SYNTHETIC ROUTE DESIGN AND SELECTION

Petr Beňovský

GENERAL ISSUES

- Academia vs. Industry (even more coordinated approach involving large numbers of chemists and supporting personnel towards a common goal);
- Moreover, “in the meantime“, under high time pressure and stress, process people need to continually improve their expertise and capability for the effective design of new synthetic routes;
- **Plan** → **Do** → **Audit** cycle → → → **Select**
- Understand sources, available time, limitations, priorities, risks, quality, quantity, budget, …

SELECT CRITERIA

S
E
L
E
C
T

Butters, M. *et al Chem. Rev. 106*, 3002 (**2006**)

SELECT CRITERIA

S
E
L
E
C
T

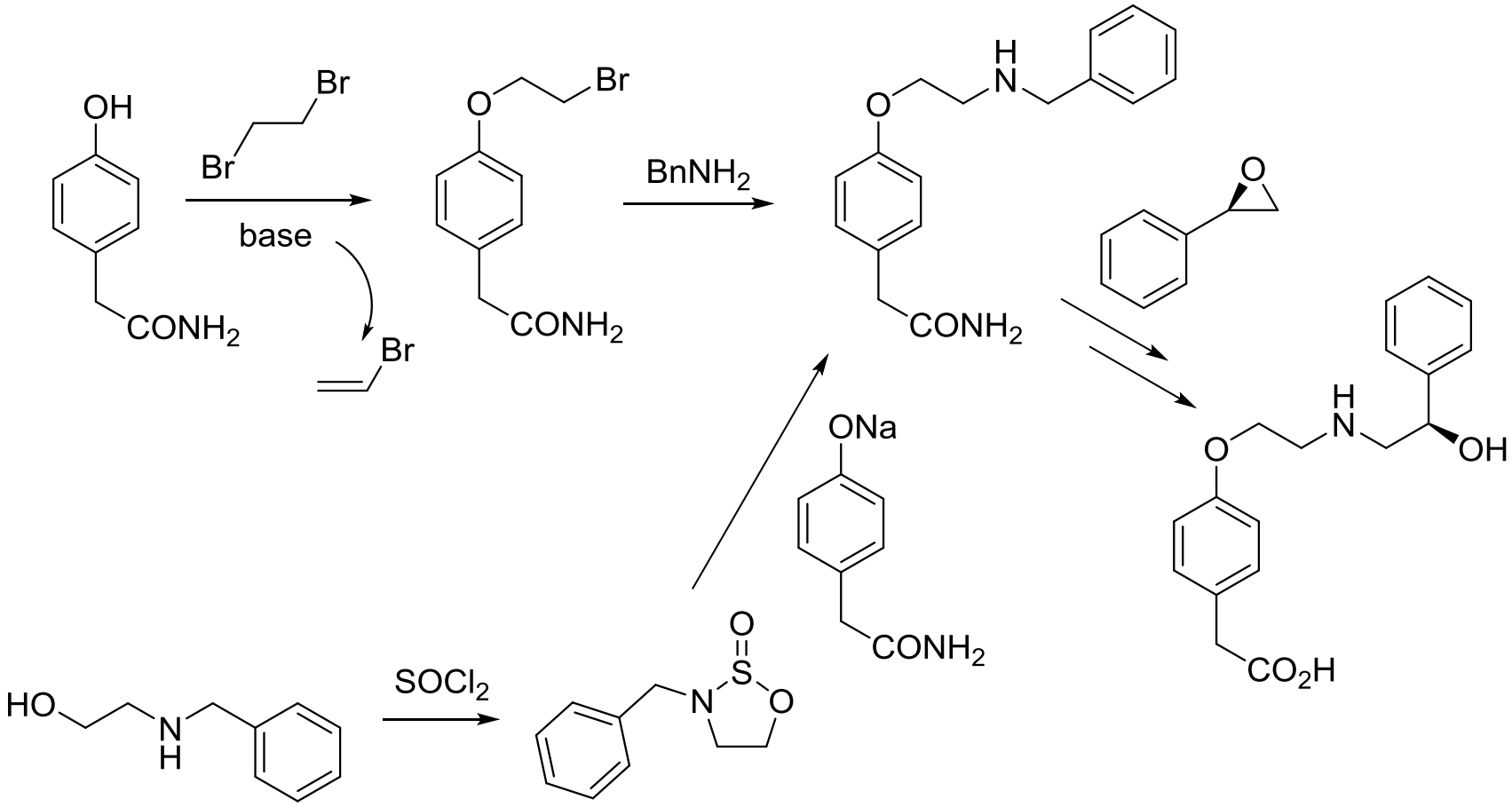
Criteria	Subcriteria	Potential Issues
SAFETY	Process, health	Thermal risk, carcinogens, sensitisers
ENVIRONMENTAL	Waste, environmental hazard	Inceneration of solvents, aquatic toxins, ozone depleting chemicals
LEGAL	Intellectual property	Indication, compound protection, process
ECONOMICS	Cost of goods, production cost, concentration	Length of the synthesis, cost of operations
CONTROL	Control of quality parameters, P-CH parameters	Meeting specifications, GMP requirements
THROUGHPUT	Time scale of manufacture	Continuity of steps, operations, transfer, availability of chemicals

Butters, M. *et al Chem. Rev. 106*, 3002 (**2006**)

SELECT CRITERIA

SAFETY

ELECT



SELECT CRITERIA

S

E N V I R O N M E N T A L

L

E

C

T

Very difficult to develop totally sustainable process with a low (or none) environmental impact

Always depends on the production volume and particular hazard

SELECT CRITERIA

SELECT

LEGAL

In civilized countries the development and commercialisation of API must be performed without breaking laws or infringing valid intellectual property;

Legal issues can arise any time and patent litigations are pretty common;

- Regulated or banned substances
- Using unacceptable quantities
- Transportation of hazardous materials
- Materials with third-party restrictions
- Patent infrigement

SELECT

LEGAL

SELECT CRITERIA

- Compound protection
- Procedural protection
- Utilization protection

Novelty (in comparison with the state of art)

Inventive step

Industrial use

SELECT CRITERIA

S E L E C T

L E G A L

Patent application

- national
- regional
- worldwide

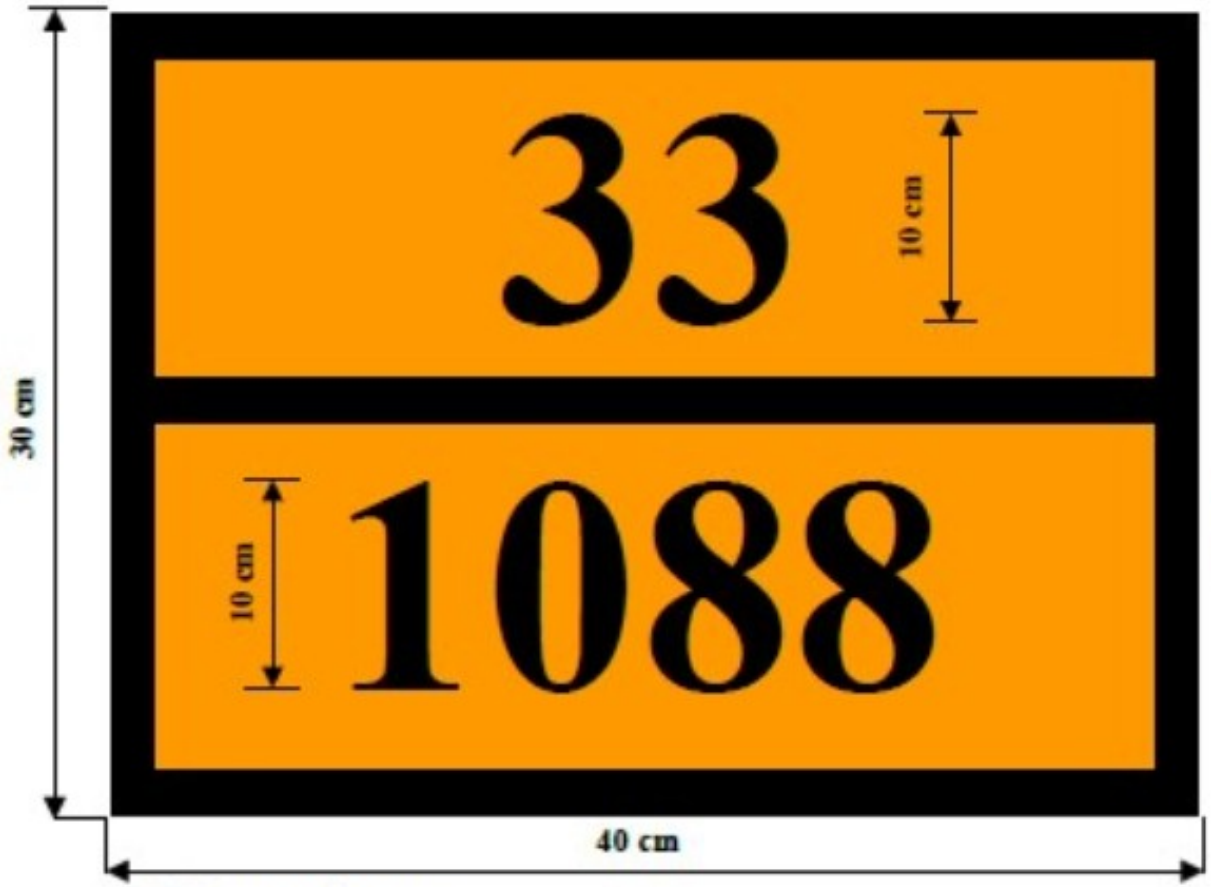
Patent does not automatically give you a right to use – you still have to make sure that it is NOT infringing the other party intellectual property

