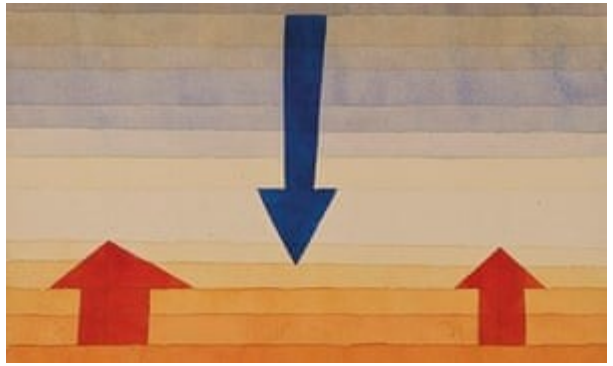
PROCESS CHEMISTRY INTRODUCTION

Petr Beňovský


Abacus Gallery



My experience has been that process chemistry is a roller-coaster ride, with tremendous highs and lows, where you learn theory and concepts, as needed, on the fly, from your colleagues and from those reference books (while meeting seemingly unattainable milestones and timelines)

Peter J.Harrington
Pharmaceutical Process Chemistry for Synthesis Rethinking the Routes to Scale-up, Wiley, 2011

DIFFERENCES BETWEEN ACADEMIC AND PROCESS CHEMISTRIES

Academic – Discovers, reveals, disputes, confirms, brings new knowledge.
Small amount of material.

Process – Selects, optimizes, seeks for efficiency, defines control points, considers efficiency and environment (also safety).
Role of chemical engineers.
Relatively large amount of material.

Outline of the class

- History of fine process chemistry, recent trends, future;
- Differences between laboratory and larger scale experiments;
- Scale-up/downscale considerations;
- Safety;
- Crystallization (solubility, metastable zone, nucleation, crystal growth, optical resolution, Viedma ripening, attrition enhanced deracemization, seeding, Ostwald ripening, new trends in crystallization);
- Polymorphism;
- Typical process operations (mixing, heat transfer, agglomeration, product isolation, distillation, drying, purification, work up, reactors);

Outline of the class (cont.)

- Continuous manufacturing, flow chemistry;
- Synthetic route selection;
- Analytical methods, Process Analytical Technology (PAT), Design of Experiments (DoE), Quality by Design (QbD), Purge Analyses;
- Environmental Aspects;
- Economy, Cost of Goods (CoG);
- Regulatory issues, patents.

Examples from recent literature about various topics within the whole lecture.

Recommended reading:

- Anderson, N.G. *Practical Process Research & Development, A Guide for Organic Chemists, 2nd Edition, Elsevier Inc. 2012; ISBN 978-0-12-386537-3*

- Hulshof, L.A. *Right First Time in Fine-Chemical Process Scale-up*, Scientific Update LLP 2013; ISBN 978-0-9533994-1-3

- Blacker, A.J.; Williams, M.T. *Pharmaceutical Process Development, Current Chemical and Engineering Challenges RSC Publishing 2011; ISBN 978-1-84973-146-1*

Examination:

Written test (total 50 points)

45 – 50 points ….. A
39 – 44 points ….. B
33 – 38 points ….. C
27 – 32 points ….. D
21 – 26 points ….. E

HISTORY, RECENT DEVELOPMENT AND FUTURE OF PROCESS (PHARMACEUTICAL) CHEMISTRY

Petr Beňovský

HISTORY OF PROCESS (PHARMACEUTICAL) CHEMISTRY

From Alchemy to Chemistry

Gesner’s treatise – 1599 – bath of Marie

HISTORY OF PROCESS (PHARMACEUTICAL) CHEMISTRY

1668 – Merck founded in Germany, nowadays one of the largest chemical and pharmaceutical companies all over the world;

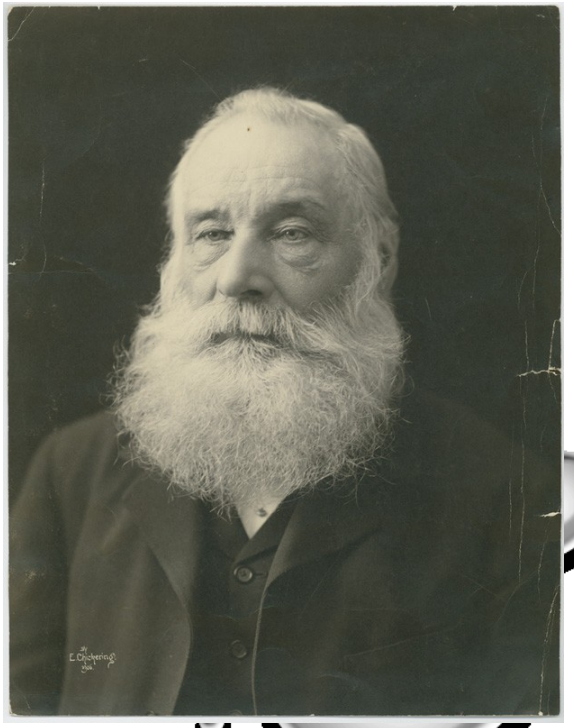
1891 – Merck US subsidiary founded (Merck & Co.), in 1917 (after WW I) expropriated and became independent American company;

1856 – William Henry Perkin assigned by his teacher (August Wilhelm von Hofmann) to attempt the synthesis of quinine from aniline. Instead, he prepared mauveine;

1876 – Eli Lilly company founded by colonel Eli Lilly in US (1923 first commercially available insulin; 1940 first mass production penicillin); first written instructions to process workers; quality controls;

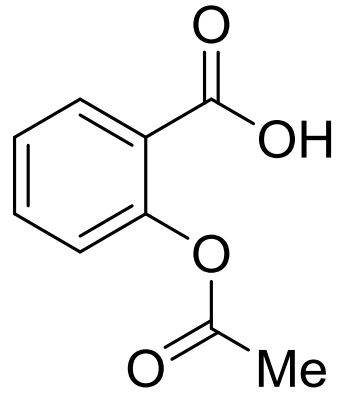
1899 – Bayer – blockbuster Aspirin® (still manufactured – about 40 000 tons per year);

1903 – Merck – diethylbarbituric acid



HISTORY OF PROCESS (PHARMACEUTICAL) CHEMISTRY

1899 – Bayer –Aspirin®;



Arthur Eichengrün (the head of pharmaceutical division);

Felix Hoffmann (a chemist);

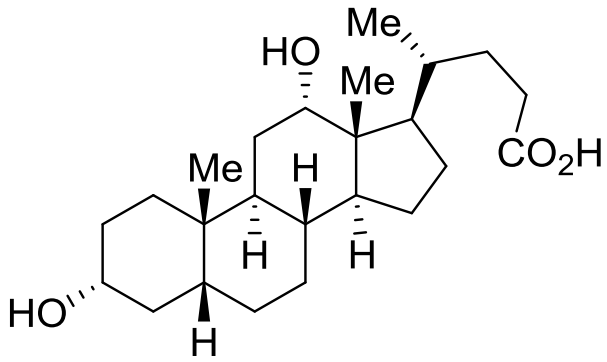
Heinrich Dreser (the head of pharmacological section responsible for the clinical studies).

