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Practical synthesis of 16α-bromo-17α-hydroxysteroids via a Raney Ni-catalyzed bromide exchange reaction

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ABSTRACT

D-ring modified glucocorticoids are attractive synthetic targets owing to their broad application in medicinal chemistry. Herein, we reported a practical synthesis of 16α-bromo-17α-hydroxysteroids from easily available 16β-bromo isomers via a Raney Ni-catalyzed bromide exchange reaction. The catalytic Finkelstein-type reaction features high yield, mild reaction condition, short reaction time and simple operation. The method provided an efficient approach to prepare 17α-hydroxy-15-pregnen-20-ones.

Glucocorticoids are of great interest in medicinal chemistry owing to their various biological activities [1]. A strong demand has been created for developing efficient methods to prepare new bioactive molecules with reduced side effects and enhanced efficacy. Substituents and stereochemistry in D ring have been proved to greatly affect the bioactivity of glucocorticoids [2]. For examples, many marketed glucocorticoids have a substituent at the 16-position, such as, dexamethasone (16α-methyl), betamethasone (16β-methyl) and budesonide (16α-hydroxyl).

Several of 17α-hydroxy-15-pregnen-20-ones (I) have revealed antiandrogenic activity [3a] and used as key intermediates in the synthesis of natural products [3d–h]. However, further exploration has been hampered by the lack of convenient synthetic methods (Fig. 1). A one-step preparation of 17α-hydroxy-16-pregnen-20-ones (I) from corresponding 15-pregnen-20-ones (II) by treatment with oxygen in the presence of strong base was first reported by Gardner in 1968 [3a], but the method suffers from low yield and harsh reaction conditions [3a–c]. To prepare the key intermediate (II) for the total synthesis of natural products, Fuchs reported a multi-step route by using allylic bromination as a key step [3d,3e] and Trost developed an alternative synthesis with a dihydroxylation/dehydration

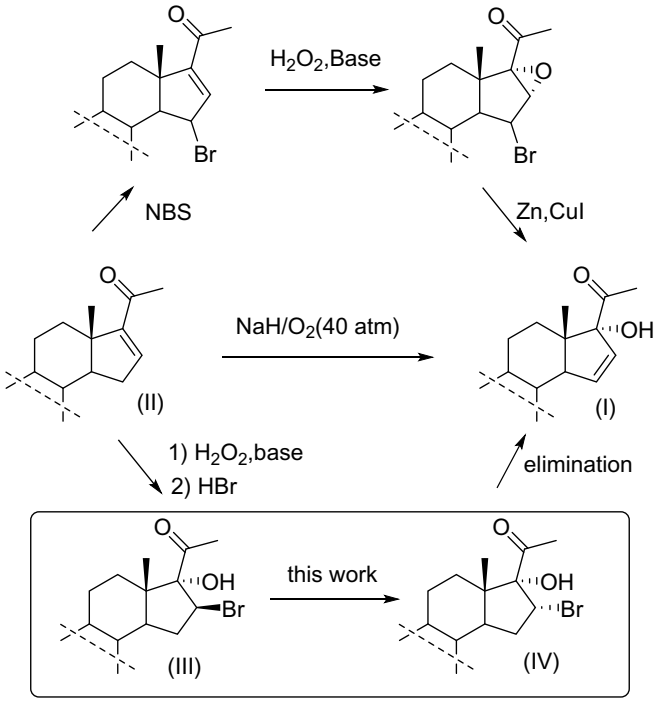

Fig. 1. Synthesis of 17α-hydroxy-15-pregnen-20-ones (I).

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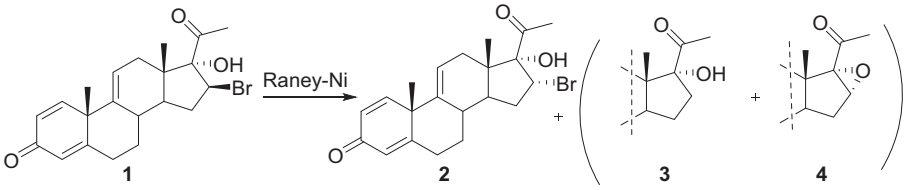
sequence [3f–h]. However, these methods generally suffer from limited substrate scope and unsatisfactory yields. Therefore, it is still highly desirable to develop a convenient method to prepare 17α-hydroxy-15-pregnen-20-ones with broad substrate scope, mild conditions and high yields.

