Simultaneously rapid deprotection of 3-acyloxy groups and reduction of D-ring ketones (nitrile) of steroids using DIBAL-H/$NiCl_2$

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An efficient preparation of hydroxysteroids by a one-pot, simultaneously rapid deprotection of 3-acyloxy groups and reduction of D-ring ketones (nitrile) of steroids using DIBAL-H in the presence of $NiCl_2$ (10 mol %) is described. The attractive features of this procedure for the preparation of the hydroxysteroid derivatives are the mild reaction conditions, short reaction time, excellent yields, clean reaction profiles, and an inexpensive catalyst system.

Keyword: hydroxysteroid, DIBAL-H, $NiCl_2$, Lewis acid

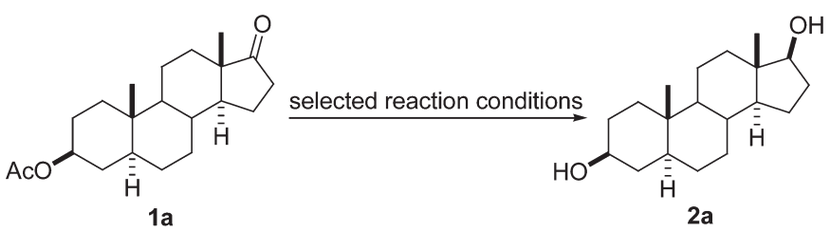
Hydroxysteroids are widespread in animal and human tissues and body fluids, and are also very important intermediates in the metabolism of natural steroids.[1] Investigations have shown that some possess special bioactivities.[2–4] For example, 5α-androstan-3β,17β-diol is a powerful inhibitor of the spread of prostate cancer cells by activation of the estrogen receptor β. 5α-Androstan-3β,17β-diol induces through estrogen receptor β, the appearance of the protein E-cadgerin which inhibits breast and prostate cancer.[5] Moreover, hydroxysteroids are an essential building block for numerous natural products, synthetic pharmaceuticals, and a wide variety of biologically active compounds. 2-Methoxyestradiol prepared from estradiol has been proven to inhibit the proliferation of various cancer cell lines. It inhibits tubulin polymerisation, and it is antiangiogenic.[6] Hydroxysteroids have also found important new applications as the key unit in conjugated anionic metalloporphyrins possessing high selectivity and the ability to work under mild conditions of enzymes. A cationic metalloporphyrin–estradiol conjugate with an anti-estradiol antibody was used as a peroxidase catalyst for oxidation reactions such as the sulfoxidation of thioanisole by H_2O_2 and it was able to catalyse the epoxidation of styrene by oxone ($KHSO_5$) in aqueous medium.[7] It is known that both reactions are typically catalysed by haem-proteins such as peroxidase and cytochrome P450, respectively.

Although a large number of methods exist for the preparation of hydroxysteroids, in general, hydroxysteroids are frequently prepared by multi-step reactions from commercial steroids.[8] For example, reduction of epiandrosterone acetate using $NaBH_4$ in methanol produced 3β-acetoxy-5α-androstan-17β-ol and then basic hydrolysis in methanol gave 5α-androstan-3β,17β-diol.[9] The development of new reductive systems directed towards the preparation of hydroxysteroids continues to be an important synthetic goal in steroid research.

In recent years, diisobutylaluminium hydride (DIBAL-H) and a catalytic amount of dichlorobis(diphenylphosphino)propane nickel [$NiCl_2$(dppp)] system has been employed as a multipurpose reducing agent for a wide range of synthetically useful reactions. It has been recently reported that the removal of the allyl group could be carried out simply and efficiently with diisobutylaluminium hydride (DIBAL-H) and a catalytic amount of dichlorobis(diphenylphosphino)propane nickel [$NiCl_2$(dppp)].[10–13] However, most examples required an expensive ligand such as bis(diphenylphosphino)propane for the catalyst. We report here a highly efficient preparation of hydroxysteroids by a one-pot, simultaneously rapid deprotection of 3-acyloxy groups and reduction of D-ring ketones (nitrile) of steroids using DIBAL-H and requiring the addition of $NiCl_2$ in only 10 mol %.

