

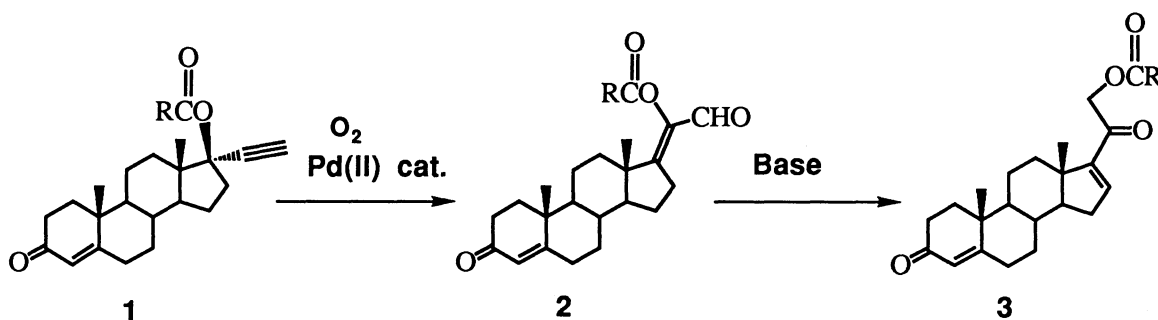
A Short and Efficient Synthetic Method for the Corticosteroid Side-Chain from 17-Keto Steroids

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21-Acyloxy-16(17)-ene-20-keto steroids were synthesized from 17-keto steroids in 4 steps using palladium(II)-catalyzed oxidative rearrangement of propargyl esters as a key reaction.

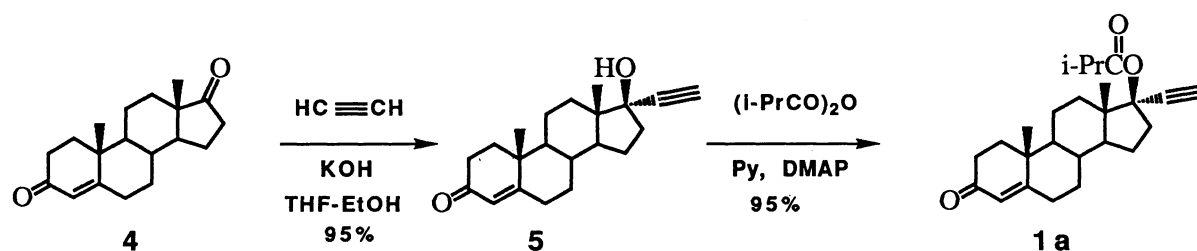
Since the development of the microbial degradation of abundant sterols to 17-keto steroids, a number of synthetic methods for the corticosteroid side-chain from 17-keto steroids have been reported.¹⁾ Among several synthetic targets for the corticosteroid side-chain, 21-hydroxy 16(17)-ene-20-keto steroids have also been important, because they are immediate precursors of the clinically important 16-substituted glucocorticoids.²⁾ However, only a few methods were reported for the synthesis of 21-hydroxy 16(17)-ene-20-keto steroids from 17-keto steroids.³⁾ We describe here a short and efficient synthetic method for 21-acyloxy-16(17)-ene-20-keto steroids from 17-keto steroids using a palladium(II)-catalyzed oxidative rearrangement of propargyl ester.

We have recently reported that propargyl esters were converted to α -acyloxy- α,β -unsaturated aldehydes catalyzed by palladium (II) under oxygen atmosphere.⁴⁾ Applying this reaction, 17 α -ethynyl-17 β -acyloxy androst-4-en-3-ones **1** were oxidized to 20-acyloxy pregna-4,17(20)-dien-3-on-21-als **2** which were easily converted to 21-acyloxy pregna-4,16(17)-diene-3,20-diones **3** using base (Scheme 1).



Scheme 1.