SELECT CRITERIA

SELECT

LEGAL

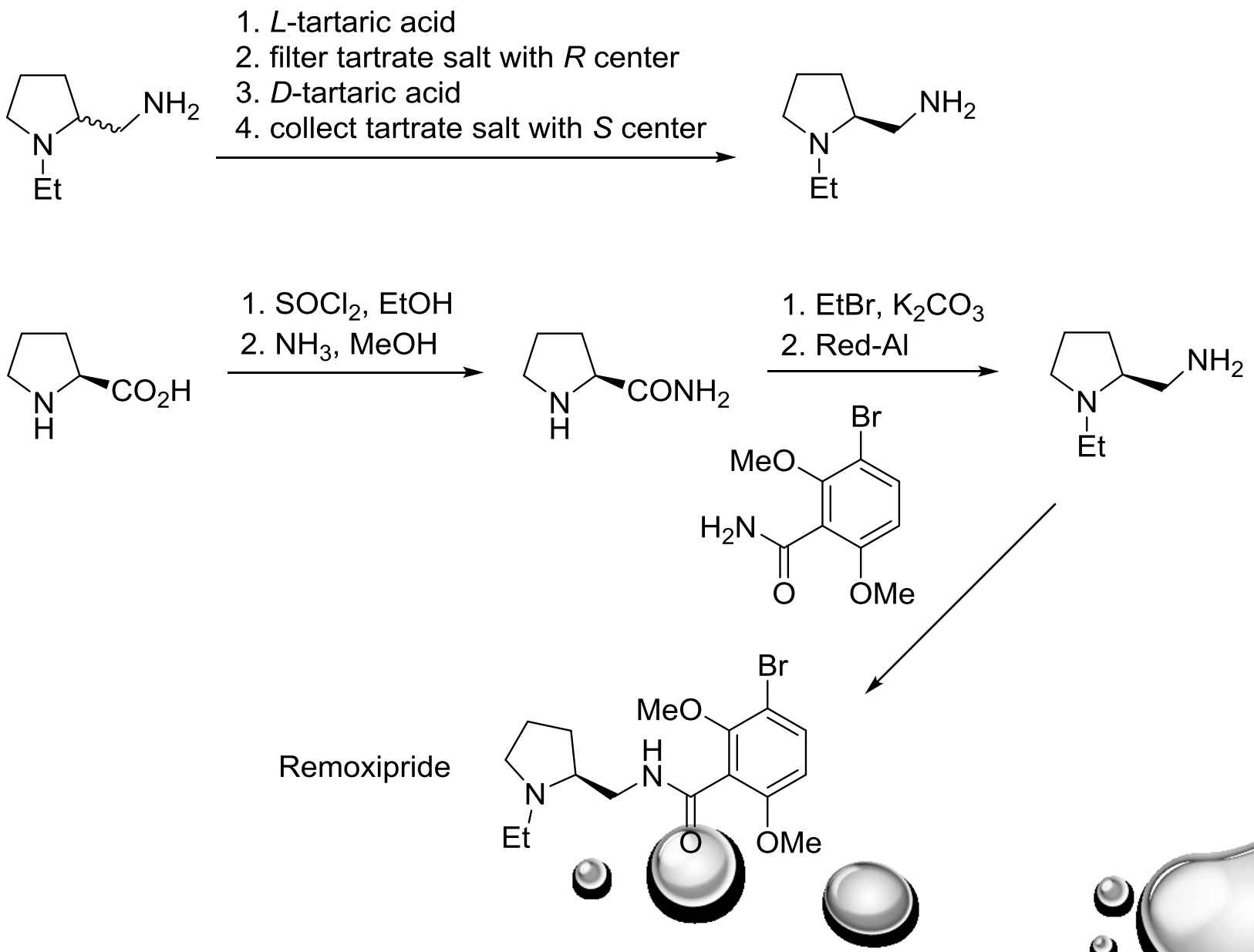
ADR



SELECT CRITERIA

SELECT

LEGAL



SELECT CRITERIA

S
E
L
C
T

E C O N O M I C S

The key factors determining the economic viability:

- Cost of goods (CoG)
- Price of the product
- Marketing costs
- Product and/or technology licensing
- Investment

CoG – the total cost involved in manufacture of a drug product (API manufacturing, formulation, packaging) expressed as a percentage of the selling price of the drug

SELECT CRITERIA

S
E
L
E
C
T

Compliance with valid guidelines of authorities for particular region (FDA, EMEA, ASEAN, ICH)

Specification that defines the acceptable quality – a must for the registration process;

C O N T R O L

Impurities – known, unknown
Mutagenic impurities – ICH M7 guideline
Solvates, stability (DVS, TGA)
Stability tests, enforced degradation studies
Polymorphism, Heavy metals
DoE, QbD, PAT

SELECT CRITERIA

S E L E C

The amount of material that can be manufactured in unit time;

Usually identified in the late stage of development for already established procedure;

T H R O U G H P U T

- Chemical yield
- Number, capacity and availability of vessels
- Reaction, work-up time
- Limiting concentration
- Number of steps
- Convergency
- Usage of special equipment

SELECT CRITERIA

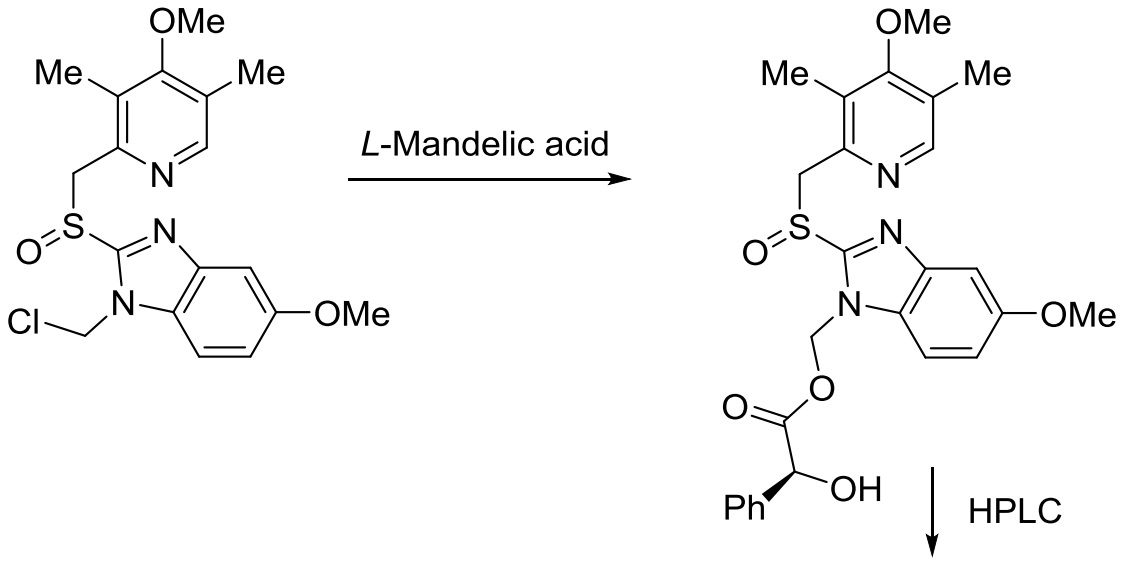
S
E
L
E
C

- Chemical yield often can be improved through a deeper undestanding of kinetics and mechanism;
- Reducing the number or the length of the most time consuming operations will improve throughput – telescoping;
- Poor solubility could be a problem;