Julian and van Dorp developed a three-step process [4] to introduce 17α-hydroxyl group to produce corticosteroids on an industrial scale from easily available 16-dehydropregnenolone acetate (16-DPA, **18**), in which 16β-bromo-17α-hydroxysteroids (III) are key intermediates. However, our attempt to prepare 17α-hydroxy-15-pregnen-20-ones (I) via direct elimination of the 16-bromo-steroid (III) was unsuccessful due to the formation of corresponding epoxides. In our previous study on the debromination of 16β-bromo-17-α-hydroxysteroid (III) with Raney Ni, it was observed that the product was often contaminated with a small amount of 16α-bromo isomer (IV) (5–10%). Conventional Finkelstein halogen exchange reaction [5] often suffers from a large excess of the halide salt, long reaction time and high reaction temperature. The unusual Raney Ni-catalyzed bromide-exchange reaction can occur under mild condition without additional inorganic bromide in spite of the low yield. The result prompted us to investigate the possibility to prepare 16α-bromosteroids (IV) from easily available 16β-isomer (III). Herein, we reported a Raney Ni-catalyzed bromide exchange reaction, which featured high yields, mild reaction condition and simple operation. On the basis of the method, 17α-Hydroxy-15-pregnen-20-one was efficiently synthesized on a 5-g scale from easily available raw material.

To explore the feasibility of the bromide-exchange, we initiated our studies with bromide **1** and Raney Ni purchased from a commercial supplier. Methanol is the most popular solvent for Raney Ni-debromination reaction, however, only provided desired bromide-exchange product in low yield. A brief screening of solvents revealed acetone as the optimal solvent for the bromide-exchange reaction. Substrate **1** was treated at room temperature with 5 equiv of Raney Ni to offer desired 16-α-bromo isomer **2** in 21% yield (Table 1, entry 1). A small amount of epoxide **4** was simulta-

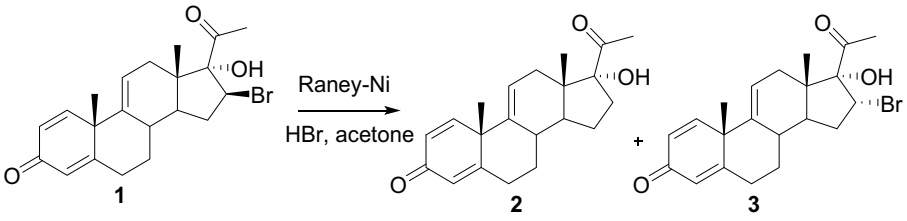
Table 1
Optimization of bromide-exchange reaction.[a]



Entry	Acid (equiv)	Raney-Ni (wt)	Time (h)	Yield[b] 2:3:4
1	——	5	4	1:3.3:0.5
2	0.5(HOAc)	5	2	1:2.5:0
3	0.5(HBr)	5	2	1:0.4:0
4	1.0(HBr)	5	2	<20% conv.
5	0.5(HBr)	3	14	1:0.04:0
6	0.5(HBr)	1	2	NR

[a] 0.25 mmol substrate, 6 mL of acetone, 25 °C.
[b] NMR yield.

Table 2
Optimization of bromide-exchange reaction.[a]



Entry[a]	Raney-Ni (wt)	Time (h)	Solvent (ml)	Yield (%)
1	3	0.5	6	83
2[b]	3	2	6	NR
3	2	10	6	95
4	1.5	14	6	68(72[c])
5	2	6	4.5	96
6	2	3	3	91
7[d]	2	2	3	—(27[c])

[a] 0.25 mmol substrate, 0.5 equiv of HBr, acetone, W2 grade Raney-Ni, rt, HPLC yield.
[b] W1 grade Raney-Ni.
[c] Conversion (%).
[d] 18 °C.

