High Performance Countercurrent Chromatography in Organic Synthesis Purification

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About Peakdale Molecular

- **Founded in 1992**
- **Based in Chapel-en-le-Frith, Derbyshire**
- **Current areas of activity**
  - Contract research, custom synthesis
  - Medicinal chemistry support, ADME
  - Parallel synthesis
  - Intermediates
  - Process development and Scale up
  - Analytical and Purification services

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Purification Strategies

- **Preparative HPLC**
  - Multiple machines for HT/small scale purification
  - UV and mass directed
  - Range of columns – NP, RP, HILIC, chiral
- **Aim - to further develop capabilities**
  - eg. Solving separation issues at larger scales
- **Long standing interest in HPCCC**
  - Orthogonality to HPLC/flash chromatography
  - Potential to scale up, lower ongoing costs

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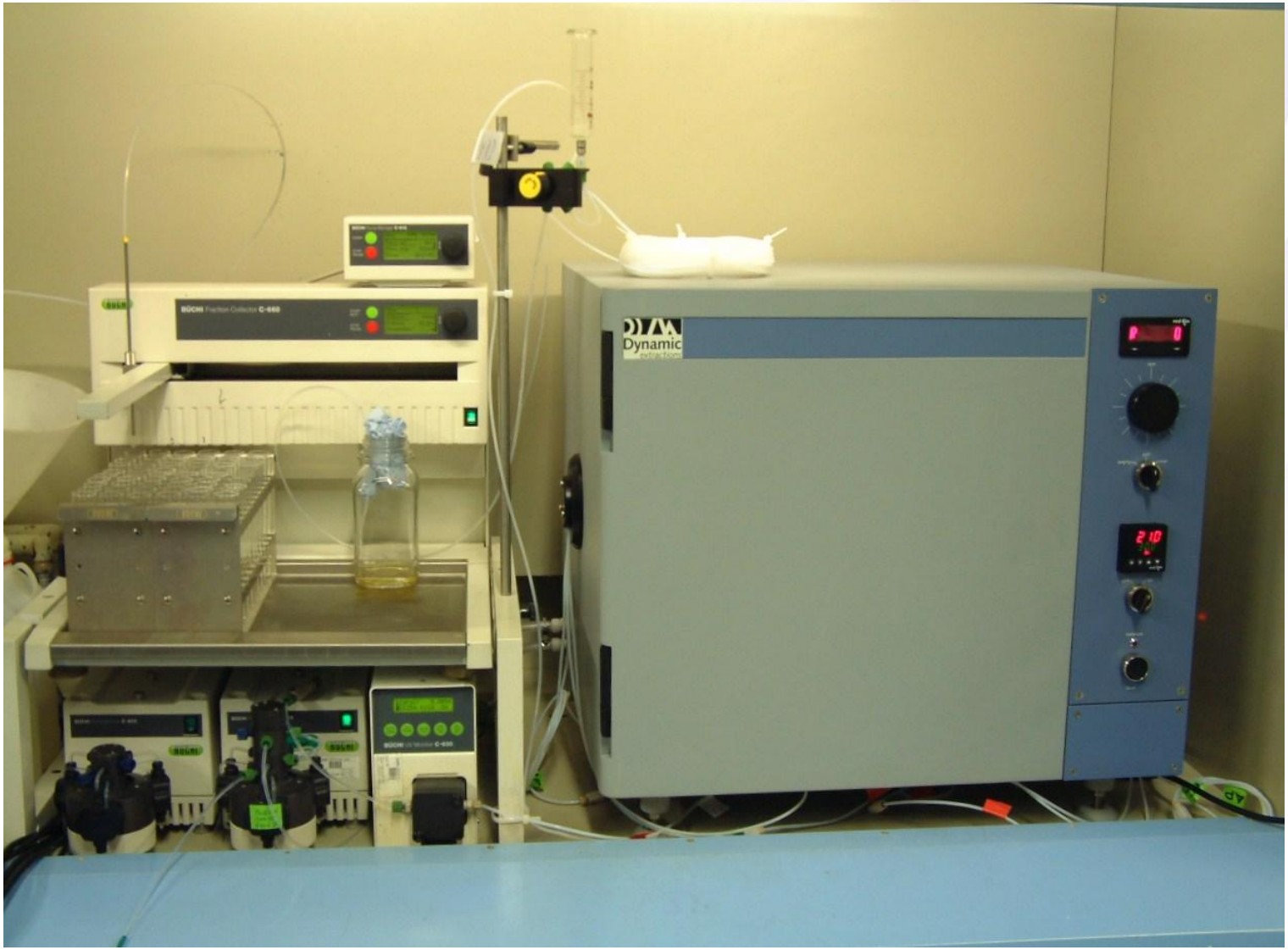