T H R O U G H P U T

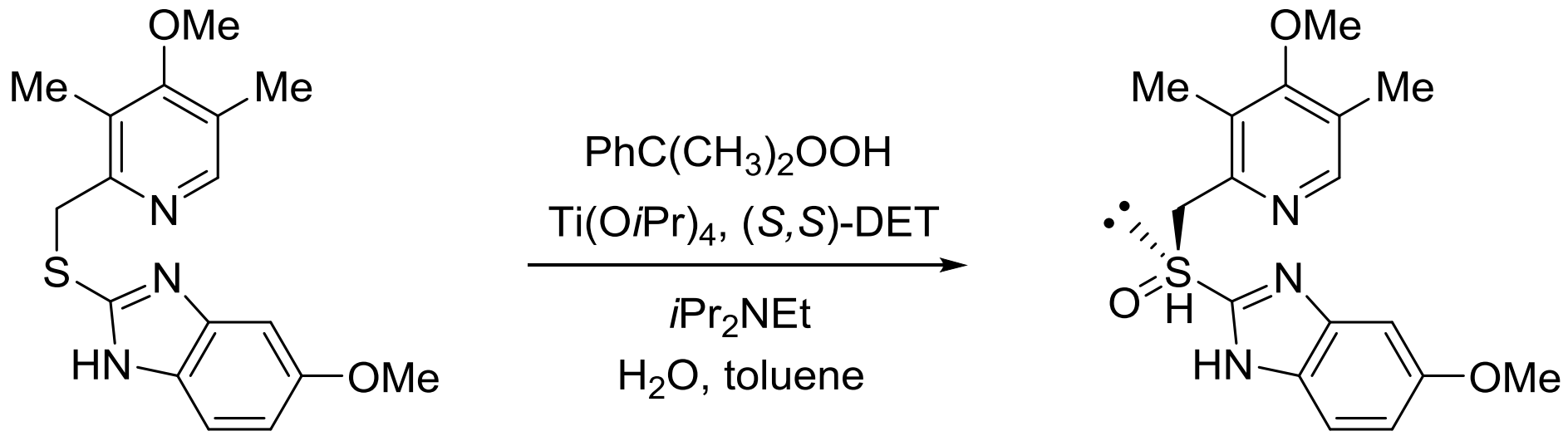
- Protecting – deprotecting sequences;

SELECT CRITERIA - THROUGHPUT



ESOMEPRAZOLE

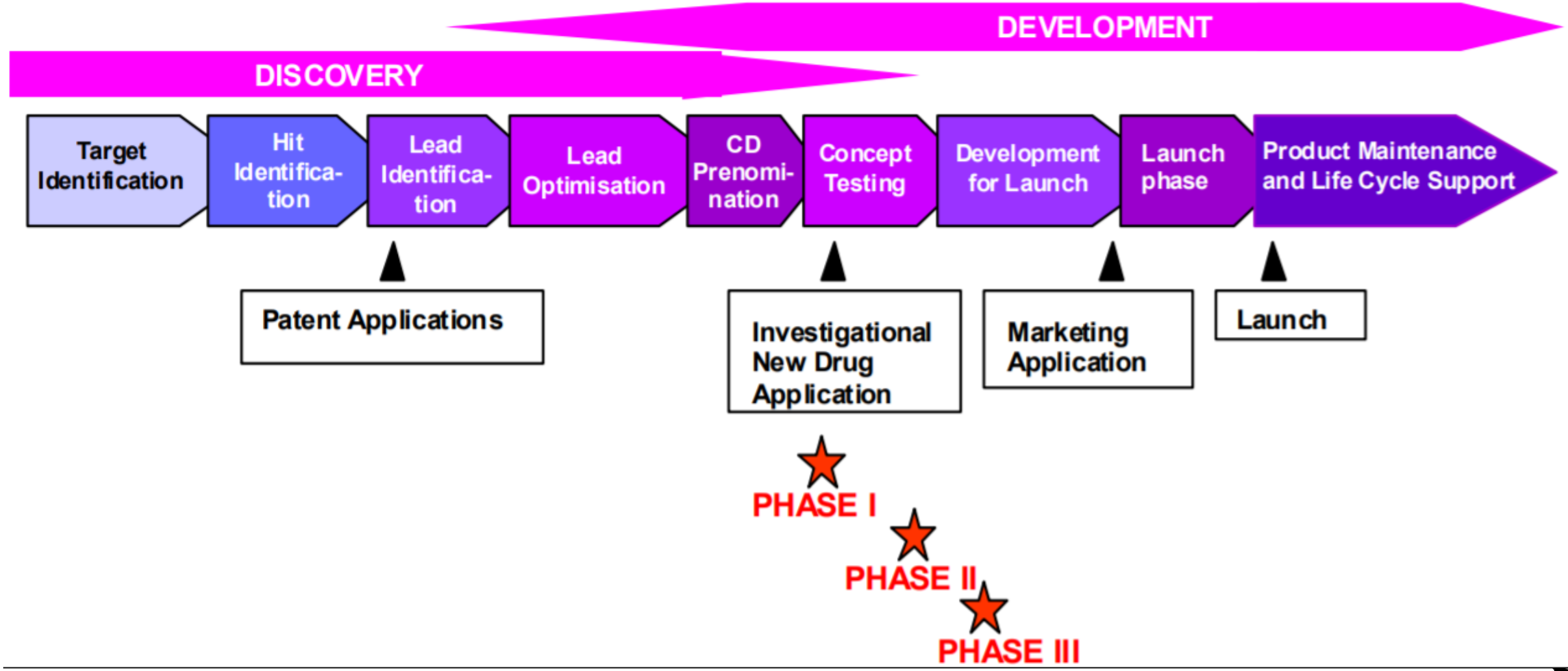
SELECT CRITERIA - THROUGHPUT



ESOMEPRAZOLE

92% conversion
> 94% ee

DEVELOPMENT PHASES



CLINICAL PHASES

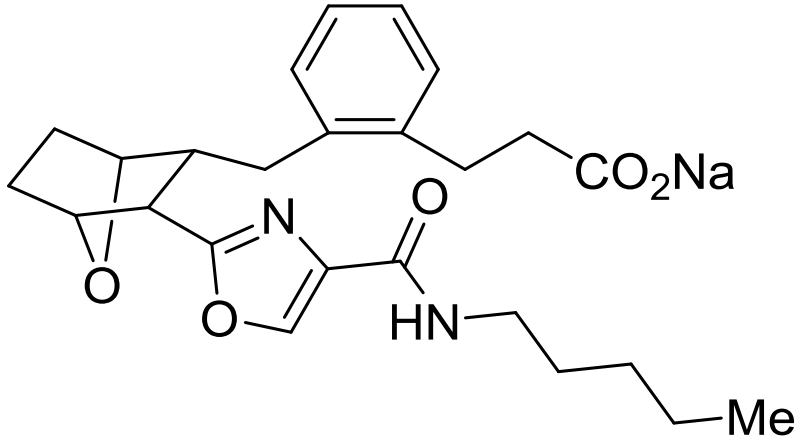
Phase 1 – safety screening (20-80 healthy volunteers) – safe dosing is determined and possible side effects identified;

Phase 2 – testing protocol is formulated (100-300 patients) – efficacy determination and further details about safety ;

Phase 3 – Final testing (1000-3000 patients) – desired effect confirmed, monitoring of side effects, comparison with known similar drugs; after successful completion of this phase a drug is usually approved and registered.

Phase 4 – Following studies after approval – gathering further pieces of information about risks, advantages and optimal dosing

A PRACTICAL SYNTHESIS OF IFETROBAN SODIUM

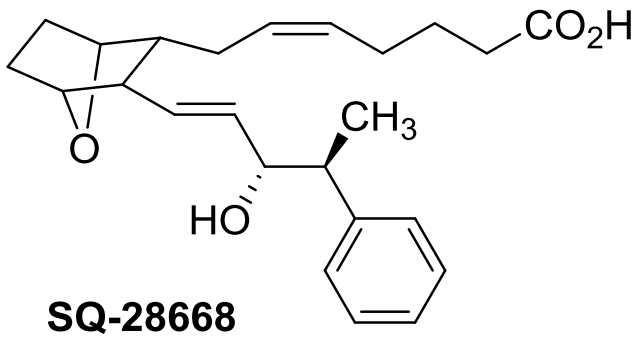


BMS-180291
IFETROBAN SODIUM

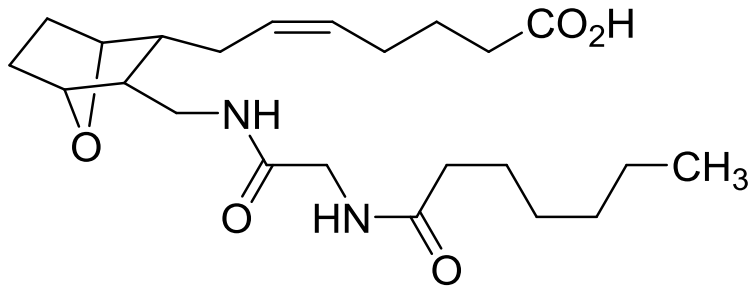
Bristol-Myers Squibb
Highly selective thromboxane A2 receptor antagonist (antithrombotic and anti-ischemic properties)
Mueller, R.H. *Process Chemistry in the Pharmaceutical Industry*, p.37, Marcel Dekker Inc. **1999**, ISBN 0-8247-1981-6

