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Tetrahedron Letters
Tetrahedron Letters 48 (2007) 4987–4989

The fragmentation reaction of 16*R*-bromopregnane-3*S*,20*S*-diol

Jing-Rong Lin,[a] Nan-Yan Zhou,[a] Qi-Hai Xu,[b] Shi-Feng Jian[a] and Wei-Sheng Tian[a,b,*]

[a]*Department of Chemistry, College of Life Sciences and Environment, Shanghai Normal University, Shanghai 200234, China*
[b]*Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin Road, Shanghai 200032, China*

Received 22 January 2007; revised 22 May 2007; accepted 22 May 2007
Available online 25 May 2007

Abstract—16*R*-Bromopregnane-3*S*,20*S*-diol reacted with potassium *t*-butoxide to afford androst-16-en-3*S*-ol in a moderate yield via fragmentation reaction. The latter is a key intermediate for the synthesis of 5α-androst-16-en-3-one, as boar sex pheromone, and other steroidal drugs. In addition, 16*R*,20*S*-epoxypregnane-3*S*-ol was also obtained as a major product by changing the reaction solvent.

Tigogenin **1** (Fig. 1) is a by-product in the hemp-making industry using sisal, and is also an environmental pollutant. Currently, about 500 tons of tigogenin are produced from industrial waste in making hemp annually in China. In connection with our project of organic synthetic chemistry based on the rational utilization of natural resource compounds (i.e., resource chemistry),[1–4] we have finished the direct degradation of tigogenin into (3*S*,16*S*,20*S*)-pregnane-3,16,20-triol **2** and 4*R*-methyl-δ-valerolactone using 30% aqueous hydrogen peroxide on a scale of 10 kg.[5,6] For the further application of pregnane-3,16,20-triol in the synthesis of medicines, pesticides and organic molecules with bioactivity, we also explored its reaction with a variety of chemicals and found that compound **2** can be easily transformed into 16*R*-bromopregnane-3*S*,20*S*-diol diacetate **3** in a good yield through regioselective acetylation–bromination.[7] In connection with this study, we continued to explore the reaction of 16*R*-bromopregnane-3*S*,20*S*-diol **4**, a hydrolysis product derived from **3** (Scheme 1), with KOBu^t. As expected, compound **4** was converted into 5α-androst-16-en-3*S*-ol (**5**) directly via a fragmentation reaction. It is obvious that this fragmentation reaction provided a new and concise method for the synthesis of 5α-androst-16-en-3-ol and its analogues from steroidal sapogenins such as tigogenin. The results about this fragmentation reaction will be reported in this Letter.

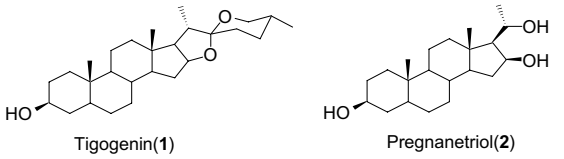
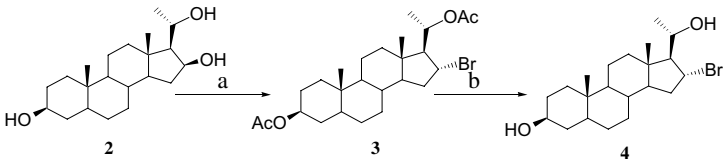


Figure 1.

Compound **4** was easily prepared in the manner depicted in Scheme 1. (3*S*,16*S*,20*S*)-Pregnane-3,16,20-triol



Scheme 1. Preparation of 16*R*-bromopregnane-3*S*,20*S*-diol (**4**). Reagents and conditions: (a) 30% HBr/HOAc, 40–45 °C, 1.5 h; (b) K_2CO_3/MeOH, 40–45 °C, 2 h, 78% in two steps from **2**.

Keywords: Tigogenin; Pregnanetriol; 16*R*-Bromopregnane-3*S*,20*S*-diol; Fragmentation.
* Corresponding author. Tel./fax: +86 21 54925176; e-mail: wstian@mail.sioc.ac.cn

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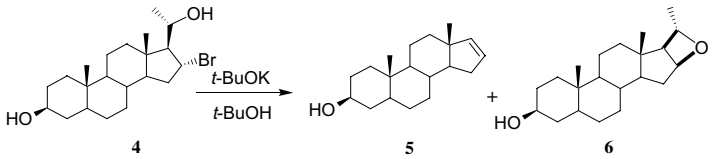
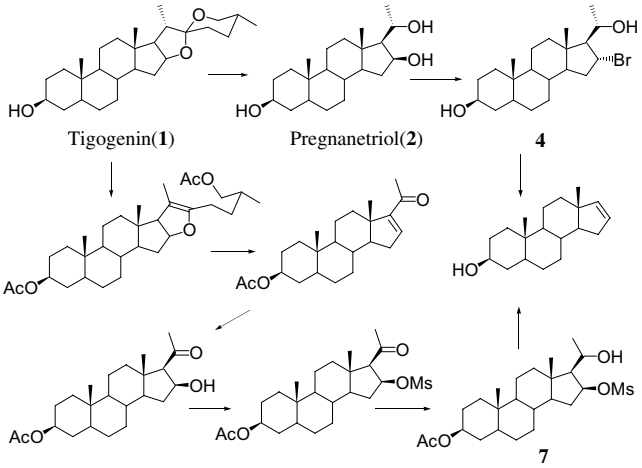
doi:10.1016/j.tetlet.2007.05.126