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HPCCC Applications

- **Purification of SNAr reaction**
- **Multigram Intermediate Purification**
- **Purification of a Labile Compound**

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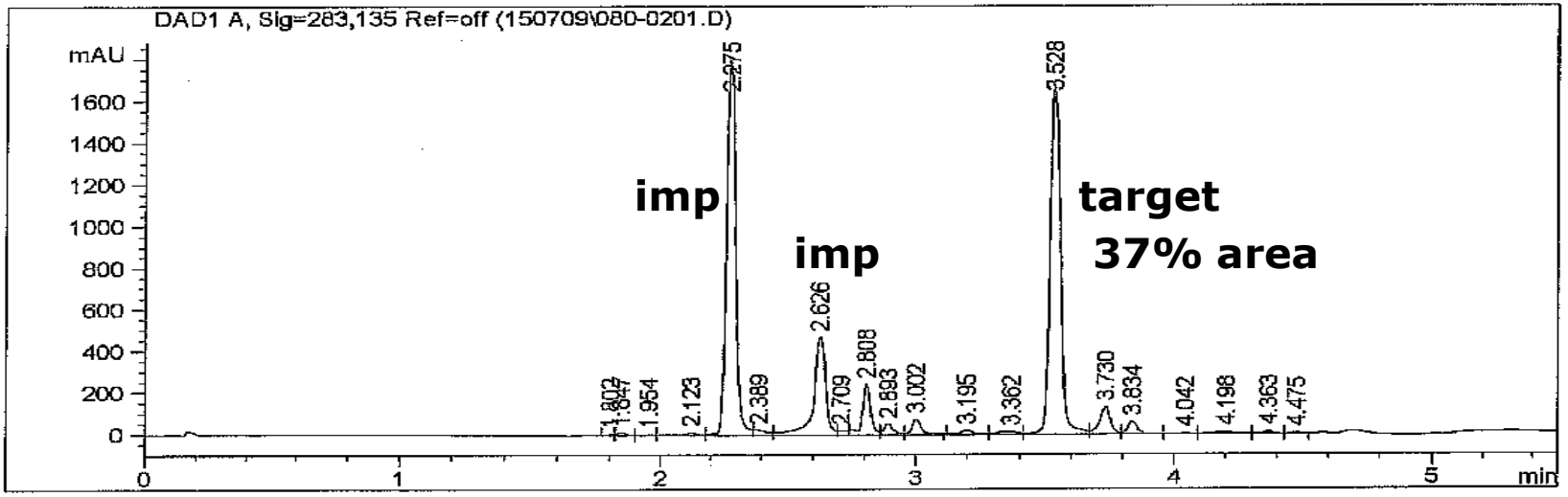
Purification of SNAr Reaction

- **Purification difficult by normal methods**
  - Flash chromatography – SM/product copolar
  - Compound would not crystallise readily
  - Objective - to purify ~10g crude mixture



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HEMWat Solvent System

System	Heptane	EtOAc	MeOH	H_2O
11	10	0	10	0
10	9	1	9	1
9	8	2	8	2
8	7	3	7	3
7	6	4	6	4
6	5	5	5	5
5	4	6	4	6
4	3	7	3	7
3	2	8	2	8
2	1	9	1	9
1	0	10	0	10