A PRACTICAL SYNTHESIS OF IFETROBAN SODIUM

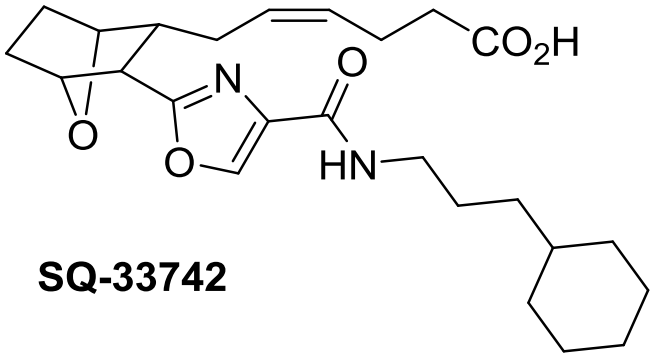
Potential new drug candidates:



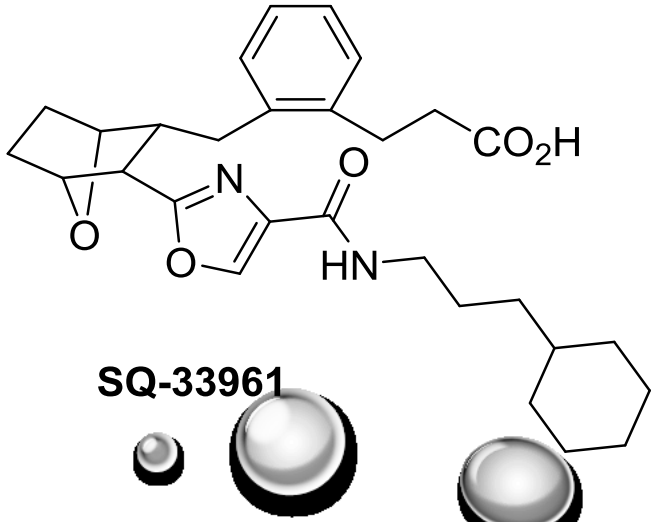
SQ-28668



SQ-30741

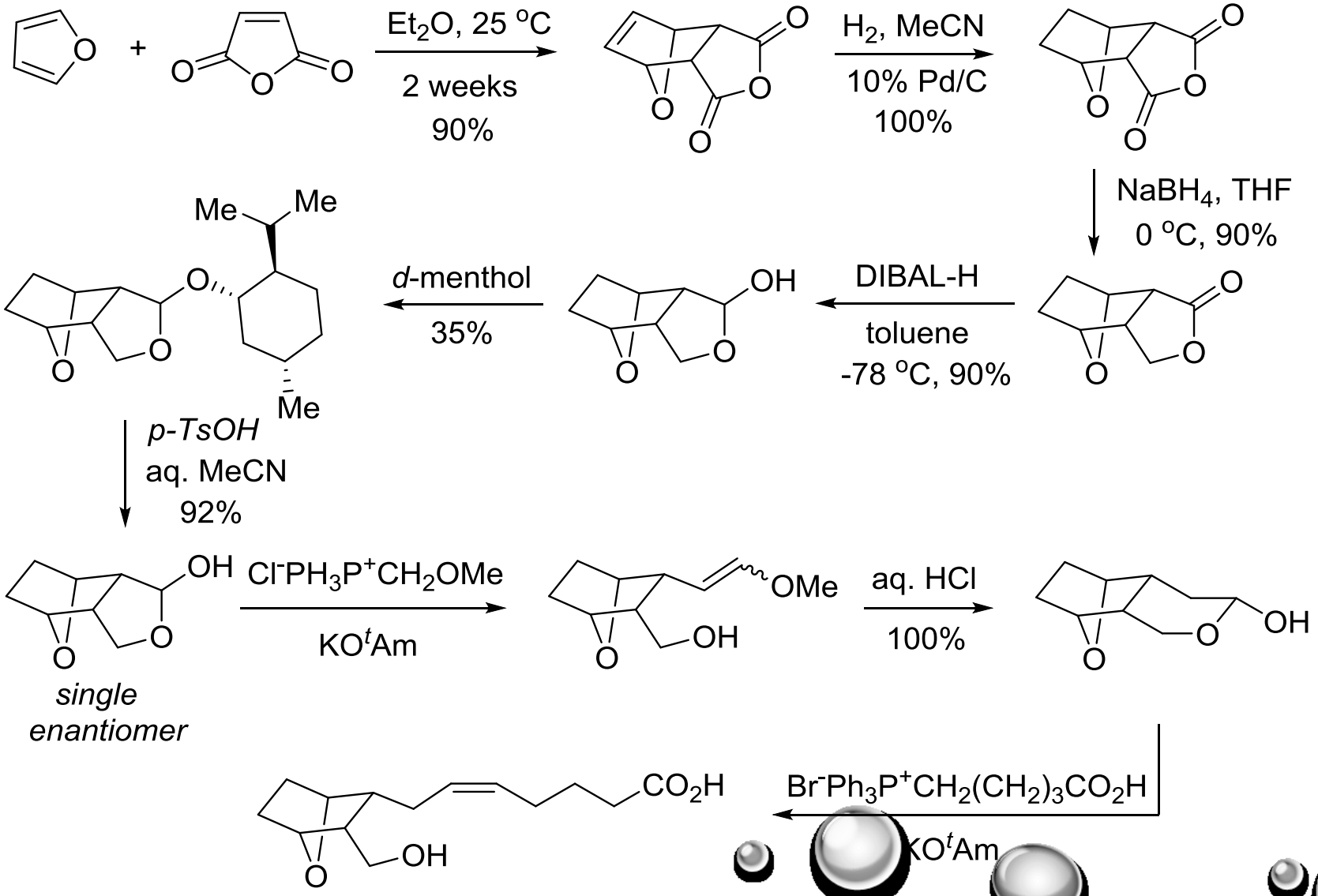


SQ-33742

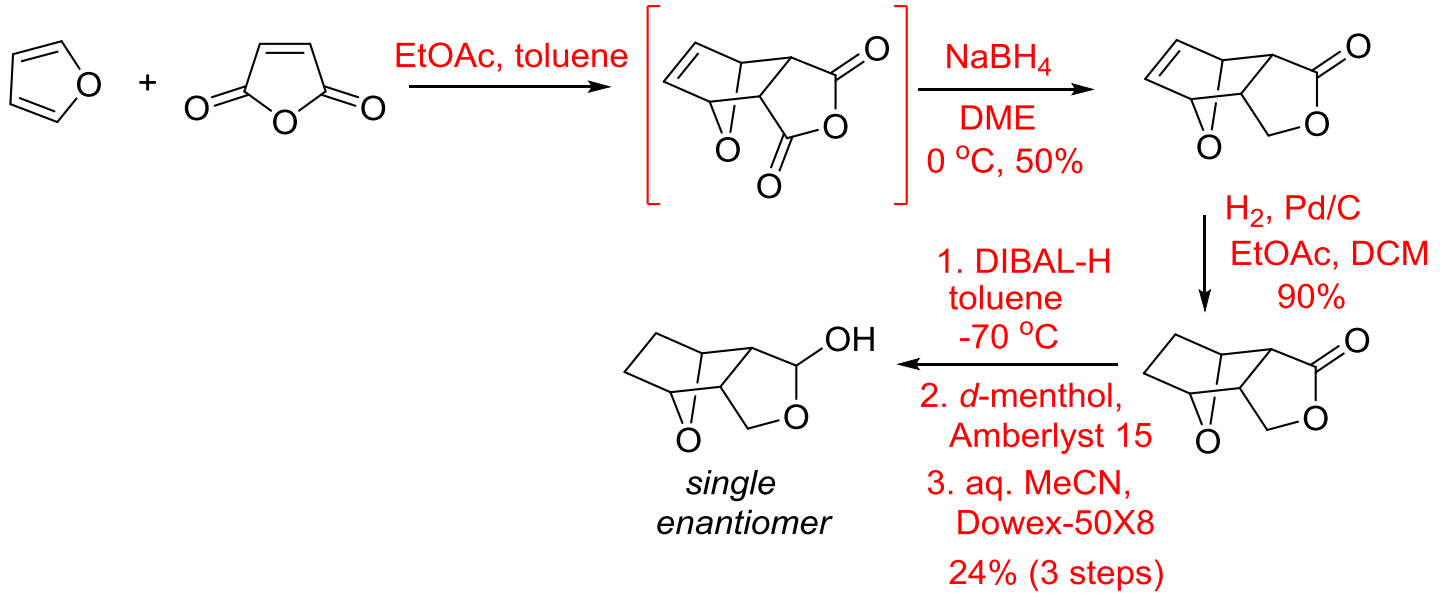


SQ-33961

A PRACTICAL SYNTHESIS OF IFETROBAN SODIUM



A PRACTICAL SYNTHESIS OF IFETROBAN SODIUM



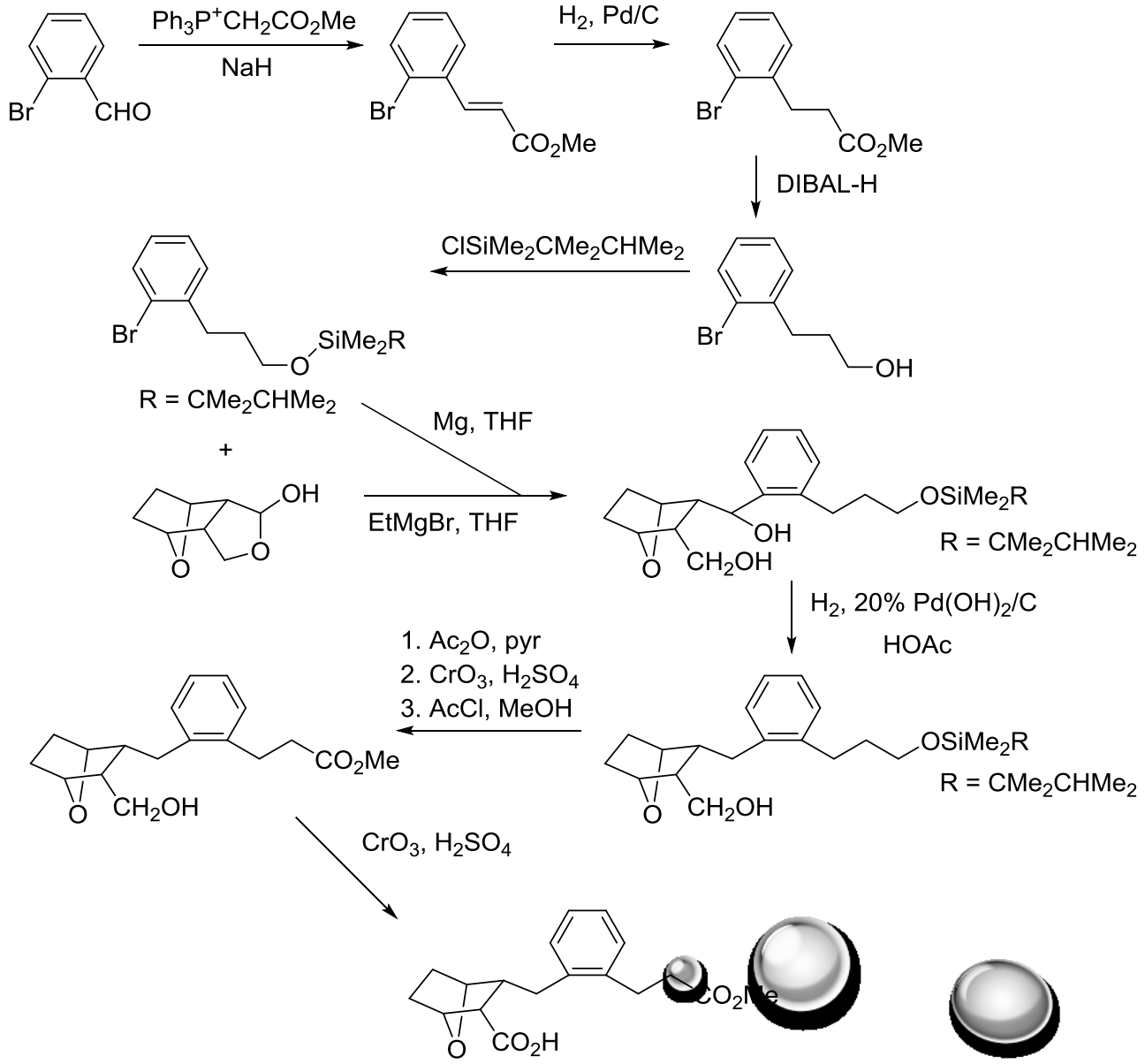
