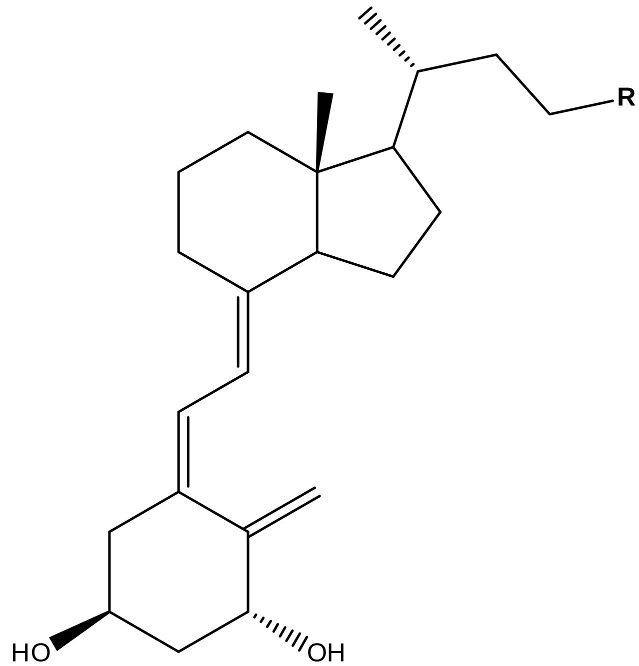
Development and Scale-up of a Photochemical Route to a Steroidal API