Desborough, M.J.R. *et al British J.Haematol. 177*, 674 (**2017**)

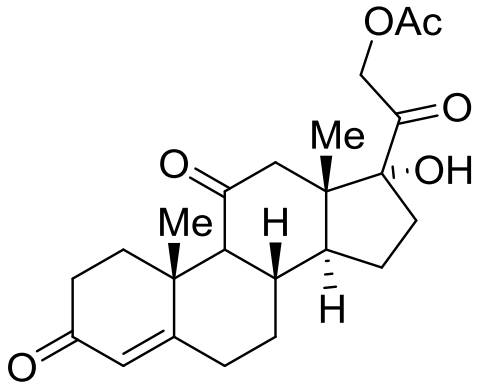
CORTISONE ACETATE

- Early 1950s – Merck the synthesis of cortisone acetate from desoxycholic acid

(*Org.Process Res.Dev.* **8**, 708 (**2004**))

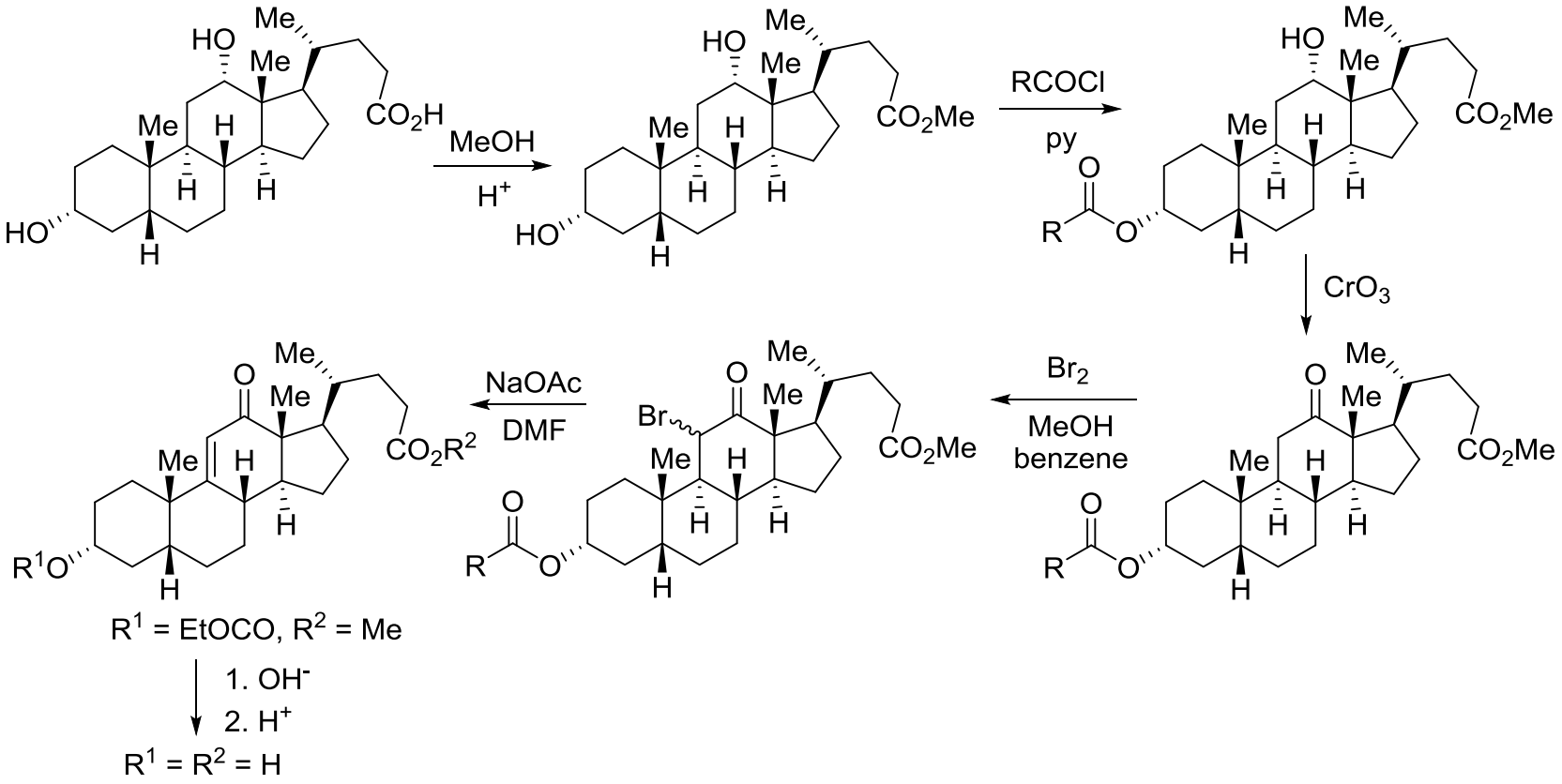