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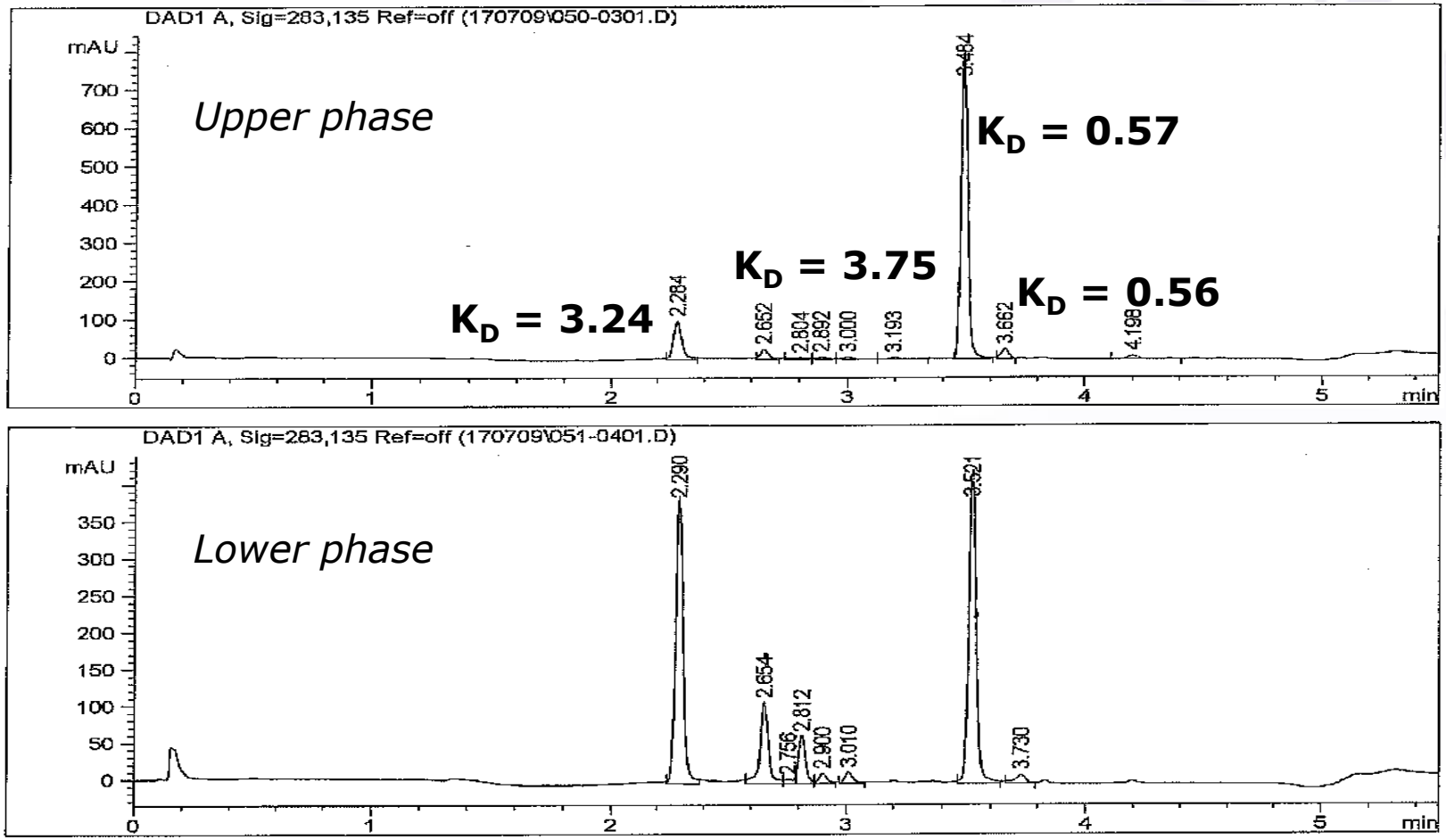
HPCCC Method Development