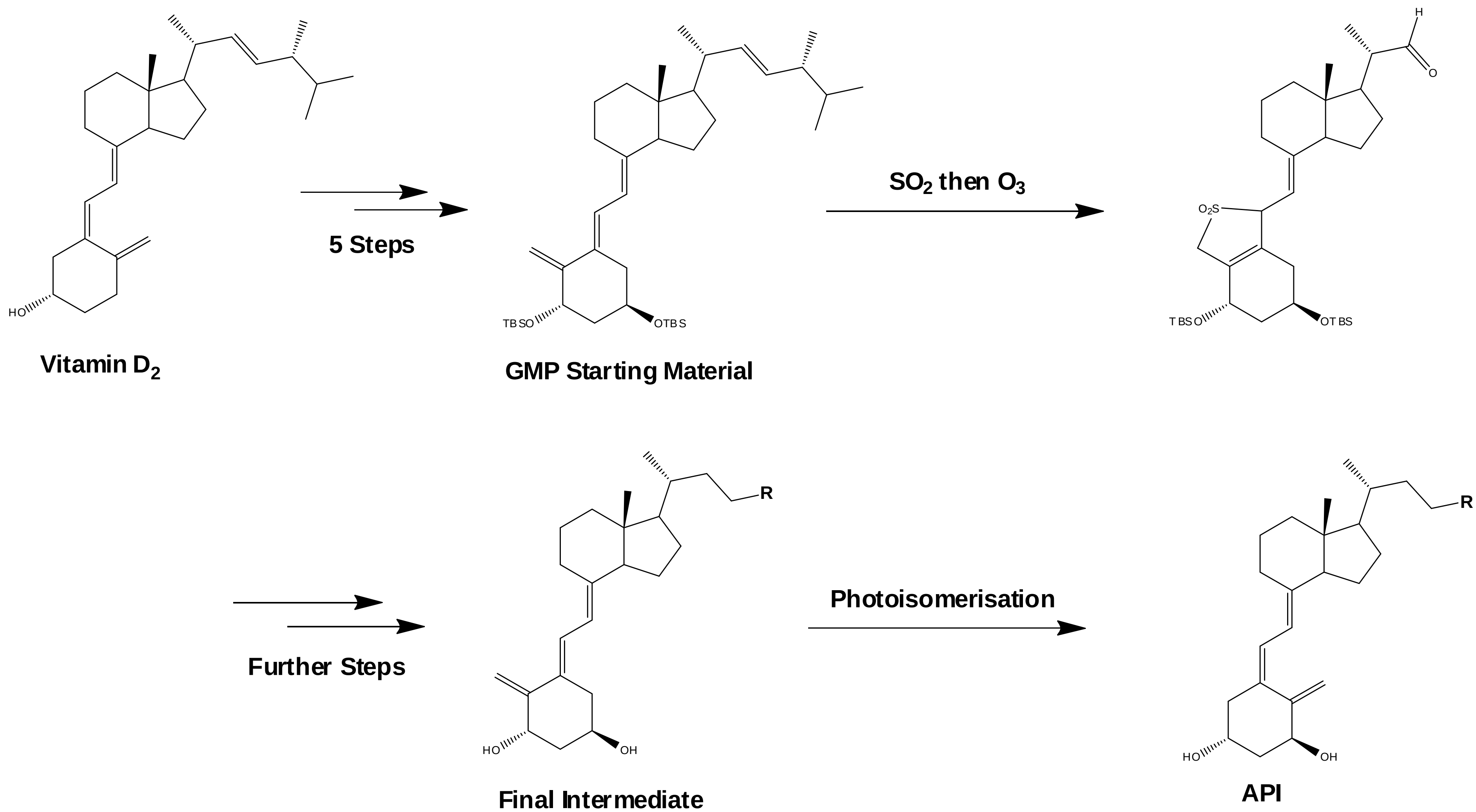
Dr Stephen Bell

Development Target

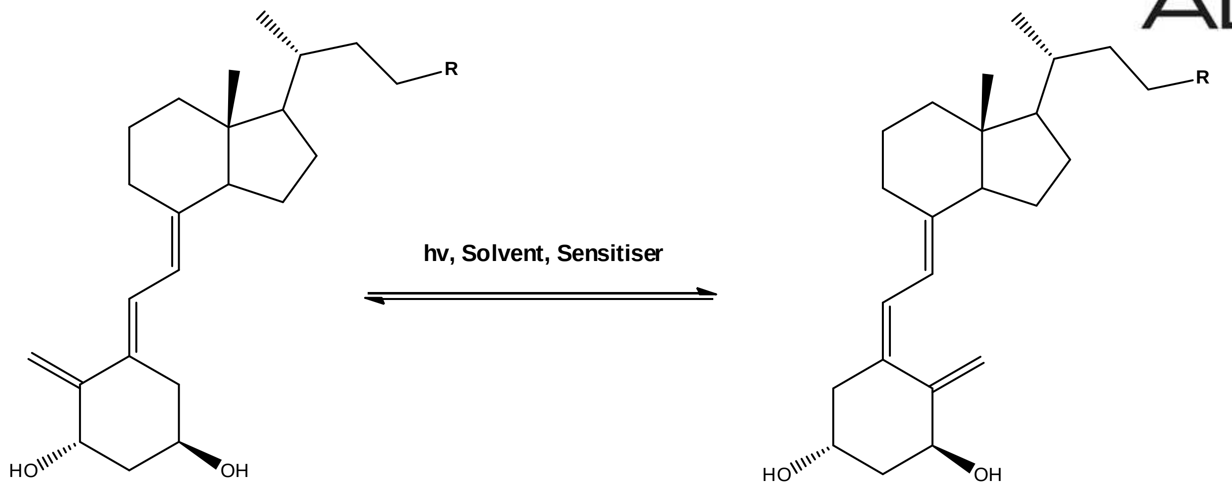


- Small volume high potency secosteroid API
- 15 Step synthesis from ergocalciferol (Vitamin D_2)
- Process needed to be capable of producing ~1-2 kg per year

Synthetic Route Summary



Photoisomerisation



Goals

- Sensitised vs direct photoisomerisation to be evaluated
- API Forming step
- Equilibrium process – target <1% SM at completion (Photostationary state)
- Close collaboration between PRD and Engineering teams