Desoxycholic Acid

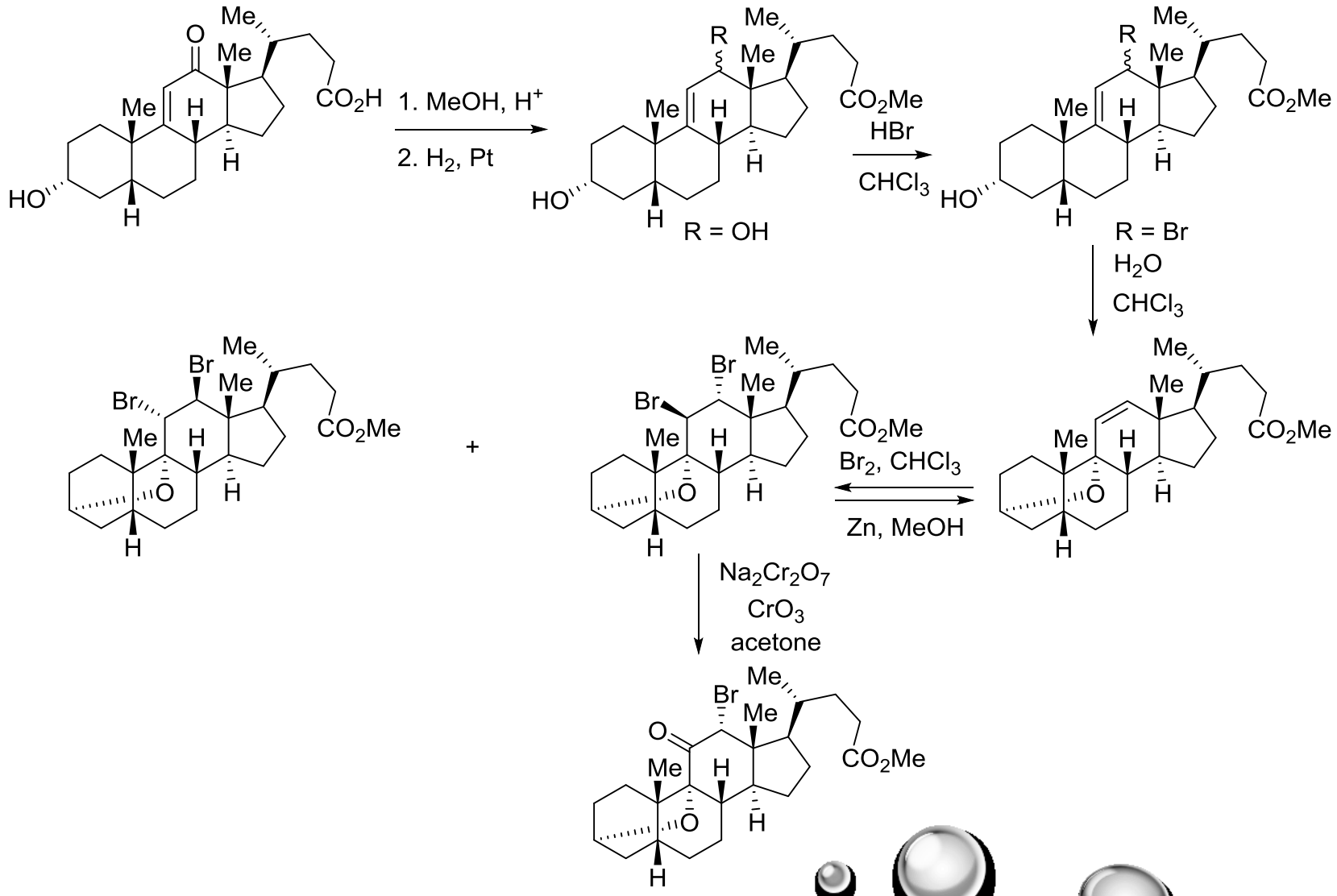


Cortisone Acetate

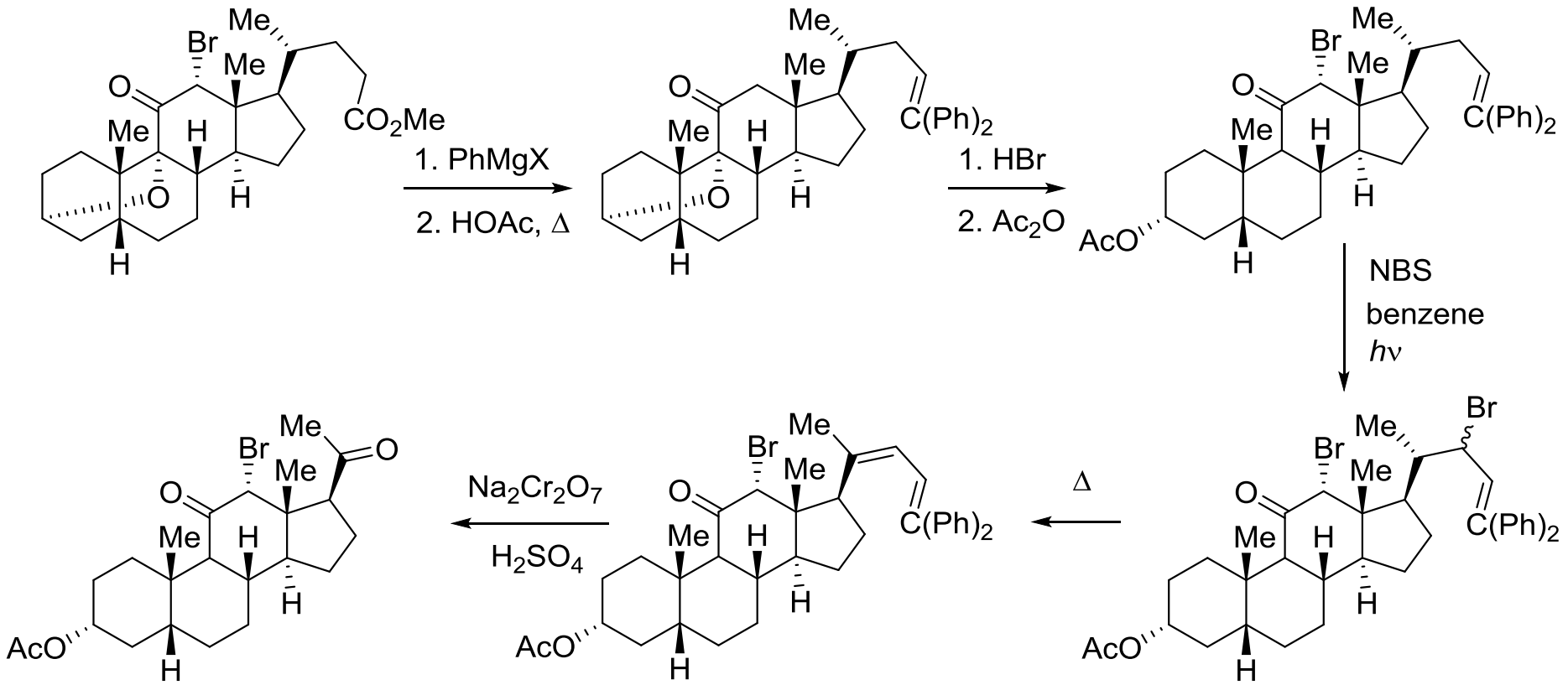
CORTISONE ACETATE



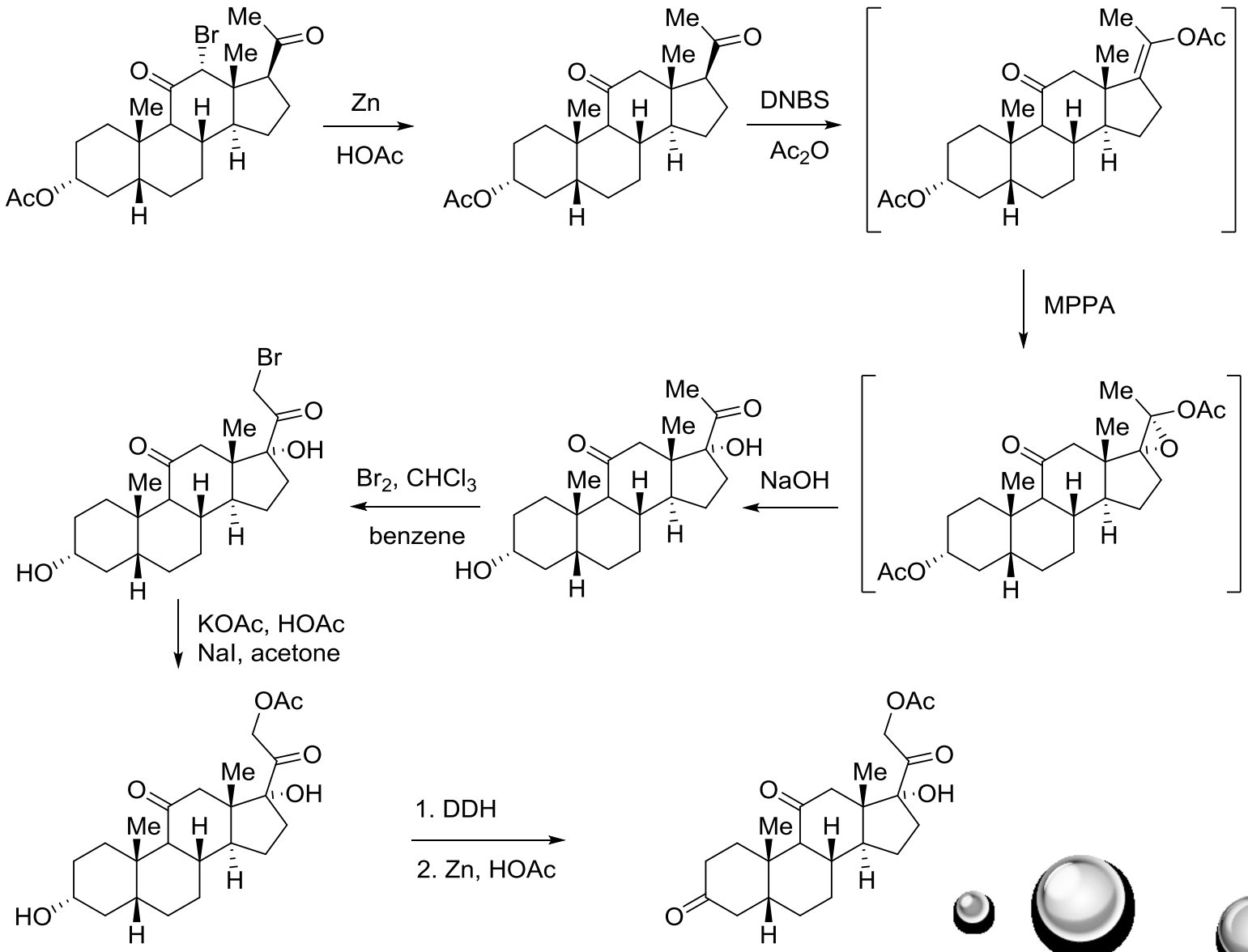
CORTISONE ACETATE



CORTISONE ACETATE



CORTISONE ACETATE

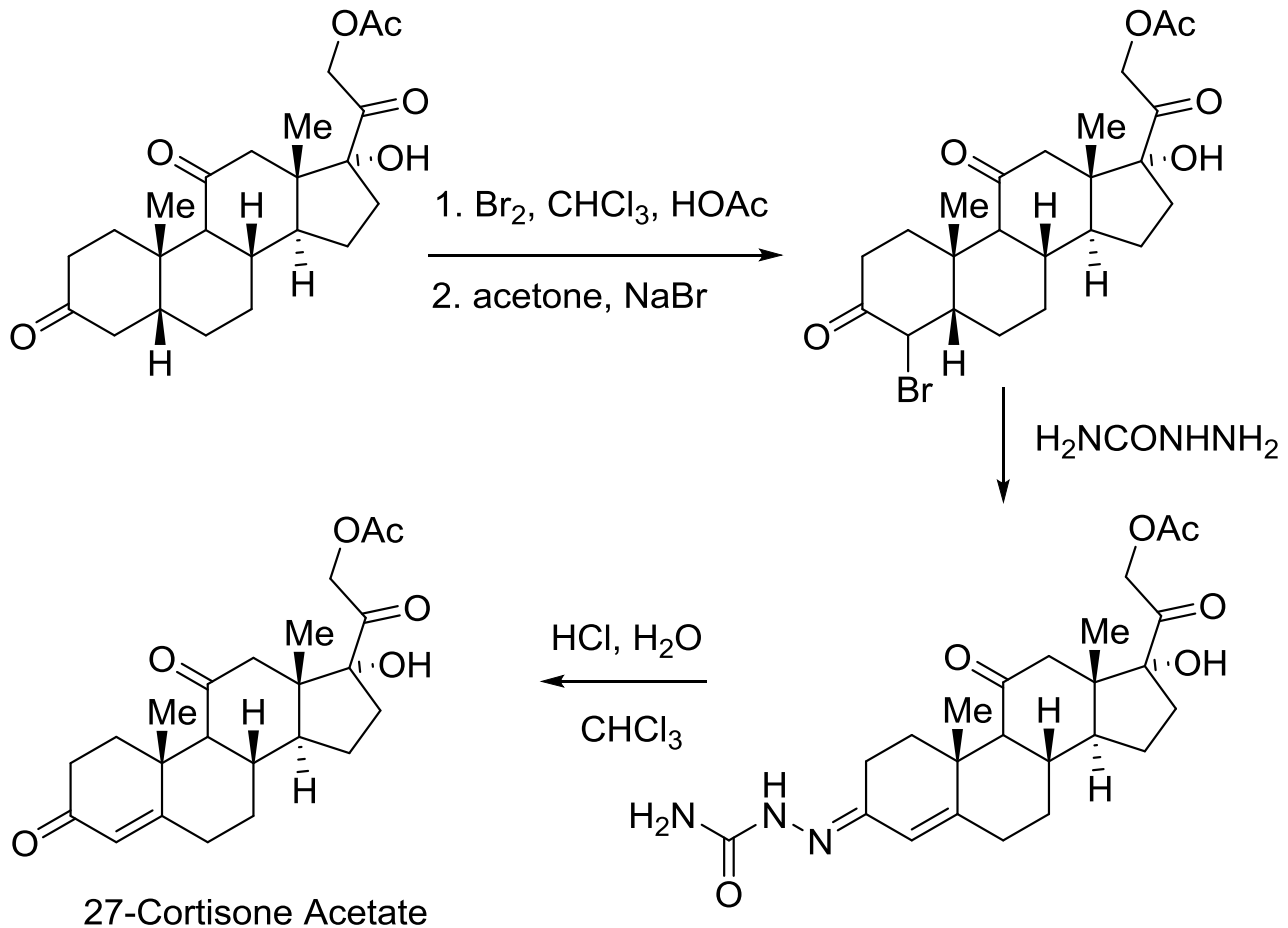


