Multikilogram enantioselective synthesis of a HCV polymerase inhibitor

Mr Andrew Gibb
Global Process Chemistry
Merck Sharp and Dohme.
Hertfordshire, UK

SCI Young Chemist in Industry
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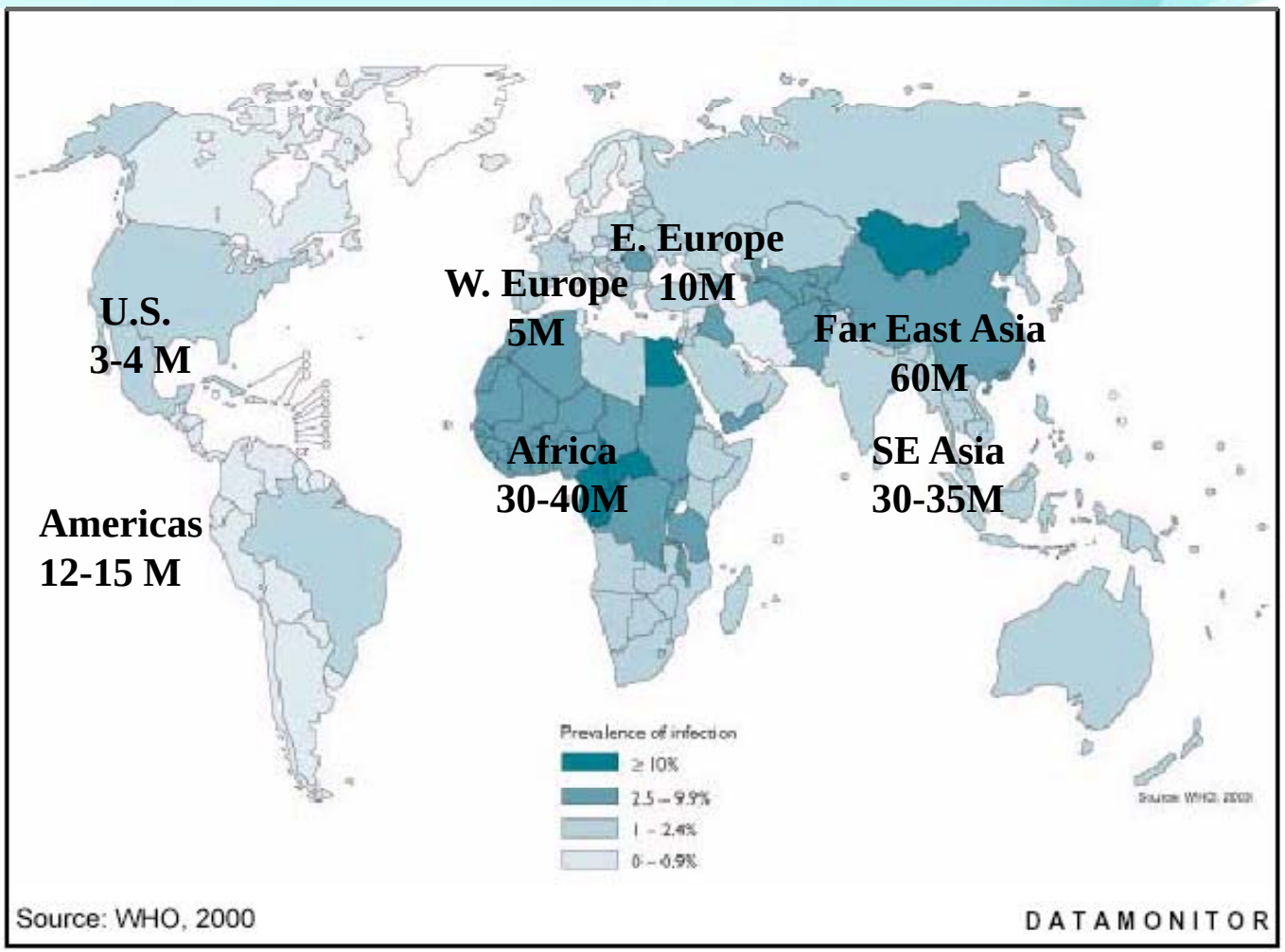
Hepatitis C Virus is a chronic viral infection that can cause liver disease

- RNA virus
- Primarily infects liver cells
- Multiple genotypes
- Primarily blood borne transmission
- RNA-dependent RNA polymerase
  - Frequent mutation and no “proofreading”
  - Selection of HCV variants

Hepatitis C: A global health problem



170 million people are chronically infected with HCV

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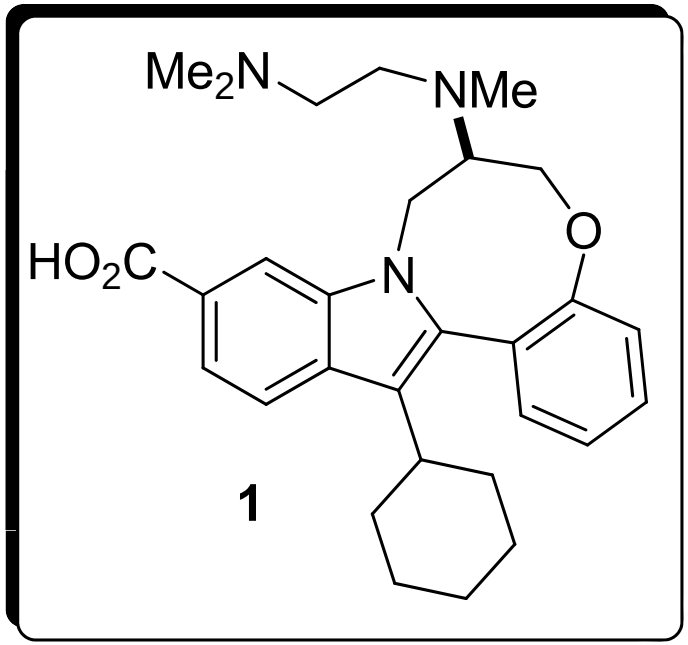
Current HCV Treatment

- Pegylated interferon alpha (PEG-IFN) plus ribavirin (RBV) for 24-48 weeks
  - Weekly subcutaneous injections of PEG-IFN
  - Twice daily oral ribavirin
- Goal is eradication of virus
  - Sustained Viral Response (SVR): undetectable HCV RNA in plasma 6 months after completion of therapy
- Significant adverse experiences associated with both ribaviran and PEG-IFN

2011: A new dawn rises for HCV patients

- Victrelis™ (Merck) and Incivek™ (Vertex) received FDA approvals in 2011.
- 1st generation NS3/4A inhibitors used with existing standard of care to substantially improve treatment rates for hepatitis C.
- The frequent mutation and genetic heterogeneity of HCV requires that new therapies continue to be developed.
- Long term goal is shift to all oral direct acting antiviral therapy.