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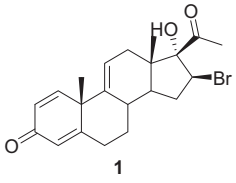
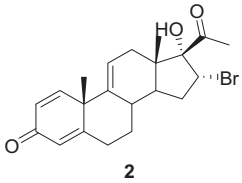
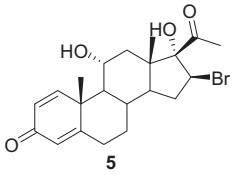
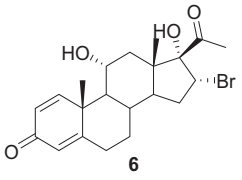
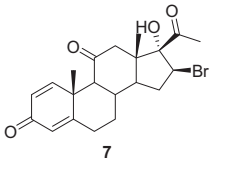
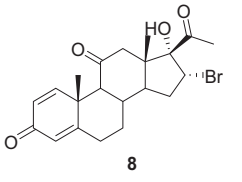
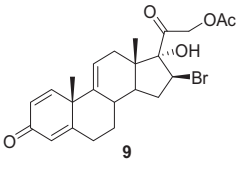
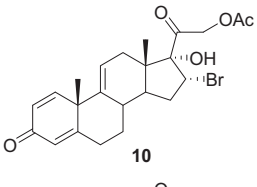
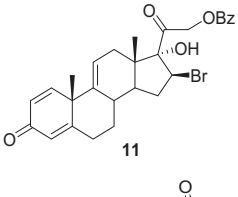
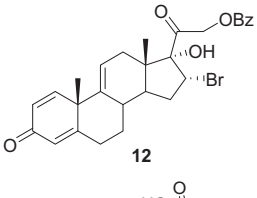
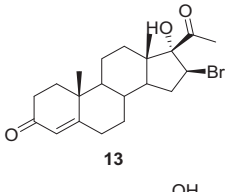
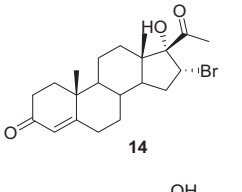
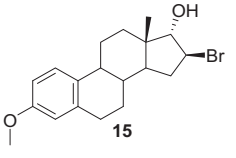
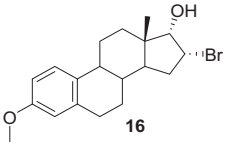
neously formed, which was proposed to be caused by basic Raney Ni and can be suppressed by adding acetic acid (entry 2). When HBr was used to replace acetic acid, the desired isomer **2** was significantly increased (entry 3). However, a further increase in the acidity led to a dramatic decrease of reaction rate (entry 4). The effect of catalyst loading amount was proved to be critical for the chemoselectivity. With 3 equiv of Raney Ni as catalyst, desired 16-α-bromo product **3** was obtained in almost quantitative yield (entry 5). A further decrease of catalyst loading led to a complete recovery of starting material **1** (entry 6).

Because Raney Ni purchased from different suppliers may exhibit different reactivity, further optimizations were performed with freshly-prepared Raney Ni (Table 2). The W2 grade Raney Ni [6a] was much more active than commercial Raney Ni (0.5 h vs 14 h, entry 1). However, W1 grade Raney Ni [6b] did not initiate the reaction (entry 2). With freshly-prepared W2 Raney Ni as catalyst, 2 equiv of catalyst loading provided the best results (entries 3, 4). Increased substrate concentration led to an increase of reaction rate (entries 5, 6). When the concentration of substrate was set to 18 mL/mmol, the best result was obtained

Table 3
Scope of substrates.[a]

Entry	Substrate	Product	Time (h)	Yield (%)[b]
1	 **1**	 **2**	6	95
2	 **5**	 **6**	8	90
3	 **7**	 **8**	6	94
4	 **9**	 **10**	6	91
5	 **11**	 **12**	2	97
6	 **13**	 **14**	17	96(83[c])
7	 **15**	 **16**	6	NR

[a] 0.5 mmol substrate, 9 mL of acetone, 2 equiv of W2 grade Raney-Ni, 25 °C.
[b] Isolated yield.
[c] Conversion (%).

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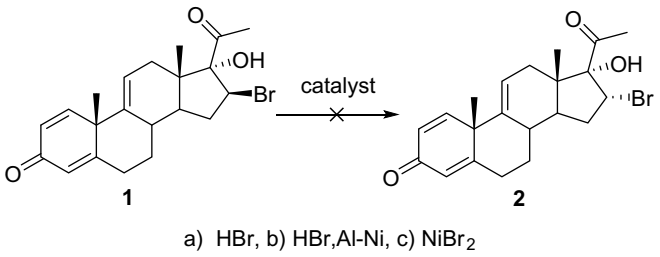
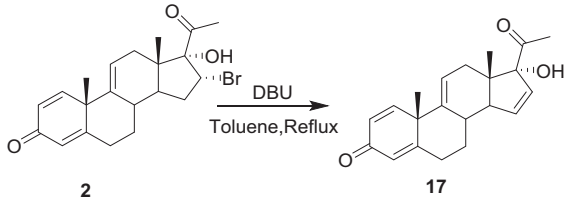
(entry 5). It is noteworthy that a slightly lower temperature led to a significant decrease in reaction rate (entry 7).

With the optimized reaction condition in hand, the substrate scope was investigated (Table 3). The reaction was proved to be robust and gave corresponding 16α-bromo products in >90% yields (entries 1–5) even with substituents at 21-postion (entries 4 and 5). The reaction of 4-ene-3-one compound **13** was sluggish, and required a long reaction time to provide desired product in an acceptable conversion (entry 6). The Finkelstein reaction is an equilibrium reaction, and the driving force of this reaction was proposed to be the formation of the thermodynamically stable product. As expectedly, substrate **15** cannot be transformed into *cis*-form product **16**.