Large supply of the product made in Kilo Lab, but at the same time first candidate SQ-28668 failed in the clinical studies;

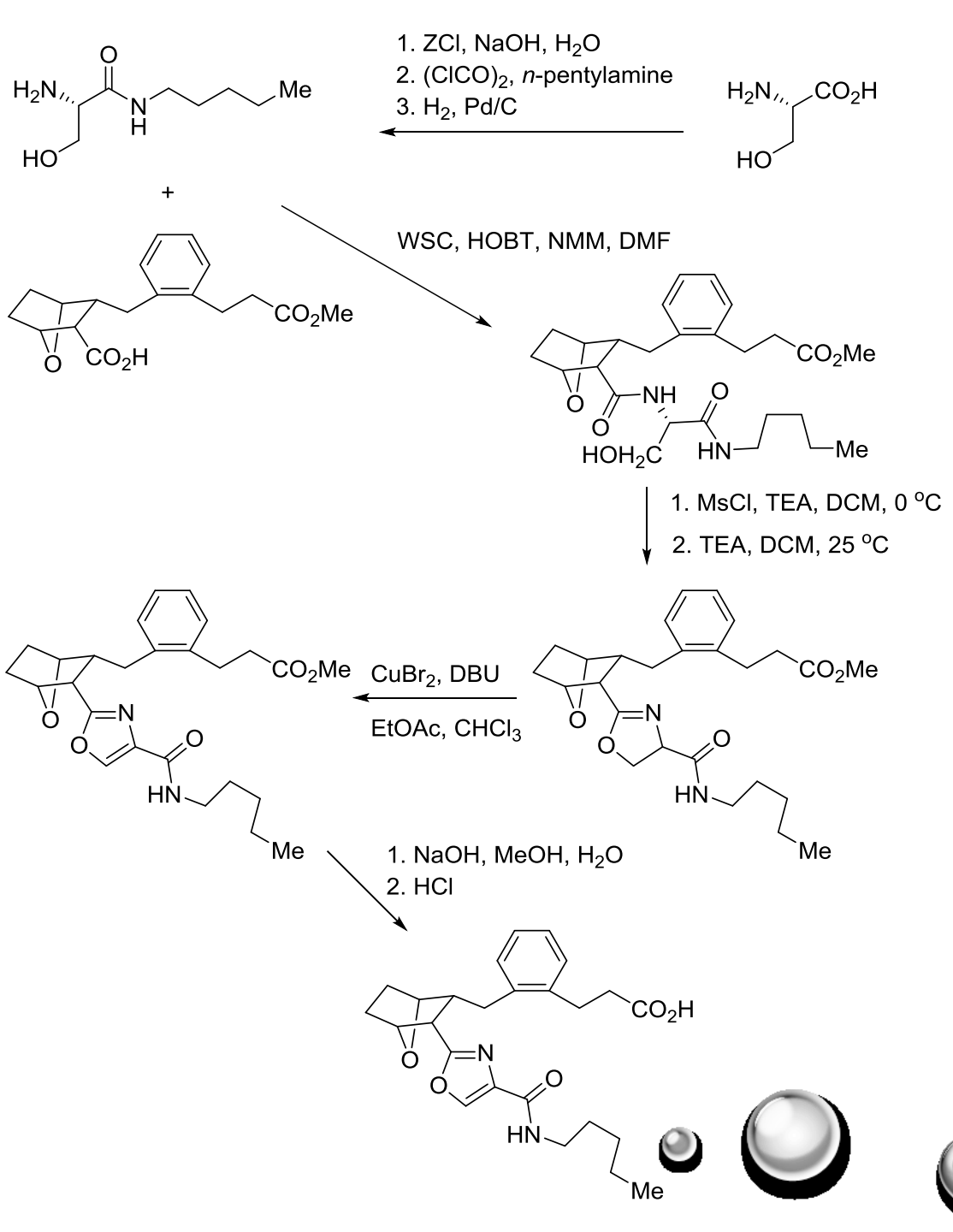
Next drug candidate was chosen (SQ-30741) – but exhibited extensive first-pass metabolism in clinic and further work was halted;

17 kg of the product still remained unutilized;

Finally, BMS-180291 selected as promising drug candidate (the product proved very useful for the start in Kilo Lab campaign).