System "10½" 19:1:19:1 heptane-EtOAc-MeOH-H_2O, 0.1% Et_3N



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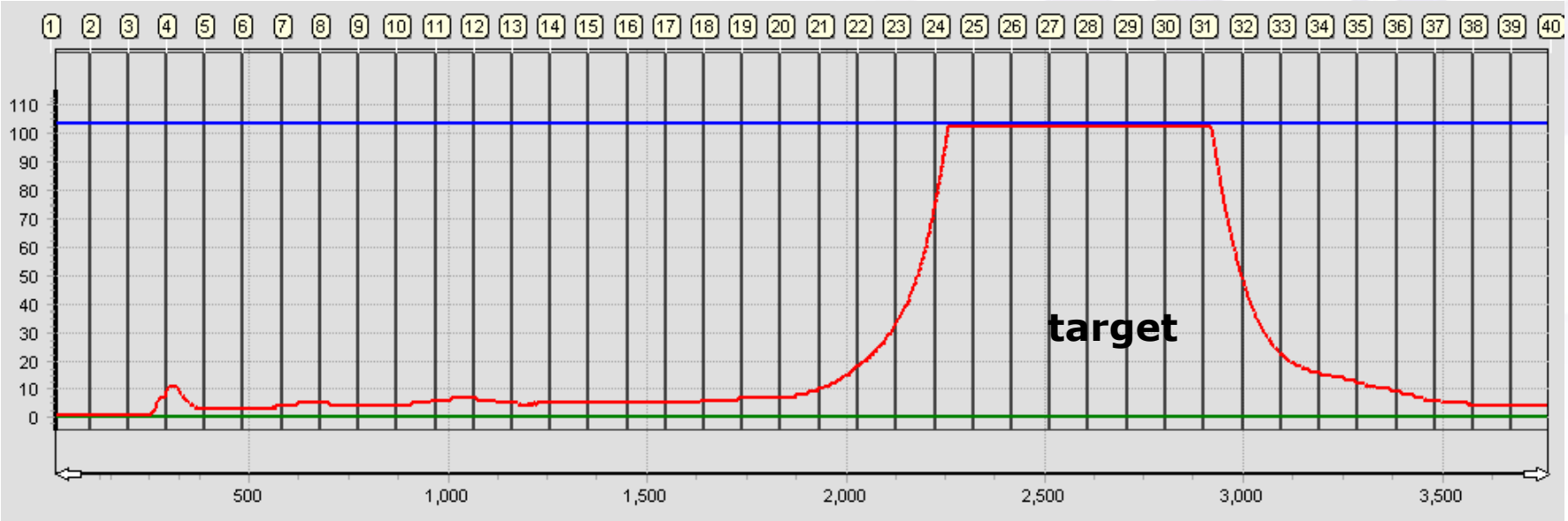
HPCCC Preparative Run



- DE Midi HPCCC, injection mass 2g
- Solvent system 19:1:19:1 heptane-EtOAc-MeOH-H_2O, 0.1% Et_3N
- Elution of upper phase at 25ml/min, S_f > 80%, run time 1hr
- F25-30 gave material of >95% purity (HPLC area)

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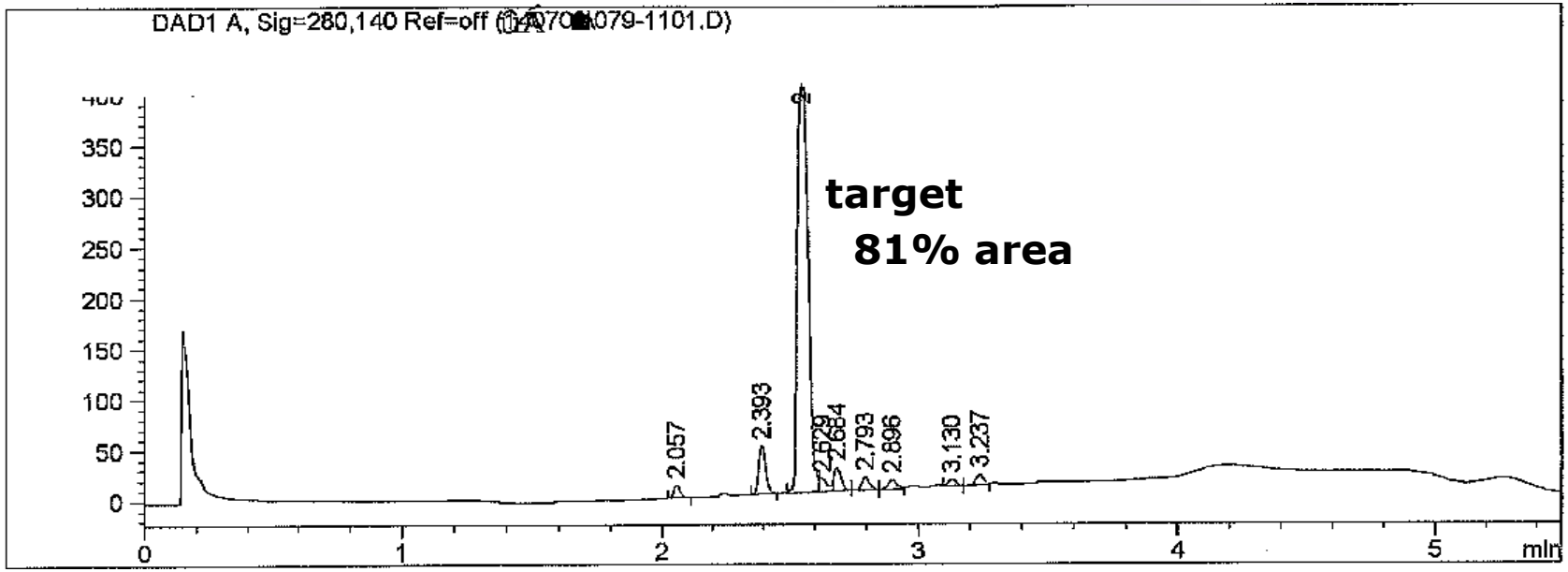
Multigram Intermediate Purification

