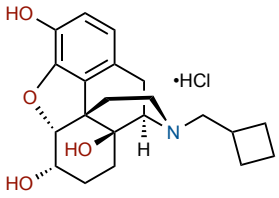
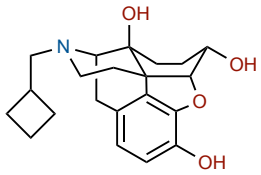
One-pot process for nalbuphine hydrochloride

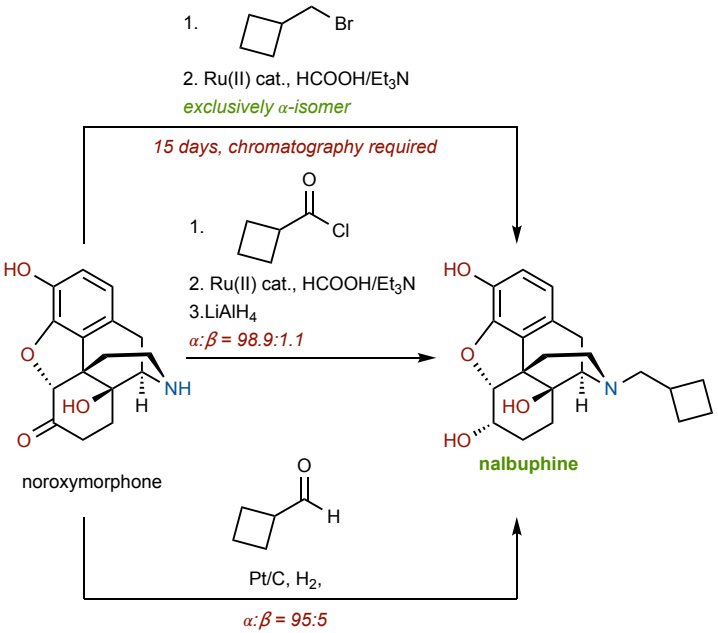


nalbuphine hydrochloride

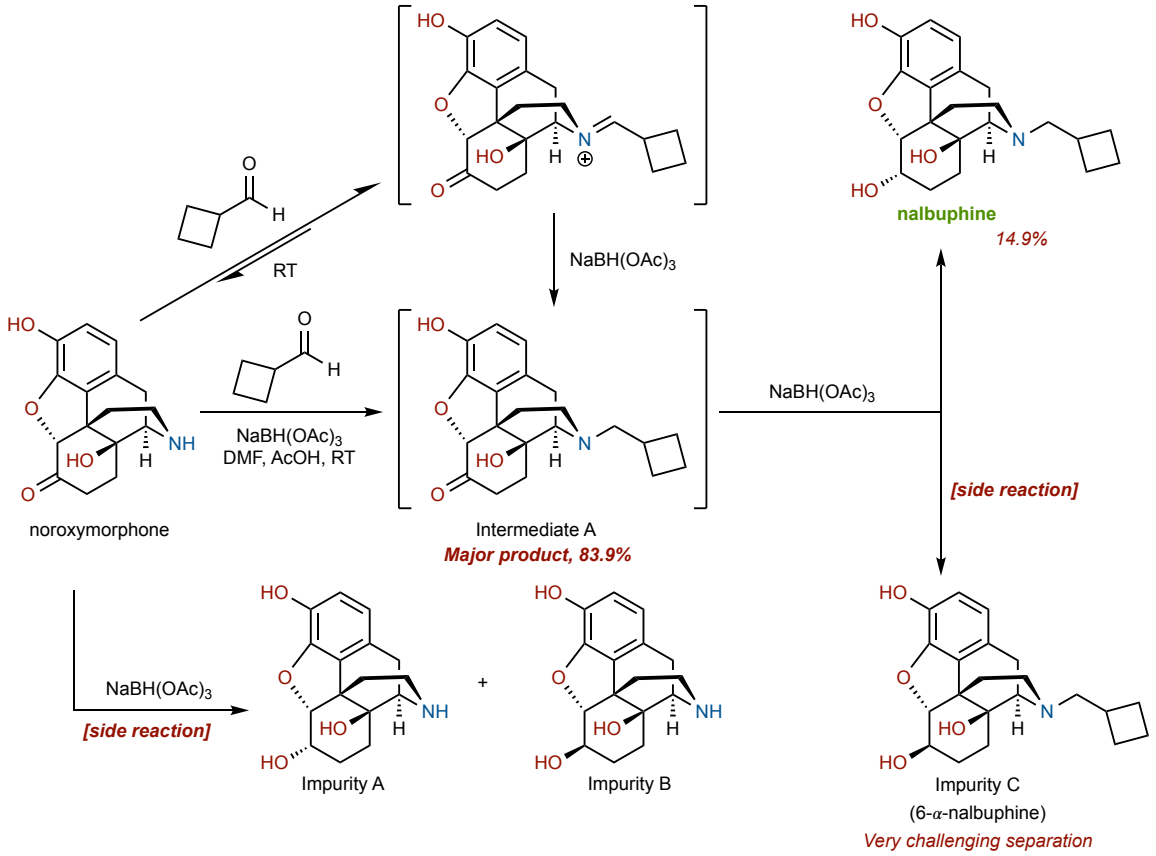


- Nalbuphine is an intravenous opiod analgesic used in the treatment of pain
- Little to no capacity for euphoria or respiratory depression
- Moderate efficacy partial agonist at μ-opioid receptor and high efficacy partial agonist of the **κ**-opioid receptor