HCV NS5B polymerase candidate

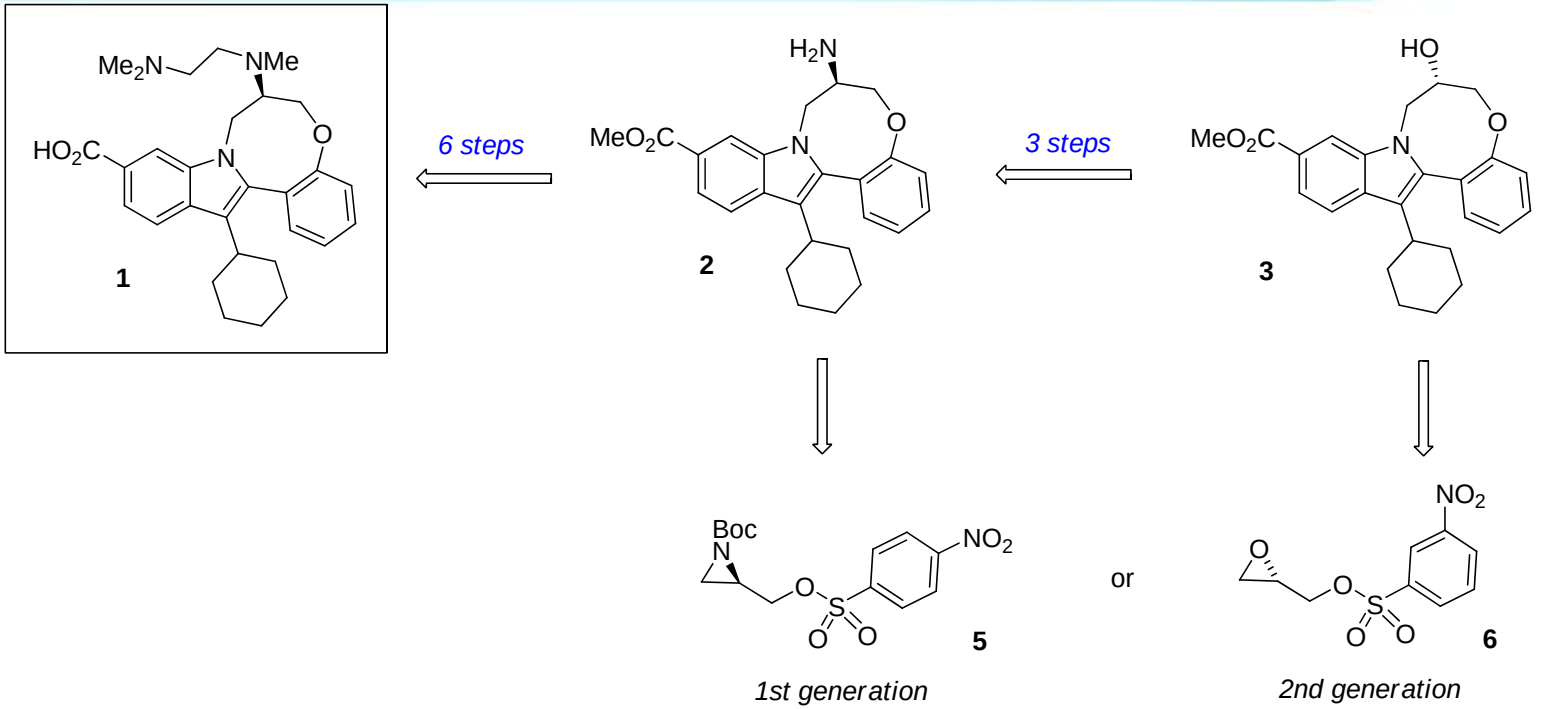


1

- Single enantiomer
- Unusual 8-membered dihydroindolo-benzoxazocine ring
- 2,3-Disubstituted pyrrole
- Zwitterionic

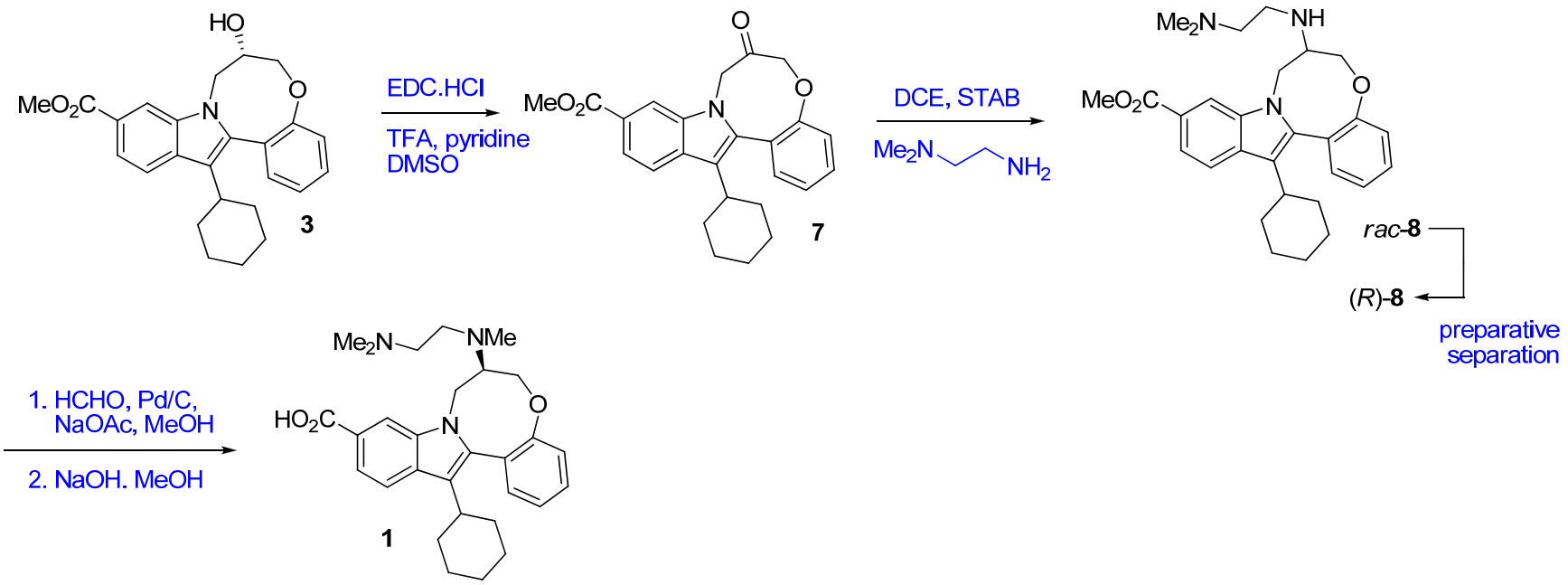
- Narjes, F. and co-workers *J. Med. Chem.* **2011**, *54*, 289

