Modern Methods for the Separation of Enantiomers - from Kilos to Tons -

Organic Process Research and Development
February 2014

CHIRAL TECHNOLOGIES INC
DAICEL GROUP

Chirality in Drug Pipeline

- Over 80% of drug candidates contain at least one chiral center

- Increasingly complex molecules, requiring more advanced production methodologies

-Three General Strategies

-Chiral Pool

-Asymmetric Synthesis

-Resolution

Challenge

- Is there an optimal approach to problem?
- No – each stage is driven by different imperatives, therefore choices are also different

Pre-Clinical

- Short-term Focus
  - –Speed is key
  - –Cost less of an issue
- Pragmatic approach
  - –Produce racemate then separate
  - –Less effort on asymmetric synthesis, chiral pool (only if quick and easy)

Clinical

- Long-term focused
  - Scalability, cost, efficiency, robustness
- "Tool Box" Approach
  - Cannot assume that any approach is invalid
  - Test all, then run economic feasibility

Chiral Separation

- Used at all stages
  - Classical Resolution
  - Chiral Chromatography

Chiral Separation

- Used at all stages
  - Classical Resolution
  - Chiral Chromatography

- Enabling Chiral Separations
  - Developing efficient methods
  - Small-scale runs (> 100kg)
  - Technology Transfer for commercial

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West Chester, PA.
23,000 sq ft Labs & Offices

Perceptions of Chromatography

- Chromatography is considered to be:
  - Last Resort
  - Temporary Solution
  - Inelegant
  - Difficult to Use

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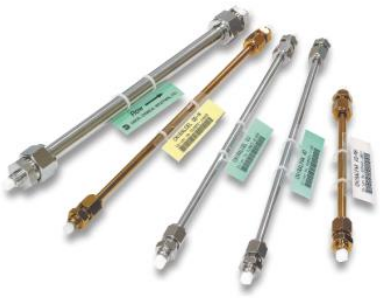
Reality of Modern Chromatography

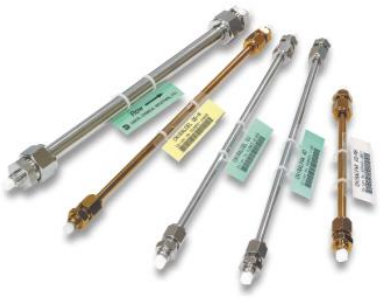
- Chromatography is;
  - Cost effective
  - Reliable
  - Scalable

Scalable Technology



Methods are developed on analytical columns

Scalable Technology



Ampac Fine Chemicals

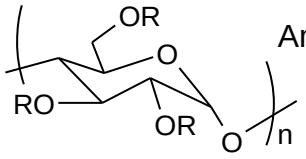
Chiral Chromatography Method Development

- Screen compound
  - Chiral Stationary Phase (CSP)
  - Mobile Phase
- Determine Optimum Combination
- Perform Loading Study
- Run Stability Tests
- Productivity = kg enantiomer/kg CSP/day

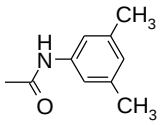
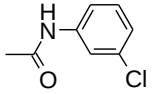
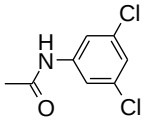
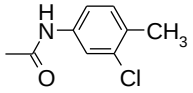
Key Points to Consider

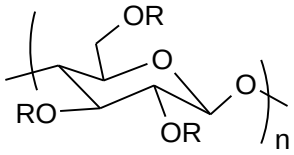
- Solubility characteristics
- Stability (chemical and stereo)
- Presence of other impurities
- API or intermediate
- Ability to racemize non-target enantiomer

Chiral Stationary Phase

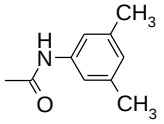
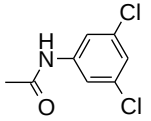


Amylose-based

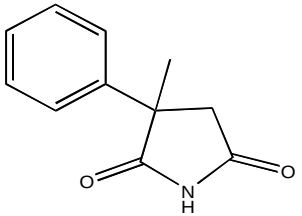
CSP	Nature	-R
CHIRALPAK IA	Immobilized	
CHIRALPAK ID	Immobilized	
CHIRALPAK IE	Immobilized	
CHIRALPAK IF	Immobilized	

