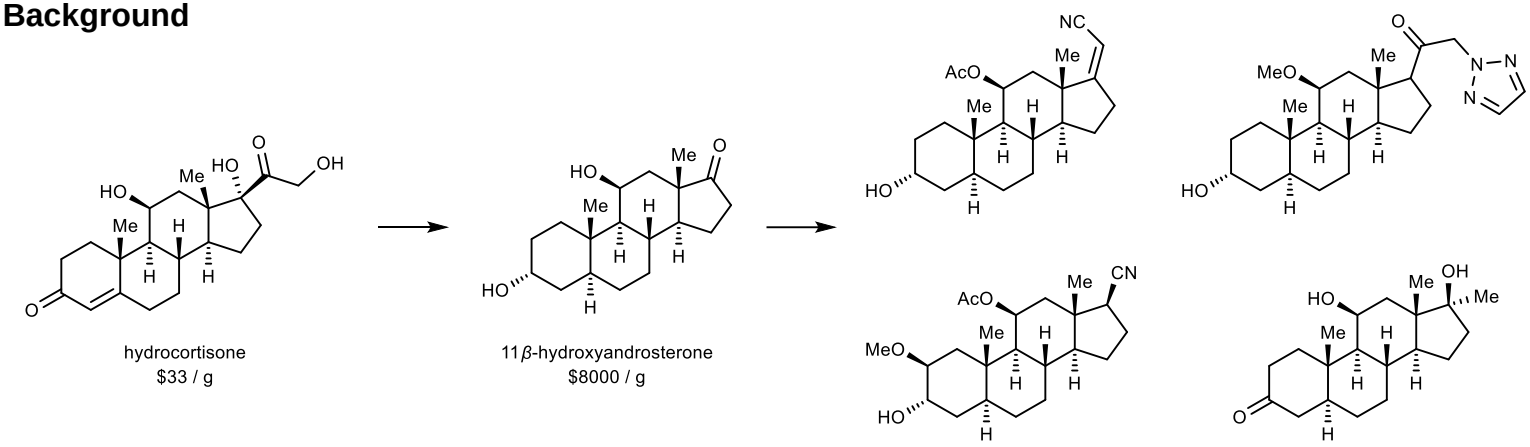
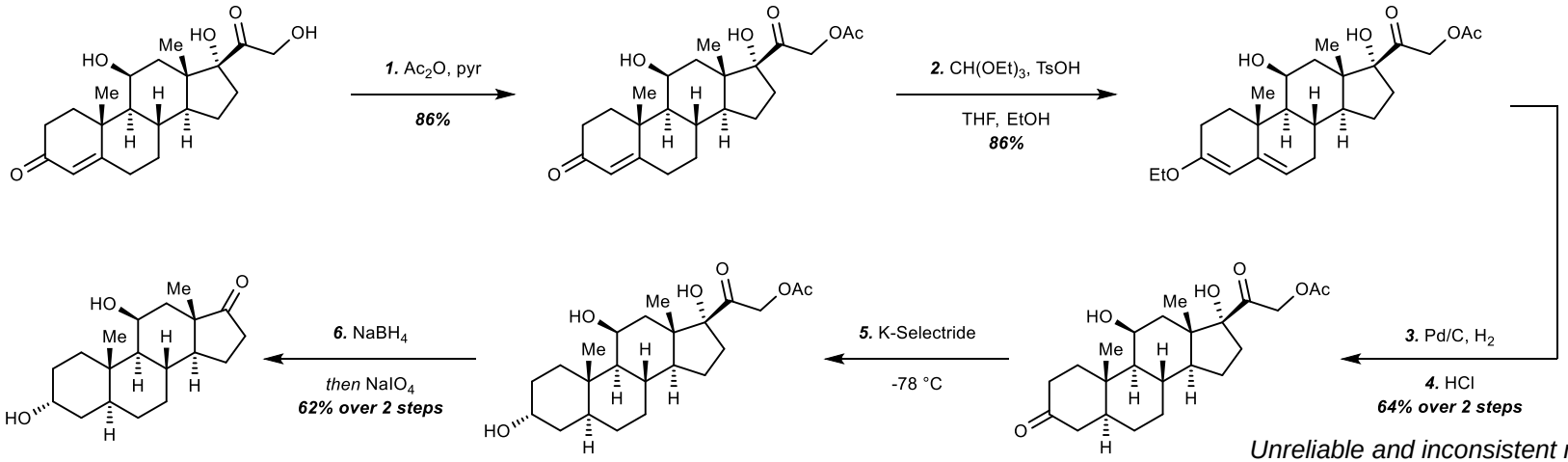
11β-Hydroxyandrosterone (CR Horizons)