Medicinal chemistry approaches



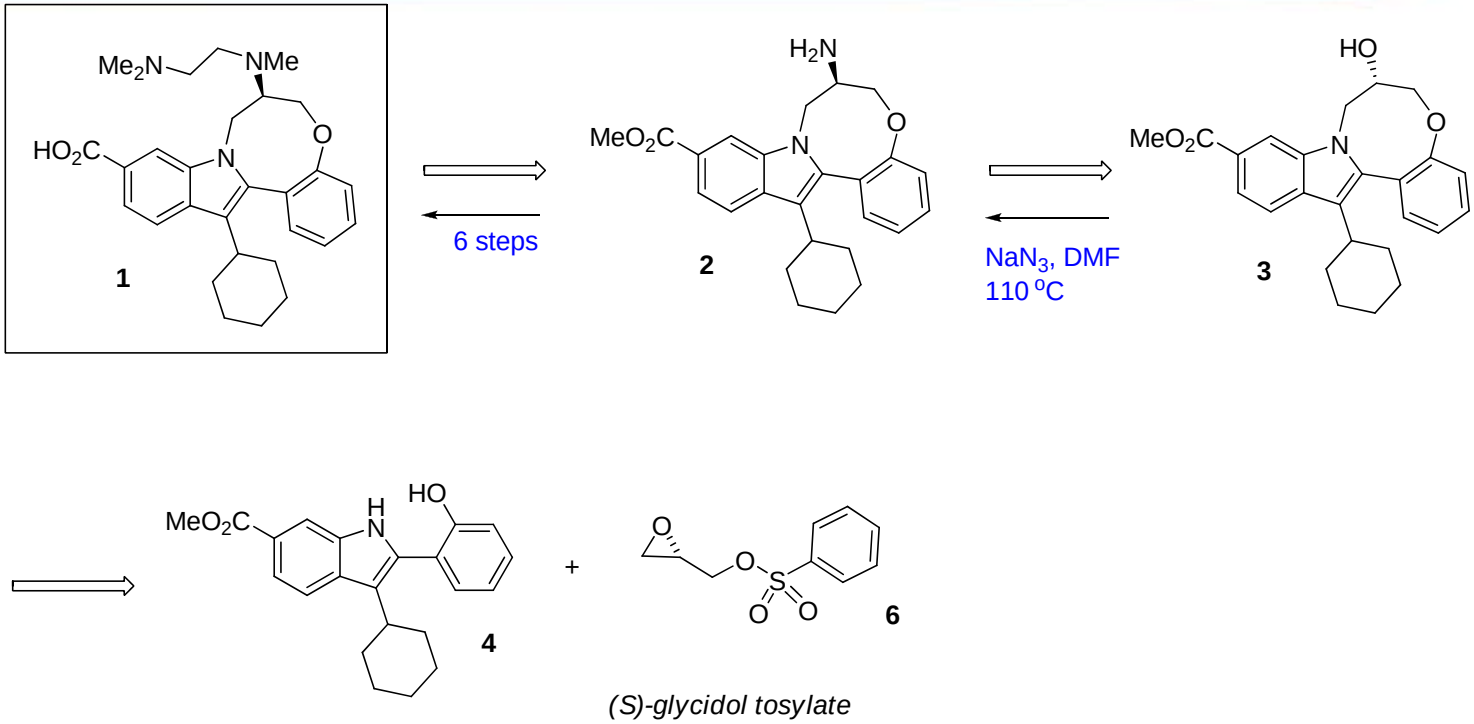
- 1,3-Dielectrophile construction of 8-membered ring.
  - Thermal instability of aziridine route *via* **5** unworkable and multiple steps with no crystalline intermediates to prepare.
  - Epoxide route *via* **6** attractive for further exploration.

Racemic synthesis of desired target



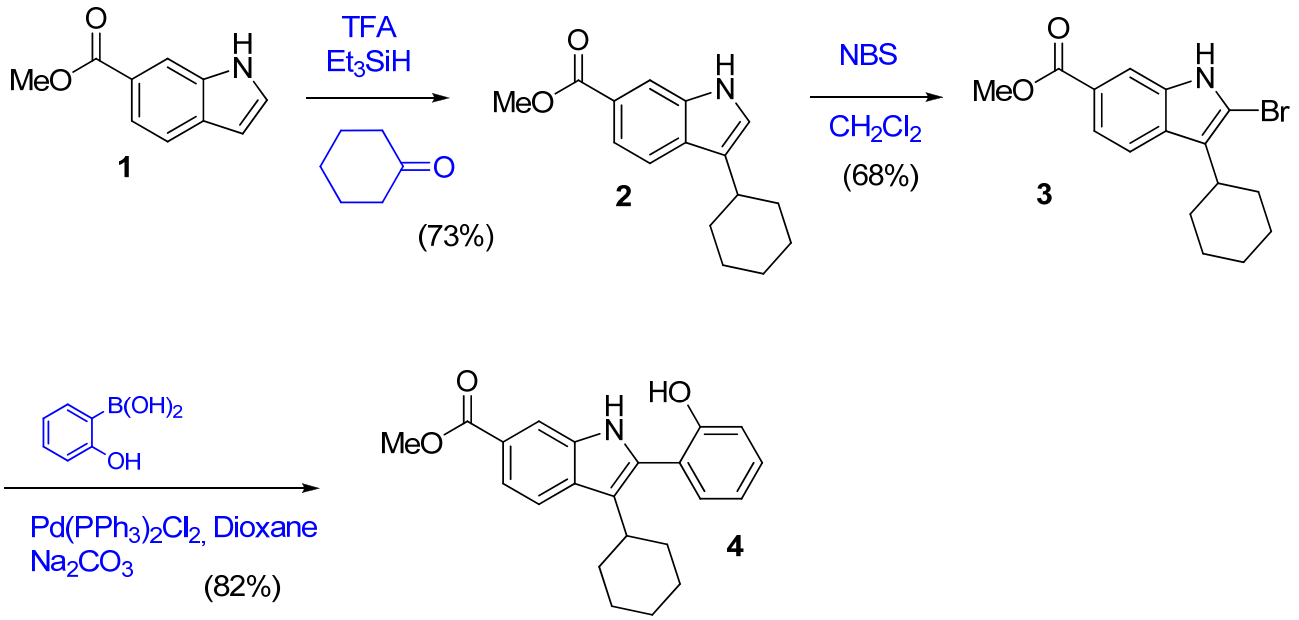
- Used to access multi-gram amounts.
- Preparative separation not viable for further kilogram scale-up.

Strategy for first kilogram scale delivery



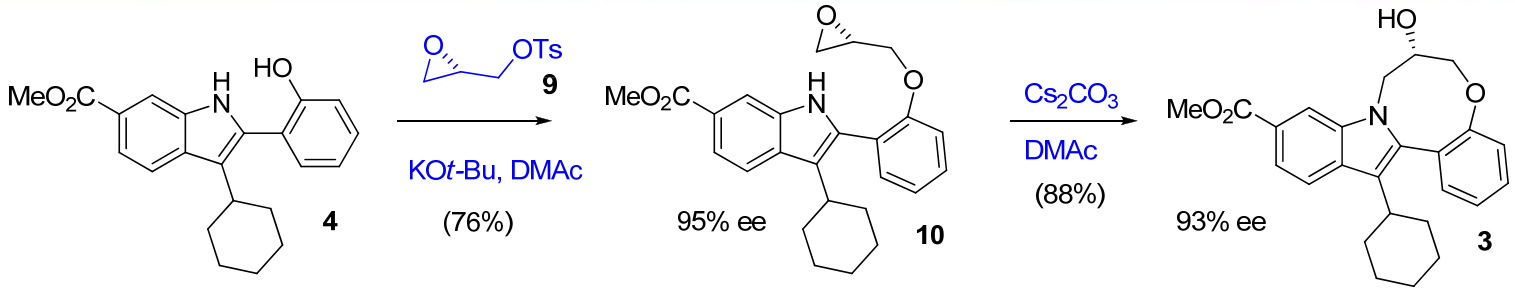
- Employ commercially available chiral pool starting material *(S)*-**6.**
- Replace high temperature azide displacement with alternative protocol.
- Develop expedited elaboration of triethylethylenediamine sidechain from primary amine **2.**

Substituted indole core synthesis



- Readily scaled and straightforward chemistry.
- 2-Hydroxyphenylboronic acid expensive and not widely available.