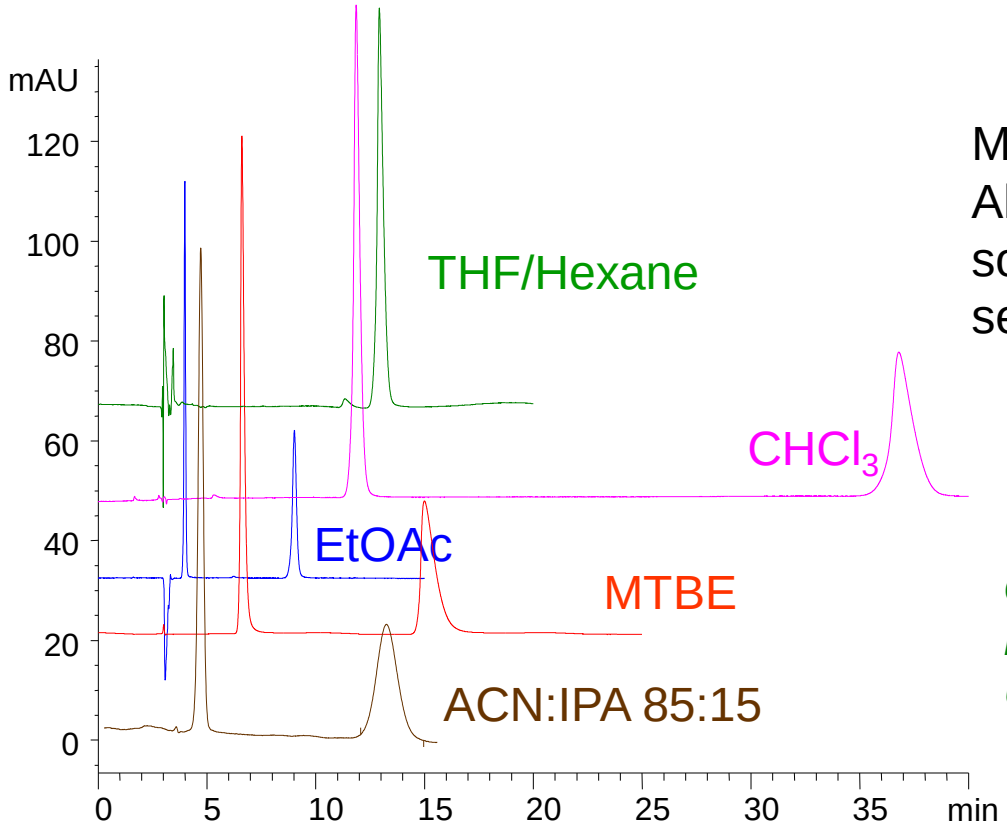


Cellulose-based

CSP	Nature	-R
CHIRALPAK IB	Immobilized	
CHIRALPAK IC	Immobilized	

Screening Study
α-Methyl-α-Phenylsuccinimide

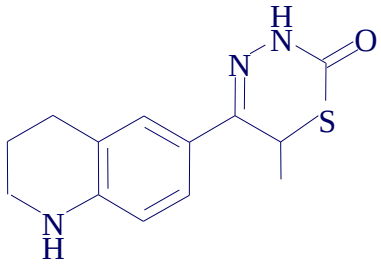




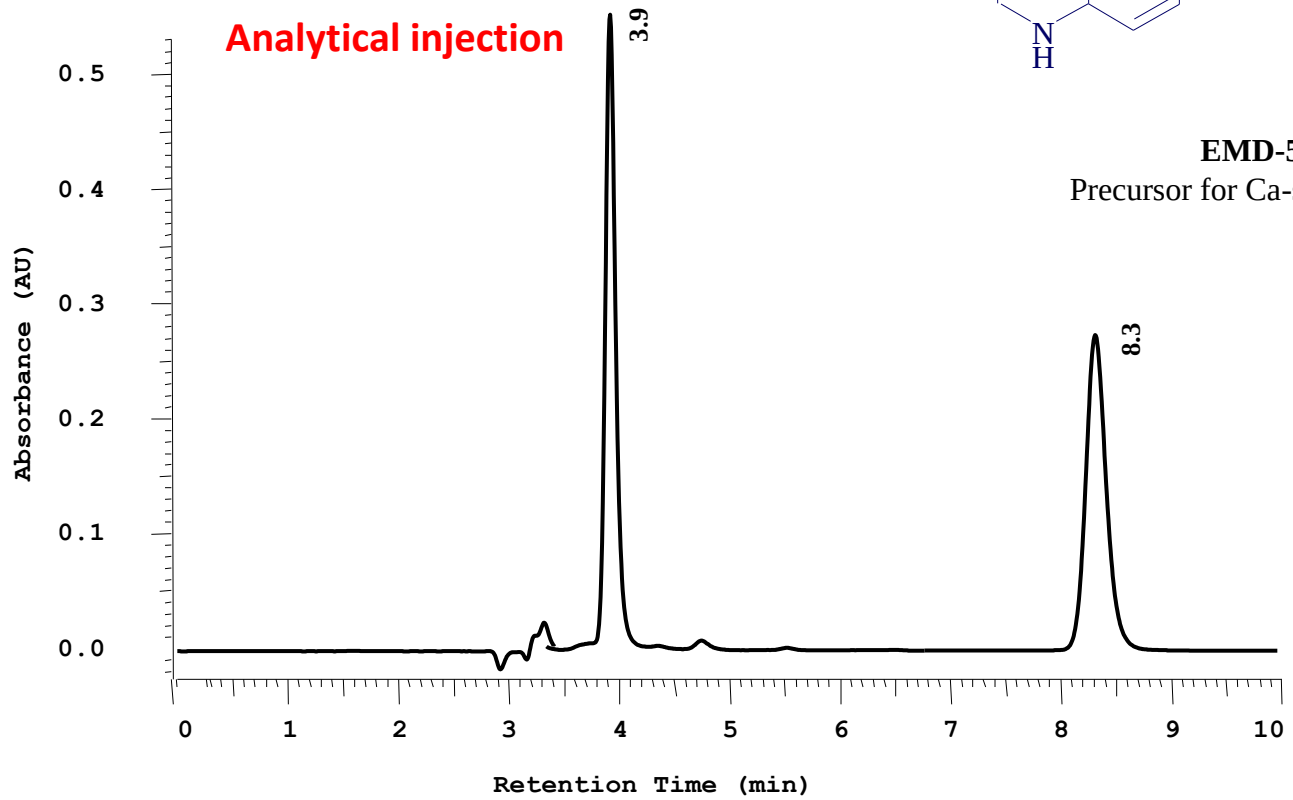
Multiple separation opportunities
Also separates with conventional solvents. Note, zero THF selectivity

CHIRALPAK IA, 250 x 4.6 mm
Flow rate 1 ml/min
UV detection 254 nm

Chiral Separation of EMD-53986



EMD-53986
Precursor for Ca-sensitizing drug



Dichloromethane/THF 70:30

F = 1 mL/min, 25°C

(Column 25 x 0.46 cm, 5 µm CSP)

Solubility in mobile phase: 45 g/L

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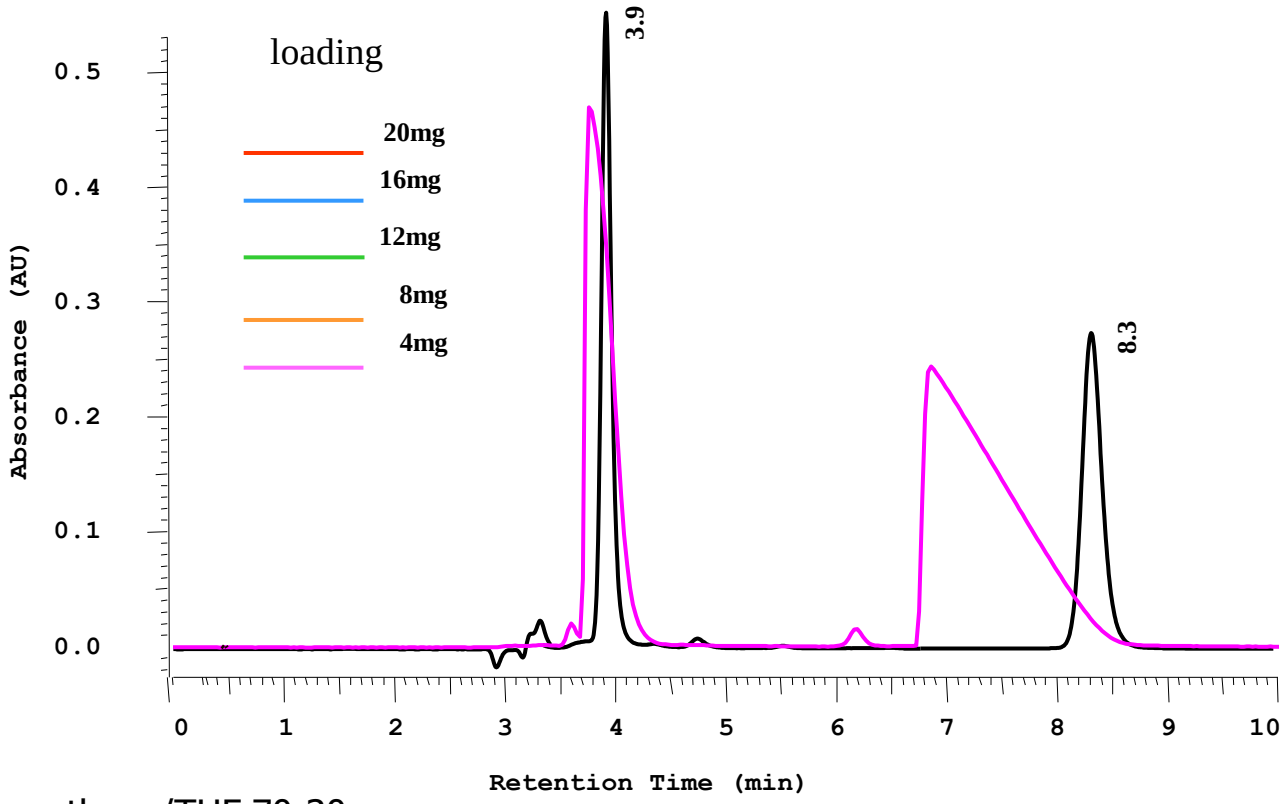
Loading Study for EMD-53986



