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The Effect of 19-Substituent on the Stereospecific Hydroxylation of Δ^5-Steroids Using Performic Acid as Oxidant

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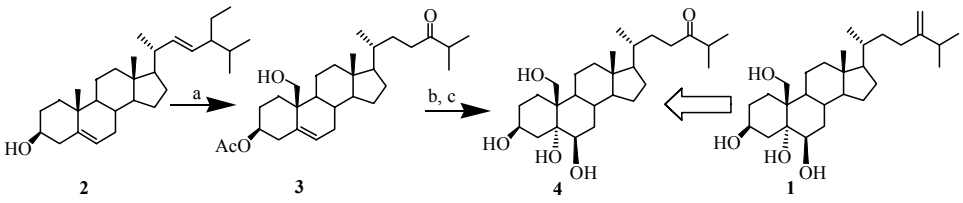
Abstract: In the studying of the stereospecific hydroxylation of different Δ^5-steroids with performic acid, followed by hydrolysis with CH_3OH/KOH, we found 19-substituting groups considerably affected the reaction and we put forward the mechanism.

Keywords: Δ^5-Steroids, performic acid, 19-substituting group, hydroxylation.

24-Methylenecholesta-3β, 5α, 6β, 19-tetrol **1**, isolated from the soft corals, *Nephthea albida and N. tiexieral verseveldt* by L. M. Zeng[1], showed significant cytotoxicity to A-549, H-29, KB and P-388 cell lines with ED_{50} values of 0.81, 0.93, 0.39 and 0.34 μg/mL, respectively[2]. We have designed a synthetic route for the synthesis of **1** as shown in **Scheme 1**.

Scheme 1



2 **3** **4** **1**

a) Ref. 3; b) $HCOOH/H_2O_2$; c) CH_3OH/KOH

In this route, the introduction of keto-containing side-chain and 19-hydroxy group was completed in 8 steps starting from stigmasterol **2** referring to the literature[3]. In the hydroxylation of 5, 6-olefin **3** to 5α, 6β-diol **4** we used performic acid as epoxidizing agent, followed by hydrolysis with CH_3OH/KOH. During the study of this conversion we found the steroid without 19-substituting group provided the expected product exclusively, while the steroid with 19-hydroxy or 19-acetoxy group provided two products in a relatively low yield.

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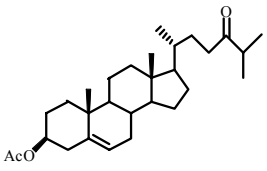
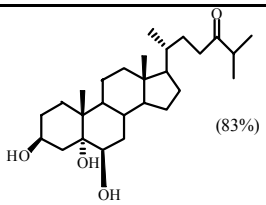
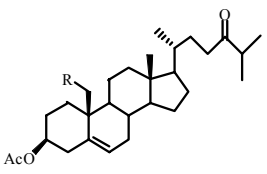
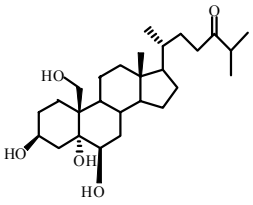
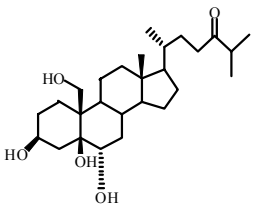
Table 1 Hydroxylation of Δ^5-steroids with performic acid as oxidant