Background



Useful intermediate for many drug molecules

Sage Therapeutics (2015, gram scale)



Unreliable and inconsistent reduction (37% in another patent)

Side reaction: enone formation

Abas, H.; Blencowe, P.; MacDonald, E.; Stanway, E.; Talbot, E. P. A.; Wang, H.; Watson, M.; Zhang, J.; Harwood, L. A. Kilogram-Scale Synthesis of 11β-Hydroxyandrosterone. *Org. Process Res. Dev.* **2024**, *28*, 2692–2701 https://doi.org/10.1021/acs.oprd.4c00084

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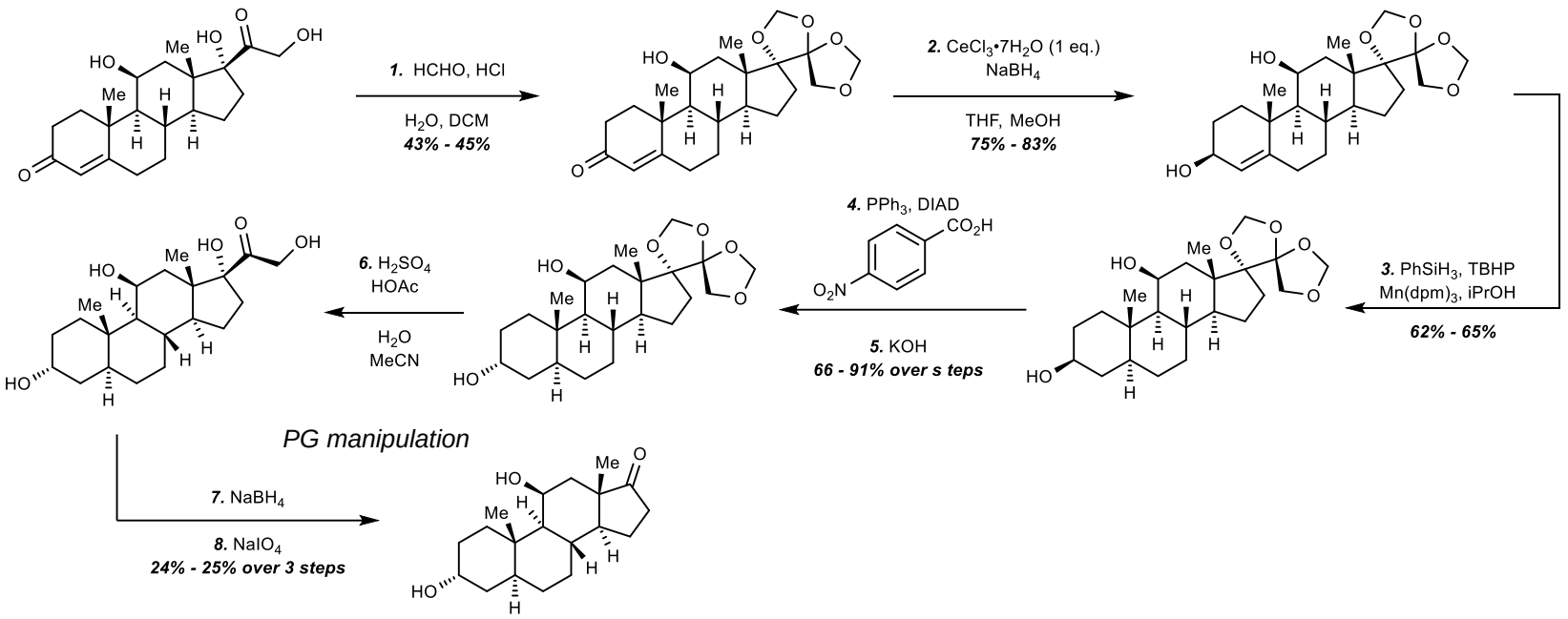
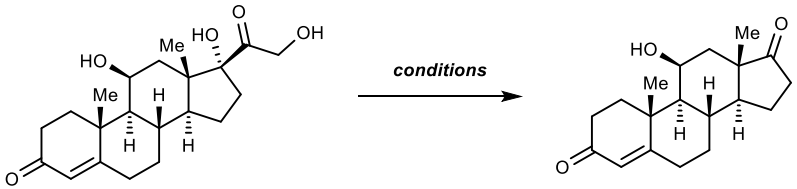
Discovery Route

