CHEMISTRY LETTERS, pp. 1705-1708, 1990.

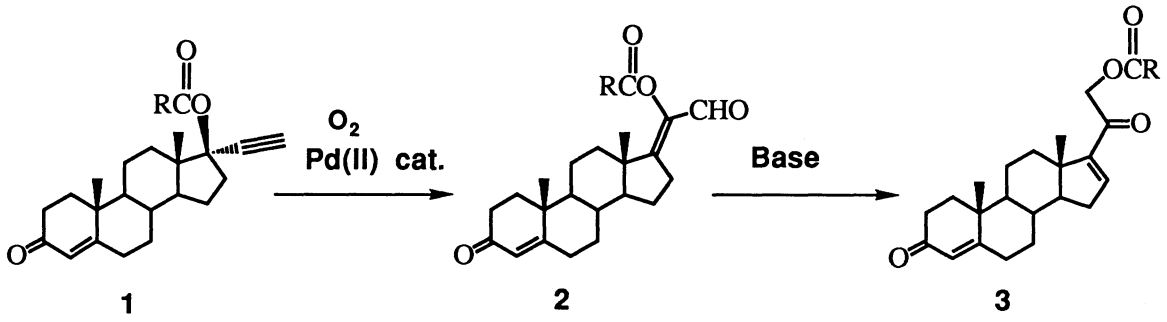
A Short and Efficient Synthetic Method for the Corticosteroid Side-Chain from 17-Keto Steroids

Hideaki KATAOKA, Kiyoshi WATANABE, Ken-ichi MIYAZAKI, Shin-ichiro TAHARA,
Ken-ichi OGU, Rikitaro MATSUOKA, and Kuniaki GOTO*
Nippon Zeon Co., Research & Development Center, 1-2-1 Yako, Kawasaki 210

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.

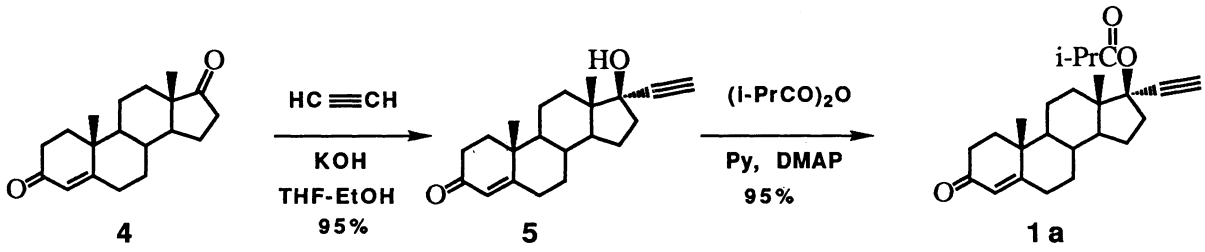
Since the development of the microbial degradation of abundant sterols to 17-keto steroids, a number of synthetic methods for the corticosteroid side-chain from 17-keto steroids have been reported.[1] Among several synthetic targets for the corticosteroid side-chain, 21-hydroxy 16(17)-ene-20-keto steroids 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, 17α-ethynyl-17β-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.

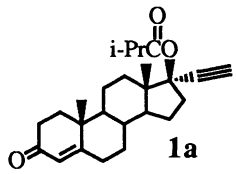
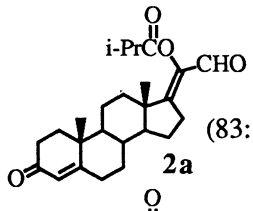
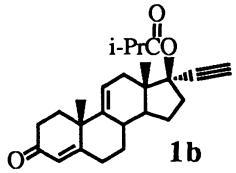
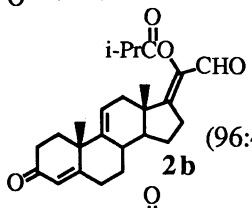
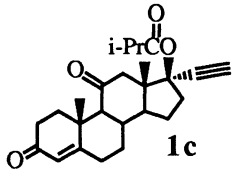
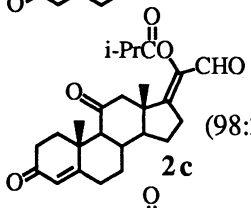
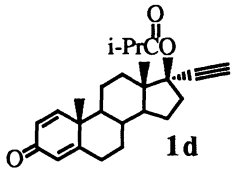
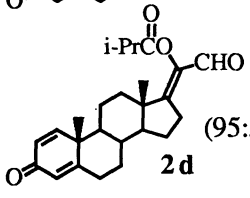
The ethynyl ester **1a** was easily obtained from androst-4-en-3-one (**4**) via the ethynyl alcohol **5** under the usual conditions (Scheme 2). Protection of the 3-keto group in the starting material was not neccesary, and the overall yield for the conversion was very high. The isobutyrate **1a** was 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.