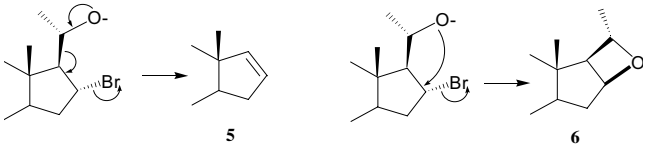
Scheme 2. Fragmentation of 16*R*-bromopregnane-3*S*,20*S*-diol (**4**).

(**2**) reacted with a 30% solution of hydrogen bromide in acetic acid at 45–50 °C to afford 16*R*-bromopregnane-3*S*,20*S*-diol diacetate **3**. Without purification, compound **3** was hydrolyzed to the corresponding 16*R*-bromopregnane-3*S*,20*S*-diol **4** in 78% overall yield from **2** in two steps of the reaction. No signal peak for acetoxy group appeared in the ^{1}H NMR and IR spectra of **4**; this implied that two acetoxy groups of **3** had been hydrolyzed. The structure of **4** was further confirmed by the mass spectrum and elemental analysis.[11]

On treatment of 16*R*-bromopregnane-3*S*,20*S*-diol **4** with 10 equiv of potassium *t*-butoxide in *t*-butyl alcohol under reflux temperature, a fragmentation product androst-16-en-3*S*-ol (**5**) was produced in 52% yield as a major product,[12] and the 16*S*,20*S*-epoxypregnane-3*S*-ol **6** was isolated simultaneously in 46% yield (Scheme 2).[13] The fragmentation product **5** was characterized by NMR and mass spectra even though it is a known compound.[8] The oxetane derivative **6** was also identified by NMR and mass spectra and elemental analysis. Evidence for the oxetane ring formation was derived from the doublet at δ 1.47 ($J = 6.4$ Hz) for the C-21 methyl protons and the multiplet at δ 4.51 for the C-16 methine proton. A similar fragmentation reaction has been reported by Matsyui and Fukushima[8b] with pregnane-3*S*,20*S*-diol 16*S*-mesylate (**7**), in which the fragmentation product **5** was only obtained in poor yield. In addition to the preparation of pregnane-3*S*,20*S*-diol 16*S*-mesylate is not convenient by comparison with 16*R*-bromopregnane-3*S*,20*S*-diol **4** (Scheme 3).



Scheme 3. The comparison of the preparation of 16*R*-pregnane-3*S*,20*S*-diol with pregnane-3,16,20-triol 16-mesylate.



Scheme 4. The possible mechanism for the formation of **5** and **6**.

A plausible mechanism for the formation of **5** and **6** is proposed (Scheme 4). The 16α derivative **4** has *anti*-clinal bond, and the concerted reaction proceeds to give the fragmentation product **5**. Oxetane ring formation may proceed by the intermediate formation of the anion of hydroxyl group, which attacks the backside of C-16 by the displacement of bromine.

The fragmentation reaction was related to the reaction temperature and the results are summarized in Table 1. As Table 1 shows, the reaction time will be shortened and the ratio of **5** and **6** will be also improved along with the raise of reaction temperature. These facts elucidate that a lower temperature is advantageous to the formation of the oxetane product, and a higher temperature is beneficial to the formation of the fragmentation product.

The amount of potassium *t*-butoxide also influenced the fragmentation reaction, but it was not so obvious (Table 2). The increment of the amount of potassium *t*-butoxide caused the yield of **5** to improve slightly, and that of **6** to decline (entries 1–3). But there was no effect on the selectivity of products by using more than

Table 1. The effect of temperature on the reaction[a]

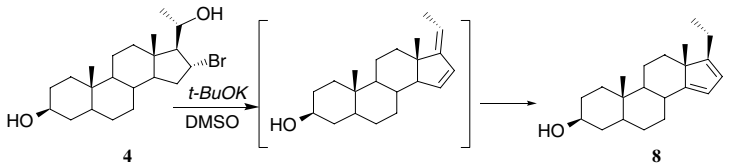
Entry	Temperature (°C)	Time (h)	Yields (%)	
			5	**6**
1	60	18	30	65
2	70	16	39	57
3	82[b]	5	52	46

[a] Reactions were carried out with 10 equiv of *t*-BuOK.
[b] Under reflux.