- Low melting, highly soluble compound
- Flash chromatography → 81% purity (HPLC area)
- Requirement is 50g material at >95% purity



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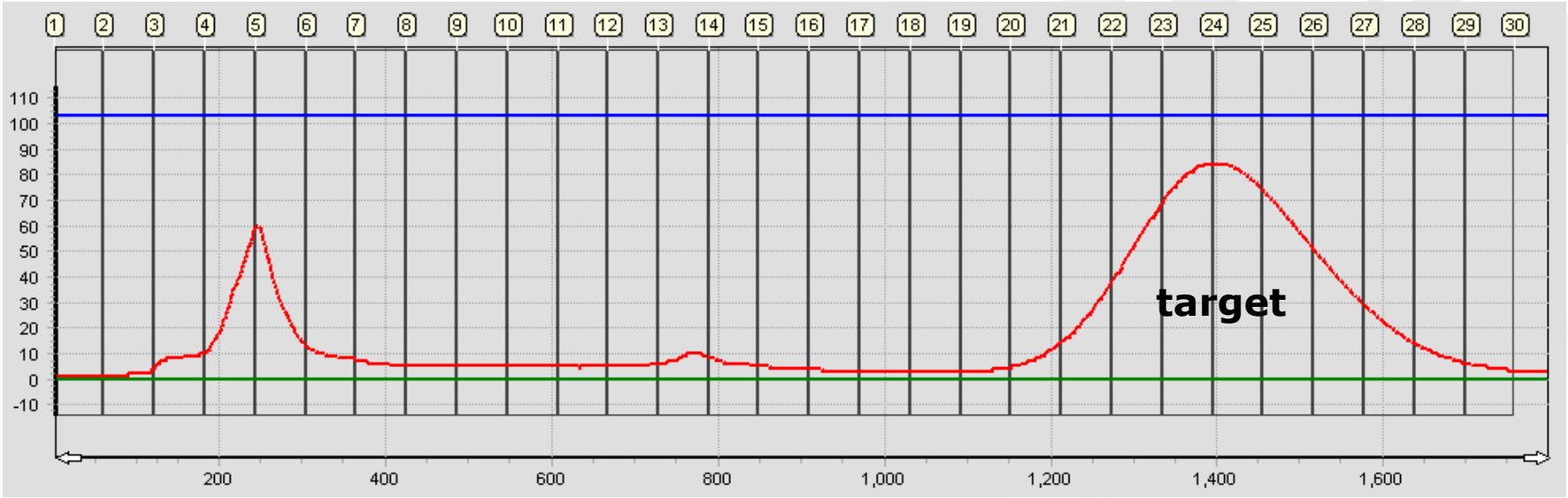
HPCCC Preparative Run



- DE Midi HPCCC, injection mass 8g
- Solvent system 3:2:3:2 heptane-EtOAc-MeOH-H_2O, 0.1% HCO_2H
- Elution of upper phase at 50ml/min, S_f > 80%, run time 30min
- F20-28 gave material of >98% purity (HPLC area)