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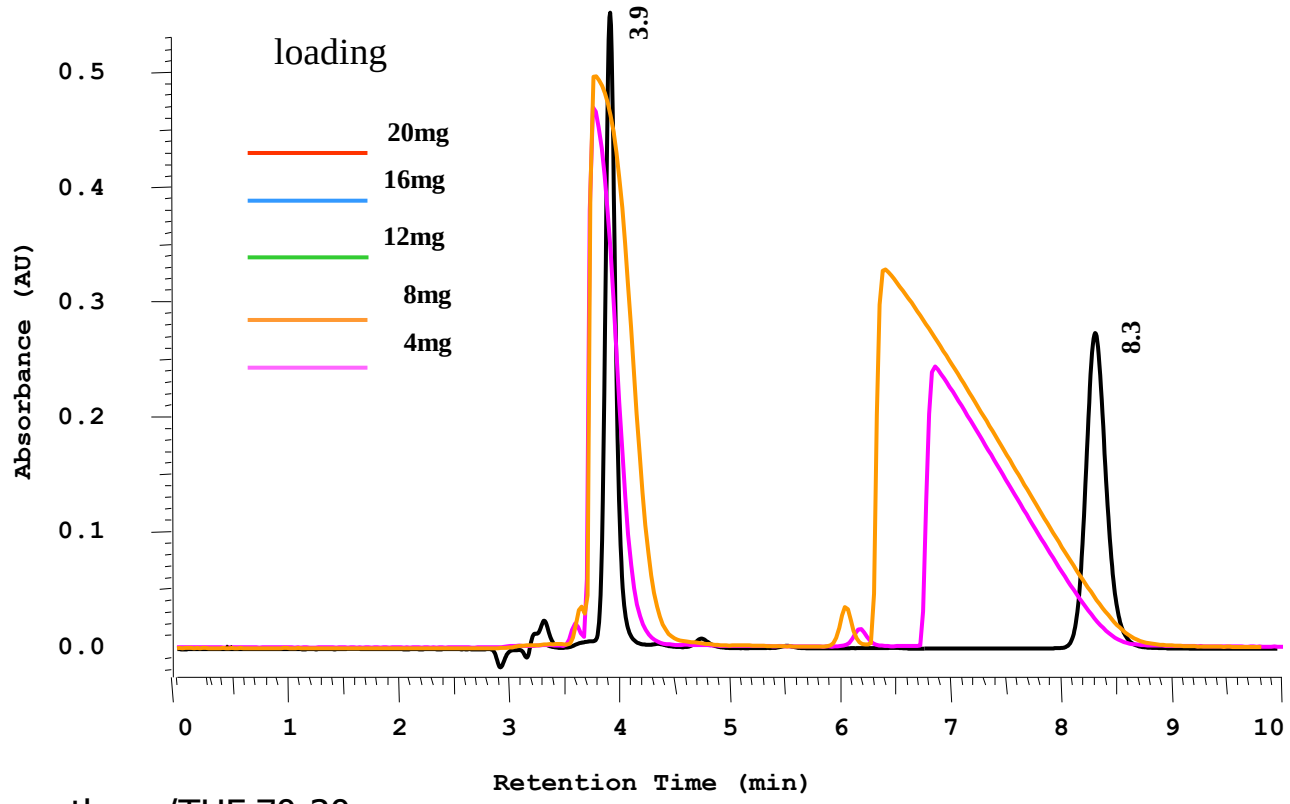

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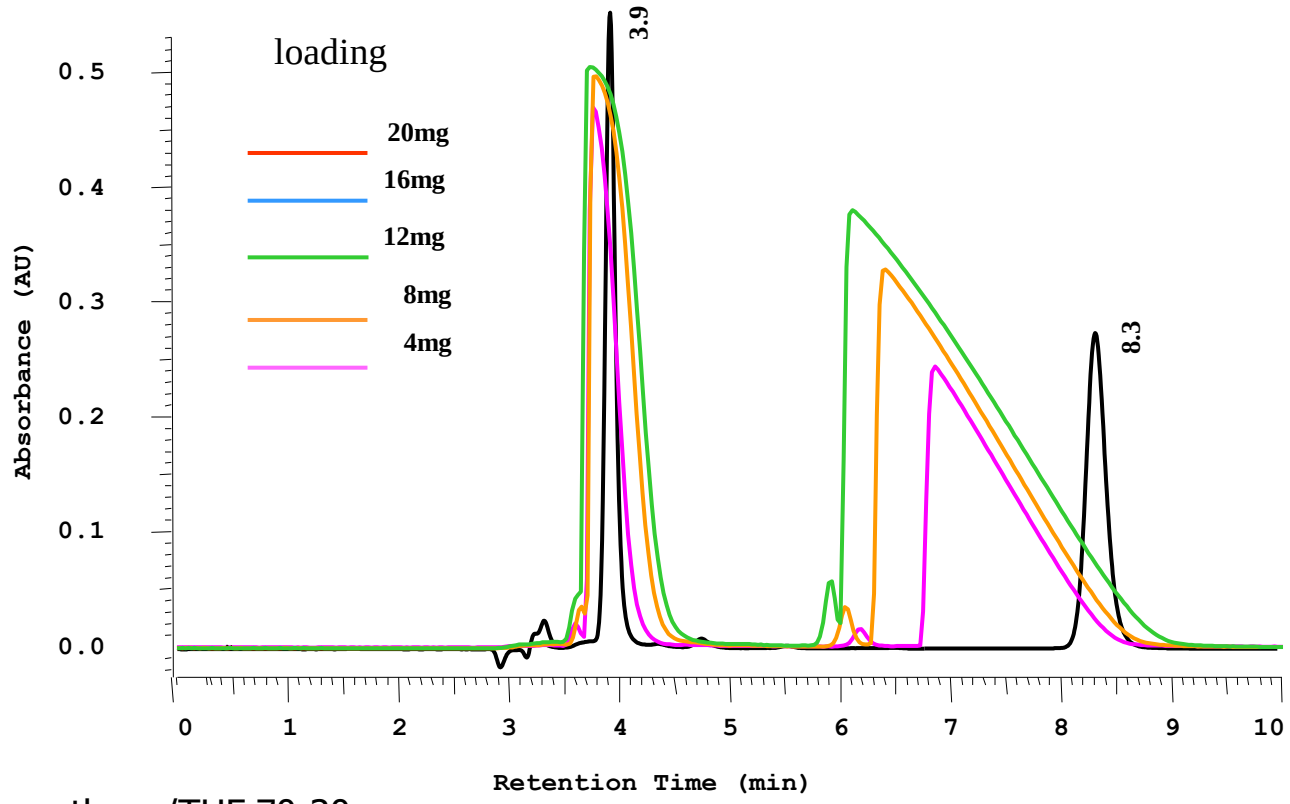

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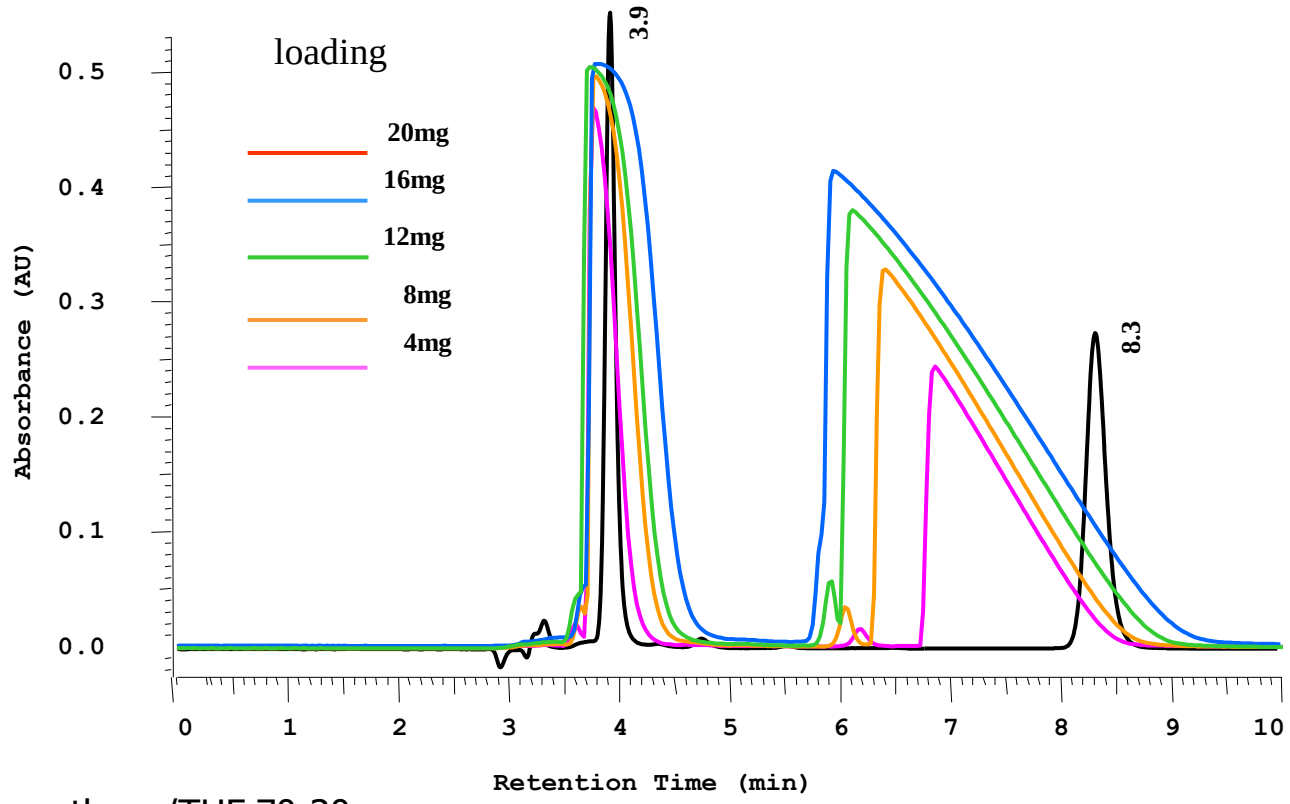