Scheme 2.

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 $PdBr_2$ catalyst in THF. After several examinations of the reaction conditions, we found that the use of K_2PdBr_4 catalyst in DME-H_2O gave better result for the oxidation. As shown in Table 1, several 17α-ethynyl-17β-isobutyryloxy-steroids **1** were converted to the corresponding aldehydes **2** in high yields using K_2PdBr_4 catalyst in DME-H_2O.

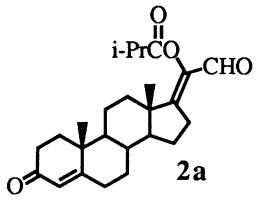
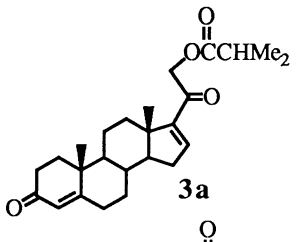
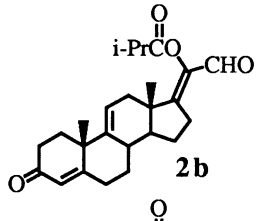
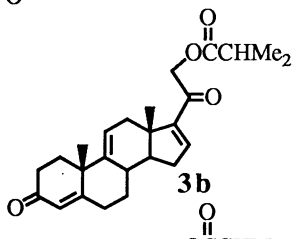
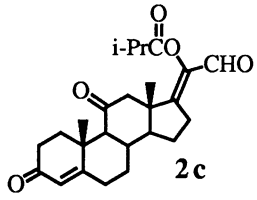
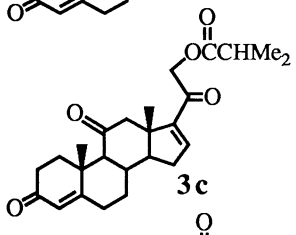
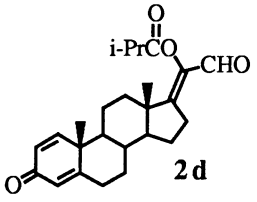
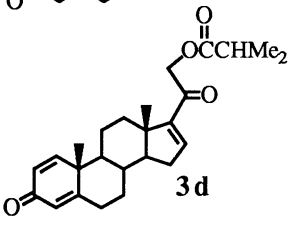
Table 1. Oxidation of 17α-ethynyl-17β-isobutyryloxy steroid **1** to 20-isobutyryloxy-17(20)-en-21-al steroid **2** using K_2PdBr_4 catalyst in DME-H_2O under O_2 atmosphere [a]

Entry	Substrate	Time / h	Aldehyde[b] (Z:E)[c]	Isolated yield / %
1	 **1a**	1	 **2a** (83:17)	95
2	 **1b**	2	 **2b** (96:4)	90
3	 **1c**	2	 **2c** (98:2)	92
4	 **1d**	1.5	 **2d** (95:5)	90

a) All reactions were carried out with 5 mol% of K_2PdBr_4 in DME-H_2O (3 equiv.) at 65 °C under O_2 (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 N_2 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.