Table 2. The effect of the amount of KOBu^t on the reaction[a]

Entry	KOBu^t (equiv)	Time (h)	Yields (%)	
			5	**6**
1	3	6	44	52
2	5	5	47	48
3	10	5	52	46
4	15	4.5	52	44

[a] Reactions were carried out under reflux condition.



Scheme 5. The elimination of 16*R*-bromopregnane-3*S*,20*S*-diol (**4**).

10 equiv of potassium *t*-butoxide (entry 4). Then, we prolonged the reaction time, and found that no change in the ratio of product **5**/**6** was observed. This implied that the reaction time had no effect on the fragmentation reaction.

The influence of the solvent was also observed. Besides *t*-butoxy alcohol, dimethyl sulfoxide and dimethyl formamide were explored, respectively. In DMF, the oxetane product **6** was superior, but in DMSO, the predominant product is pregnan-14,16-dien-3*S*-ol (**8**), an elimination-rearrangement product of **4** (Scheme 5). Moreover, the effect of a base such as sodium hydride, lithium aluminium hydride and lithium diisopropylamide was examined. But no satisfactory results were obtained as expected.

In conclusion, the reaction of 16*R*-bromopregnane-3*S*,20*S*-diol with potassium *t*-butoxide has been investigated in detail. According to the reaction condition used, fragmentation, intramolecular etherification and elimination-rearrangement of 16*R*-bromopregnane-3*S*,20*S*-diol with potassium *t*-butoxide occurred, respectively. The desired fragmentation reaction provided a new and concise method for the synthesis of 5α-androst-16-en-3-ol and its analogues from steroidal sapogenins such as tigogenin. The fragmentation product **5** is a key intermediate for the synthesis of 5α-androst-16-en-3-one, as boar sex pheromone.[9] The application of this fragmentation reaction for the synthesis of Pavaulon,[10] a steroidal muscle relaxant, is currently in progress in this laboratory.

Acknowledgements

We are grateful for financial support of this work by the National Science Foundation (Nos. 29372077, 20472052), Shanghai Municipal Education Commission (No. 05DZ18).

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11. *The spectral data of 16R-bromopregnane-3S,20S-diol* (**4**): Mp 165–167 °C, $[\alpha]_D^{25}$ +9.19 (*c* 0.77, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 4.51–4.42 (m, 1H, 16-H), 3.89–3.82 (m, 1H, 20-H), 3.65–3.57 (m, 1H, 3-H), 0.80 (s, 3H, 18-Me), 0.65 (s, 3H, 19-Me); IR (KBr): 3415, 2921, 2847, 1442, 1372, 1041 cm^{-1}; MS (EI) *m*/*z* (intensity): 381 (M^+-18), 365 (M^+-34), 301 (M^+-98). Anal. Calcd for $C_{21}H_{35}O_2Br$: C, 63.15; H, 8.83. Found: C, 63.36; H, 8.47.
12. *The spectral data of androst-16-en-3S-ol* (**5**): Mp 125–127 °C, $[\alpha]_D^{25}$ +13.29 (*c* 1.30, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 5.84–5.83 (m, 1H, 16-H), 5.69 (d, $J = 1.6$ Hz, 1H, 17-H), 3.63–3.56 (m, 1H, 3-H), 0.85 (s, 3H, 18-Me), 0.74 (s, 3H, 19-Me); ^{13}C NMR (400 MHz, $CDCl_3$): δ 144.19, 129.51, 71.52, 56.33, 55.42, 45.80, 45.31, 38.44, 37.08, 36.17, 36.00, 34.34, 32.36, 32.24, 31.74, 28.93, 21.45, 17.31, 12.57; IR (KBr): 3346, 3040, 2938, 1611, 1450, 1368, 1041, 706 cm^{-1}; MS (EI) *m*/*z* (intensity): 292 (M^++18), 257 (M^+-17).
13. *The spectral data of 16S,20S-epoxypregnane-3S-ol* (**6**): Mp 194–196 °C, $[\alpha]_D^{25}$ +19.56 (*c* 1.39, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 5.16–5.10 (m, 1H, 20-H), 4.54–4.49 (m, 1H, 16-H), 3.63–3.56 (m, 1H, 3-H), 1.47 (d, $J = 6.4$ Hz, 3H, 21-Me), 1.18 (s, 3H, 18-Me), 0.83 (s, 3H, 19-Me); ^{13}C NMR (400 MHz, $CDCl_3$): δ 83.85, 76.50, 71.28, 57.06, 56.28, 54.58, 45.05, 40.68, 40.09, 38.35, 37.22, 35.80, 35.13, 34.83, 32.75, 31.67, 28.84, 23.33, 21.59, 16.13, 12.56; IR (KBr): 3444, 2925, 2848, 1446, 1377, 1054, 706 cm^{-1}; MS (EI) *m*/*z* (intensity): 319 (M^++1), 302 (M^+-16), 301 (M^+-17). Anal. Calcd for $C_{21}H_{34}O_2$: C, 79.19; H, 10.76. Found: C, 78.79; H, 10.36.