8-Membered benzoxazocine ring construction

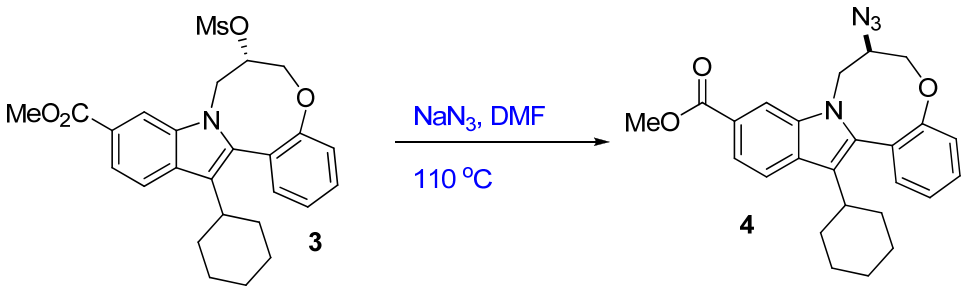


- Heavily optimised to minimise dimeric and dialkylated impurities.
- First step:
  - Slow, reverse addition of preformed phenoxide into epoxide at 65 ºC.
  - Addition of EtOAc prior to water addition gave smooth direct crystallisation of **10**.
  - MTBE swish of product to remove unreacted glycidol tosylate. Typical 10A% of **3** formed under reaction conditions**.**

- Second step:
  - Slow reverse addition of **10** into cesium carbonate at 65 ºC to promote intra- vs intermolecular cyclisation.
  - Direct crystallisation by water addition following addition of IPAc as co-solvent.

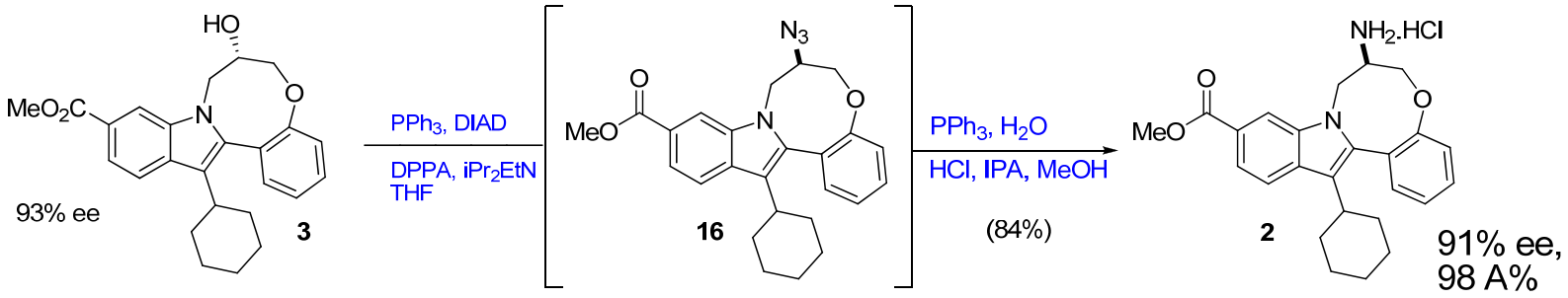
- One-pot 2-step telescoped through process suffered from low yields.
- (*S*)-Epichlorohydrin cheaper but led to racemic **3**.

Transformation of alcohol to primary amine : medchem



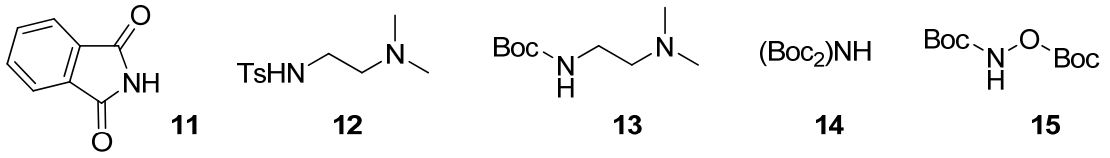
- High temperature displacement : safety concerns.
- β-elimination also a competitive side reaction.
- What about Mitsunobu based protocol using diphenylphosphoryl azide?

Mitsunobu inversion with diphenylphosphoryl azide (DPPA)



DIAD : Diisopropylazodicarboxylate

- Dramatic reactivity enhancement : inversion takes place at 15 ºC vs 110 ºC!
- Telescoped Staudinger azide reduction through addition of further Ph_3P then water to avoid any handling of intermediate azide.
- Simple direct crystallisation of HCl salt from IPA/MeOH sheds all of the 2 mol Ph_3PO byproduct. No distillation required at any point.
- Other *N*-nucleophiles evaluated did not afford desired inversion products.