Results and discussion

Many reductions of steroids have recently been reported in the presence of Lewis acids as promoting reagents. Continuing our research on such reactions, we have investigated the simultaneously rapid deprotection of 3-acyloxy groups and the reduction of D-ring ketone (nitrile) of steroids using a new reductive system: DIBAL-H/$NiCl_2$. The solvent, time, and Lewis acid were varied to optimise the reaction conditions. We first selected (3β,5α)-3-acetoxyandrostan- 17-one (**1a**) to prepare (3β,5α,17β)-androstane-3,17-diol (**2a**) via the reduction reaction with DIBAL-H without any catalyst However, a yield of only 74% of the desired product was obtained (Table 1, entry 1). We then attempted to carry out this reaction with DIBAL-H in the presence of some Lewis acids such as $NiCl_2$, $ZnCl_2$ and $FeCl_3$ (Table 1, entries 2, 3 and 4). DIBAL-H/$NiCl_2$ system proved to be superior, producing the best yield of **2a**. Only 87% and 81% yield was obtained in the presence of $ZnCl_2$ and $FeCl_3$ respectively under the same reaction conditions. Furthermore, when the reaction time was reduced to 10 min 90% yield of **2a** was obtained (Table 1, entry 5). Thus the most appropriate reaction time was 15 min. Among the solvents tested, dichloromethane gave the best result. Low yields were obtained when hexane or toluene was employed as



1a **2a**

Scheme 1 Simultaneously deprotection of 3-acyloxy groups and reduction of 17-ketone of **1a** under varies selected reaction conditions.

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Table 1 The optimum reaction conditions were selected [a]

Entry	Reaction conditions	Yield (%)[b]
1	DIBAL-H /CH_2Cl_2/–78 °C/45 min	74
2	DIBAL-H/$NiCl_2$/CH_2Cl_2/–78 °C/15 min	99
3	DIBAL-H/$ZnCl_2$/CH_2Cl_2/–78 °C/15 min	83
4	DIBAL-H/$FeCl_3$/CH_2Cl_2/–78 °C/15 min	81
5	DIBAL-H/$NiCl_2$/CH_2Cl_2/–78 °C/10 min	90
6	DIBAL-H/$NiCl_2$/hexanes/–78 °C/15 min	87
7	DIBAL-H/$NiCl_2$/toluene/–78 °C/15 min	92
8	DIBAL-H/$NiCl_2$/CH_2Cl_2/–45 °C/15 min	86
9	DIBAL-H/5 mol %$NiCl_2$/CH_2Cl_2/–78 °C/15 min	95[c]

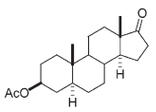
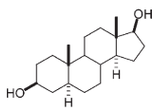
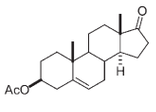
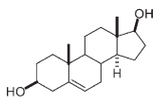
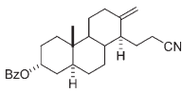
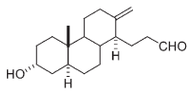
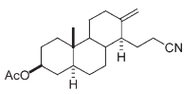
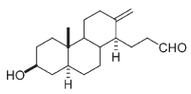
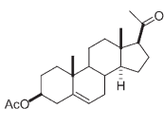
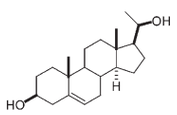
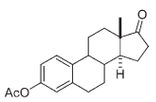
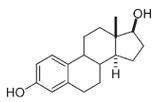
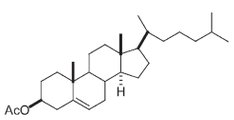
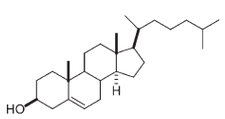
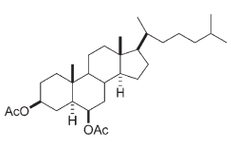
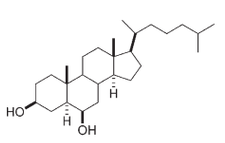
[a](3β,5α)-3-acetoxyandrostan-17-one (**1a**) (1.5 mmol), DIBALH (4.5 mmol), Lewis acid (0.15 mmol), solvent (30 mL), –78°C – –45°C, 10–45 min.
[b]Isolated yields.
[c]Lewis acid $NiCl_2$ (0.075 mmol).

