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Oxidation of Hecogenin and Diosgenin Derivatives with Dimethyldioxirane

Bao Kun ZHU[1], Hong Bin ZHANG[1], Yu Shun ZHANG[1],
Hui Min ZHONG[2], Jian Ping LIU[1]*

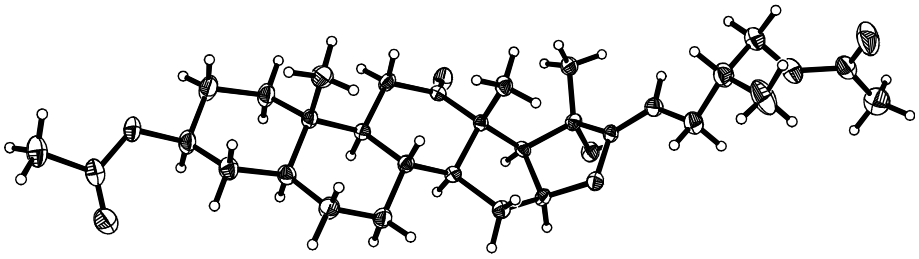
[1]The School of Pharmacy, Center for Advanced Studies of Medicinal and Organic Chemistry, Yunnan University, Kunming 650091
[2]The School of Chemistry, Qingdao Sci. & Techn. Univ., Qingdao 266042

Abstract: Diacetyl derivative of hecogenin **1** was oxidized to unsaturated ketone **5** *via* allylic alcohol **3** when it reacted with dimethyldioxirane (DMDO). The structure of **3** was confirmed by X-ray crystal analysis and the highly regioselectivity of DMDO to different olefin bonds was also observed when diosgenin derivative **6** was treated with DMDO.

Keywords: Oxidation, dimethyldioxirane, hecogenin, diosgenin, derivative.

Dimethyldioxirane (DMDO), as one of the most interesting environment benign oxidizing reagents, has been used for many years[1-5]. Numerous acid or base sensitive molecules have been made available for the first time by the application of DMDO in the synthetic chemistry as the reactions were carried out on the neutral conditions[6,7]. Iida and co-workers had reported the oxidation of DMDO with different steroids[8]. They focused the reactions on the A, B, C and D rings of the steroids and got some interesting results but they did not report the changes of steroid side chains in their research. Here we report the reactions of DMDO with side chains of hecogenin and diosgenin derivatives (**1** and **6**) as part of our program of synthesis of bioactive interesting compounds from easy obtained natural materials.

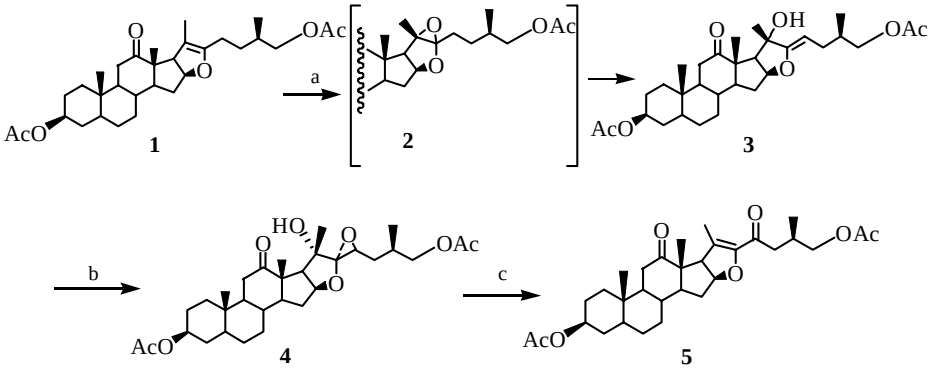
Figure 1 The X-ray structure of compound **3**