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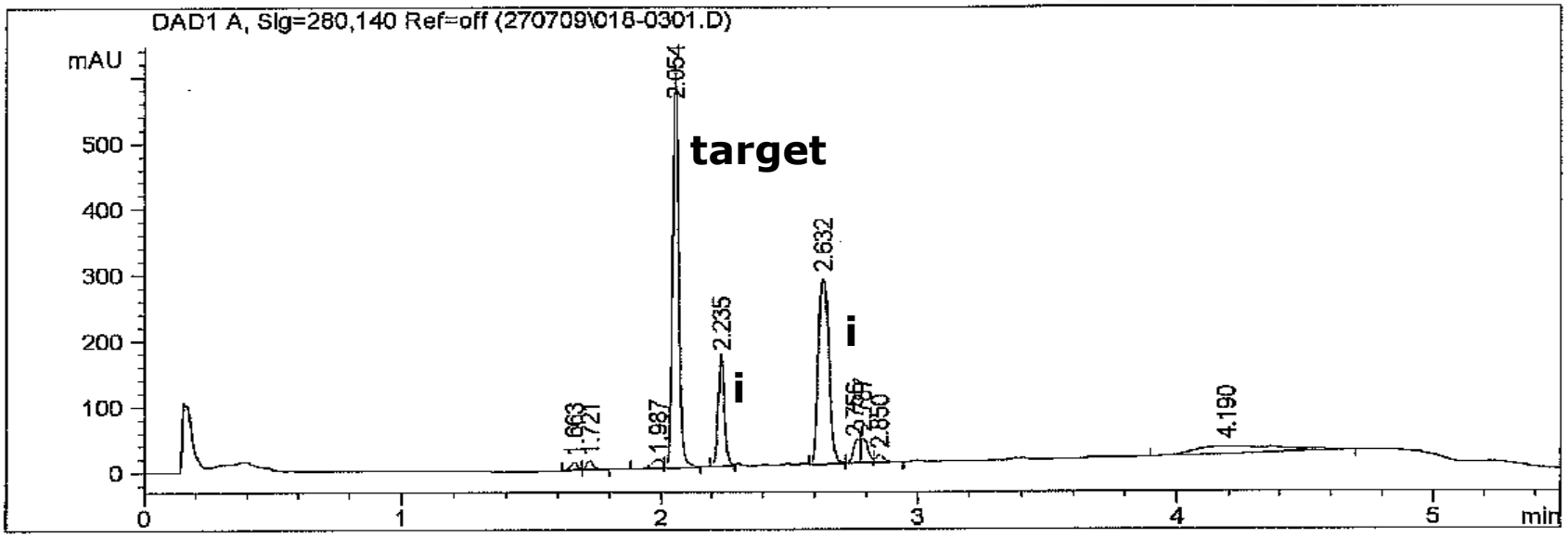
Purification of a Labile Compound

- **Project requirement**
  - 1g of material, >95% purity (HPLC area)
  - Flash chromatography – not separable
  - Preparative HPLC (RP) - unstable to evaporation



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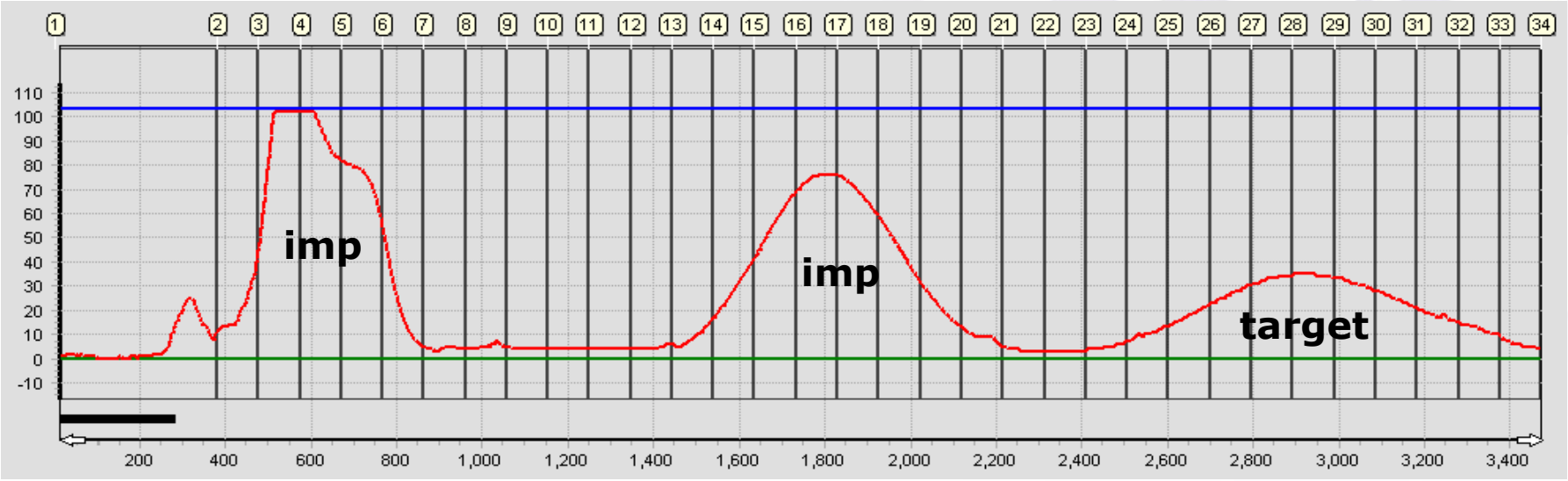
HPCCC Preparative Run