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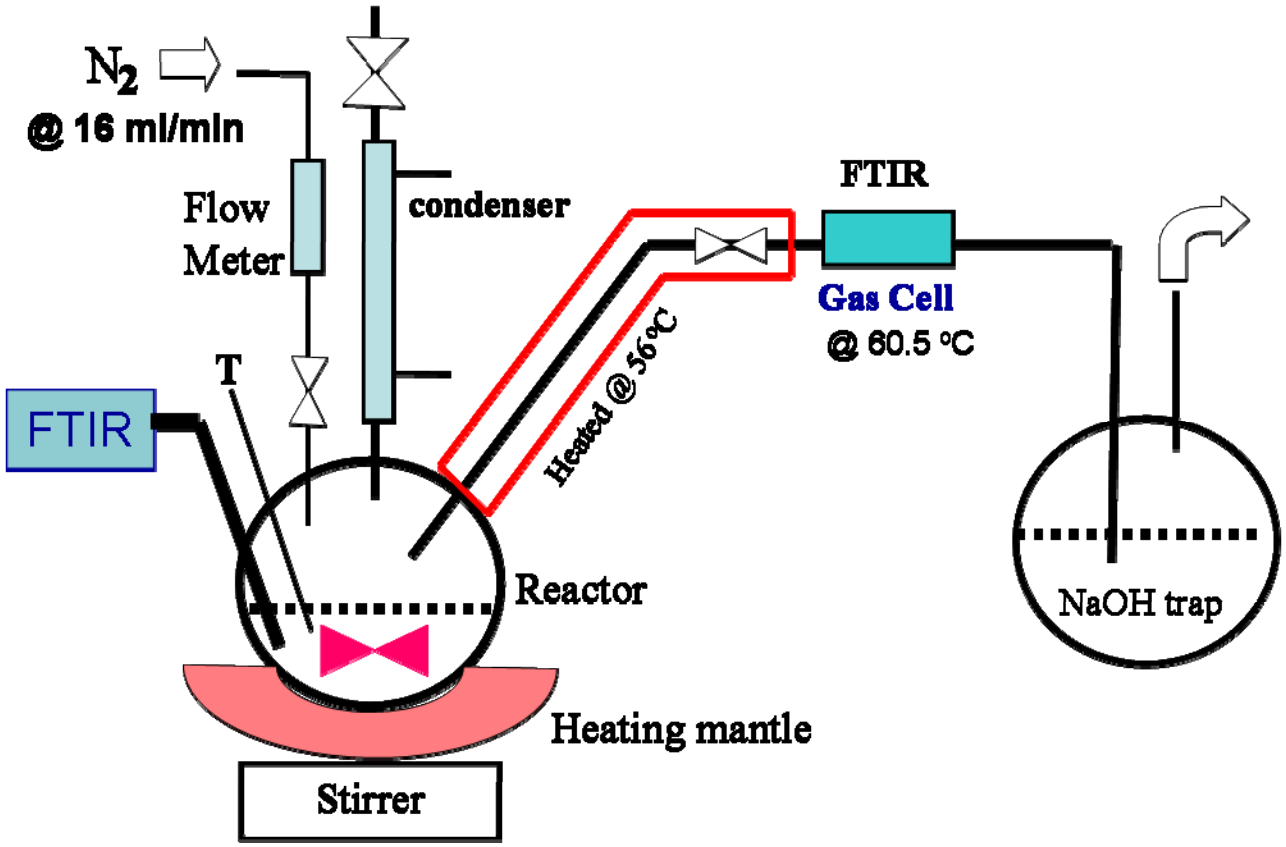
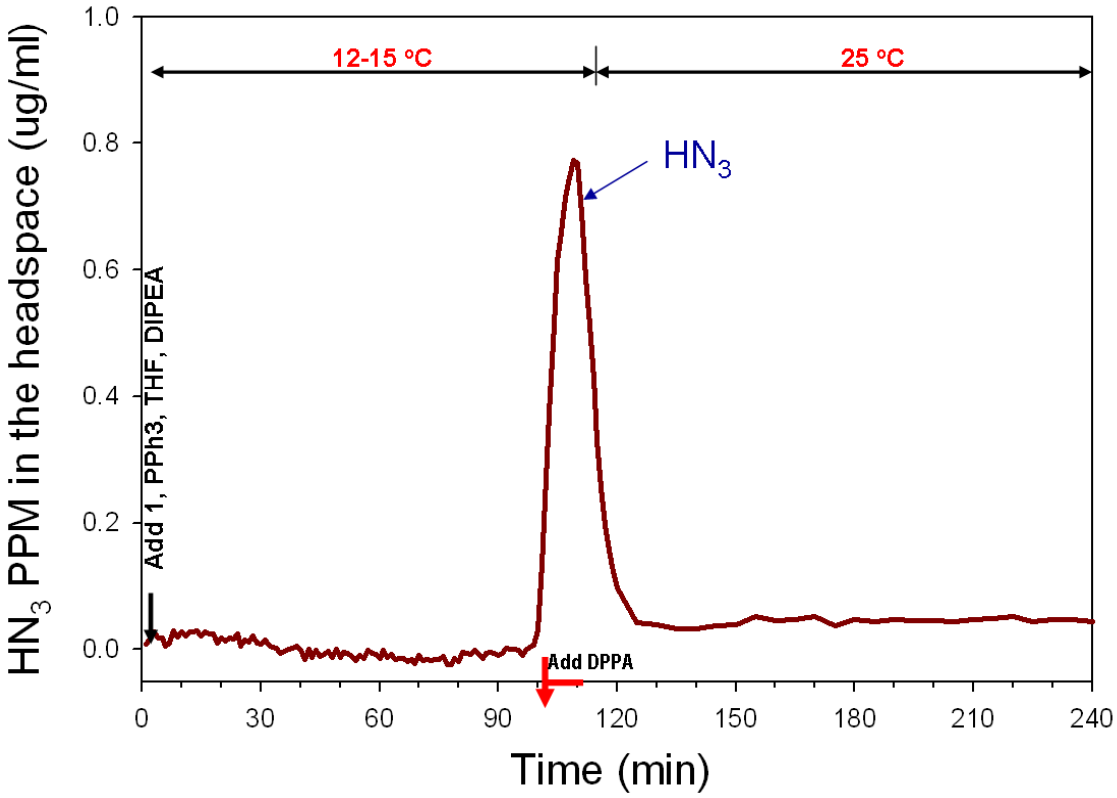
Hydrazoic acid headspace measurements



Hydrazoic acid headspace measurements



• Process run in the presence of 1.2 equiv. of *i*-Pr_2NEt to avoid HN_3 in the headspace as well as with nitrogen sweep.