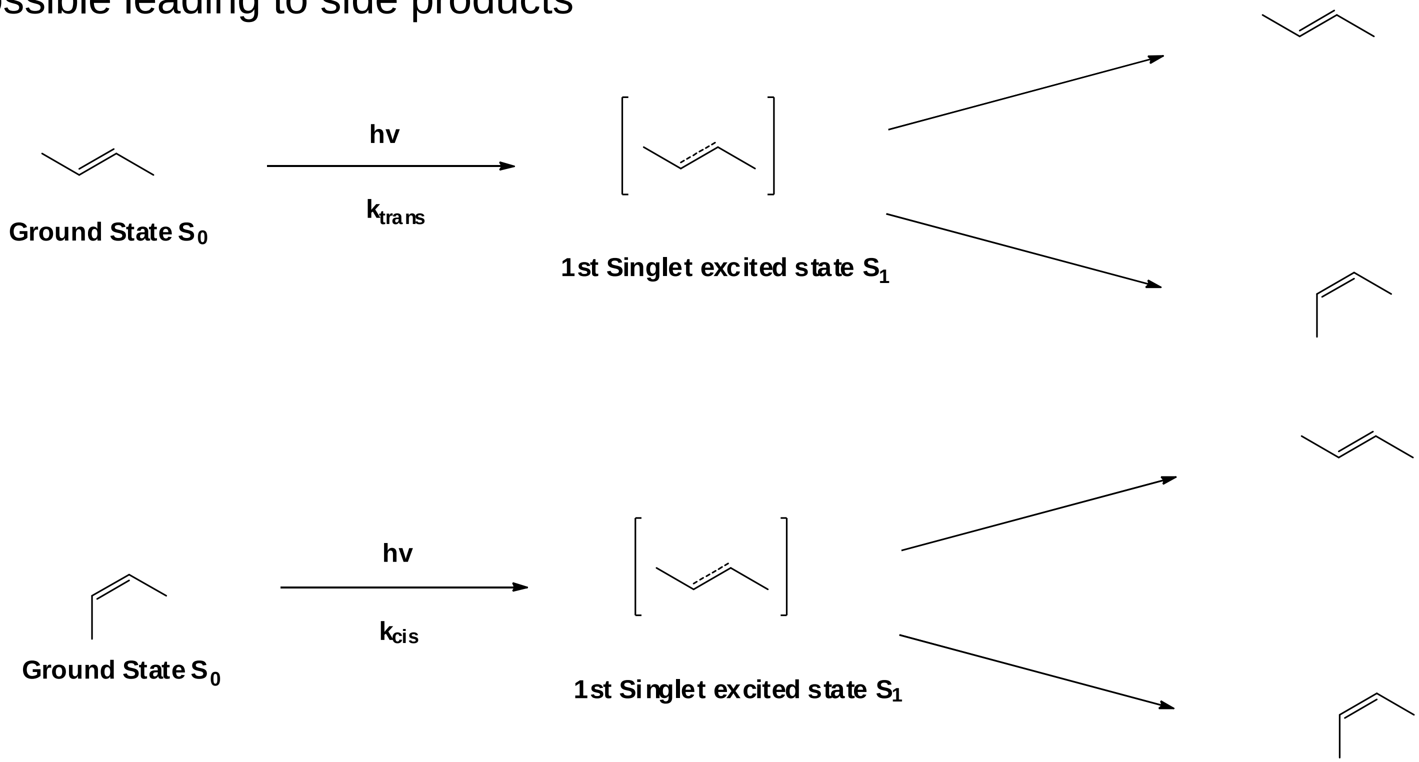
Challenges

- Literature reports typically only carried out on 100 mg to ~5 g scale
- Quantities of late stage intermediate initially very limited
- Previous in house photochemical experience limited eg radical initiation and singlet O_2
- Did not initially possess any UV lab equipment
- Need for rational design