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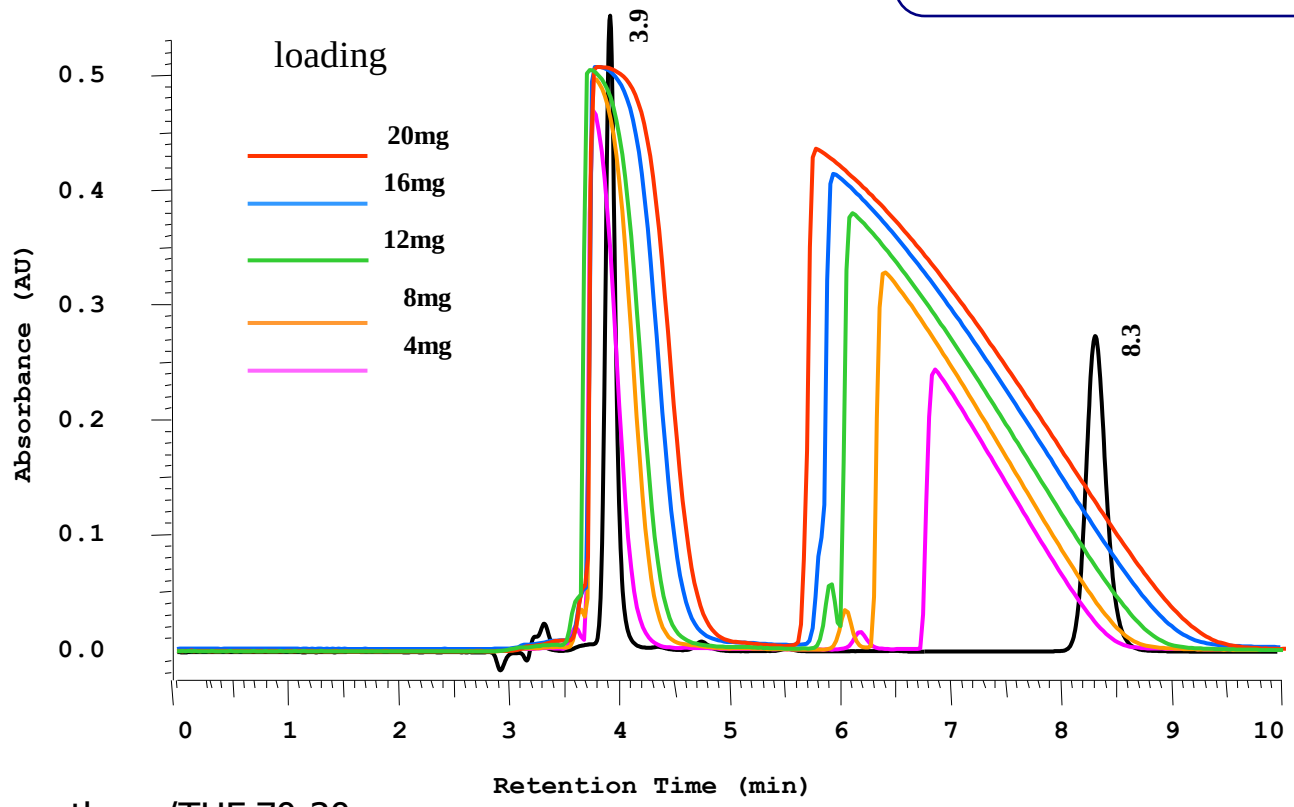
Loading Study for EMD-53986

Estimated productivity:
2.8kg enantiomer/kg CSP/day



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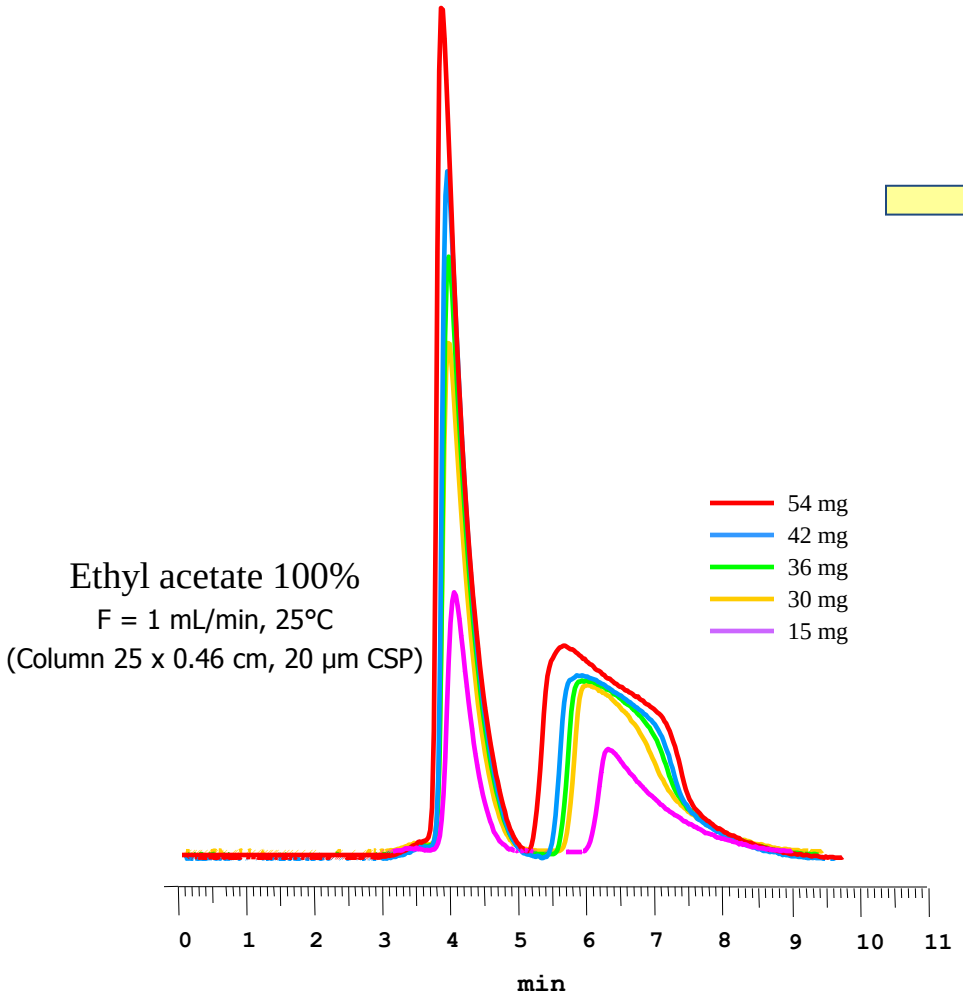
Preparative chromatography

HPLC (batch)

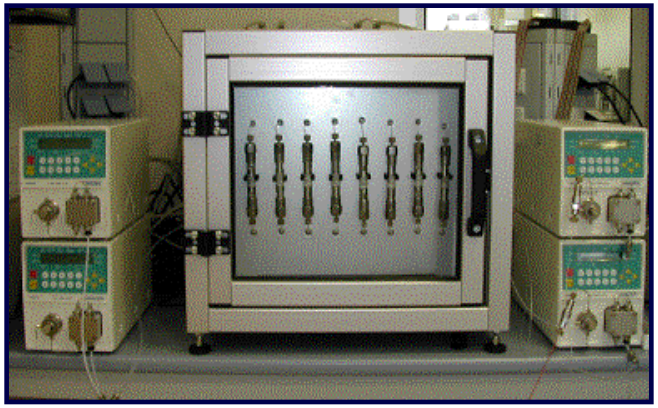
SMB (continuous)