Wrong epimer formed



Optimization of Decarbonylation



Reagent(s)	Solvent	Time (h)	Conversion (%)	HPLC Yield (%)
$NaBH_4$ then $NaIO_4$	EtOH	12	100	57
$NaBH_4$ then $VO(acac)_2$	EtOH	12	100	0
NaOMe	dioxane	3	94	85
		10	100	89
NaOEt	EtOH	3	24	15
		10	57	42
NaOtBu	tBuOH	3	*decomposition*	
NaOMe	dioxane	16	94	73%[a]

[a]: isolation yield at 2.5 kg scale, under 110 °C

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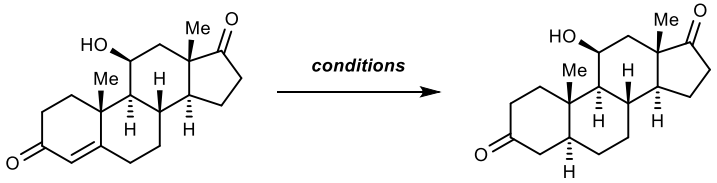
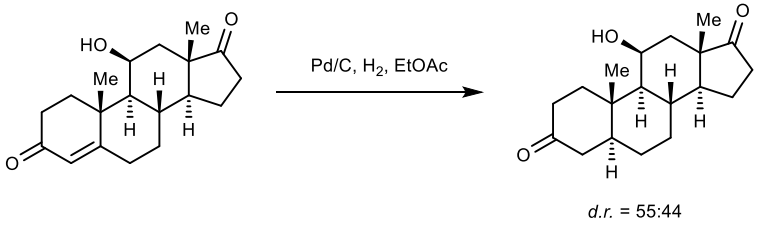
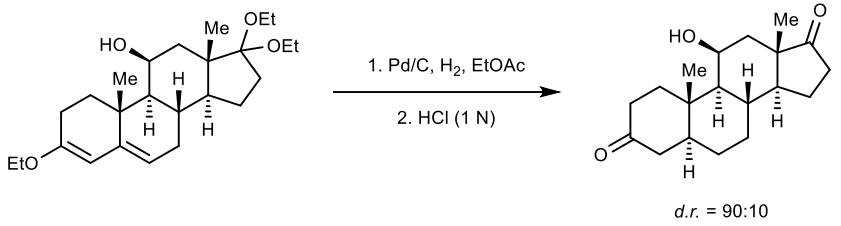
11β-Hydroxyandrosterone (CR Horizons)