the solvent (Table 1, entries 6 and 7). After some experimentation, it was found that the model reaction using the reaction temperature –78 °C produced the corresponding compound **2a** in excellent yield. However, when the reaction temperature was raised to –45 °C the yield of **2a** was reduced to 86% (Table 1, entry 8). Some dependence was also observed on the amount of $NiCl_2$ that was used. A satisfactory result was obtained in the presence of 5 mol % $NiCl_2$ (Table 1, entry 9), and an almost quantitative yield of the product was obtained when the catalyst loading was increased to 10 mol % (Table 1, entry 2).

The scope and limitations of this reaction under the optimised conditions were explored using a variety of steroids, as summarised in Table 2. In general, the acyl group was removed easily from 3- or 6-acyloxyposition of the steroids. The reduction of D-ring bearing ketone functional group at different positions was completed smoothly in less than 15 min to generate the corresponding products in excellent yields. However the nitrile group was reduced by DIBAL-H in the presence of $NiCl_2$ over a longer period (15 to 30 min) and afforded the corresponding aliphatic aldehydes in high yields. (Scheme 2) Studies showed that the esters were reduced to aldehydes via the formation of an intermediate hemiacetal by 1 equiv. DIBAL-H,[14] and the esters might be reduced directly to alcohols via the formation of distinct alkoxyalumino intermediates using 2 to 4 equiv. of DIBAL-H.[15] After the completion of reduction reaction, the work-up procedure was normally carried out t by adding dilute hydrochloric acid which not only destroyed excess DIBAL-H and disrupted the reductant-aluminum complex but also catalysed the hydrolysis of the intermediate hemiacetal.

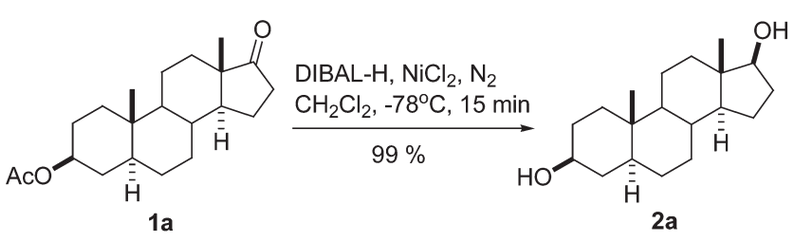
In conclusion, a novel and efficient preparation of hydroxysteroids by a one-pot, simultaneously rapid deprotection of 3-acyloxy groups and the reduction of D-ring ketone (nitrile) of steroids using DIBAL-H and requiring the addition of $NiCl_2$ in only 10 mol % has been described. The attractive features of this procedure are the mild reaction conditions, short reaction time, high efficiency (in excellent yields), clean reaction profiles, and inexpensive catalyst system. The novelty and synthetic utility of this methodology has been demonstrated by the efficient synthesis of hydroxysteroid derivatives.