Glutethimide



Productivity:
> 11 kg enantiomer/kg CSP/day

Productivity demonstrated
under SMB conditions



Solubility in mobile phase: 300 g/L

Case Studies

- Two Clinical Development Projects

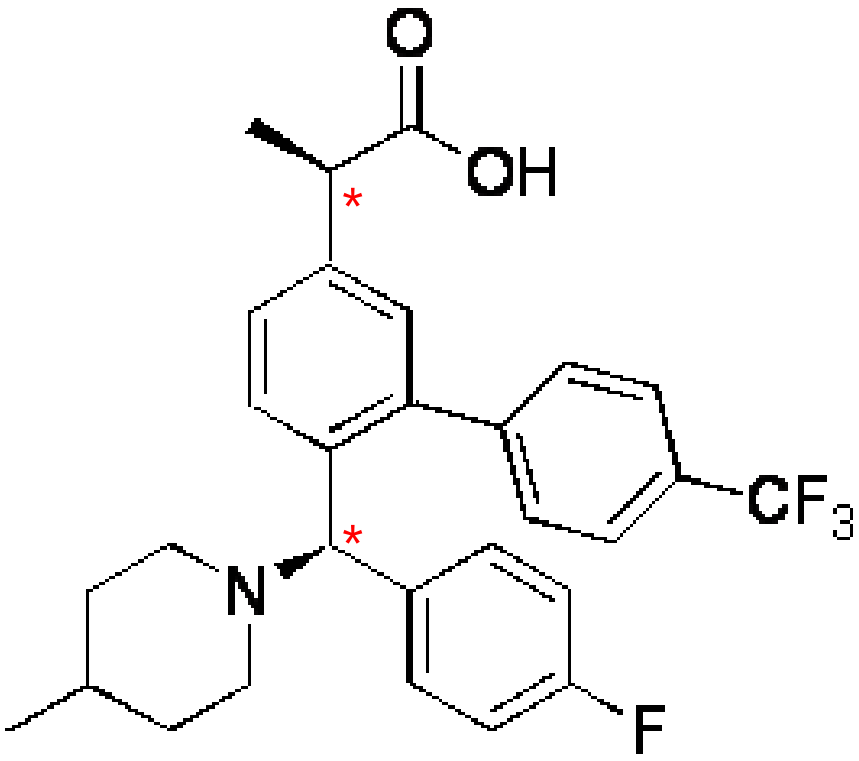
  1) Continuous Enantio-Enrichment

  2) Stage-Appropriate Technology

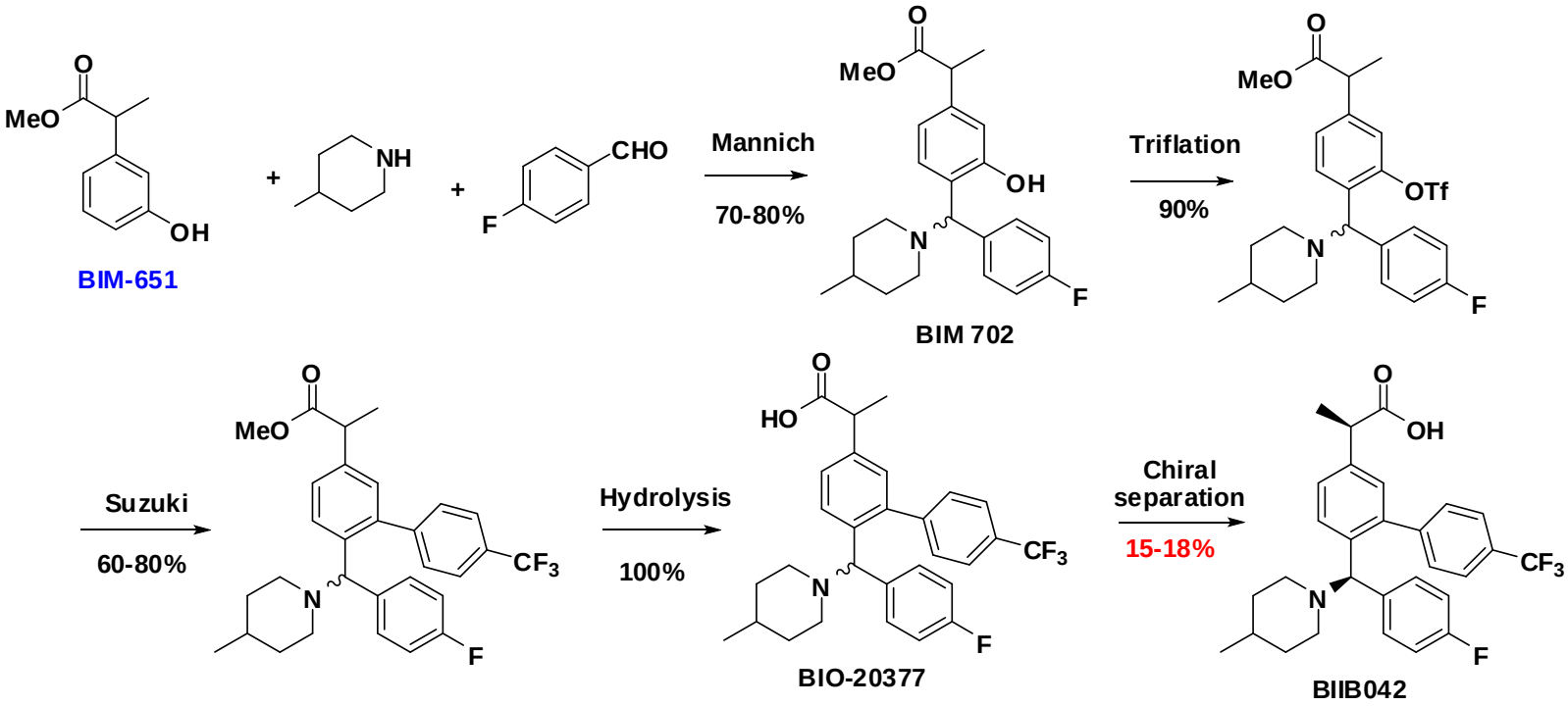
1) Continuous Enantio-Enrichment

- Biogen Idec Alzheimer's Drug
  - BIIB042
  - Two chiral centers
  - Continuous process developed

BIIB042 Structure

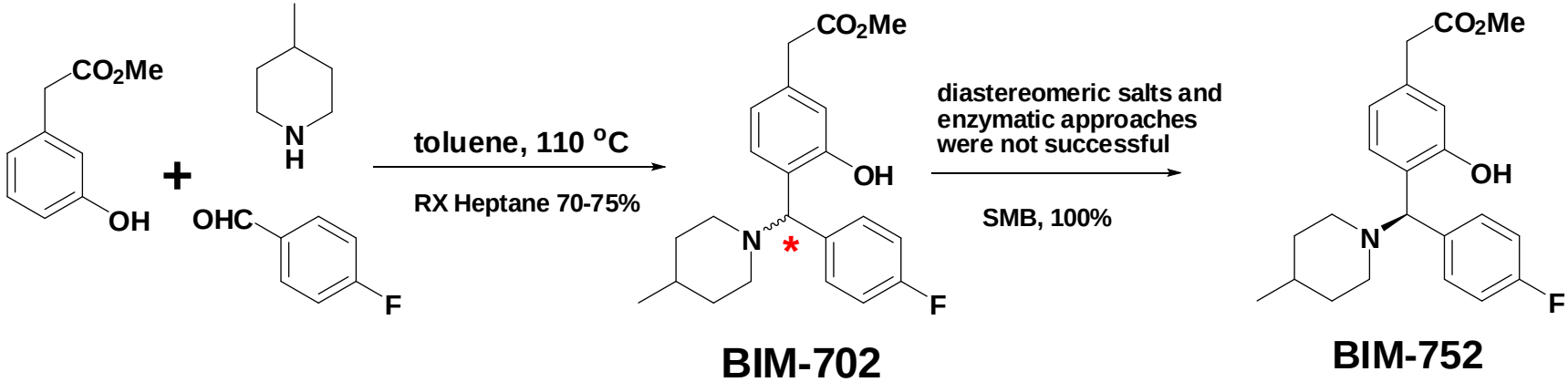


Initial Drug Discovery Approach



The Mannich reaction established the framework for **BIIB042** in the first step producing **BIM-702,** and chiral chromatography was employed to separate the four stereoisomers.