DNBS = 3,5-dinitrobenzene-sulfonic acid

MPPA = monoperoxophthalic acid

DDH = dibromodimethyl hydantoin

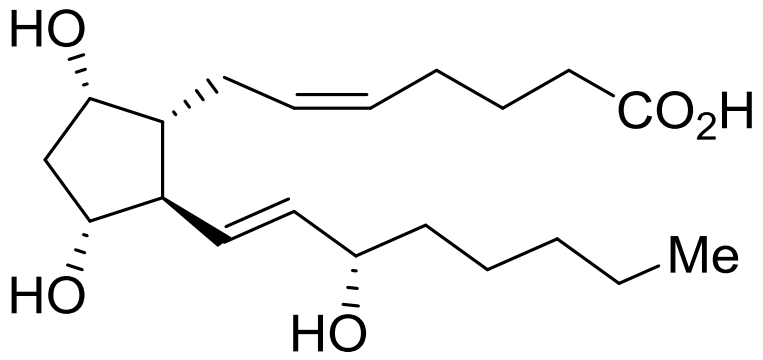
CORTISONE ACETATE



27-Cortisone Acetate

HISTORY OF PROCESS (PHARMACEUTICAL) CHEMISTRY

1960s – Upjohn and ICI companies developed synthetic routes to prostaglandins

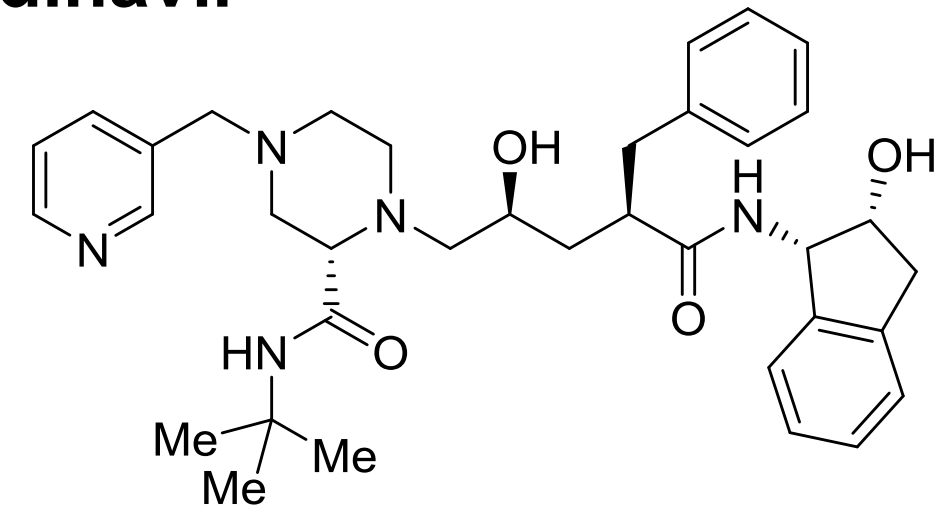


Prostaglandin $F_2\alpha$

1960s to 1980s – the advent of asymmetric synthesis (Sharpless, Jacobsen, the Monsanto process – asymmetric hydrogenation, Takasago – asymmetric isomerisation)

