PtO_2 to give 13 and 14. Chlorination of **13** and **14** with $SOCl_2$–pyridine gave the corresponding chloride **15** and **16** respectively which was obtained by reduction of **9** and **10**.

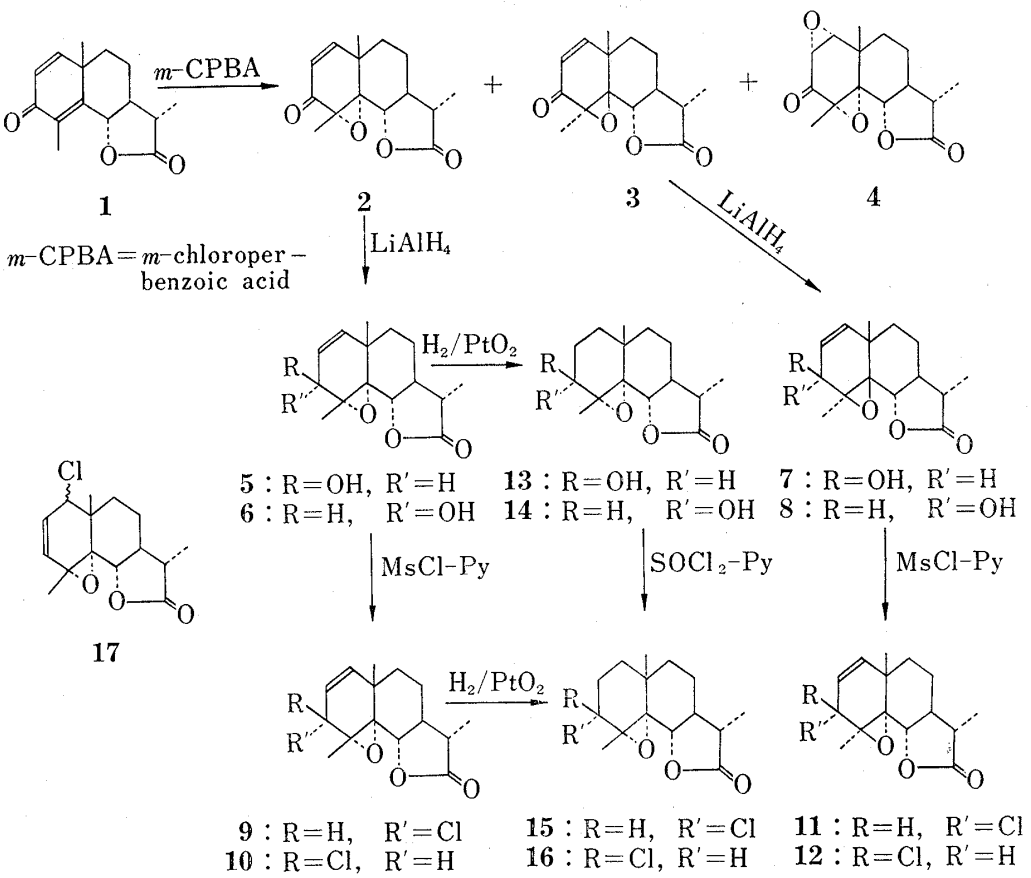

Chart 2

Inversion of the configuration of C_3–H during the chlorination was verified by the comparison of the coupling constants of C_3–H of the original alcohol (**5**) and the chloride (**9**).

By the same treatment, the other three alcohols (**6**, **7** and **8**) were also converted stereospecifically into the corresponding chlorides (**10**, **11** and **12**) having the inverted configuration of C_3–H (**10**; yield 85.6%, mp 189°, NMR ($CDCl_3$) δ: 4.55 (1H, d, J=5.0 Hz; C_3–H), 5.34 (1H, d, J=10.0 Hz; C_1–H), 5.64 (1H, dd, J=10.0, 5.0 Hz; C_2–H), **11**; yield 90.8%, mp 223—224°, NMR ($CDCl_3$) δ: 4.70 (1H, m, C_3–H), 5.29 (1H, dd, J=10.0, 2.0 Hz; C_1–H), 5.47 (1H, dd, J=10.0, 2.0 Hz; C_2–H), **12**; yield 98.0%, mp 176—178°, NMR ($CDCl_3$) δ: 4.56 (1H, d, J=5.0 Hz; C_3–H), 5.24 (1H, d, J=10.5 Hz; C_1–H), 5.64 (1H, dd, J=10.5, 5.0 Hz; C_2–H). Further

3) S. Sternhell, *Quart. Rev.*, **1969**, 236.

studies on this abnormal, stereospecific chlorination and reactivities of the chlorides are now in progress.

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Rikagaku Kenkyusho
The Institute of Physical and Chemical Research
Wako-shi, Saitama, 351, Japan

Yasuo Fujimoto
Takeshi Shimizu
Takashi Tatsuno

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