The ethynyl ester **1a** was easily obtained from androst-4-en-3-one (**4**) via the ethynyl alcohol **5** under the usual conditions (Scheme 2). Protection of the 3-keto group in the starting material was not necessary, and the overall yield for the conversion was very high. The isobutyrate **1a** was chosen for the ester moiety from our previous studies on the next oxidation reaction.⁴⁾ Other ethynyl esters **1 b-d** were also synthesized by this method in high overall yields.



Oxidation of the ethynyl ester **1a** to the aldehyde **2a** was performed using Pd(II) catalyst according to our previous study,⁴⁾ and the aldehyde **2a** was afforded in 85% yield using PdBr₂ catalyst in THF. After several examinations of the reaction conditions, we found that the use of K₂PdBr₄ catalyst in DME-H₂O gave better result for the oxidation. As shown in Table 1, several 17 α -ethynyl-17 β -isobutyryloxy-steroids **1** were converted to the corresponding aldehydes **2** in high yields using K₂PdBr₄ catalyst in DME-H₂O.

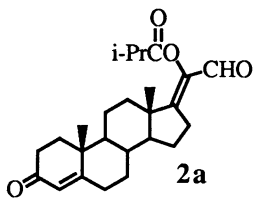
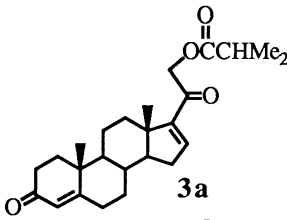
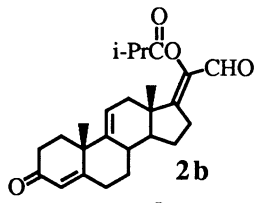
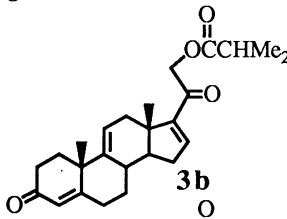
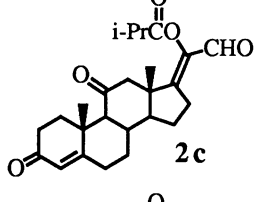
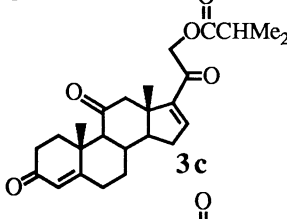
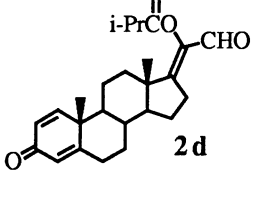
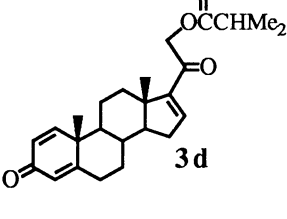
Table 1. Oxidation of 17 α -ethynyl-17 β -isobutyryloxy steroid **1** to 20-isobutyryloxy-17(20)-en-21-al steroid **2** using K₂PdBr₄ catalyst in DME-H₂O under O₂ atmosphere ^{a)}

Entry	Substrate	Time / h	Aldehyde ^{b)} (Z:E) ^{c)}	Isolated yield / %
1		1	 (83:17)	95
2		2	 (96:4)	90
3		2	 (98:2)	92
4		1.5	 (95:5)	90

a) All reactions were carried out with 5 mol% of K₂PdBr₄ in DME-H₂O (3 equiv.) at 65 °C under O₂ (1 atm). b) All the products gave satisfactory NMR, IR, and mass spectra. c) Z:E ratios were determined by ¹H NMR (500 MHz).

The base-catalyzed rearrangement of the aldehydes **2** to 21-acyloxy-16(17)-ene-20-keto steroids **3** was already reported.⁵⁾ However the yield of the conversion by the known procedure was not satisfactory for the practical use (about 60% yield; KOAc, DMF, 60 °C). After screening the reaction conditions, we found that the use of DBU in EtOAc gave better results for the rearrangement. As shown in Table 2, several aldehydes **2** were converted to the corresponding 21-acyloxy-16(17)-ene-20-keto steroids **3** in high yields using DBU in EtOAc.