HISTORY OF PROCESS (PHARMACEUTICAL) CHEMISTRY

1990s - Merck - **Indinavir**



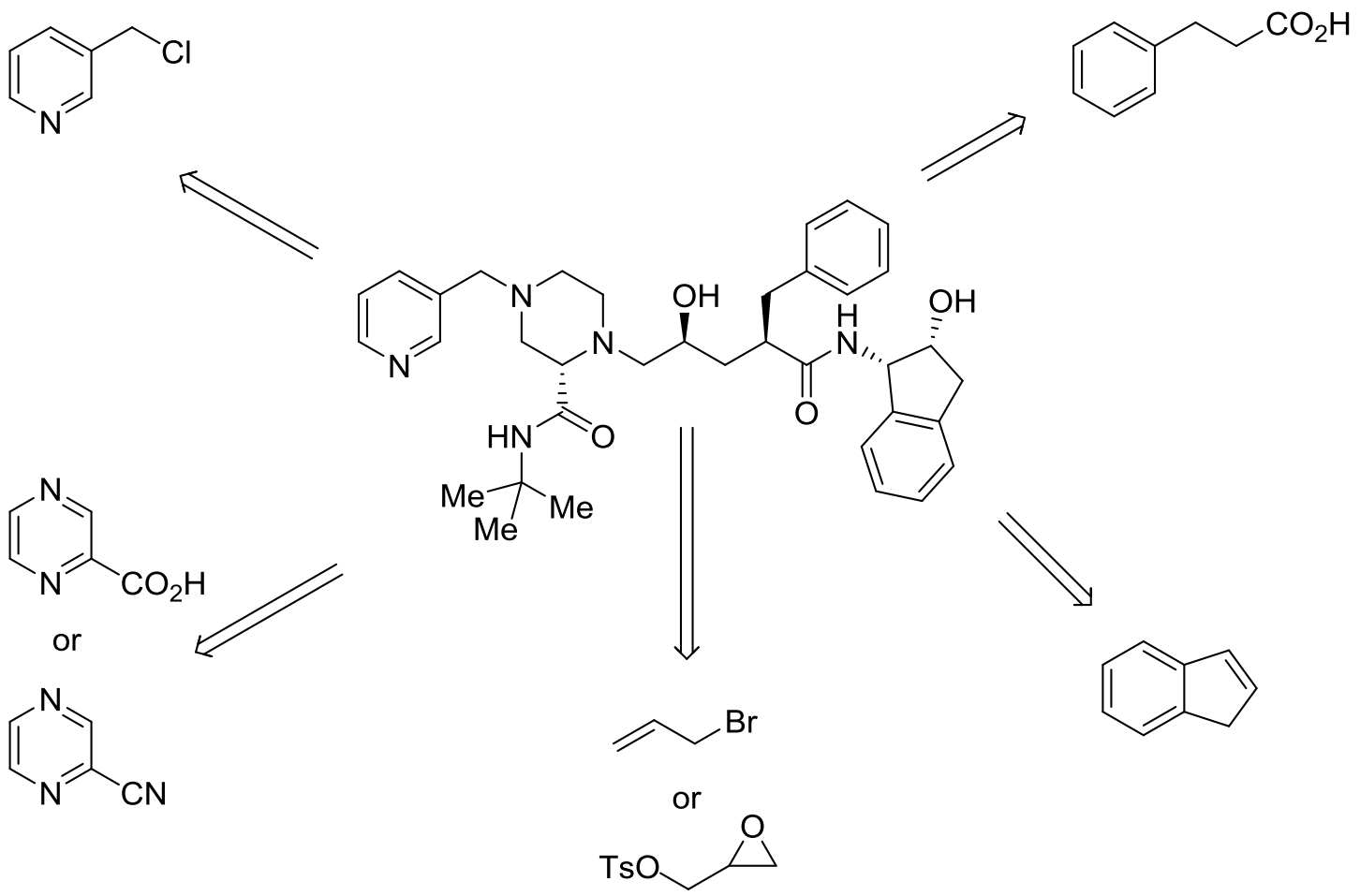
Indinavir

Treatment of HIV – AIDS related diseases;

Very large dose – 2.4 g per day, i.e. cca 1 kg per year per person;

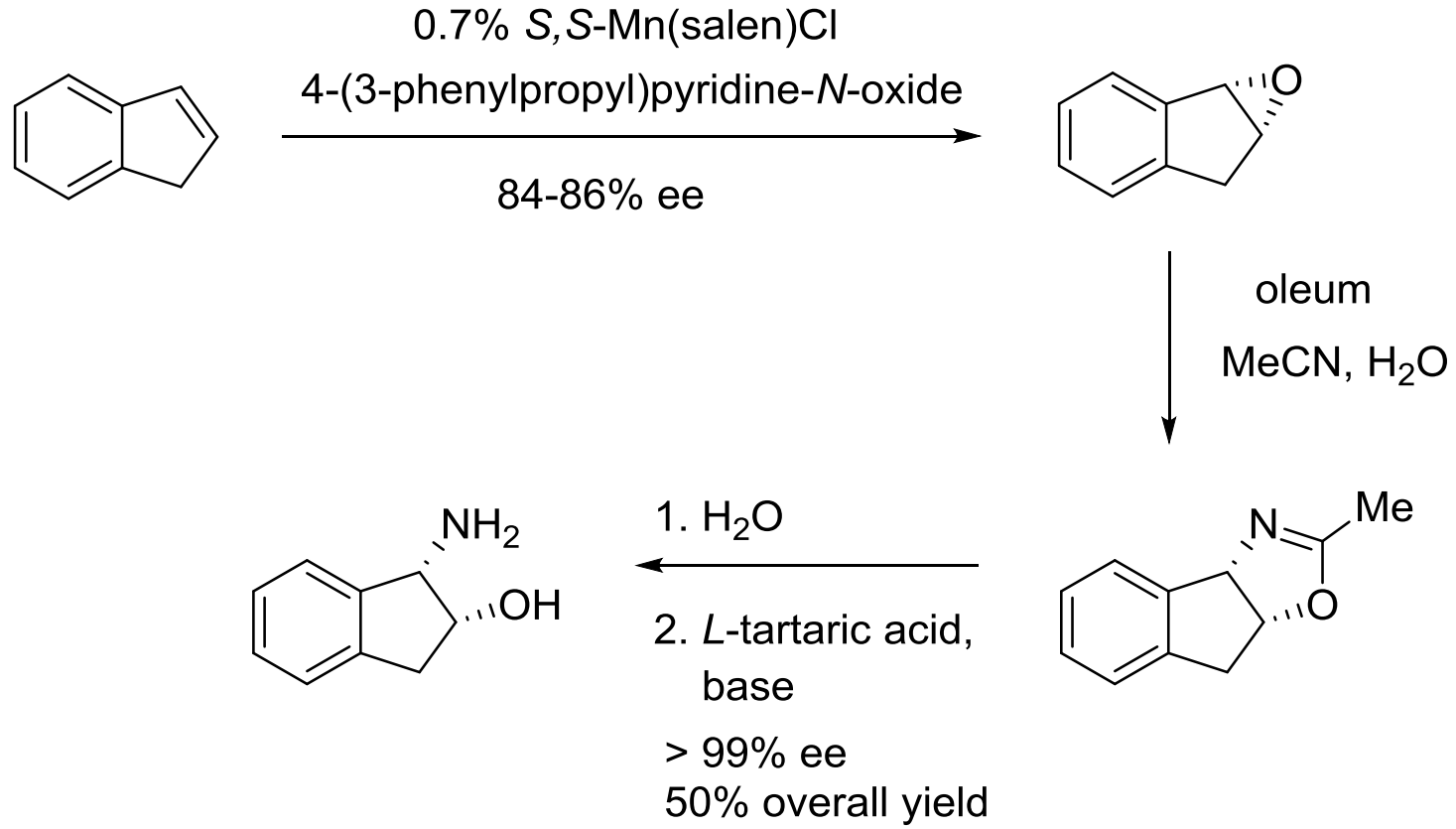
Challenge to design a synthesis that could be executed on a scale approaching that of commodity chemicals.