A PRACTICAL SYNTHESIS OF IFETROBAN SODIUM




1. ZCl, NaOH, H_2O
2. $(ClCO)_2$, *n*-pentylamine
3. H_2, Pd/C
WSC, HOBT, NMM, DMF
1. MsCl, TEA, DCM, 0 °C
2. TEA, DCM, 25 °C
$CuBr_2$, DBU
EtOAc, $CHCl_3$
1. NaOH, MeOH, H_2O
2. HCl

A PRACTICAL SYNTHESIS OF IFETROBAN SODIUM

SUMMARY (so far):

23 steps, synthesis is convergent but the longest linear sequence consists of 16 steps;

Overall yield < 3%

10 steps involve oxidation stage adjustment

Resolution process

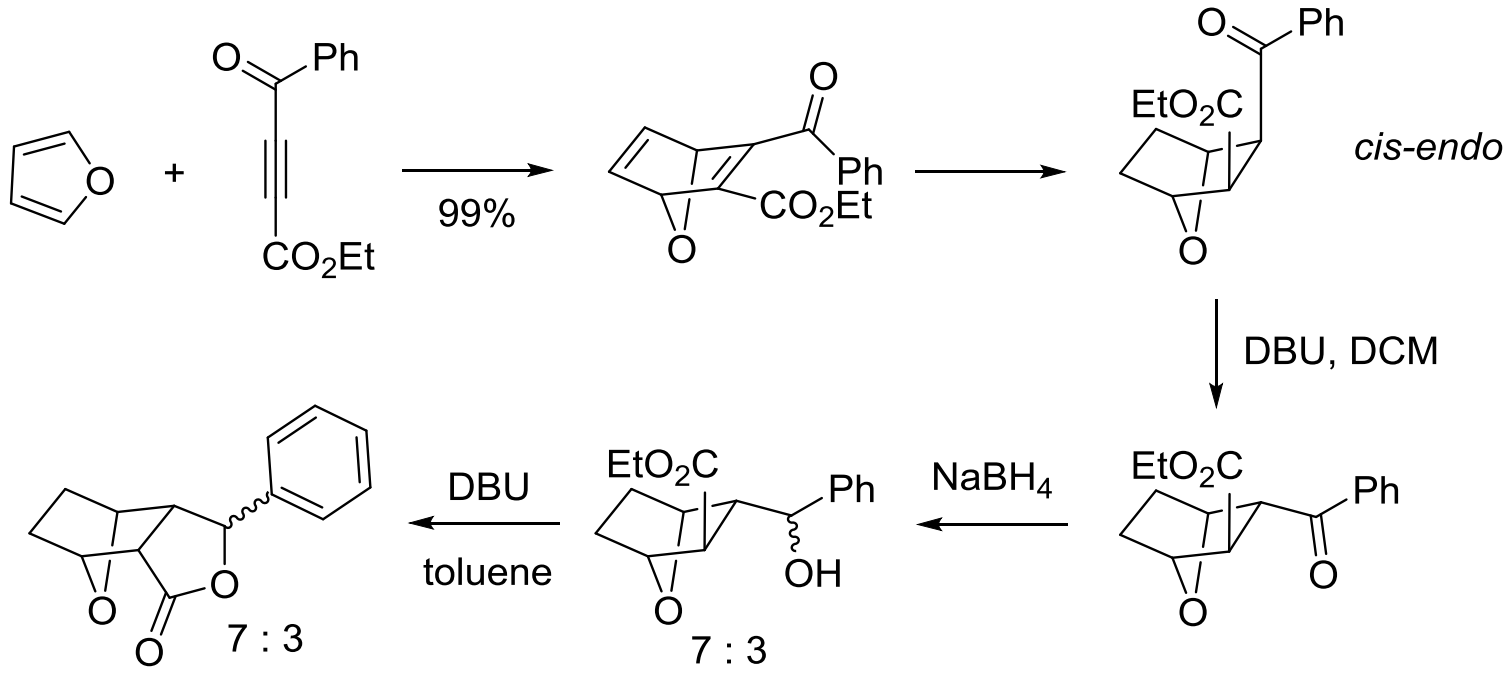
BMS-18029 seemed to be promising drug candidate in preliminary tests

„Quick-fixes“ in original route to get more material (20 kg by a combination of Kilo Lab and Pilot Plant efforts);

In the meantime Process Research activities started to identify a better route

A PRACTICAL SYNTHESIS OF IFETROBAN SODIUM

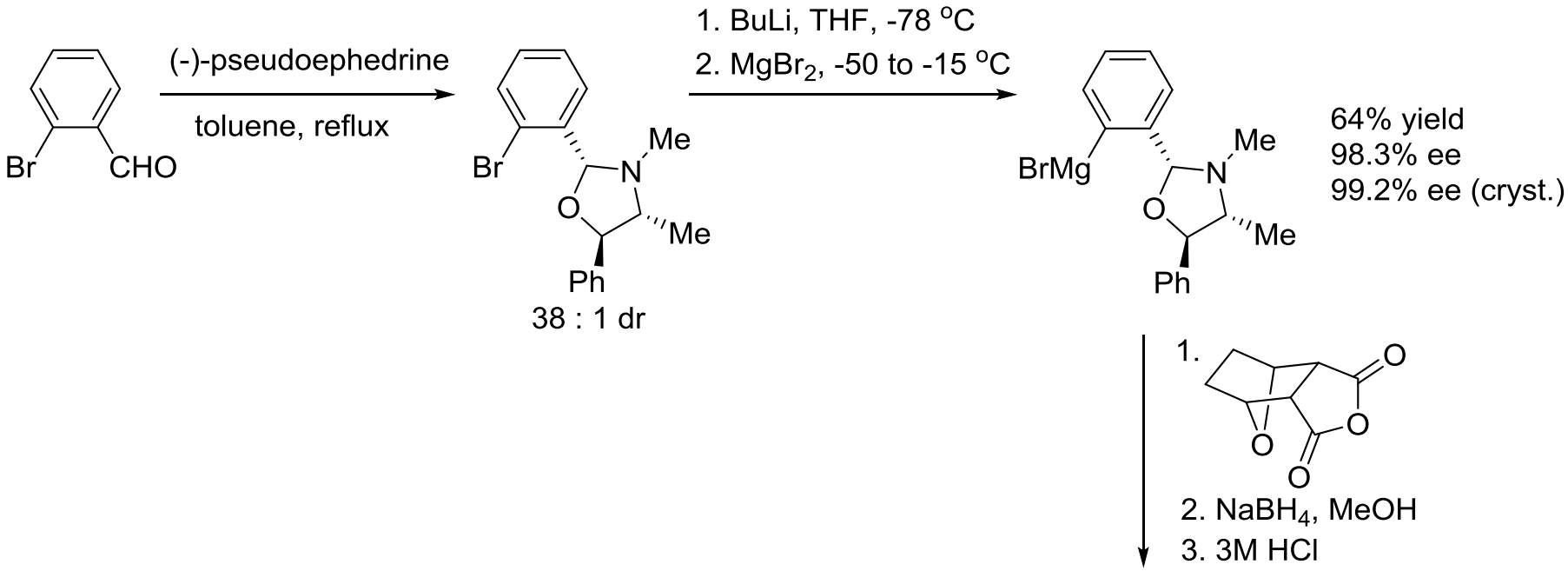
- Model alternative Diels-Alder approach:



Would require synthetic approach to starting propargylic derivative

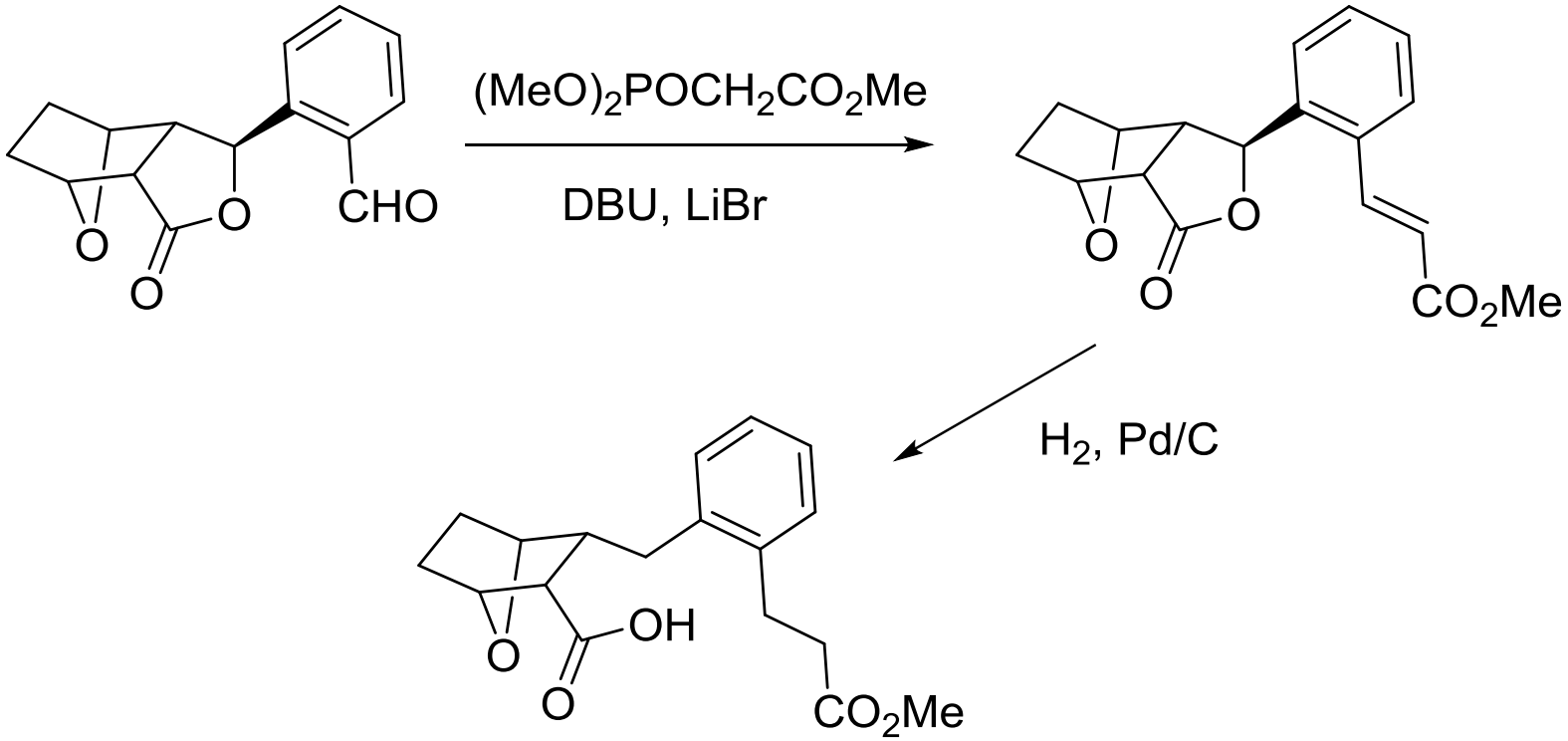
A PRACTICAL SYNTHESIS OF IFETROBAN SODIUM

Stereoselective approaches (to avoid resolution):



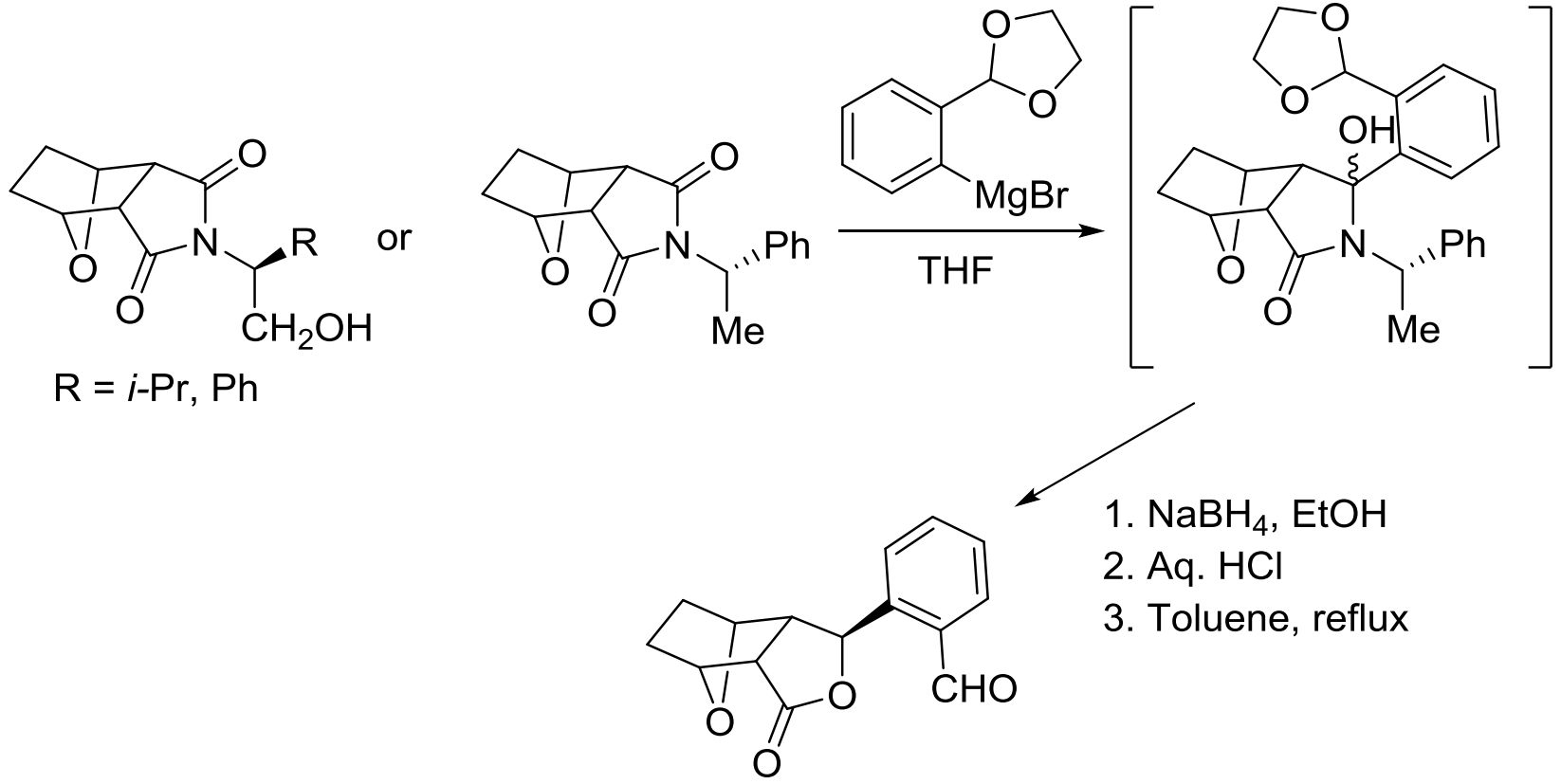
99.7 : 0.3 - very selective borohydride reduction
(the presence of magnesium ion during the reduction)
In the absence of magnesium ion only 60 : 40 mixture
of epimers at the benzylic carbon atom

A PRACTICAL SYNTHESIS OF IFETROBAN SODIUM



More efficient than the original synthetic pathway;
Safety concerns;
The yield in the Grignard to lactone conversion was lower than practical

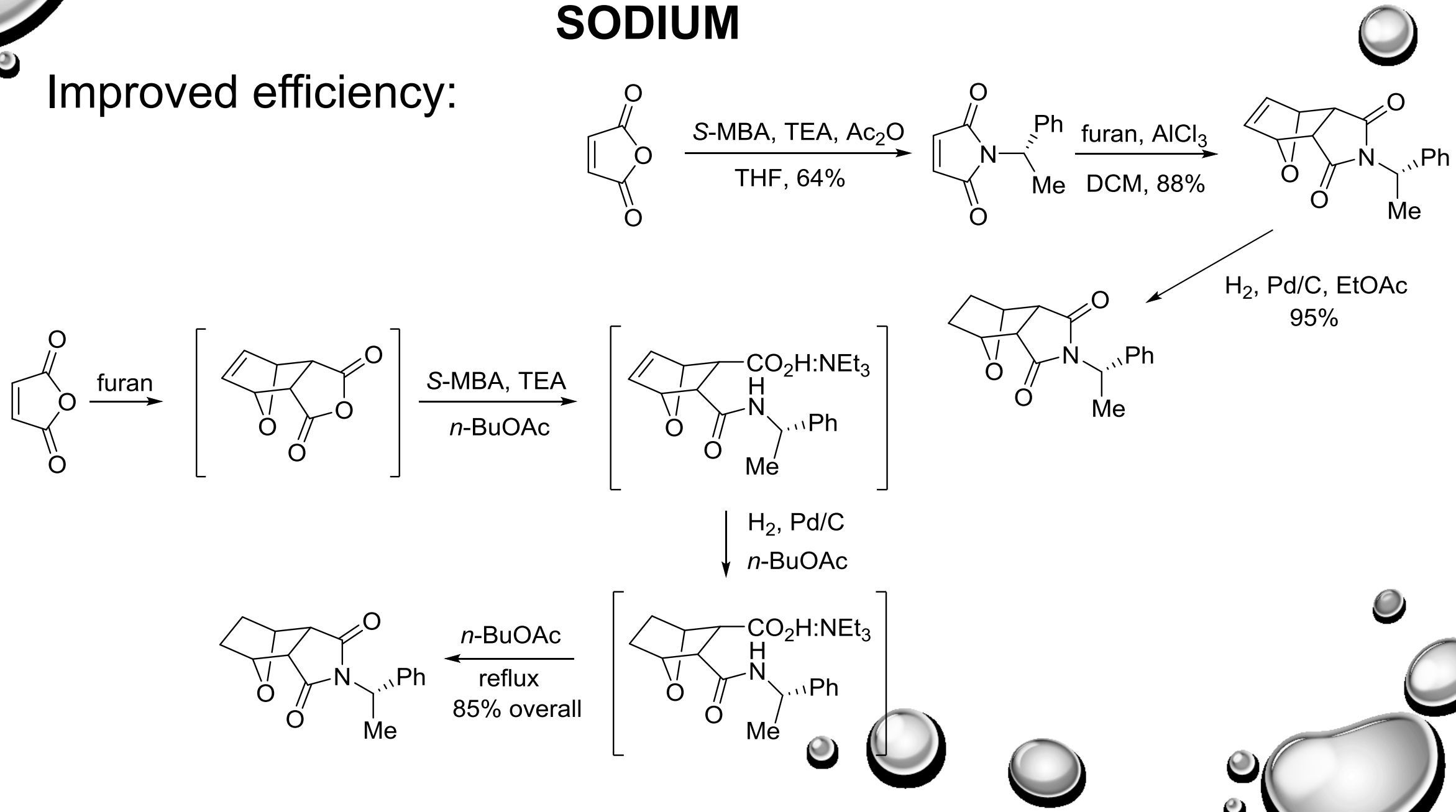
A PRACTICAL SYNTHESIS OF IFETROBAN SODIUM