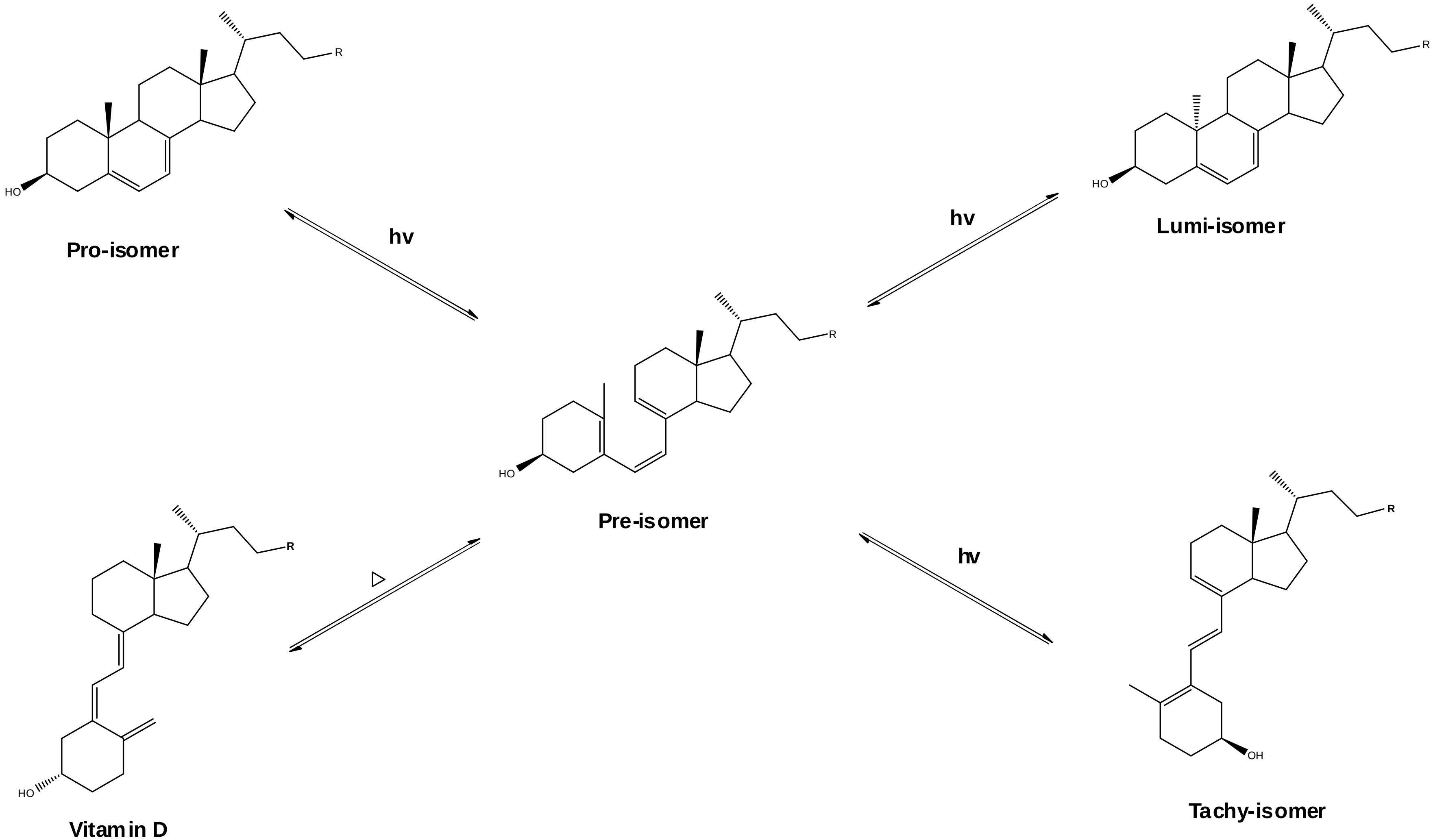
Types of Photoisomerisation

Direct

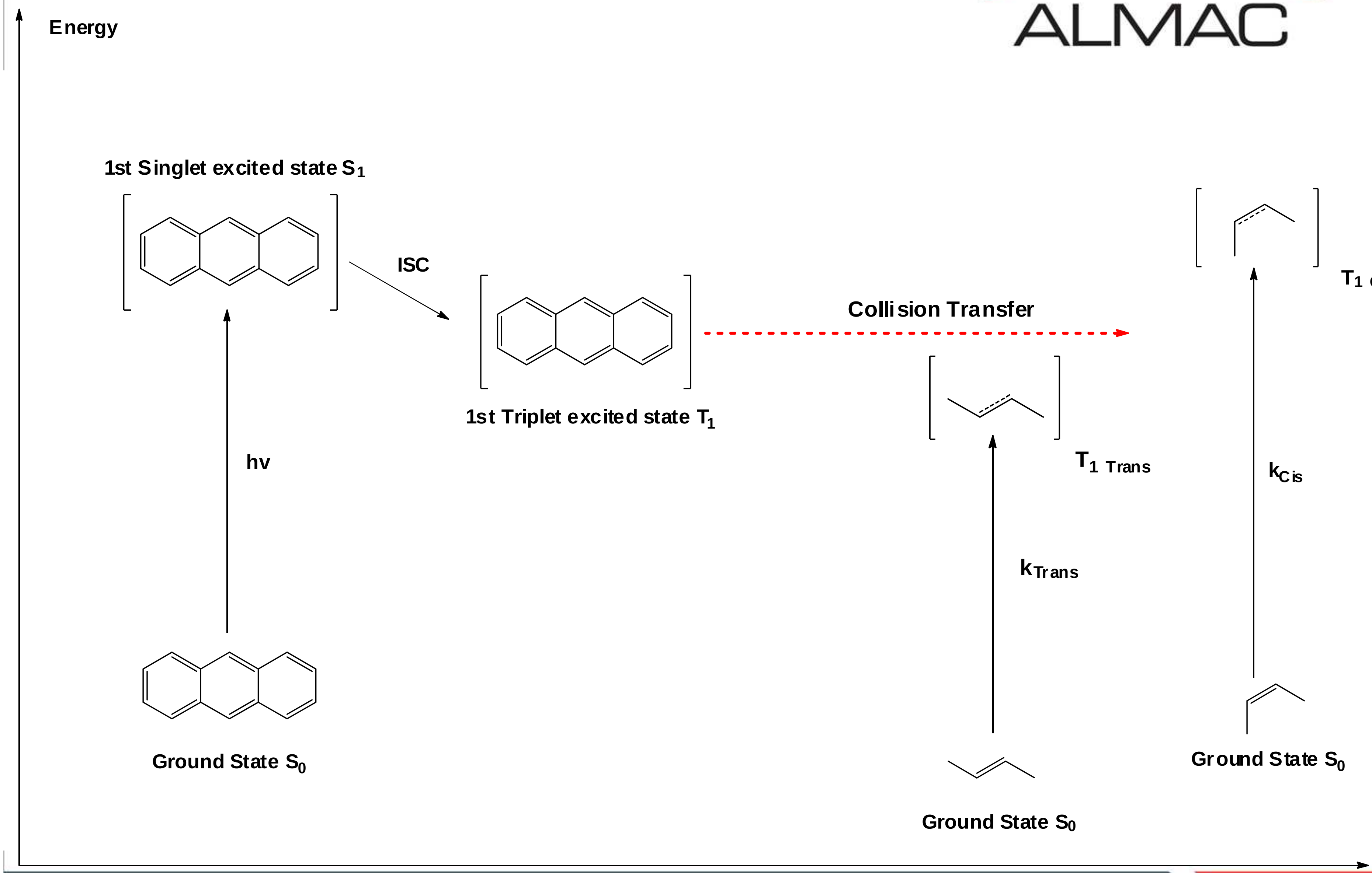
- Substrate absorbs light to give first singlet excited state - no barrier to rotation
- Decay of singlet can give either isomer, equilibrium mixture depends on the relative rates of activation of the two isomers by light – $k_{trans} >> k_{cis}$
- 1st Singlet excited state is highly reactive and many other reaction pathways possible leading to side products



Photochemistry of Vitamin D



Sensitised Photoisomerisation

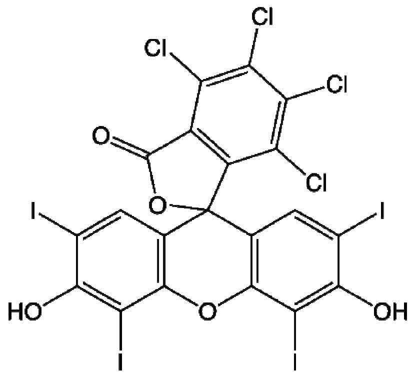


Sensitised Process Summary

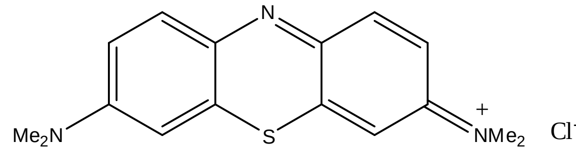
- Sensitiser molecule absorbs light at a wavelength where the substrate does not
  – hence less side products
- Singlet excited state of sensitiser decays rapidly to longer lived triplet state
  – fast intersystem crossing
- Triplet sensitiser collides with substrate transferring its energy and triplet spin state
- Sensitiser functions as a photochemical catalyst/energy carrier
- Decay of triplet state of substrate can give either isomer,
  equilibrium mixture depends on the relative rates of energy transfer to the isomers during collision with the activated sensitiser
- $k_{trans} >> k_{cis}$ depends on the triplet energy level of the sensitiser