Table 2. Rearrangement of 20-isobutyryloxy-pregna-4,17(20)-dien-3-on-21-al **2** to 21-isobutyryloxy-pregna-4,16(17)-dien-20-one **3** using DBU in EtOAc ^{a)}

Entry	Substrate	Time / h	Product ^{b)}	Isolated yield / %
1	 2a	8	 3a	95
2	 2b	6	 3b	90
3 ^{c)}	 2c	7	 3c	85
4	 2d	6	 3d	90

a) All reactions were carried out at 50 °C in dry EtOAc under N₂ using 0.5 mmol of the starting material and 0.5 equiv. of DBU unless otherwise noted. b) All the products gave satisfactory NMR, IR, and mass spectra. c) A mixture of EtOAc and DMF (10 : 1) was used as the solvent.

Using the above mentioned procedure, 21-acyloxy 16(17)-ene-20-keto steroids were afforded in 4 steps from cheaply available 17-keto androstan steroids in high over all yields.

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- 6) Analytical data : **1b** ; Mp 182-184 °C; $[\alpha]_D^{25}$ -2.01° (c 1.0, CHCl₃); ¹H NMR (500 MHz, CDCl₃) : δ 5.75 (s, 1H, olefinic), 5.58 (m, 1H, olefinic), 2.90-1.10 (m, 16H, CH, CH₂), 2.60 (s, 1H, acetylenic), 1.36 (s, 3H, CH₃), 1.17 (d, J=7.3 Hz, 6H, isobutyryl CH₃), 0.86 (s, 3H, CH₃); IR (KBr) 3300, 2110, 1745, 1665, 1615, 1200, 1165, 1015, 685, 630 cm⁻¹. **2b** ; Mp 153-155 °C; $[\alpha]_D^{25}$ +131.5° (c 0.5, CHCl₃); ¹H NMR (500 MHz, CDCl₃) : δ 9.60 (s, 1H, CHO), 5.76 (s, 1H, olefinic), 5.52 (m, 1H, olefinic), 3.20-2.80 (m, 2H, C-16 CH₂), 2.82-2.72 (m, 1H, CHMe₂), 2.65-1.10 (m, 15H, CH, CH₂), 1.36 (s, 3H, C-18 CH₃), 1.31 (d, J=6.7 Hz, 3H, isobutyryl CH₃), 1.30 (d, J=6.7 Hz, 3H, isobutyryl CH₃), 0.95 (s, 3H, C-19 CH₃); IR (KBr) 1755, 1685, 1670, 1615, 1135, 865 cm⁻¹ ; MS Found 396.2300, Calcd for C₂₅H₃₂O₄ 396.2301. **3b** ; Mp 110-111 °C; $[\alpha]_D^{25}$ +167.1° (c 0.5, CHCl₃); ¹H NMR (500 MHz, CDCl₃) : δ 6.77 (s, 1H, olefinic), 5.76 (s, 1H, olefinic), 5.55 (m, 1H, olefinic), 5.03 (d, J=16 Hz, 1H, C-21 Ha), 4.90 (d, J=16 Hz, 1H, C-21 Hb), 2.75-2.65 (m, 1H, CHMe₂), 2.65-1.10 (m, 14H, CH, CH₂), 1.36 (s, 3H, C-18 CH₃), 1.24 (d, J=7.3 Hz, 6H, isobutyryl CH₃), 0.89 (s, 3H, C-19 CH₃); IR (KBr) 1730, 1670, 1610, 1585, 960, 935, 790 cm⁻¹ ; MS Found 396.2324, Calcd for C₂₅H₃₂O₄ 396.2301.

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