Formation of First Chiral Center

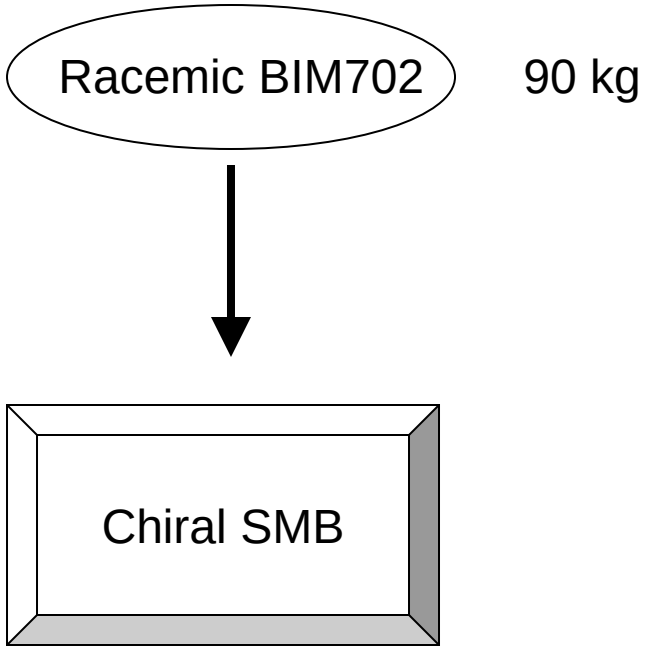


Chiral SMB Approach

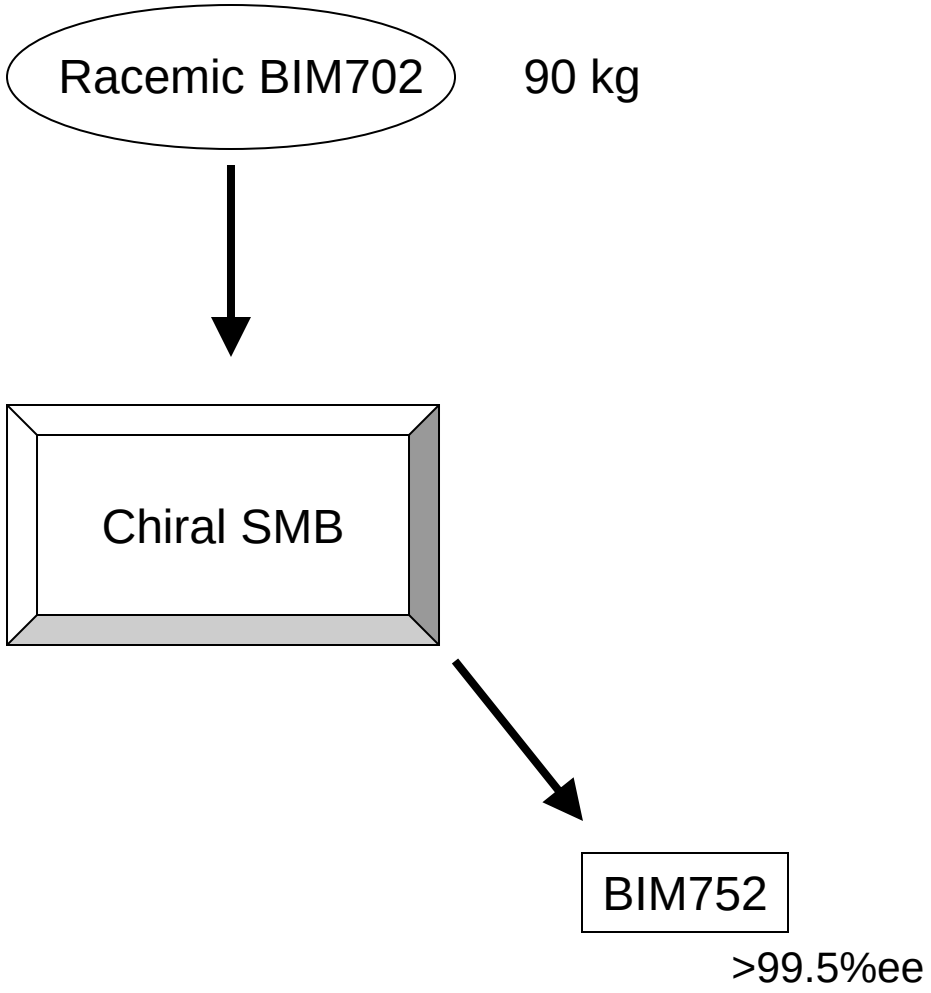
- Screened against matrix of chiral stationary phases/solvents
    - Best method; AD CSP with Hexane/IPA