* E-mail: jpliu@ynu.edu.cn

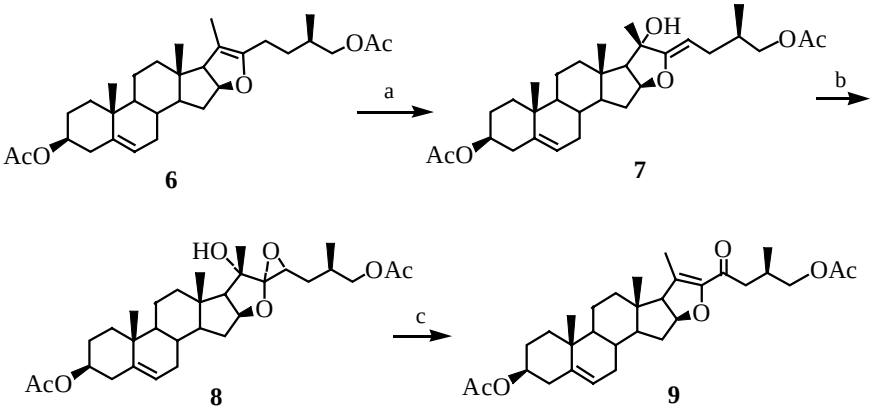
Our aim was to find some environment benign reagents, such as DMDO and ozone, to replace the reagents containing heavy metal in the modifications of the steroid side chain. Diacetyl derivative of hecogenin **1**[9] was used as first starting substrate in our study. When **1** was mixed with DMDO at low temperature, the product **3**[10] was isolated at a very good yield and no C-H oxidizing insertion product was obtained. It was expected presumably that **3** should be formed from epoxide **2** *via* opening of epoxide ring and proton removal or migration. We had tried several times at different conditions but failed to get the intermediate **2**. Finally, the whole structure and stereochemistry of **3** was confirmed by single crystal X-ray crystallography[11] (**Figure 1**). The conformations of newly formed chiral carbon (C20) and C22-C23 double bond in **3** were agreed with the similar results previously reported by Morzycki *et al.*[12,13] but there was no direct evidence provided in their reports.

Scheme 1 Reaction of hecogenin derivatives with DMDO



(a) DMDO, acetone, 0℃, 98%; (b) oxone, $NaHCO_3$, acetone, H_2O, rt, 82%; (c) HCl, H_2O, 60℃, 91%.

Scheme 2 Reaction of diosgenin derivatives with DMDO



(a) oxone, $NaHCO_3$, acetone, H_2O, -10℃, 81%; (b) oxone, $NaHCO_3$, acetone, H_2O, rt, 78%; (c) HCl, H_2O, 60℃, 93%.

Further treatment of **3** with oxone at room temperature afforded epoxide **4** in a satisfactory yield. Unsaturated ketone **5**[14] was formed when epoxide **4** was exposed to acid (**Scheme 1**). Presumably, the conversion of **4** to **5** should include 1,2-hydride shift and dehydration processes but we could not isolate any intermediate. The ketone **5** could also be obtained directly when **1** was reacted with MCPBA or ozone, but there were more by-products formed in the reactions and the yields were lower according to our studies.

The similar results were also observed when diacetate **1** was replaced by diosgenin derivative **6** in the oxidation reactions. The ketone **9** was formed from allylic alcohol **7** *via* epoxide **8**[15]. One of the interesting fact observed in the transformation was the highly regioselectivity of DMDO to different olefin bonds as there was no any C5-C6 double bond oxidized product isolated in the reactions (**Scheme 2**).