- Novel, one-pot protocol reported for nalbuphine hydrochloride synthesis reported in *Org Process Res. Dev*. **2020**, ASAP, DOI: 10.1021/acs.oprd.0c00321

Classic process approaches towards nalbuphine:



Mallinkckrodt one-pot protocol:



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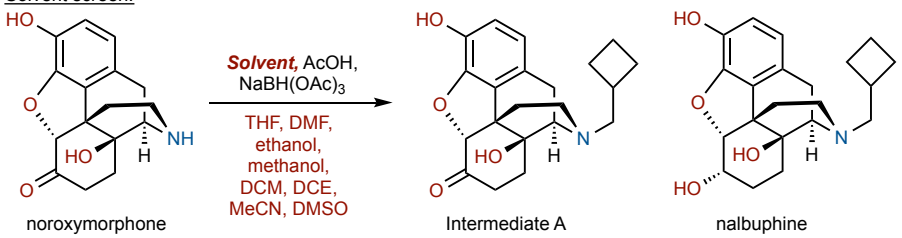
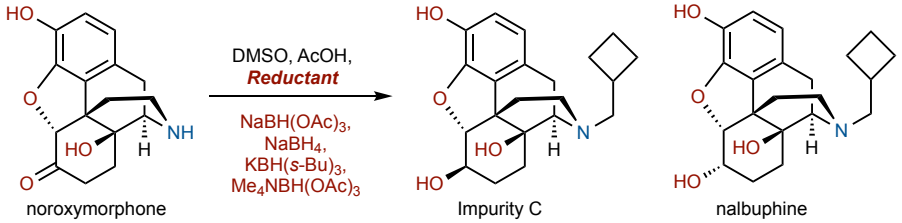
Solvent screen:



Only DMF and DMSO afford full conversion of noroxymorphone:
DMF - 84.90 : 15.10
DMSO - 70.31 : 29.69

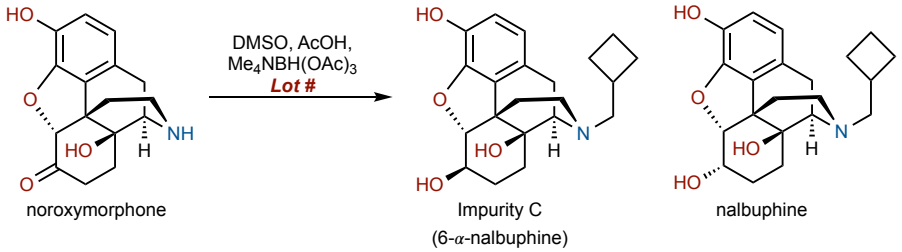
Reductant screen - yield:



- It was observed that 4.0 equiv. of reductant required for full conversion of Intermediate A
- Multiple portions gave superior results over single addition
- Notably, $NaBH_4$ gave 20.65 : 79.35 ratio of epimers
- 5 portions totalling 4.0 equiv. of $Me_4NBH(OAc)_3$ gave 99.79% of nalbuphine

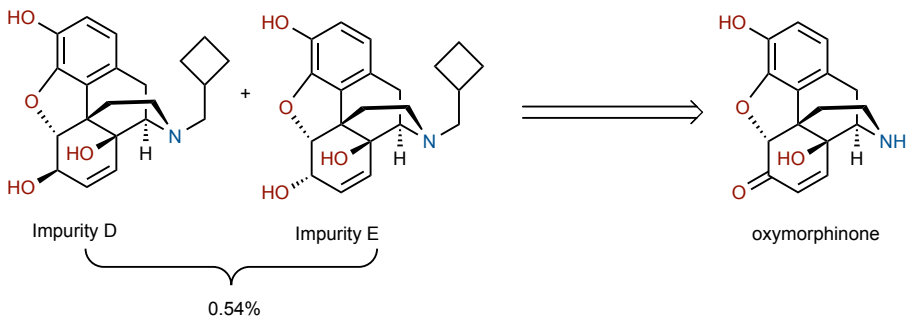
Reductant screen - stereoselectivity:

The results of previous screen found irreproducible with different batches of reductant



As the synthesis of $Me_4NBH(OAc)_3$ begins from $NaBH_4$, the purity of $Me_4NBH(OAc)_3$ from different vendors was measured. $Me_4NBH(OAc)_3$ with >99.9% purity gave 99.5% desired product, while $Me_4NBH(OAc)_3$ at 91.3% purity gave 3.03% of epimer.

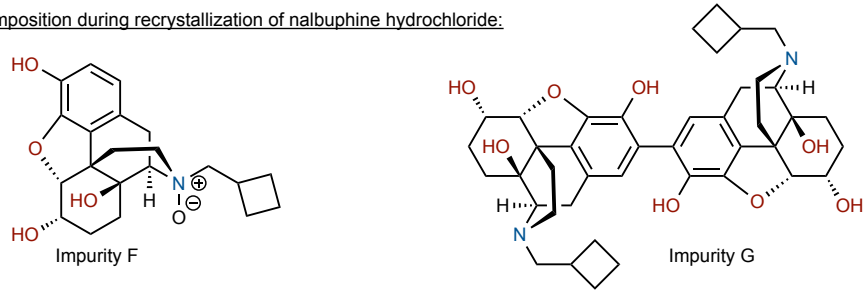
Purity of starting material:



Impurities D and E were observed and confirmed by synthesis. Their presumed origin is contamination of oxymorphinone in commercially sourced noroxymorphone due to incomplete hydrogenation following 1,4-oxidation of thebaine. Hydrogenation of starting material could only decrease impurity content to 0.24%

Purification of noroxymorphone could be performed *in situ* by reslurrying in THF/H_2O at RT

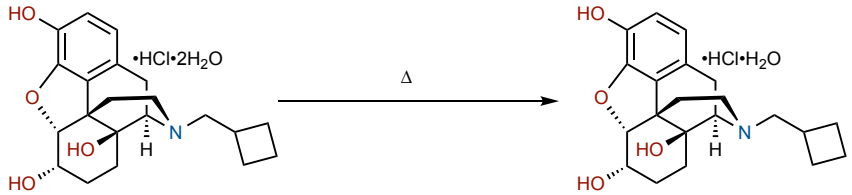
Decomposition during recrystallization of nalbuphine hydrochloride:



Impurities F and G were observed during initial crystallization attempts in THF/H_2O under ambient light. Morphinans with free phenol groups have known photoinstability and dimerize through phenolic coupling. Traced peroxides formed in THF sufficient for amine *N*-oxidation.

The use of pure H_2O with rigorous exclusion of light sufficient to avoid these reactions.

Multiple nalbuphine hydrochloride polymorphic forms:



XRPD reveals major product to be unstable polymorphic form B (dihydrate), which was found to convert quantitatively to monohydrated form C upon sustained heating.