Table 2 Varies steroids bearing 3-acyloxy and D-ring ketone (or nitrile) were treated with DIBAL-H/$NiCl_2$ system

Entry	Starting steroid(**1**)	Product steroid(**2**)	Time /min	Yield /%
a			15	99
b			15	99
c			30	90
d			30	92
e			12	99
f			15	99
g			15	98
h			15	96

Experimental

All melting points were determined on a Yanaco melting point apparatus and are uncorrected. IR spectra were recorded on a Nicolet FT-IR 5DX spectrometer as KBr pellets. The ^1H NMR and ^{13}C NMR



Scheme 2 Typical reaction of steroids using DIBAL-H/$NiCl_2$ system.

spectra were recorded on a Bruker ACF-300 spectrometer with TMS as internal reference. The *J* values are given in hertz. Optical rotations were determined on a Perkin-Elmer 343 polarimeter. The elemental analyses were performed on a Perkin-Elmer 240C instrument.

General procedure for the simultaneously rapid deprotection of 3-acyloxys group and reduction of D-ring ketones (nitrile) of steroids using DIBAL-H/$NiCl_2$

DIBALH (3.0 mL, 4.5 mmol, 1.5 M in toluene) and $NiCl_2$ (19.5 mg, 0.15 mmol) was added to a solution of the steroid (1.5 mmol) in dichloromethane (30 mL) under N_2 at –78 °C. After an appropriate reaction time (TLC showed that the starting material disappeared completely), 1 N HCl (12 mL) was added. The reaction mixture was warmed to room temperature and poured into water (50 mL) and extracted with CH_2Cl_2 (3 × 15 mL). The combined organic phases were washed with water (2 × 15 mL). Evaporation of the solvent gave a white solid or an oil which was purified by chromatography (silica gel, 10% EtOAc in CH_2Cl_2) to yield the anticipated steroids.

*(3*β,5α,17β*)-Androstane-3,17-diol* (**2a**): Prepared from (3β,5α)-3-acetoxyandrostan- 17-one (**1a**) according to the above procedure. **2a** (99% yield) was obtained as needles: m.p. 168–170 °C ($CHCl_3$), lit. m.p. 161°C[16]; 163–165°C[9]; $[\alpha]^{20}_D$ = +6.20° (c = 0.550, $CHCl_3$); IR 3473, 3391, 3236, 1444, 1072, 1055, 1026 cm^{-1}; ^1H NMR δ 3.62 (m, 2H), 2.05 (m, 1H), 0.82 (s, 3H), 0.73 (s, 3H); ^{13}C NMR δ 81.93, 71.25, 54.46, 51.00, 44.90, 42.97, 38.16, 37.02, 36.73(2C), 35.53, 31.60, 30.49, 28.55, 23.36, 20.81, 12.32, 11.11. Anal. Calcd for $C_{19}H_{32}O_2$: C, 78.03; H, 11.03. Found: C, 78.15; H, 11.20%.

*(3*β,17β*)-Androst-5-ene-3,17-diol* (**2b**): Prepared from (3β)-3-acetoxyandrost-5-en- 17-one (**1b**) according to the above procedure. **2b** (99% yield) was obtained as needles: m.p. 180–181°C (EtOAc) (lit.[8] 181°C, EtOAc); $[\alpha]^{20}_D$ = –51.31° (c = 0.267, MeOH); IR 3474, 3386, 3216, 1667, 1462, 1434, 1082, 1051, 1028 cm^{-1}; ^1H NMR (300 Hz, $CDCl_3$) δ 5.35 (d, *J* = 4.8 Hz, 1H), 3.65 (t, *J* = 8.7 Hz, 1H), 3.52 (m, 1H), 2.27 (m, 2H), 2.04 (m, 2H), 1.02 (s, 3H), 0.76 (s, 3H); ^{13}C NMR (75 Hz, CD_3OD) δ 142.48, 122.40, 82.62, 72.56, 52.85, 52.05, 44.00, 43.19, 38.74, 38.04, 37.92, 33.47, 32.79, 32.44, 30.78, 24.52, 21.97, 20.07, 11.67. Anal. Calcd for $C_{19}H_{30}O_2$: C, 78.57; H, 10.41. Found: C, 78.65; H, 10.20%.