With *S*-valinol or *S*-phenylglycinol auxiliaries 65% yield; 72% ee;
Relatively inexpensive chiral auxiliary *S*-methylbenzylamine provided selectivity 94 : 6 (>99 : 1 after crystallization) in 89% yield.
Serine derived chiral auxiliaries gave lower yields and stereoselectivity.

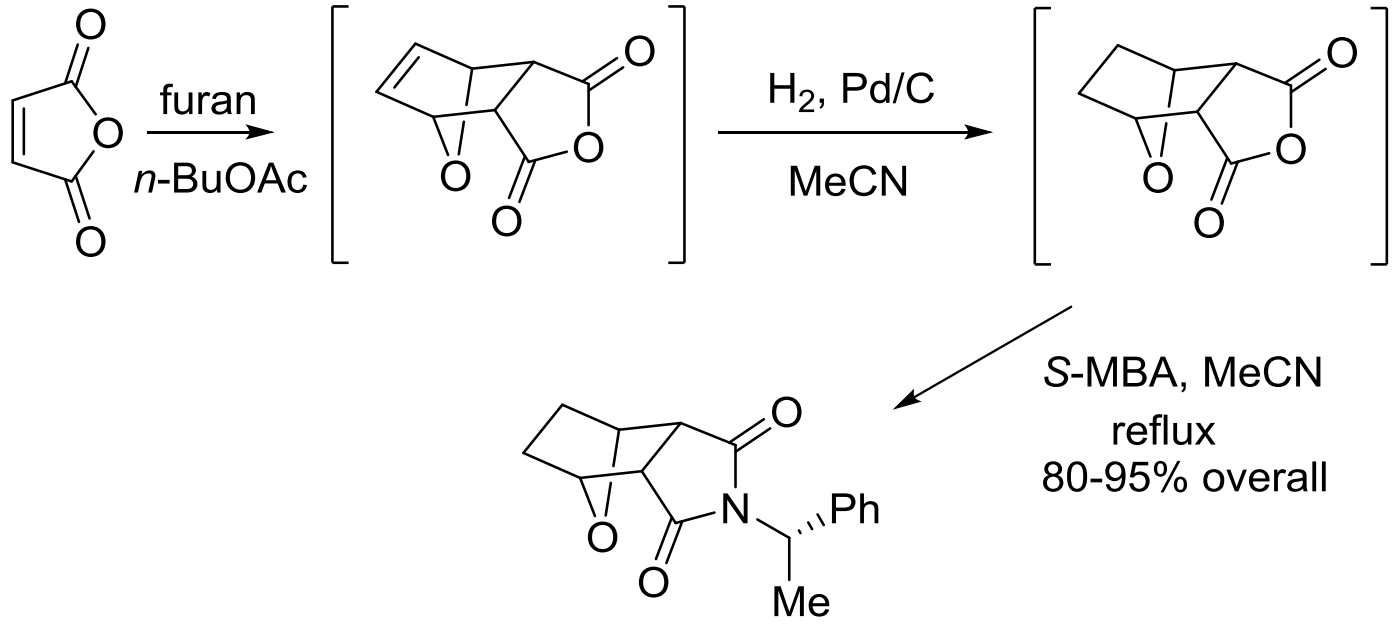
A PRACTICAL SYNTHESIS OF IFETROBAN SODIUM

Improved efficiency:



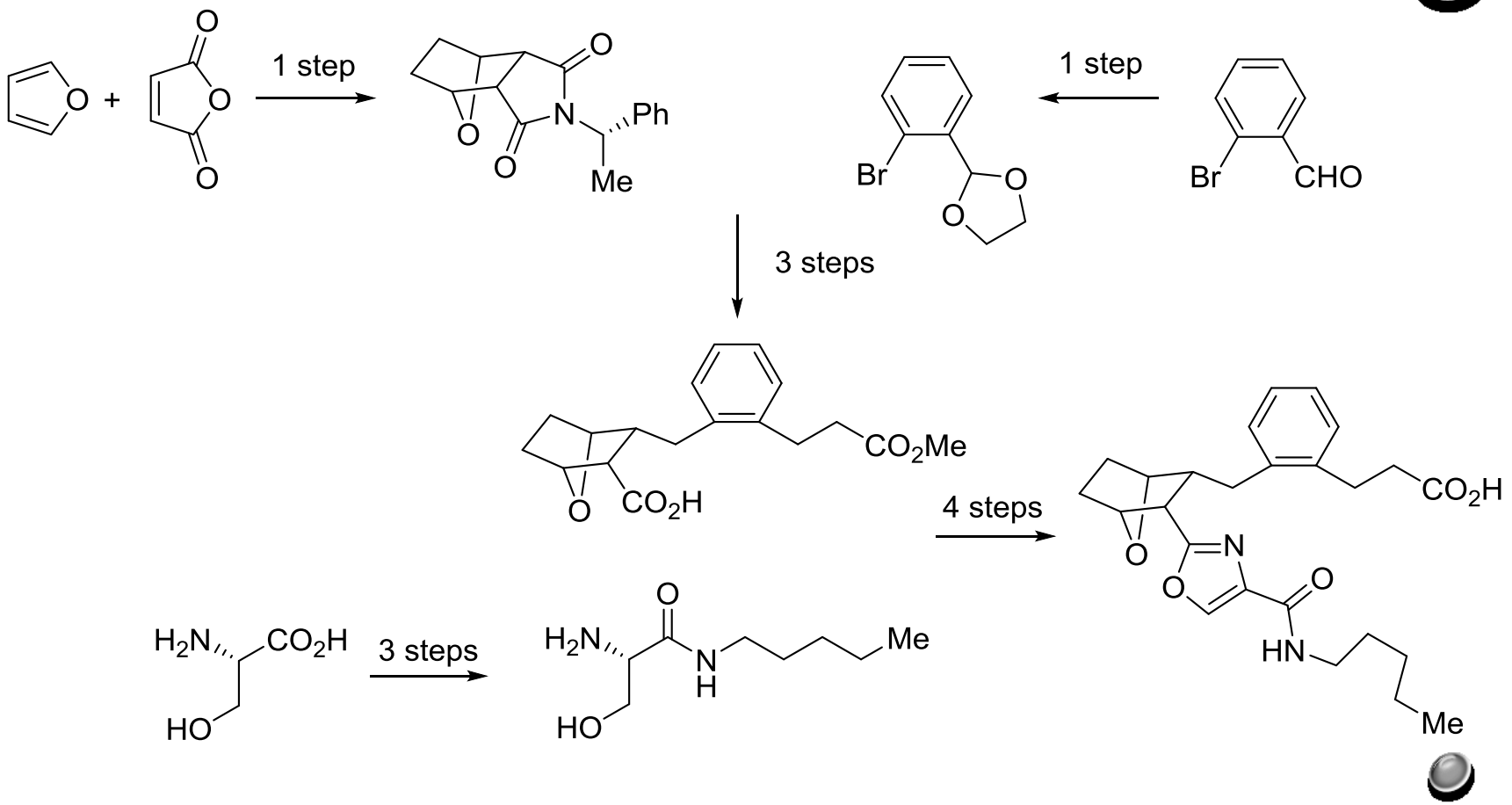
A PRACTICAL SYNTHESIS OF IFETROBAN SODIUM

- Still improving efficiency:



A PRACTICAL SYNTHESIS OF IFETROBAN SODIUM

SUMMARY:



12 convergent steps; 3 oxidation-reduction reactions left from 10;
83 researchers.
Overall yield 28%;