References

1) M.Biollaz,W.Haeflinger,E.Velarde, P.Crabbe, and J.H.Fried,*J.Chem.Soc.,Chem.Commun.*,**1971**,1322 ; D.O.Olsen and J.H.Babler, *J.Org.Chem.*, **40**, 255 (1975); G.Ortar, E.Morera, A.Romeo, *ibid.*, **43**, 2927 (1978); M.B.Erman, I.S.Aulchenko, L.A.Kheifits, V.G.Dulova, J.N.Novikov, and M.E.Volpin, *Tetrahedron Lett.*, **34**, 2981 (1976); H.Pauling, D.A.Andrews, and N.C.Hindley, *Helv.Chim.Acta.*, **59**, 1233 (1976); R.H.Wollenberg and R.Peries, *Tetrahedron Lett.*, **37**, 297 (1979); D.H.R.Barton, W.B.Motherwell, and S.Z.Zard, *J.Chem.Soc., Chem.Commun.*, **1981**, 774 ; L.Nedelec, V.Torelli, and M.Hardy, *ibid.*, **1981**, 775; A.R.Daniewski and W.Wojciechowska, *J.Org.Chem.*, **47**, 2993 (1982); *Synthesis*, **1984**, 132 ; G.Neef, U.Eder, A.Seeger, and R.Wiechert, *Chem. Ber.*, **113**, 1184 (1980); D.J.Aberhart and C.Hsu, *J.Org.Chem.*, **43**, 4374 (1978); G.Haffer, U.Eder, G.Neef, G.Sauer, and R.Wiechert, *Chem.Ber.*, **111**, 1533 (1978); R.W.Freerksen, M.L.Raggio, C.A.Thoms, and D.S.Watt, *J.Org.Chem.*, **44**, 702 (1979); M.Gumulka, A.Kurek, and J.Wicha, *Pol.J.Chem.*, **1982**, 56 ; I.Nitta, S.Fujimori, and H.Ueno, *Bull.Chem.Soc.Jpn.*, **58**, 978 (1985); V.H.VanRheenen and K.P.Shephard, *J.Org.Chem.*, **44**, 1582 (1979); I.Nitta, S.Fujimori, T.Haruyama, S.Inoue, and H.Ueno, *Bull.Chem.Soc.Jpn.*, **58**, 981 (1985); S.Solyom, K.Szilagyli, and L.Toldy, *Liebigs Ann.Chem.*, **1987**, 153.

2) R.E.Schaub, G.R.Allen Jr., and M.J.Weiss, *J.Am.Chem.Soc.*, **81**, 4962 (1959); D.Taub, R.D.Hoffsommer, and H.L.Slates, *ibid.*, **82**, 4012 (1960); J.E.Huber, U.S.Patent 4530795; Y.Horiguchi, E.Nakamura, and I.Kuwajima, *J.Org.Chem.*, **51**, 4323 (1986); Y.Horiguchi, E.Nakamura, and I.Kuwajima, *J.Am.Chem.Soc.*, **111**, 6257 (1989).

3) D.Leusen and A.M.Leusen, *Tetrahedron Lett.*, **25**, 2581 (1984); D.H.R.Barton and W.B.Motherwell, EP 87359; E.J.Hessler and V.H.VanRheenen, U.S.Patent 4216159.

4) H.Kataoka, K.Watanabe, and K.Goto, *Tetrahedron Lett.* in press.

5) H.Hofmeister, H.Laurent, G.A.Hoyer, and R.Wiechert, *Chem.Ber.*, **107**, 1235 (1974).

6) Analytical data : **1b** ; Mp 182-184 °C; $[\alpha]_D^{25}$ -2.01° (*c* 1.0,$CHCl_3$); ^1H NMR (500 MHz,$CDCl_3$) : δ 5.75 (s,1H,olefinc), 5.58 (m,1H,olefinic), 2.90-1.10 (m,16H,CH,CH_2), 2.60 (s,1H,acetylenic), 1.36 (s,3H,CH_3), 1.17 (d,J=7.3 Hz,6H,isobutyryl CH_3), 0.86 (s,3H,CH_3); 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,$CHCl_3$); ^1H NMR (500 MHz,$CDCl_3$) : δ 9.60 (s,1H,CHO), 5.76 (S,1H,olefinic), 5.52 (m,1H,olefinic), 3.20-2.80 (m,2H,C-16 CH_2), 2.82-2.72 (m,1H,$CHMe_2$), 2.65-1.10 (m,15H,CH,CH_2), 1.36 (s,3H,C-18 CH_3), 1.31 (d,J=6.7 Hz,3H,isobutyryl CH_3), 1.30 (d,J=6.7 Hz,3H,isobutyryl CH_3), 0.95 (s,3H,C-19 CH_3); IR (KBr) 1755, 1685, 1670, 1615, 1135, 865 cm^{-1} ; MS Found 396.2300, Calcd for $C_{25}H_{32}O_4$ 396.2301. **3b** ; Mp 110-111 °C; $[\alpha]_D^{25}$ +167.1° (*c* 0.5, $CHCl_3$); ^1H NMR (500 MHz,$CDCl_3$) : 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,$CHMe_2$), 2.65-1.10 (m,14H,CH,CH_2), 1.36 (s,3H,C-18 CH_3), 1.24 (d,J=7.3 Hz,6H,isobutyryl CH_3), 0.89 (s,3H,C-19 CH_3); IR (KBr) 1730, 1670, 1610, 1585, 960, 935, 790 cm^{-1} ; MS Found 396.2324, Calcd for $C_{25}H_{32}O_4$ 396.2301.

(Received July 5, 1990)