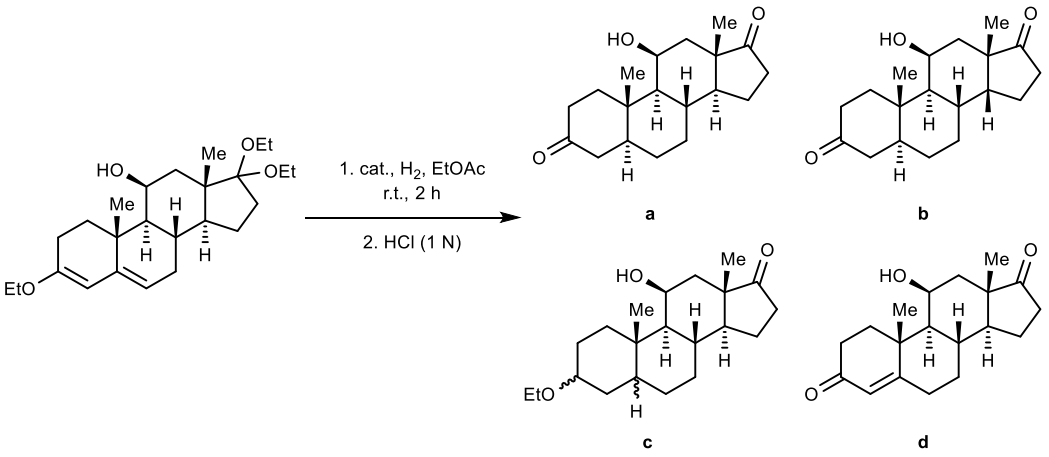
Optimization of Hydrogenation



Conditions	Time (h)	Conversion (%)	Ratio (SM / Pdt)
$Fe(acac)_2$ (1 eq.), $PhSiH_3$, TBHP, DCM, r.t.	overnight	0	-
$Mn(dpm)_3$ (0.1 eq.), $PhSiH_3$, TBHP, THF, r.t.	overnight	8	12.9:1.1
$Mn(dpm)_3$ (0.1 eq.), $PhSiH_3$, TBHP IPA:EtOAc:DCM, r.t.	overnight	11	22.0:2.8







Catalyst (loading in wt%)	Base	HPLC Yield (a / b / c / d)
20 wt% $Pd(OH)_2$/C (10%)	-	57.5 / 23.5 / 11.8 / 0
5 wt% $Pd/BaSO_4$ (30%)	-	25.2 / 30.7 / 0 / 55
5 wt% Pt/C (10%)	-	52.1 / 20.2 / 27.7 / 0
10 wt% Pd/C (5%)	-	45.1 / 8.7 / 40 / 2
5 wt% Rh/C (10%)	-	72.6 / 2.5 / 19.9 / 1.2
5 wt% Rh/C (10%)	$CaCO_3$ (1 eq.)	47.8 / 5 / 39.1 / 0
5 wt% Rh/C (10%)	Et_3N (1 eq.)	45.8 / 2.5 / 0 / 51.2
5 wt% Rh/C (10%)	Et_3N (2 eq.)	0.1 / 0.5 / 0 / 99.2
5 wt% Rh/C (20%)	Et_3N (0.5 eq.)	45.7 / 1.6 / 0.2 / 52.3
5 wt% Rh/C (30%)	Et_3N (0.5 eq.)	92.3 / 1.5 / 4.7 / 0
5 wt% Rh/C (35%)	Et_3N (0.5 eq.)	96.3 / 1.9 / 1.3 / 0
5 wt% Rh/C (40%)	Et_3N (0.5 eq.)	95.4 / 1.9 / 1 / 0