INDINAVIR (cont.)



Hudlický, T.; Reed J.W. *The Way of Synthesis;* Wiley 2007

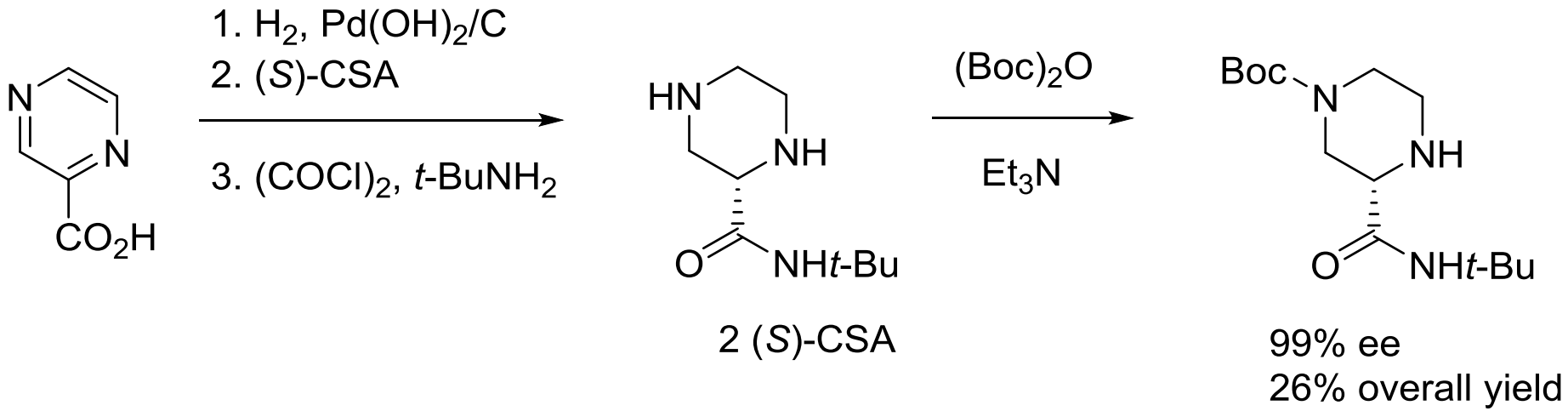
INDINAVIR (cont.)



Senanayake, C.H. *et al* *Tetrahedron Lett. 36*, 3993 (**1995**)

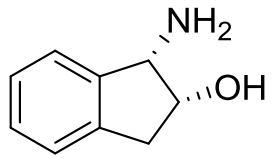
Hudlický, T.; Reed J.W. *The Way of Synthesis* Wiley 2007

INDINAVIR (cont.)



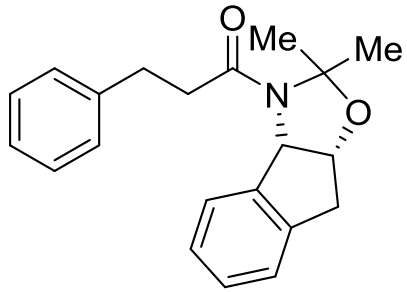
Rossen, K. *et al* *Tetrahedron Lett. 36*, 6419 (**1995**)
Hudlický, T.; Reed J.W. *The Way of Synthesis* Wiley 2007

INDINAVIR (cont.)