Substrate	Products (yield)	
	 (83%)	
5	**6**	
		
3 R = HO	**4** (41%)	**7** (15%)
3a R = CH_3COO	**4** (21%)	**7** (20%)

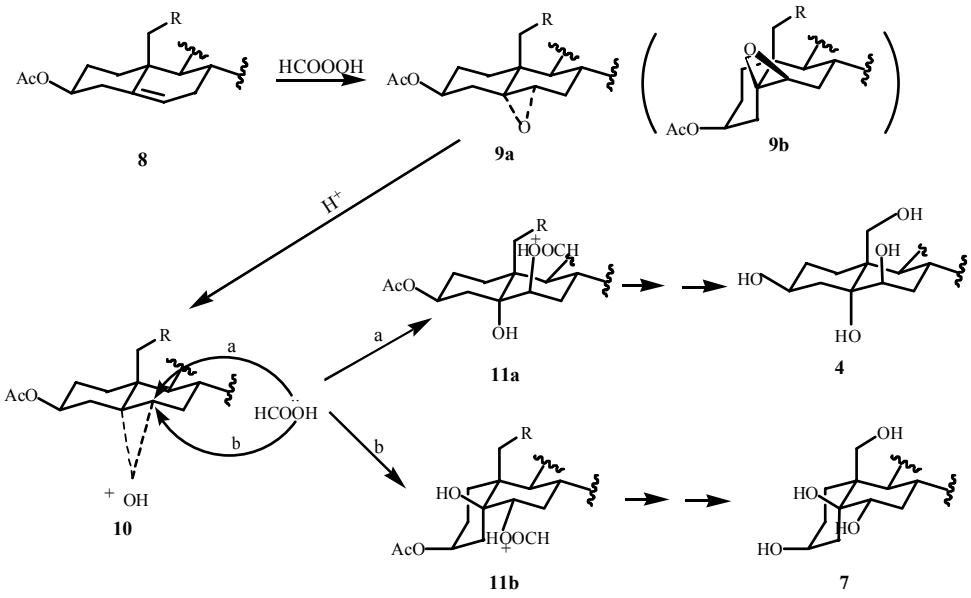
As shown in **Table 1**, the Δ^5-steroidal hydroxylation of compound **5** by employing J. Romo's method[4] with performic acid, followed by hydrolysis with CH_3OH/KOH, gave compound **6** in a yield comparable to the literature. However, 19-subsituted compounds **3** and **3a**, subjected to the similar situation, gave two products **4** and **7** (tracked by TLC and separated by silica gel chromatography, benzene/acetone=1/1) in a relatively low yield.

It is interesting that these two compounds (**4** and **7**) have the same molecular formula $C_{27}H_{46}O_5$ (determined by Micro-analysis and FAB-mass spectrometry) and all have one primary, two secondary and one tertiary alcohols (determined by ^{1}H NMR, ^{13}C NMR and DEPT). According to their NMR spectral data[5,6] and literature survey[1,7], we confirmed these two compounds being configurational isomers, cholest-24-oxo-3β, 5α, 6β, 19-tetrol **4** and cholest-24-oxo-3β, 5β, 6α, 19-tetrol **7**.

We suggested that the steric hindrance of 19-substituting groups might be the explanation, here we proposed the mechanism for the formation of compound **4** and **7** (**Scheme 2**).

The reaction of performic acid with Δ^5-steroids **8** produces the 5α, 6α- and 5β, 6β-epoxides (**9a** and **9b**) with the epoxidation taking place predominantly from the α-face of the molecule[8]. The protonation of the α-epoxide **9a** will lead to the formation of oxonium intermediate **10**, which are susceptible to nucleoplic attack. Intermediate **10** is expected to be particularly reactive at its relatively unhindered 6-position by nucleopile HCOOH[9] either from the α-face or the β-face, to lead to two products, **11a** and **11b**. The hydrolysis of **11a** and **11b** with CH_3OH/KOH produces **4** and **7** respectively. If R is hydrogen, the approach of the nucleophile in the intermediate **10** is preferred from the β-face because of the *trans*-A/B ring system unchanged. If R is hydroxy or acetoxy group, steric factor suggested that the attack from the β-face might be sterically restricted, while the attack from the α-face will lead to the formation of compound **7**, which has a relatively unstable *cis*-A/B ring system.

Scheme 2



Steric effect of 19-substituting group on the cleavage of epoxide, only rings A and B are shown

In conclusion, the existence of R group increases the steric hindrance on the β-face, and it reduces the approaching of nucleophile from the β-face to the extent that the approaching from the α-face may not be neglected.