- Determined optimum process parameters
    - Yield, %ee

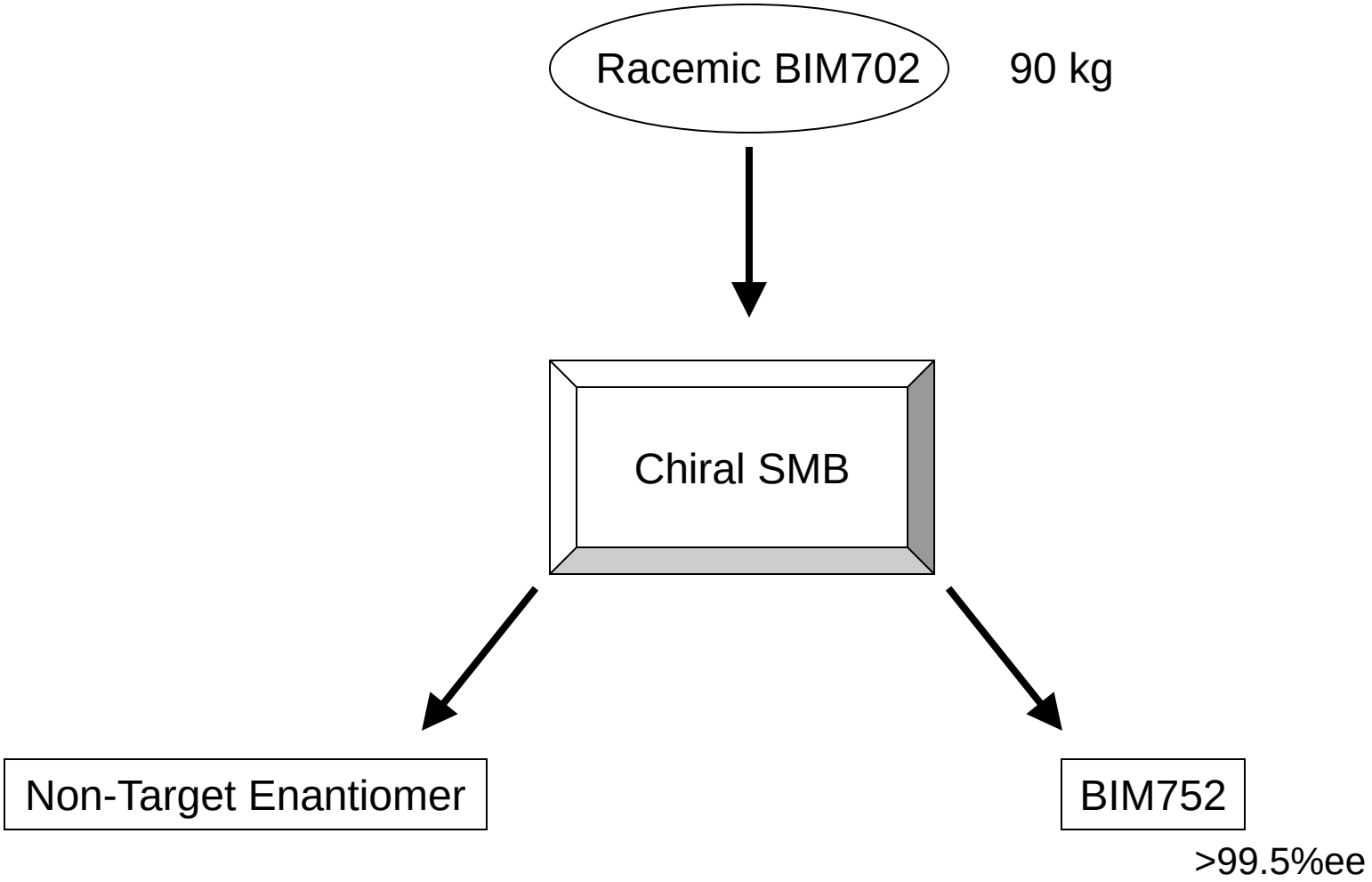
Continuous SMB Process



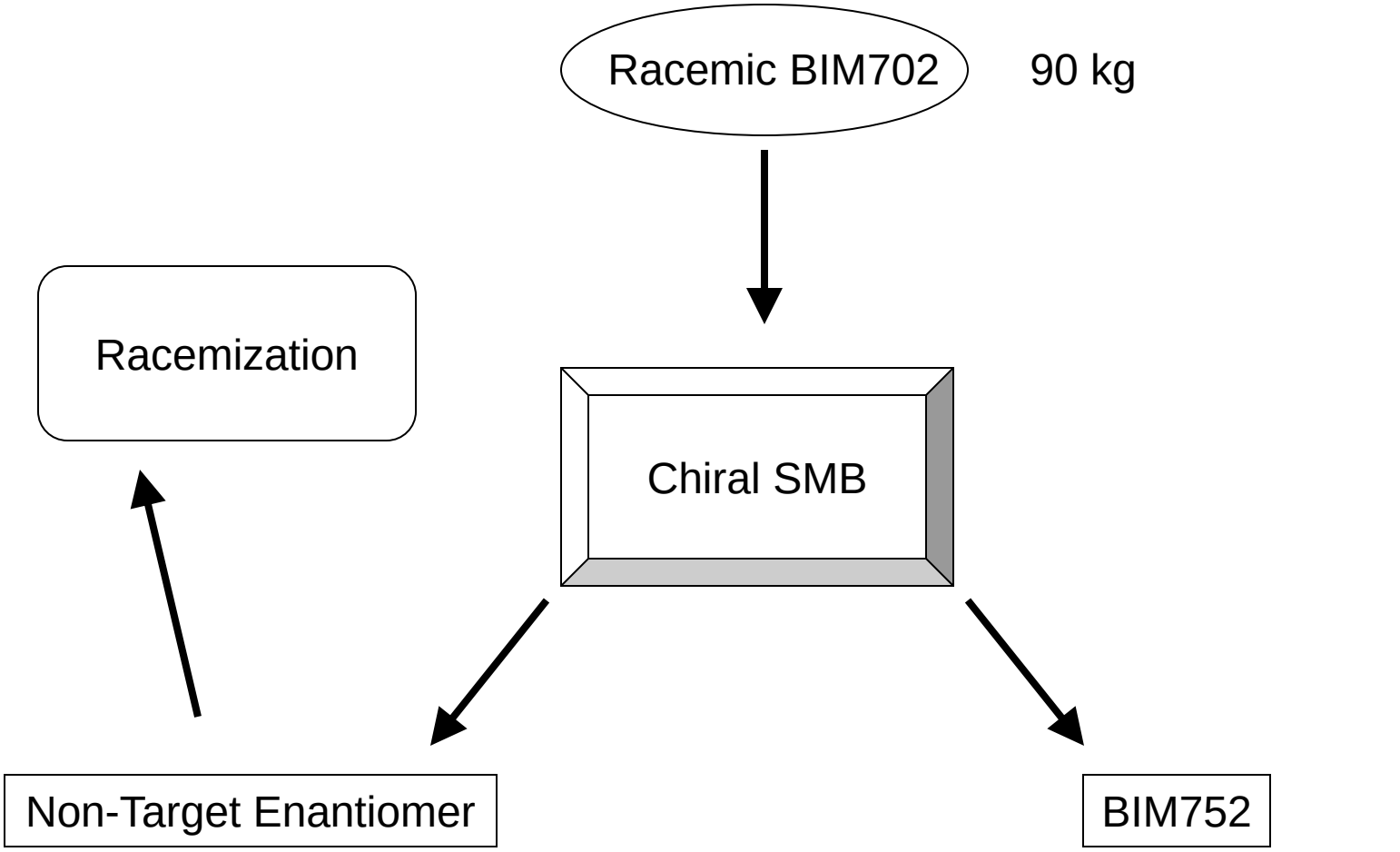
Continuous SMB Process



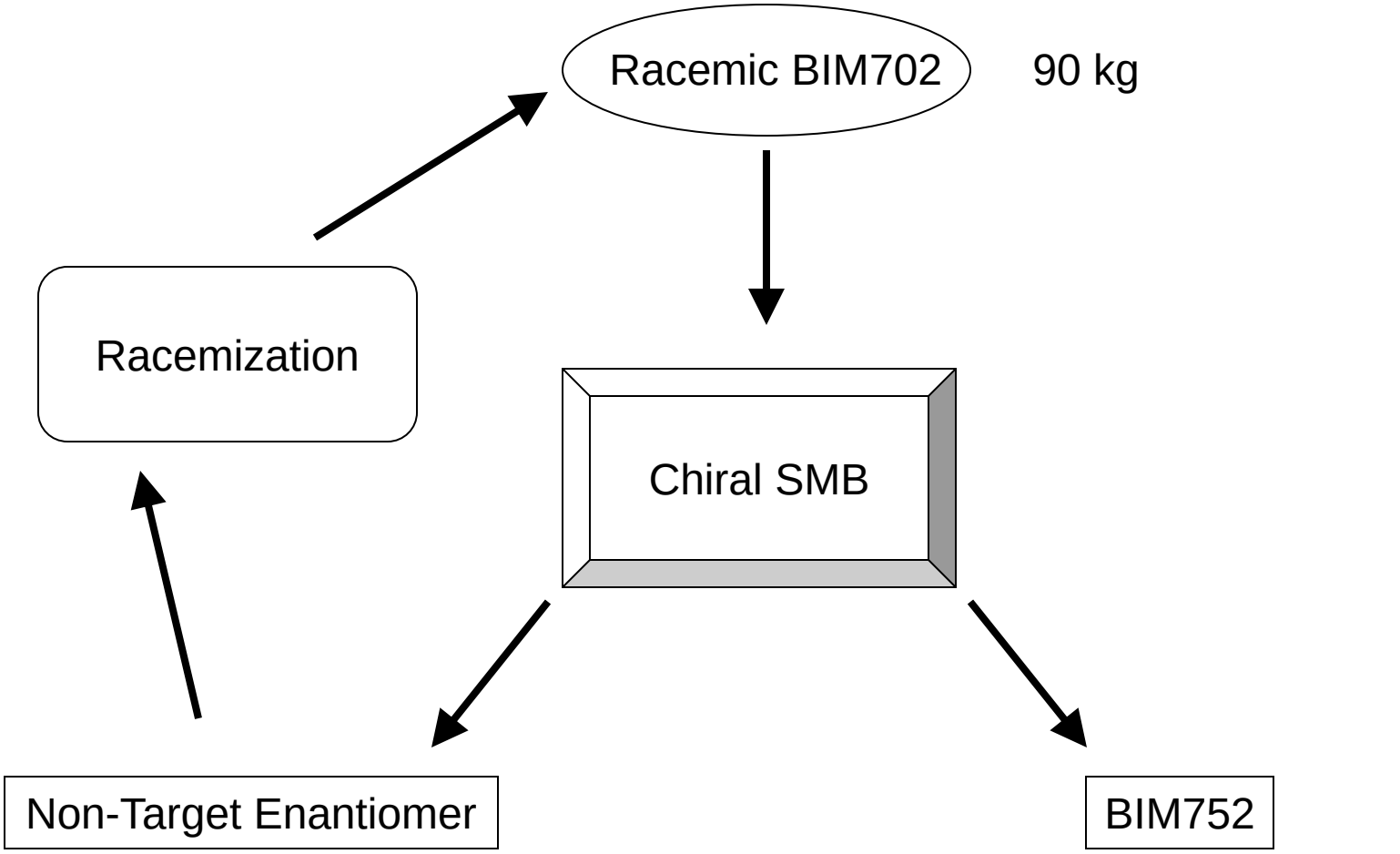
Continuous SMB Process



Continuous SMB Process

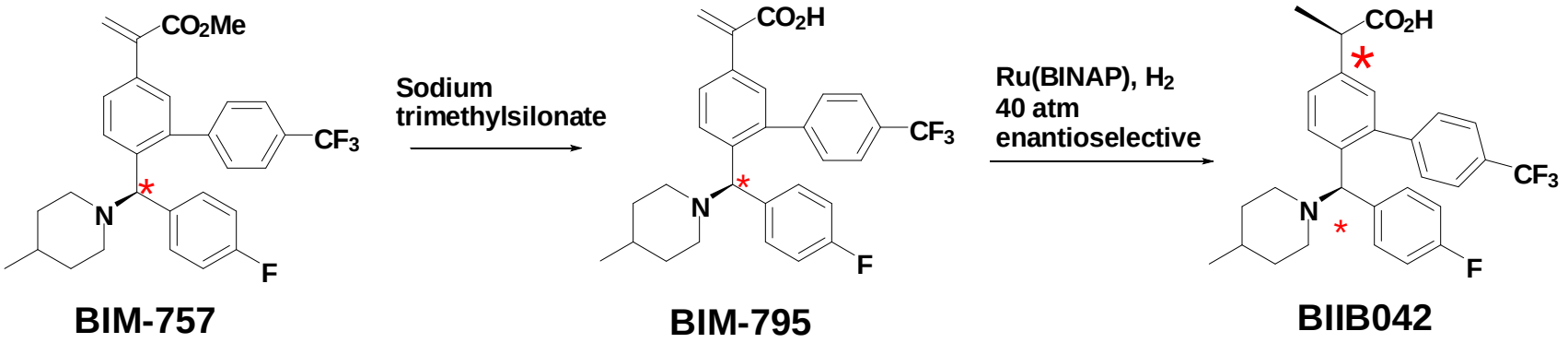


Continuous SMB Process



Lab Scale SMB

Second Chiral Center



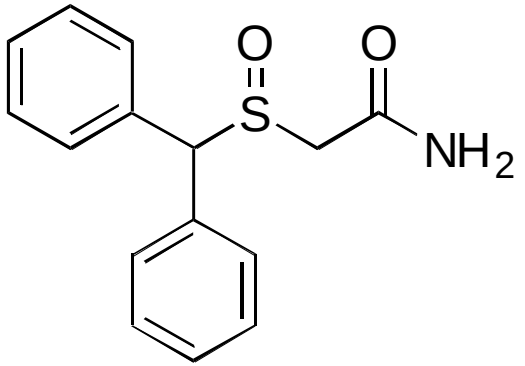
>95% ee via catalytic hydrogenation (Ru)

2) Stage-Appropriate Technology

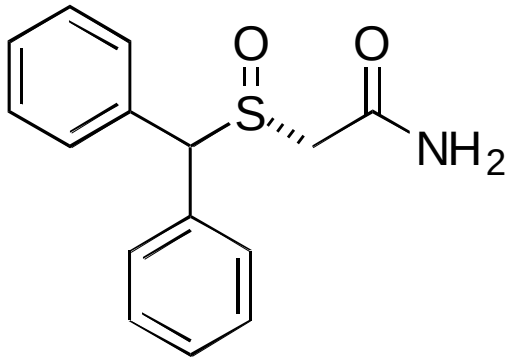
- Development of Armodafinil
- Cephalon (Teva)

Stage-Appropriate Technology

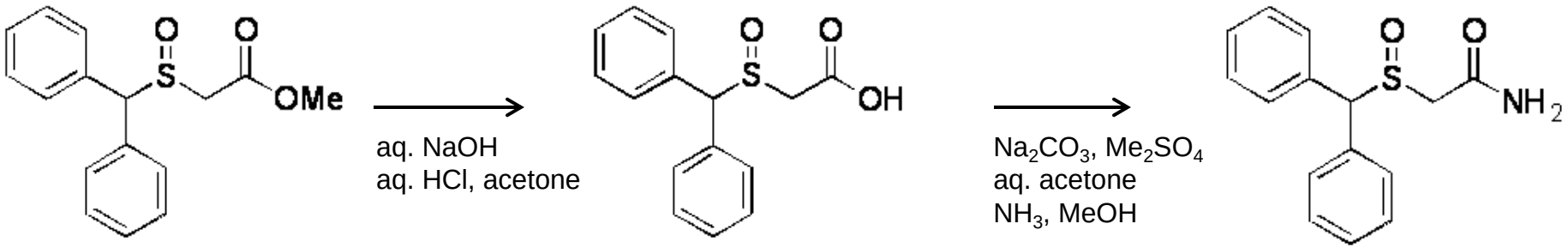
- Modafinil (Provigil)
  - Approved for treatment of apnea, narcolepsy, shift work disorder
  - Racemic API



- Armodafinil (Nuvigil)
  - (R)-Enantiomer
  - Second generation therapy



Pre-Clinical Phase



DMSAM **Modafinic Acid** **Modafinil**

- Modafinic Acid was the best candidate for classical resolution

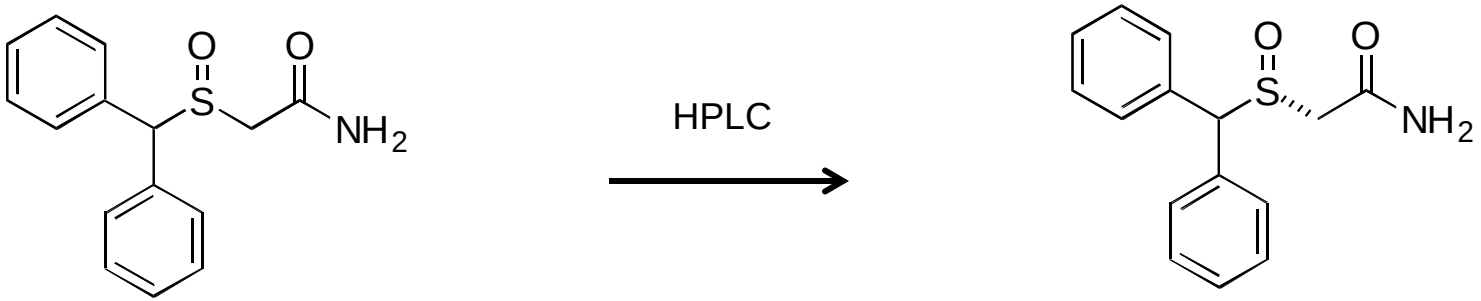
- Easily converted to R-Modafinil

Pre-Clinical Phase

- 85 kgs prepared via crystallization
  - ~98% ee
  - Conversion to R-Modafinil
  - Non-ideal system due to
    - Product degradation
    - Cost inputs