3-((2R,4aS,4bS,8S,8aS,10aS)-*Tetradecahydro-2-hydroxy-4a-methyl-7-methylenephenanthren-8-yl)propanal* (**2c**):[17] Prepared from (1S,4aS,4bS,7R,8aS,10aS)-1-(2-cyanoethyl)-tetradecahydro-4b-methyl-2-methylenephenanthren-7-yl benzoate (**1c**) according to the above procedure. **2c** (90 % yield) was obtained as an oil: $[\alpha]^{20}_D$ = –24.58° (c = 0.8625, $CHCl_3$); IR 3401, 3080, 2718, 1722, 1643 cm^{-1}; ^1H NMR δ 9.71 (t, *J* = 1.2 Hz, 1H), 4.67 (s, 1H), 4.41 (s, 1H), 3.97 (m, 1H), 0.63 (s, 3H); ^{13}C NMR δ 202.74, 150.60, 104.69, 66.06, 53.17, 47.63, 41.92, 38.25, 36.82, 36.18, 35.47, 31.95, 31.51, 28.72, 28.25, 27.14, 19.26, 10.90. Anal. Calcd for $C_{19}H_{30}O_2$: C, 78.57; H, 10.41. Found: C, 78.70; H, 10.24%.

3-((2S,4aS,4bS,8S,8aS,10aS)-Tetradecahydro-2-hydroxy-4a-methyl-7-methylenephenanthren-8-yl)propanal (**2d**): Prepared from (1S,4aS,4bS,7S,8aS,10aS)-1-(2-cyanoethyl)-tetradecahydro-4b-methyl-2-methylenephenanthren-7-yl acetate (**1d**) according to the above procedure. **2d** (92 % yield) was obtained as an oil: $[\alpha]^{20}_D$ = –21.10° (c = 4.322, $CHCl_3$); IR 3391, 3080, 2720, 1722, 1643 cm^{-1}; ^1H NMR δ 9.77 (t, *J* = 1.2 Hz, 1H), 4.73 (s, 1H), 4.47 (s, 1H), 3.59 (m, 1H), 0.73 (s, 3H); ^{13}C NMR δ 202.74, 150.45, 104.81, 70.88, 53.22, 47.60, 44.03, 42.00, 41.33, 37.72, 36.84, 36.78, 35.65, 31.60, 31.16, 28.38, 27.58, 19.31, 12.04. Anal. Calcd for $C_{19}H_{30}O_2$: C, 78.57; H, 10.41. Found: C, 78.75; H, 10.20%.

*(3*β, *17*β, *20*β*)-Pregn-5-en-3,20-diol* (**2e**): Prepared from (3β, 17β)-3-acetoxypregn-5-en-20-one (**1e**) according to the above procedure. **2e** (99 % yield) was obtained as needles: m.p. 211–212°C (MetOH) (lit.[18–19] 211–211.5°C, EtOH); $[\alpha]^{20}_D$ = –77.42° (c = 0.186, MeOH); IR 3422, 3386, 1639, 1464, 1436, 1376, 1053 cm^{-1}; ^1H NMR (300 Hz, CD_3OD) δ 5.34 (d, *J* = 5.1 Hz, 1H), 3.63 (m, 1H), 3.38 (m, 1H), 1.10 (d, *J* = 6.3 Hz, 3H), 1.03 (s, 3H), 0.78 (s, 3H); ^{13}C NMR (75 Hz, CD_3OD) δ 142.44, 122.54, 72.59, 70.99, 59.49, 57.86, 52.02, 43.64, 43.19, 40.95, 38.72, 37.87, 33.30, 33.26, 32.45, 26.96, 25.76, 23.92, 22.19, 20.04, 12.74. Anal. Calcd for $C_{21}H_{34}O_2$: C, 79.19; H, 10.76. Found: C, 79.05; H, 10.50%.