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References and Notes

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10. The data of **3**: ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 4.84 (m, 1H, H-16), 4.64 (m, 1H, H-3), 4.28 (t, 1H, *J* = 7.7 Hz, H-23), 3.87 (m, 2H, H-26), 2.67 (d, 1H, *J* = 6.4 Hz, H-17), 2.42 (t, 1H, *J* = 13.5 Hz, H-11), 2.27-2.24 (m, 2H), 2.17 (d, 1H, *J* = 13.9 Hz, H'-11), 2.02, 1.99 (s, 2×3H, 2×OAc), 1.48 (s, 3H, 21-CH_3), 1.06 (s, 3H, 18-CH_3), 0.89 (d, 3H, *J* = 6.7 Hz, 27-CH_3), 0.88 (s, 3H, 19-CH_3). ^{13}C NMR (75 MHz, $CDCl_3$, δ ppm): 212.3 (C12), 171.2, 170.5(2×OAc), 162.3 (C22), 91.9 (C23), 82.5 (C16), 77.2 (C20), 73.1 (C3), 69.0 (C26), 58.9 (C17), 56.7 (CH), 55.7 (CH), 54.5 (C13), 44.4 (CH), 37.3 (CH_2), 36.3 (CH_2), 36.0 (C10), 33.8 (CH), 33.6 (CH_2), 33.1 (CH), 32.5 (CH_2), 31.0 (CH_2), 28.6 (CH_2), 28.1 (CH_2), 27.2 (CH_2), 21.7 (21-CH_3), 21.3, 20.9 (2×OAc), 16.9, 13.2 (18-CH_3, 27-CH_3), 11.8 (19-CH_3). HR-MS ($C_{31}H_{46}O_7Na$) calcd. 553.3141, found: 553.3146.
11. Crystallographic parameters have been deposited in the editorial office of CCL.
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14. The data of **5**: ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 4.80 (m, 1H, H-16), 4.68 (m, 1H, H-3), 3.97-3.90 (m, 2H, H-26), 3.44 (d, 1H, *J* = 10.6 Hz, H-17), 2.65 (m, 1H, H-11), 2.44-2.37 (m, 4H), 2.02, 2.01 (s, 3×3H, 2×OAc, 21-CH_3), 0.96 (s, 3H, 18-CH_3), 0.94 (d, 3H, *J* = 6.1 Hz, 27-CH_3), 0.92 (s, 3H, 19-CH_3). ^{13}C NMR (75 MHz, $CDCl_3$, δ ppm) 212.4 (C12), 194.6 (C23), 171.0, 170.5 (2×OAc), 148.8 (C20), 123.1 (C22), 82.9 (C16), 73.0 (C3), 68.7 (C26),

57.9 (C13), 57.1 (C17), 55.4 (CH), 54.2 (CH), 44.4 (CH), 44.1 (CH_2), 37.8 (CH_2), 36.3 (CH_2), 36.1 (C10), 34.1 (CH), 33.8 (2×CH_2), 34.6 (CH_2), 28.4 (CH), 28.1 (CH_2), 27.2 (CH_2), 21.4, 20.9 (2×OAc), 17.0 (21-CH_3), 14.0, 12.8 (18-CH_3, 27-CH_3), 11.9 (19-CH_3). HR-MS ($C_{31}H_{44}O_7Na$) calcd. 551.2984, found: 551.2975.

15. The structures of compounds **7**, **8** and **9** were all confirmed by NMR and MS data. Here the data of **9** were presented: ^{1}H NMR (300 MHz, $CDCl_3$ δ ppm): 5.83 (brs, 1H, H-6), 4.85 (m, 1H, H-16), 4.60 (m, 1H, H-3), 3.94-3.90 (m, 2H, H-26), 2.03, 2.02 (s, 3×3H, 2×OAc, 21-CH_3), 0.96 (s, 3H, 18-CH_3), 0.95 (d, 3H, J = 4.2 Hz, 27-CH_3), 0.72 (s, 3H, 19-CH_3). ^{13}C NMR (75 MHz, $CDCl_3$ δ ppm): 195.2 (C23), 171.2, 170.7 (2×OAc), 148.4 (C20), 139.9 (C5), 123.8 (C22), 122.2 (C6), 84.7 (C16), 73.9 (C3), 68.8 (C26), 65.6 (C17), 55.1 (CH), 50.0 (CH), 44.4 (C13), 44.2 (CH_2), 39.5 (CH_2), 38.2 (CH_2), 37.1 (CH_2), 36.8 (C10), 34.5 (CH_2), 32.2 (CH_2), 31.3 (CH), 28.5 (CH), 27.8 (CH_2), 21.5, 21.0 (2×OAc), 21.0 (CH_2) 19.5 (21-CH_3), 17.2 (19-CH_3), 14.1 (27-CH_3), 13.3 (18-CH_3). HR-MS ($C_{31}H_{44}O_6$+H) calcd. 513.3211, found: 513.3214.

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