- 2:3:2:3 heptane-EtOAc-MeOH-water, 0.1% HCO_2H
- DE Midi HPCCC, injection mass 1g
- Elution of upper phase at 25ml/min, S_f > 85%, run time 1hr
- F23-32 gave material of >98% purity (HPLC area)

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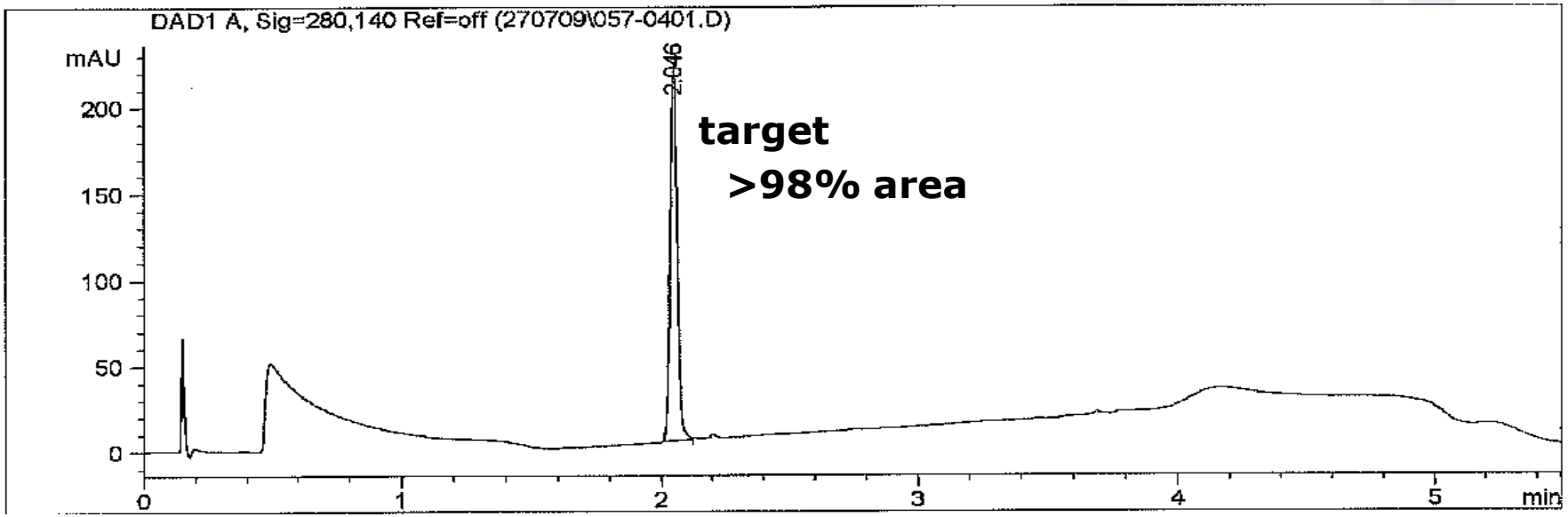
Isolated Material



- **Normal phase elution key to success**
  - Allowed evaporation with minimal decomposition

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Conclusions

- **HPCCC is a promising addition to the purification toolkit**
  - Works well in many situations
  - High loadability, essentially complete material recovery
  - Low solvent usage
- **Challenges**
  - HEMWat doesn’t work for everything
  - Surfactants and emulsifiers present specific issues

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Many thanks for your time

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