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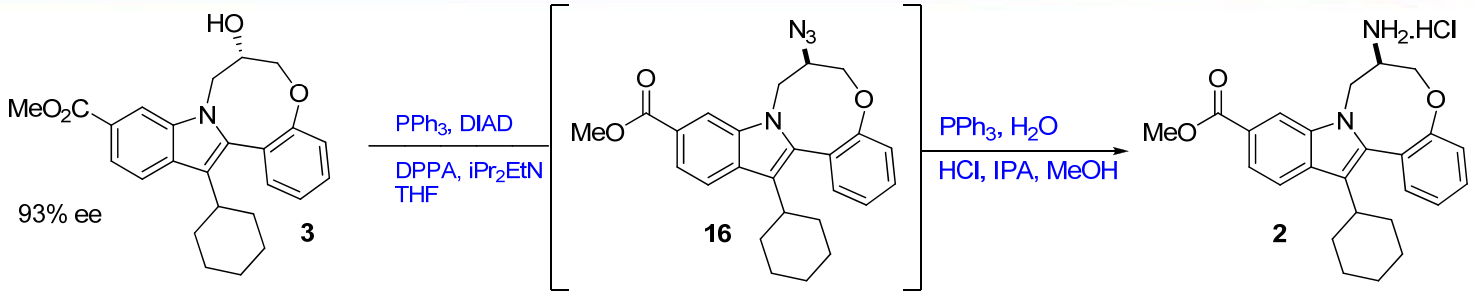
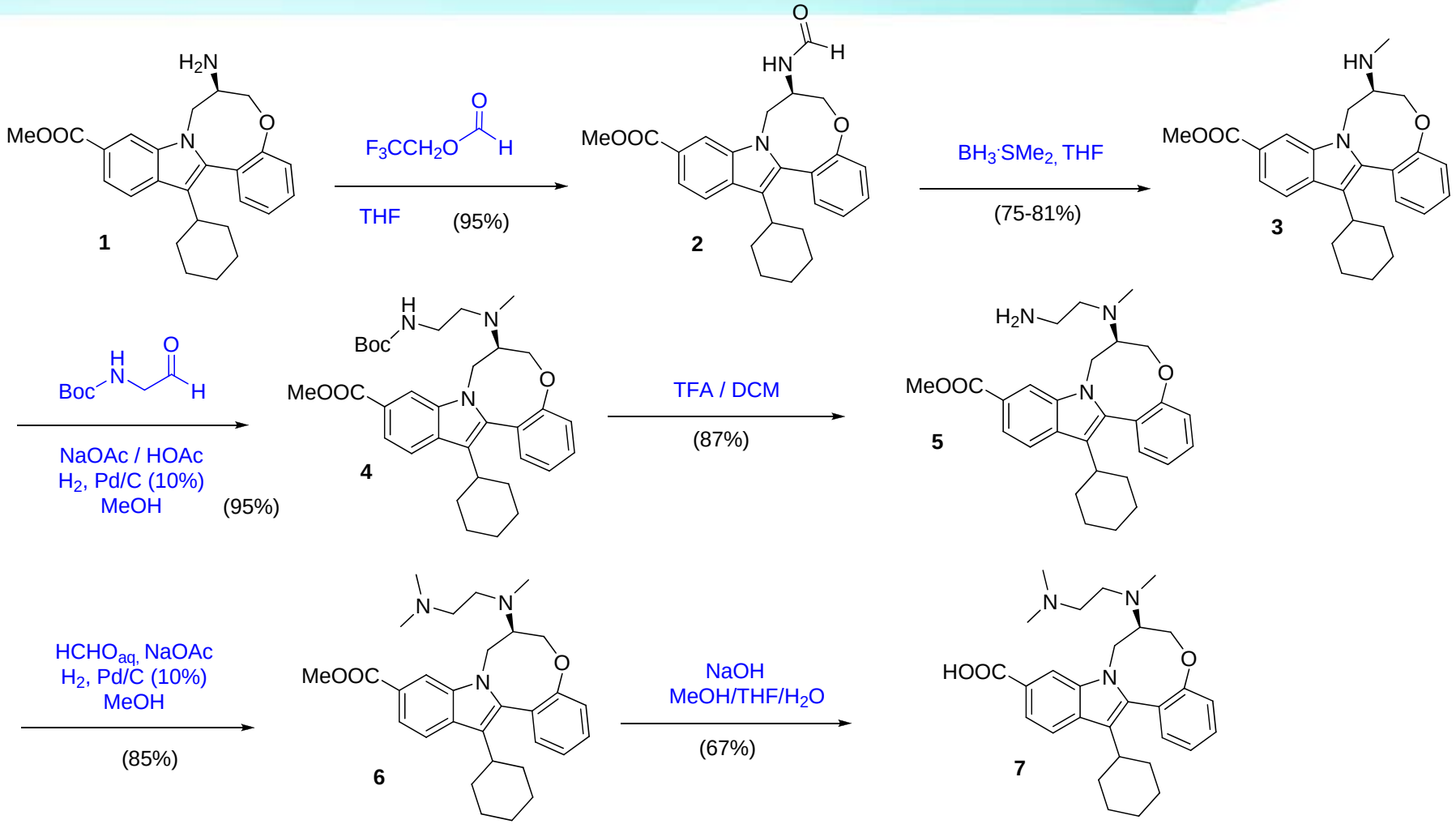
RC-1 Calorimetry measurements



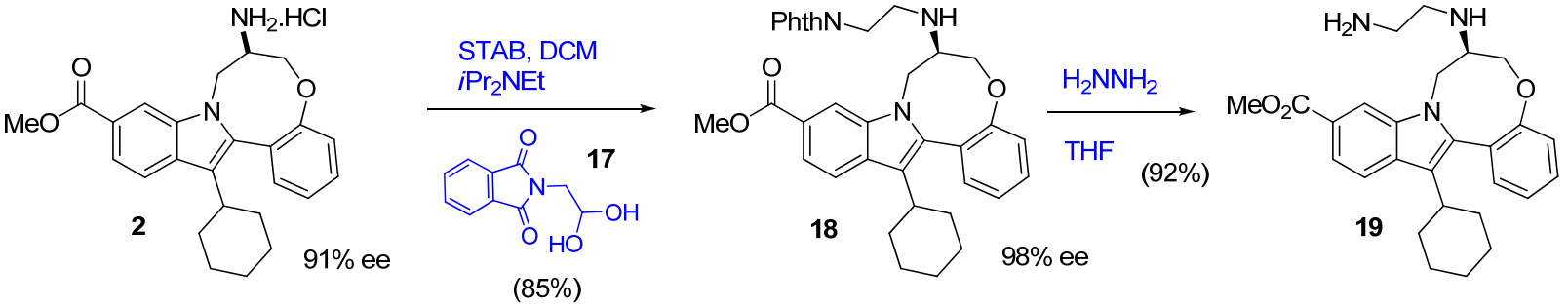
BATCH OPERATION	HEAT OF REACTION (kJ mol^{-1} of alcohol 3)	ADIABATIC ΔT (°C)	COMMENTS
Addition of DIAD	-173.1	23.3	Addition rate controlled. Accumulation <5% (addition over 20 minutes at 10 °C)
Addition of DPPA	-149.3	18.5	70% accumulation (addition over 6 minutes at 15 °C)
Addition of THF solution of Ph_3P	-277.7	30.5	~50% accumulation (addition over 12 minutes at 25 °C)
Addition of water	-11.8	1.3	-

Trimethylethylene diamine sidechain installation: medchem



- 6 steps, linear with Boc glycine aldehyde not readily available

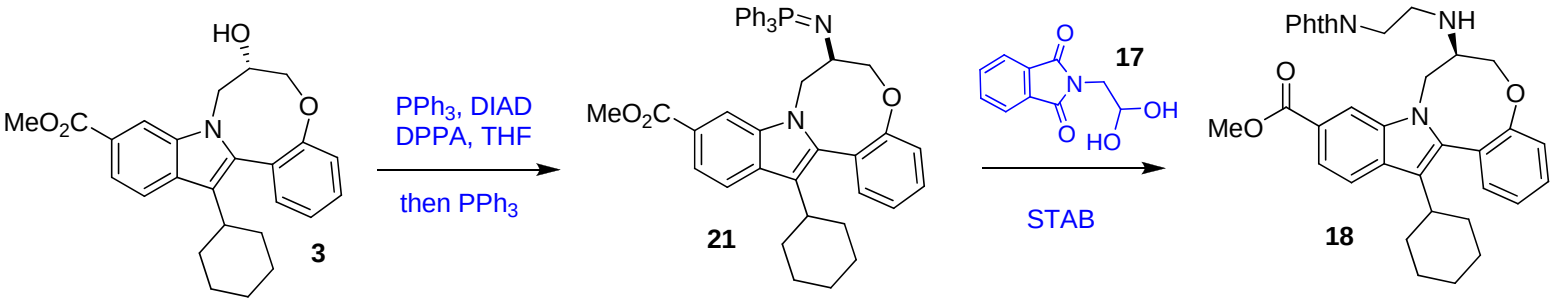
Trimethylethylene diamine sidechain installation



• Crystallisation of **18** from acetonitrile leads to ee upgrade to 98% through rejection of racemic mother liquors.