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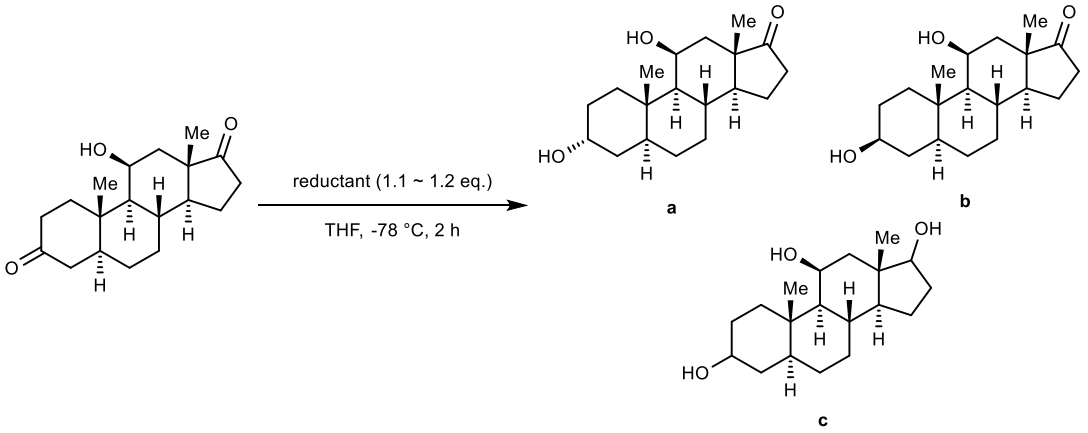
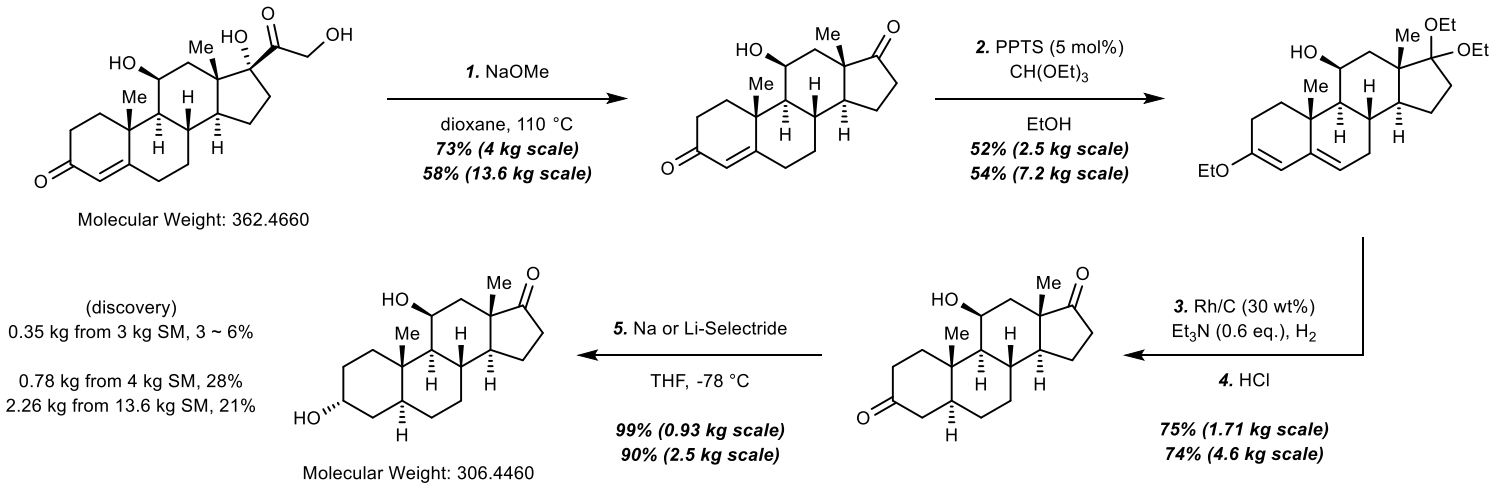
11β-Hydroxyandrosterone (CR Horizons)

Optimization of Reduction



Reductant	HPLC Yield (a + b / c, *d.r.* of a / b)
$LiEt_3BH$	58 / 6, 1:18
$NaEt_3BH$	56 / 0, -
Li-Selectride	67 / 32, 1:1
Na-Selectride	97 / 2, 23:1
K-Selectride-1	93 / 7, 8.3:1
K-Selectride-2	97 / 1, 8.7 /1

Process Route



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