Scheme 1. Bromide exchange reaction with other catalysts.

Table 4
Optimization of elimination reaction.[a]



Entry	Reagent (equiv)	Solvent	Temp. (°C)	Time (h)	Conversion (%)
1	Li_2CO_3/LiBr(5)	DMF	170	4	>99
2	Li_2CO_3(5)	DMF	170	2	<10
3	DBU(5)	Toluene	135	4	40
4[b]	DBU(33)	Toluene	135	8	99(94[c])

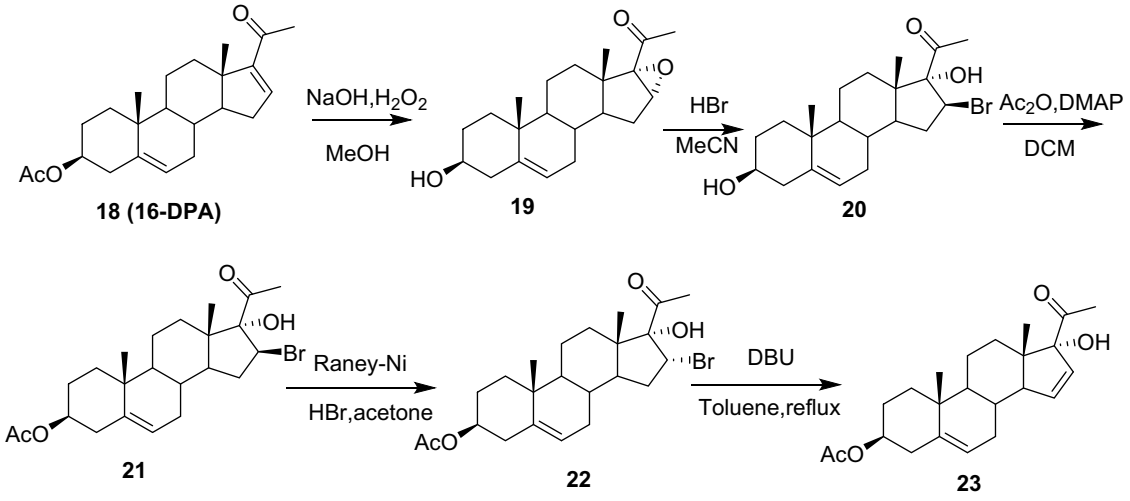
[a] Reaction conditions: 0.1 mmol substrate, 5 equiv of catalyst, 1 mL of solvent, NMR yield.
[b] 0.5 mL of DBU(33equiv), 0.5 mL of toluene.
[c] Isolated yield.

Although the details of reaction mechanism are not yet clear, control experiments showed that Raney Ni was indispensable to the bromide exchange reaction. No reaction was observed with HBr, nickel-aluminium alloy or nickel salt as catalyst (Scheme 1). It is noteworthy that the exchange reaction of 16-chloro or 16-iodo-steroids did not occur under same condition.

With 16α-bromo-17α-hydroxysteroids in hand, we next attempted to prepare 17α-hydroxy-15-pregnen-20-ones via direct elimination (Table 4). As expectedly, classical elimination condition with Li_2CO_3/LiBr [7] gave the epoxy **4** as major product (>80%, entry 1). However, the elimination reaction did not occur in the absence of LiBr (entry 2). The reaction with DBU at high temperature [8] offered desired 17α-hydroxy-15-pregnen-20-one **17** as sole product (entry 3). Complete conversion was observed with 33 equiv of DBU after 8 h, and the desired product **17** was obtained in 94% isolated yield (entry 4).

To illustrate the practical utility of our method, preparation of 17α-hydroxy-15-pregnen-20-one from commercially available 16-dehydropregnenolone acetate (16-DPA, **18**) was realized on a 5 g scale (Scheme 2). Raw material **18** (16-DPA) was transformed into bromide **20** with an almost quantitatively yield according to the conventional method [4]. The direct inversion reaction of bromide **20** was unsuccessful due to its poor solubility in acetone. After acetylation of **20**, the Raney Ni-catalyzed bromide exchange reaction proceeded smoothly to afford the corresponding 16α-bromide **22**, which reacted with DBU to furnish Δ^{15}-steroid **23** in 69% overall yield (5 steps).

In summary, a novel Raney Ni-catalyzed bromide exchange reaction has been developed and applied to the synthesis of 16α-bromo-17α-hydroxysteroids. The method provides an efficient approach for the preparation of 17α-hydroxy-15-pregnen-20-ones from easily available raw materials. Further investigation on the reaction mechanism is under progress.



Scheme 2. Synthesis of Δ^{15}-steroid from 16-DPA.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2019.05.049.

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