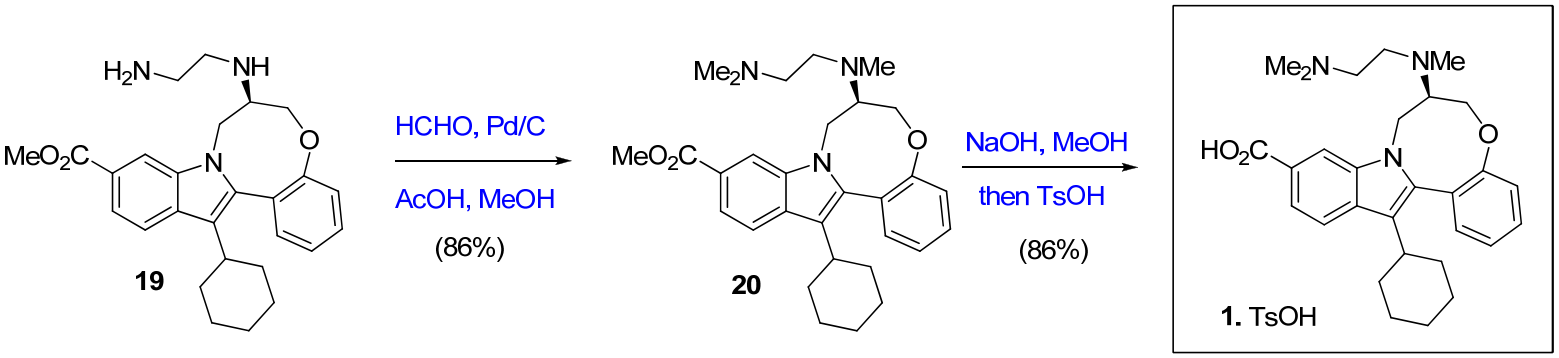
• Hydrazinolysis developed to address issues of genotoxicity and headspace liberation during batch concentration.

One-pot Mitsunobu/Staudinger/Aza-Wittig



- One-pot telescoped through process demonstrated to be viable but not developed due to time constraints.

Reductive trimethylation and final isolation

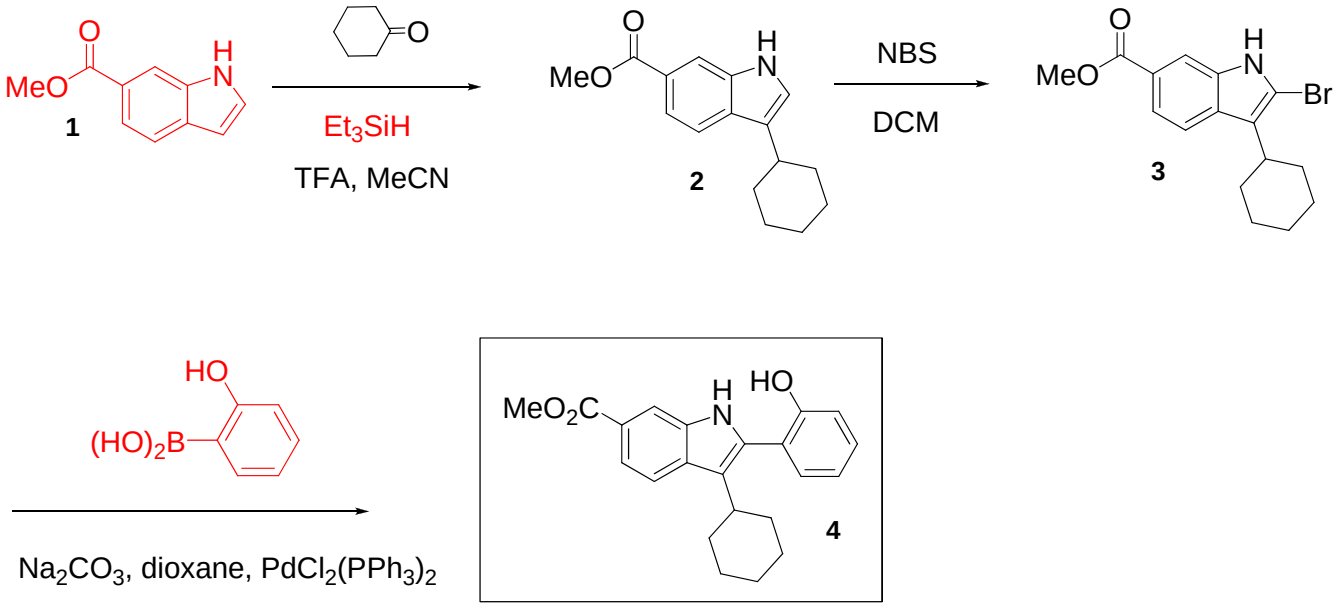


- High pressure required for triple methylation (90 psi H_2). Direct isolation by pH adjustment to crystallise **20**.

- >5 kg drug substance prepared at >99 A%, >99% ee as tosylate salt.

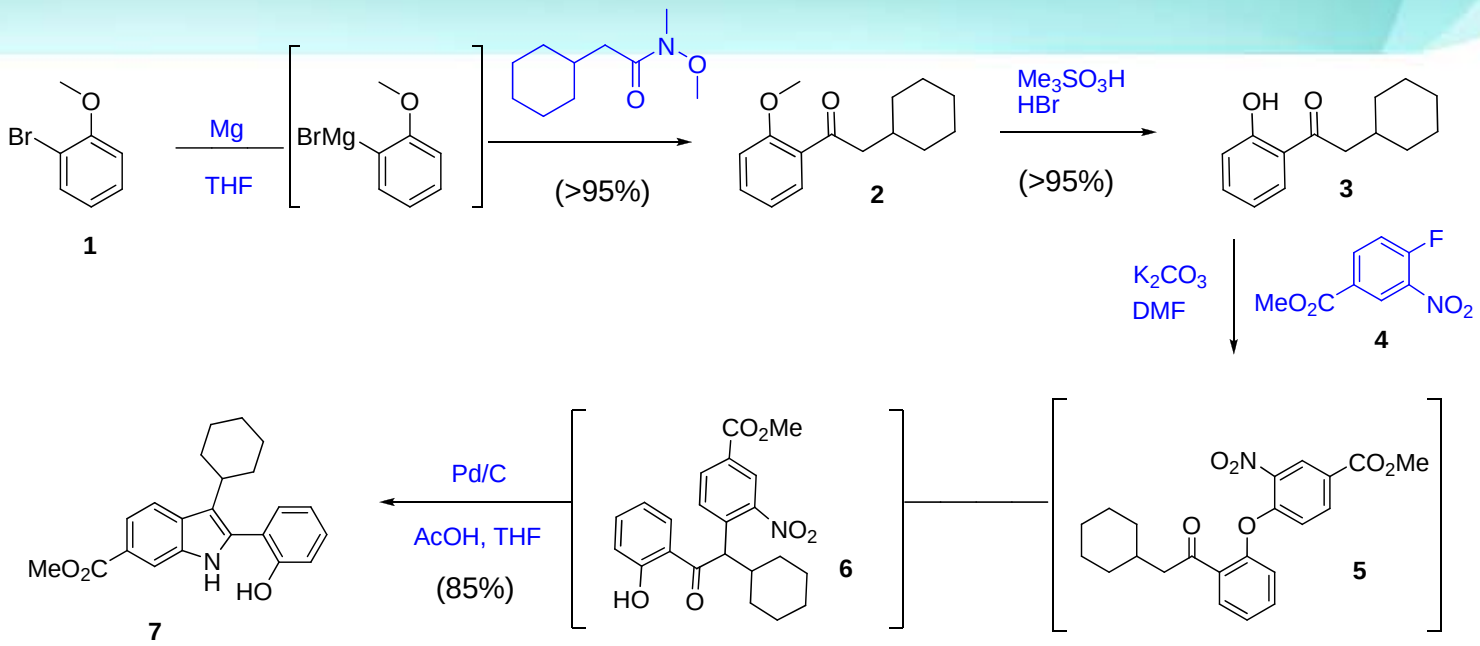
Jeremy P. Scott* and co-workers *Org. Process Res. Dev.* **2011,** *15*, 1116 (Special Issue: Asymmetric Synthesis on Large Scale 2011)