*17*β*-Estradiol* (**2f**): Prepared from 3-acetoxy-1,3,5(10)-estratrien-17-one (**1f**) according to the above procedure. **2f** (99 % yield) was obtained as needles: m.p. 174–176°C (MeOH) (lit.[20] 178–179.5°C); $[\alpha]^{20}_D$ = +80.10° (c = 0.586, dioxane); IR 3531, 3403, 1614, 1585, 1497, 1449, 1251, 1054 cm^{-1}; ^1H NMR (300 Hz, CD_3OD) δ 7.06 (d, *J* = 8.7 Hz, 1H), 6.52 (d, *J* = 8.7 Hz, 1H), 6.47 (s, 1H), 3.64 (t, *J* = 8.4 Hz, 1H), 2.74 (m, 2H), 2.06 (m, 1H), 0.76 (s, 3H); ^{13}C NMR (75 Hz, CD_3OD) δ 156.04, 138.95, 132.77, 127.37, 116.20, 113.87, 82.67, 51.44, 45.51, 44.52, 40.67, 38.18, 30.86(2C), 28.69, 27.75, 24.18, 11.86. Anal. Calcd for $C_{18}H_{24}O_2$: C, 79.37; H, 8.88. Found: C, 79.15; H, 8.70%.

Cholesterol (**2g**): Prepared from 3-acetylcholesterol (**1g**) according to the above procedure. **2g** (98 % yield) was obtained as needles: m.p. 148–150°C (EtOAc) (lit.[21] 148–150°C, EtOAc); $[\alpha]^{20}_D$ = –39.10° (c = 0.886, $CHCl_3$); IR 3430, 1466, 1376, 1057 cm^{-1}; ^1H NMR (300 Hz, $CDCl_3$): δ 3.35 (d, *J* = 5.1 Hz, 1H), 3.52 (m, 1H), 1.01 (s, 3H), 0.91 (d, *J* = 6.3 Hz, 3H), 0.86 (d, *J* = 6.3 Hz, 6H), 0.68 (s, 3H); ^{13}C NMR (75 Hz, $CDCl_3$): δ 140.74, 121.69, 71.76, 56.72, 56.11, 50.09, 42.27(2C), 39.74, 39.48, 37.22, 36.46, 36.15, 35.76, 31.86(2C), 31.63, 28.20, 27.92, 24.25, 23.80, 22.80, 22.54, 21.05, 19.37, 18.68, 11.82. Anal. Calcd for $C_{27}H_{46}O$: C, 83.87; H, 11.99. Found: C, 83.65; H, 11.70%.

*6*β*-Hydroxy cholestanol* (**2h**): Prepared from 3β,6β-diacetoxy-5a-cholestane (**1h**) according to the above procedure. **2h** (96 % yield) was obtained as needles: m.p. 168–150°C (EtOAc) (lit.[22] 168°C, EtOAc); $[\alpha]^{20}_D$ = –32.16° (c = 0.572, $CHCl_3$); IR 3438, 1400, 1380, 1006, 980, 786 cm^{-1}; ^1H NMR (300 Hz, $CDCl_3$): δ 3.88 (m, 1H), 3.60 (m, 1H), 1.03 (s, 3H), 0.95 (d, *J* = 6.3 Hz, 3H), 0.91 (d, *J* = 6.3 Hz, 6H), 0.65 (s, 3H); ^{13}C NMR (75 Hz, $CDCl_3$): δ = 71.88, 71.20, 57.18, 56.78, 53.86, 47.22, 42.52(2C), 40.60, 39.78, 39.22, 37.30, 35.88, 35.76, 35.42, 31.36(2C), 30.40, 28.70, 27.86, 24.58, 23.53, 23.19, 21.06, 19.42, 16.50, 12.18. Anal. Calcd for $C_{27}H_{48}O_2$: C, 80.14; H, 11.96; found C 80.02, H 11.78%.

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