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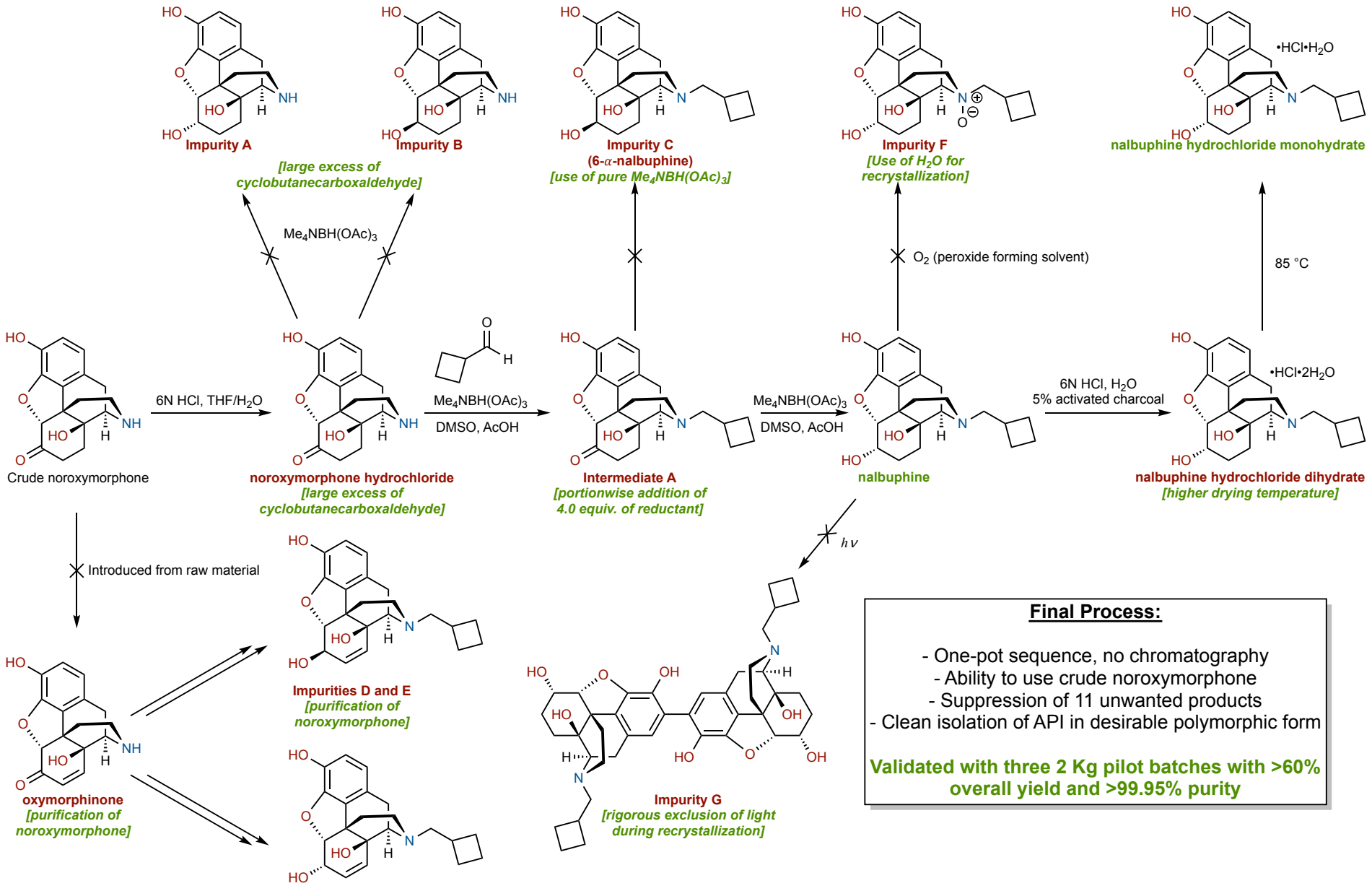

Final Process:

- One-pot sequence, no chromatography
- Ability to use crude noroxymorphone
- Suppression of 11 unwanted products
- Clean isolation of API in desirable polymorphic form

Validated with three 2 Kg pilot batches with >60% overall yield and >99.95% purity