Long term route development : indole core



- Cost basis too high to support long term manufacture.
- Supply chain for phenylhydroxyboronic acid unreliable and slow.

Smiles rearrangement to prepare indole core



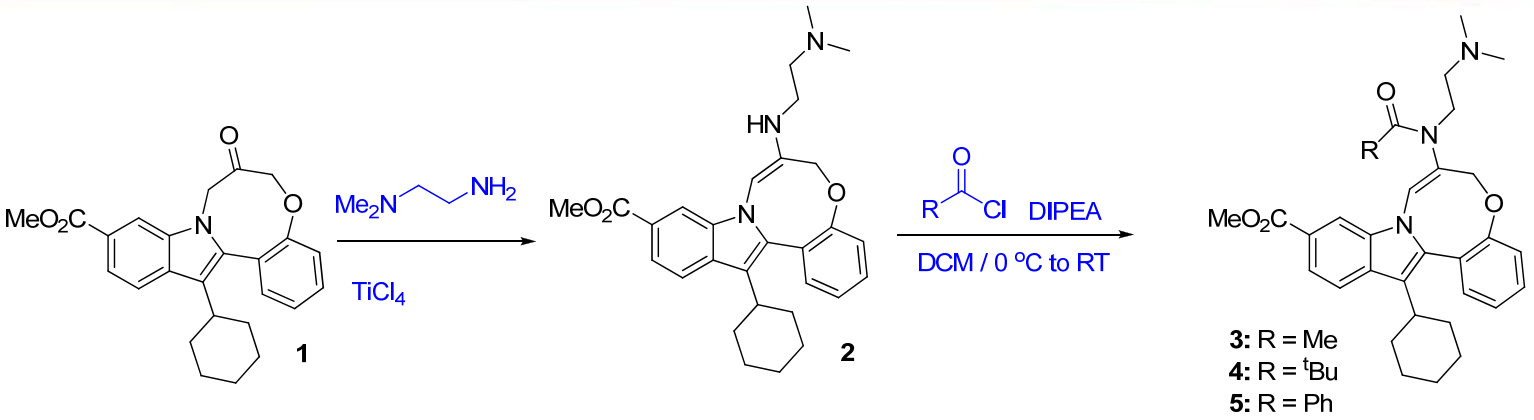
- Grignard prepared using elemental Mg.

- Ketone formation and demethylation high yielding allowing for 4-step telescoped through process to the desired indole product.

- Raw material cost basis significantly lower vs previous route.
- **> 50 kg of indole, 59% overall from cyclohexylacetic acid.**

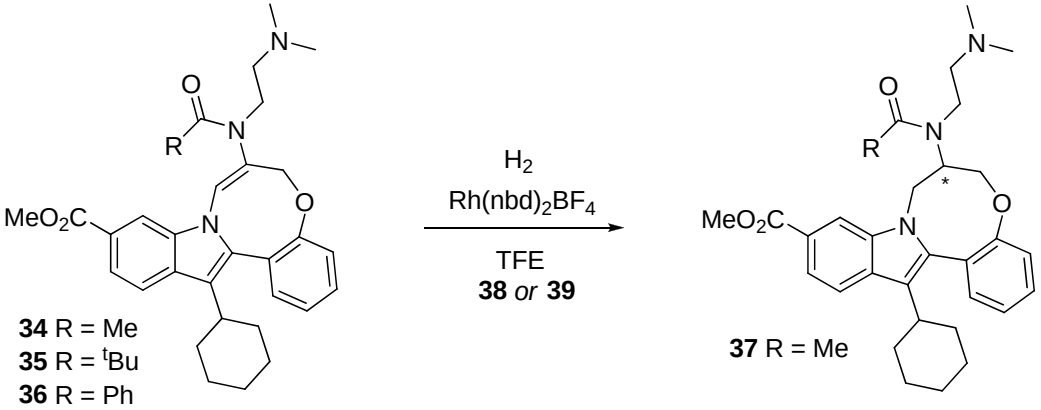
A Gibb* and co-workers, Org. Process Res. Dev. **2012**, 16, 1947-1952

Asymmetric approaches based on enamide reduction



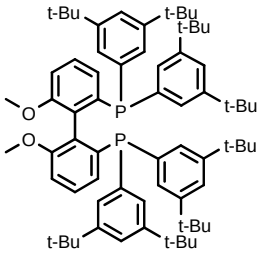
- Ketone **1** fully converted to imine in the presence of $TiCl_4$ (0.5 equiv.) and *N,N*-dimethyl ethylenediamine.
- Acylation gave the phenyl, methyl and trimethylacyl enamides.
- Enamine and enamide regiochemistry confirmed by NMR.

Proof of concept for enamide reduction



34 R = Me
35 R = ^{t}Bu
36 R = Ph

37 R = Me



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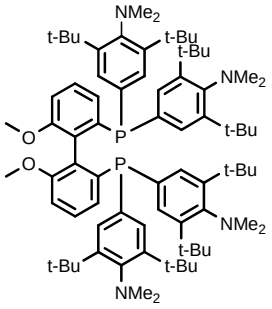
38



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39

- R=Me; $Rh(nbd)_2BF_4$ with ligands **38** or **39** each gave full conversion and 95% ee.
- Enamine reductions gave only low ee's.

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Summary

- Efficient construction of the 8-membered dihydroindolobenzoxazocine ring.
- Practical room temperature azidation under Mitsunobu conditions.
- Expedited construction of the trimethylethylenediamine sidechain.
- Multikilogram demonstration to prepare >5 kg of drug substance.
- Alternative indole core synthesis via Smiles rearrangement demonstrated.
- Alternative enantioselective route evaluted by asymmetric enamide hydrogenation.

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