Acknowledgment

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References and Notes

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4. J. Romo, G. Rosenkranz, C. Djerassi, F. Sondheimer, *Steriods*, **1954,** *19*,1509.
5. The physical data of compound **4**: Anal. Calcd. for $C_{27}H_{46}O_5$: (%) C 72.06, H 10.08 Found: C 71.54, H 10.23; FAB-MS *m/z* 451 $(M+H)^+$; IR (KBr, cm^{-1}) 3327, 2941, 2869, 1707, 1464, 1380, 1047, 976; ^{1}H-NMR (DMSO-d_6, ppm) 0.66 (s, 3H, H-18), 0.86 (d, 3H, *J* = 6.5Hz, H-21), 0.99 (d, 6H, *J* = 7.0Hz, H-26 and H-27), 2.60 (m, 1H, *J* = 7.0Hz, H-25), 3.27 (m, 1H, H-6), 3.52 (dd, 1H, *J* = 12.0, 6.0Hz, H_a-19), 3.69 (s, 1H, 5α-OH), 3.85 (m, 1H, H-3), 3.99 (dd, 1H, *J* = 12.0, 3.5Hz, H_b-19), 4.11 (d, 1H, *J* = 5.5Hz, 3-OH), 4.50 (m, 1H, 19-OH), 5.02 (dd, 1H, *J* = 5.0, 1.5Hz, 6-OH); ^{13}C-NMR (Pyridine-d_5, ppm) 12.8 (CH_3), 18.4 (CH_3), 18.5 (CH_3), 18.7 (CH_3), 22.5 (CH_2), 24.5 (CH_2), 28.5 (CH_2), 29.7 (CH_2), 30.3 (CH_2), 32.4 (CH), 32.6 (CH_2), 35.0 (CH_2), 35.8 (CH), 37.4 (CH_2), 40.9 (CH), 41.2 (CH_2), 42.9 (C), 43.5 (CH_2), 43.8 (C), 46.4 (CH), 56.4 (CH), 57.6 (CH), 64.7 (CH_2), 67.4 (CH), 75.8 (CH), 76.2 (C), 214.2 (C).

6. The physical data of compound **7**: Anal. Calcd. for $C_{27}H_{46}O_5$: (%) C 72.06, H 10.08 Found: C 71.34, H 10.40; FAB-MS *m/z* 451 $(M+H)^+$; IR (KBr, cm^{-1}) 3409, 2937, 2871, 1709, 1463, 1381, 1047, 988; ^{1}H-NMR (DMSO-d_6, ppm) 0.61 (s, 3H, H-18), 0.85 (d, 3H, *J* = 6.5Hz, H-21), 0.99 (d, 6H, *J* = 7.0Hz, H-26 and H-27), 2.60 (m, 1H, *J* = 7.0Hz, H-25), 3.48 (dd, 1H, *J* = 11.0, 6.0Hz, H_a-19), 3.73 (dt, 1H, *J* = 11.5, 4.5Hz, H-6), 3.83 (dd, 1H, *J* = 11.0, 3.5Hz, H_b-19); 3.98 (brs, half width 8.5Hz, 1H, H-3); 4.04 (d, 1H, *J* = 4.0Hz, 3-OH), 4.67 (dd, 1H, *J* = 6.0, 3.5Hz, 19-OH), 5.11 (d, 1H, *J* = 5.0Hz, 6-OH), 5.33 (s, 1H, 5-OH); ^{13}C-NMR (Pyridine-d_5, ppm) 12.2 (CH_3), 18.4 (CH_3), 18.5 (CH_3), 18.7 (CH_3), 20.6 (CH_2), 21.9 (CH_2), 24.4 (CH_2), 28.3 (CH_2), 28.4 (CH_2), 30.2 (CH_2), 30.9 (CH_2), 34.2 (CH), 35.6 (CH), 36.8 (CH_2), 37.4 (CH_2), 40.5 (CH_2), 40.9 (CH), 42.9 (C), 43.2 (CH), 43.9 (C), 56.1 (CH), 57.1 (CH), 65.7 (CH_2), 67.0 (CH), 72.1 (CH), 81.6 (C), 214.2 (C).
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