    - High labor component

Clinical Phase

- Chiral HPLC/SMB study on Modafinil
  - Screened CSPs
  - HPLC and SMB methods developed
- 60kg of Phase I material produced
  - Single column HPLC
  - >99.0%ee



Clinical Phase

- 550kg Phase II/III material produced
  - Chiral SMB
  - Optical purity >99.2%ee
  - Chemical purity >99.7%

- Over 10 MT of racemate processed via SMB
  - Novasep operation
  - Process ran on 300mm and 450mm systems
  - Stabile, robust process

Commercial Launch

- Asymmetric Oxidation Results
  - 75% isolated yield
  - >99.5% optical purity
- Significantly longer development than chromatography
- Favorable economics
- Launch of Armodafinil was accelerated due to stage-appropriate technologies

Development of Armodafinil

- Three different methods employed

- Pre-Clinical – Classical Resolution
- Clinical Trials – Chiral SMB
- Commercial Launch – Asymmetric Synthesis

- Result – Speed to Market

Conclusions

- Chiral Chromatography can offer advantages
  - Effective from mgs to MTs
  - Predictable scale factors
  - Ability to “dial in” desired %ee

Acknowledgements

Thank You Partners

- Biogen Idec
- Teva (Cephalon)
- Novasep

move easily …

move reliably …

move quickly …

move ahead

DAICEL

Chiral Technologies