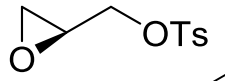


1. $PhCH_2CH_2COCl$

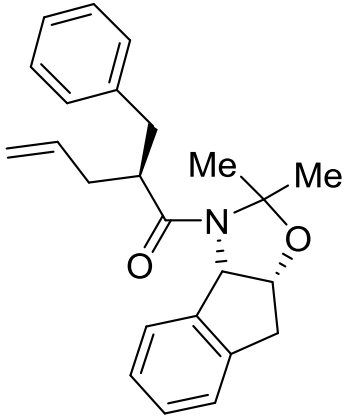
2. 2-methoxypropene
   MeOH



LHMDS
allyl bromide



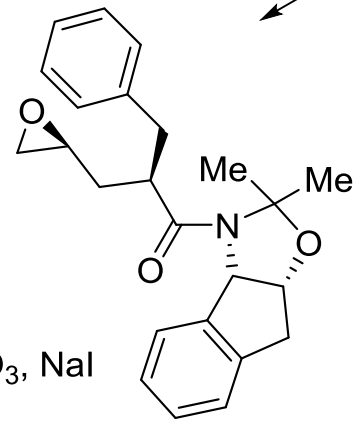
LHMDS

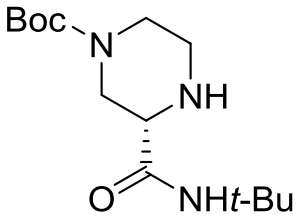


97% de
95% yield

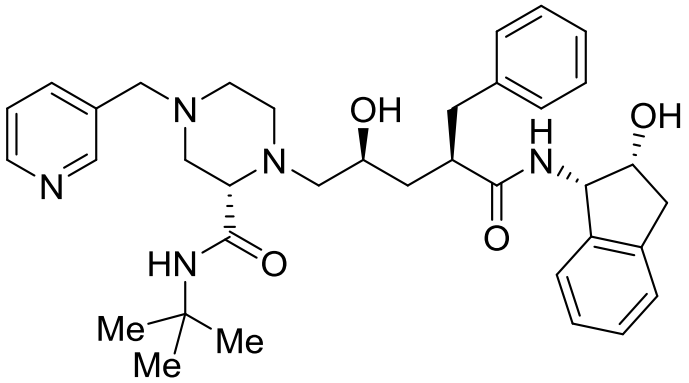
1. NCS, NaI,
   aq. $NaHCO_3$

2. NaOMe



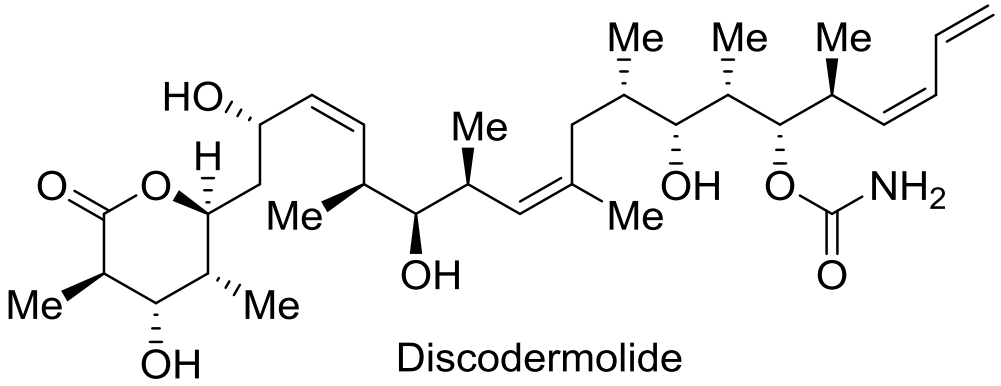


1. MeOH, 80 °C, 98%
2. HCl, MeOH
3. picolyl chloride, $KHCO_3$, NaI
4. H_2SO_4, EtOH



HISTORY OF PROCESS (PHARMACEUTICAL) CHEMISTRY

- 2004 – Novartis – **Discodermolide** – large scale production (60 g) – 39 steps – 17 chromatographic purifications – 43 chemists participation – over 20 months (!!)



Discodermolide

A polyketide natural product;
One of the most potent promoters of tubulin assembly;
A potent inhibitor of tumor cell growth in several MDR (multidrug resistence) cancer cell lines;
Attempts to do semi-synthesis by a fermentation process failed;

HISTORY OF PROCESS (PHARMACEUTICAL) CHEMISTRY

MATERIAL – limitation in materials, equipment and commercial suppliers;
METHODOLOGY – relatively good portfolio of various reactions, but often harsh reaction conditions;
CHEMICALS – difficult to get broad range of commercially available starting material;
ANALYTICAL SUPPORT – degradation methods, tedious
INSTRUMENTS – very limited, later spectroscopy (UV/VIS, IR, optical rotation)
FINANCIAL SUPPORT – money from science enthusiasts, maybe some societies or companies (focused on particular field of interest)
SAFETY – significant improvement and systematic evaluation of possible risks over last 40 years

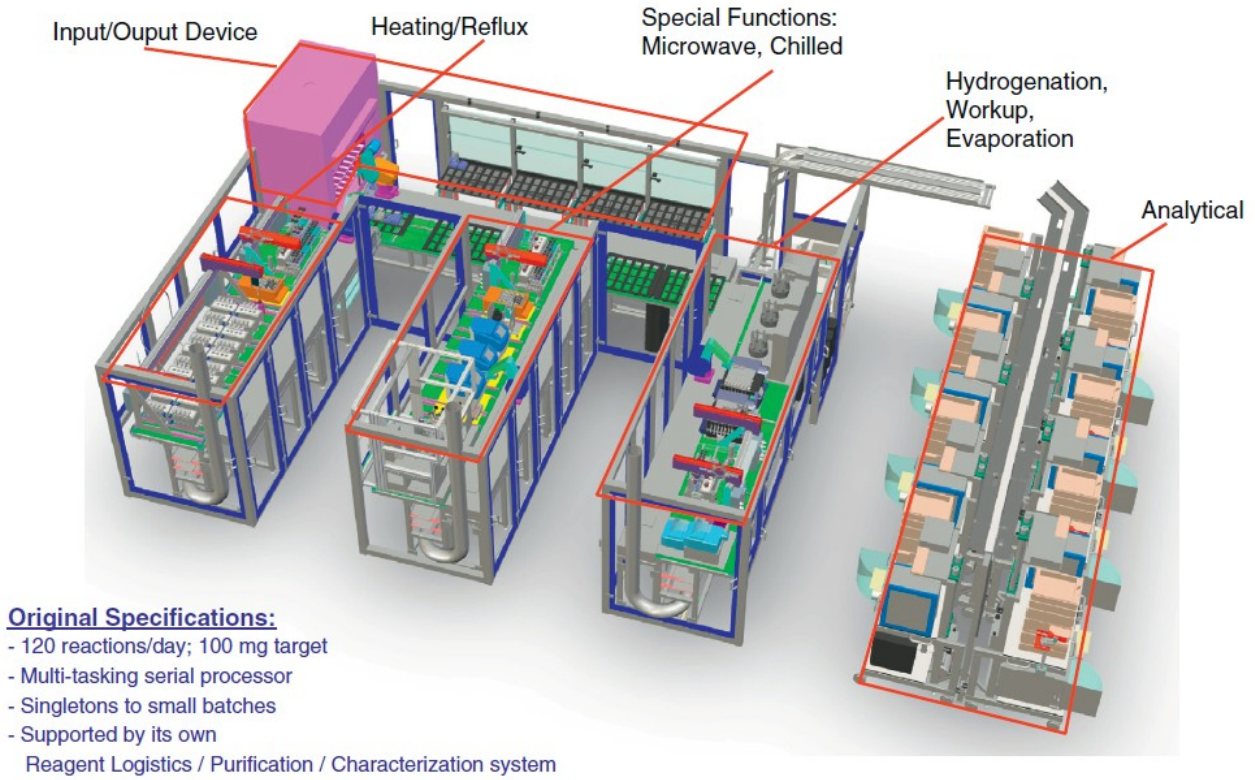
RECENT DEVELOPMENT

- Increased regulatory expectations – even more focused on the patient's safety – more controls and deeper process understanding;
- Automated platforms and robotics – high throughput methods;
- Cooperation of process chemists with academics;
- Green chemistry, sustainability;
- Continuous production (finally !!), flow chemistry;
- Powerful software enables better modeling;
- Biotechnologies

THE FUTURE

- Intensification of the research and development work;
- Automation; continuous manufacturing;
- Real-time measurement – Process Analytical Technology (PAT);
- Shift from the Quality by Certificate (QbC) to Quality by Design (QbD)
- Outsourcing;
- University spin-offs – contract synthesis and cooperation;
- More environmental oriented

THE FUTURE



Drug Discovery Today 18, 795 (**2013**)

THE FUTURE

Drug Discovery Today 18, 795 (**2013**)