Examples of Sensitisers

Visible Light

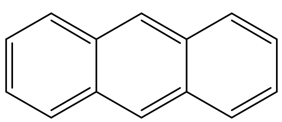


Rose Bengal

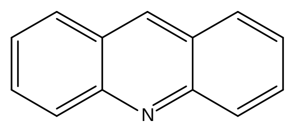


Methylene Blue

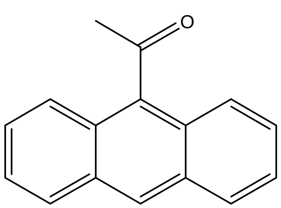
UV Light



Anthracene

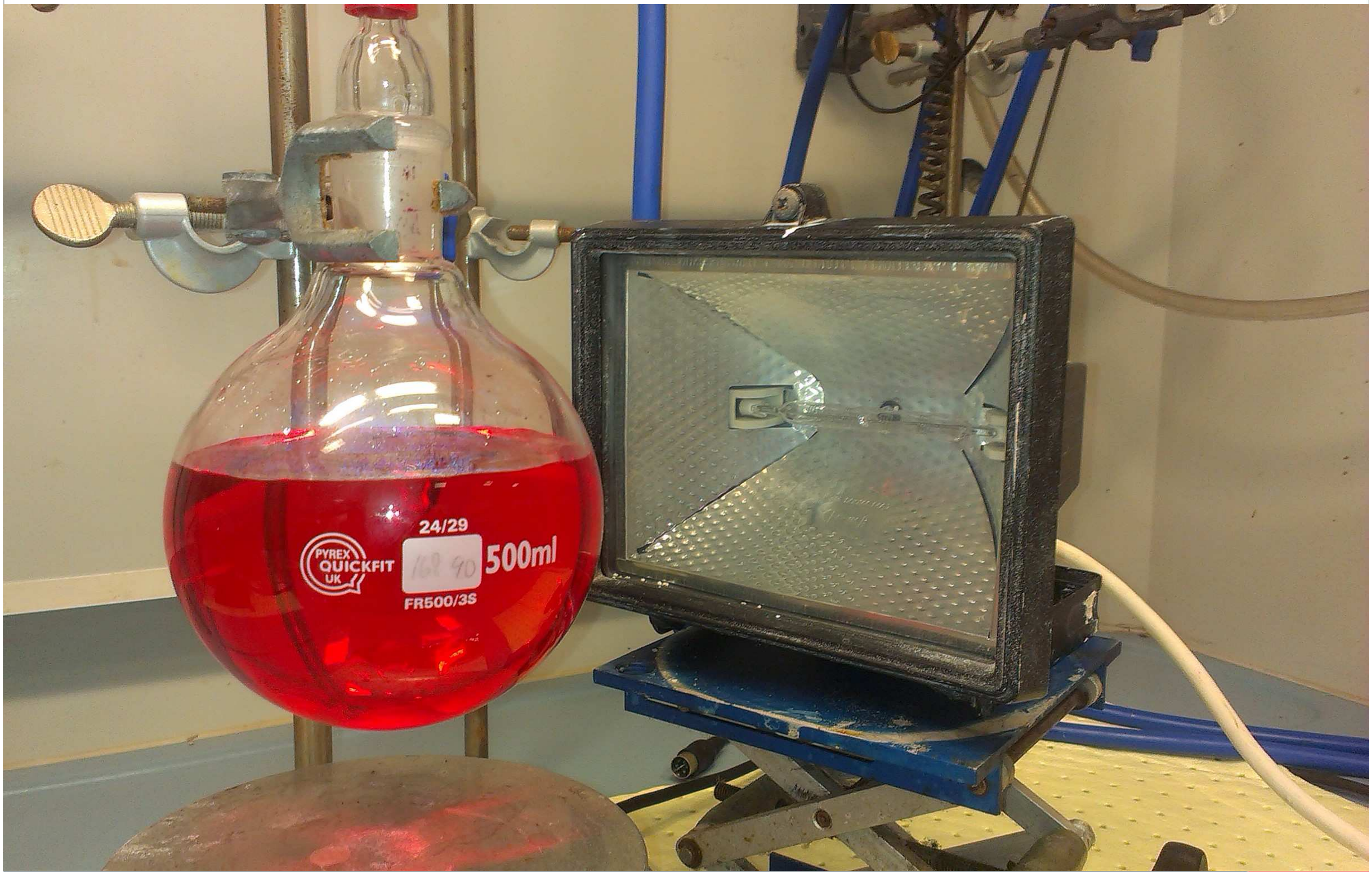


Acridine

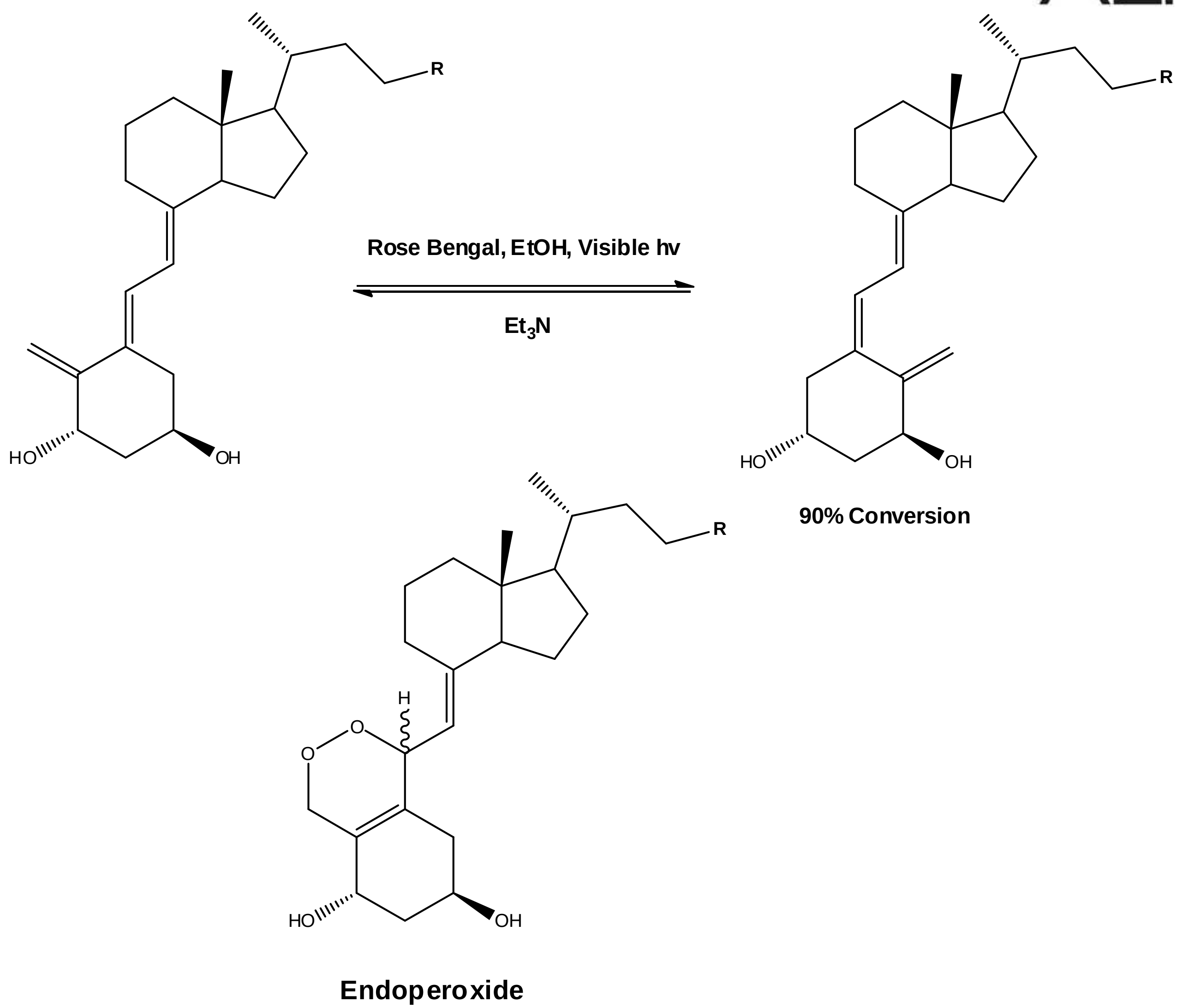


9-Acetylanthracene

Visible Light Studies

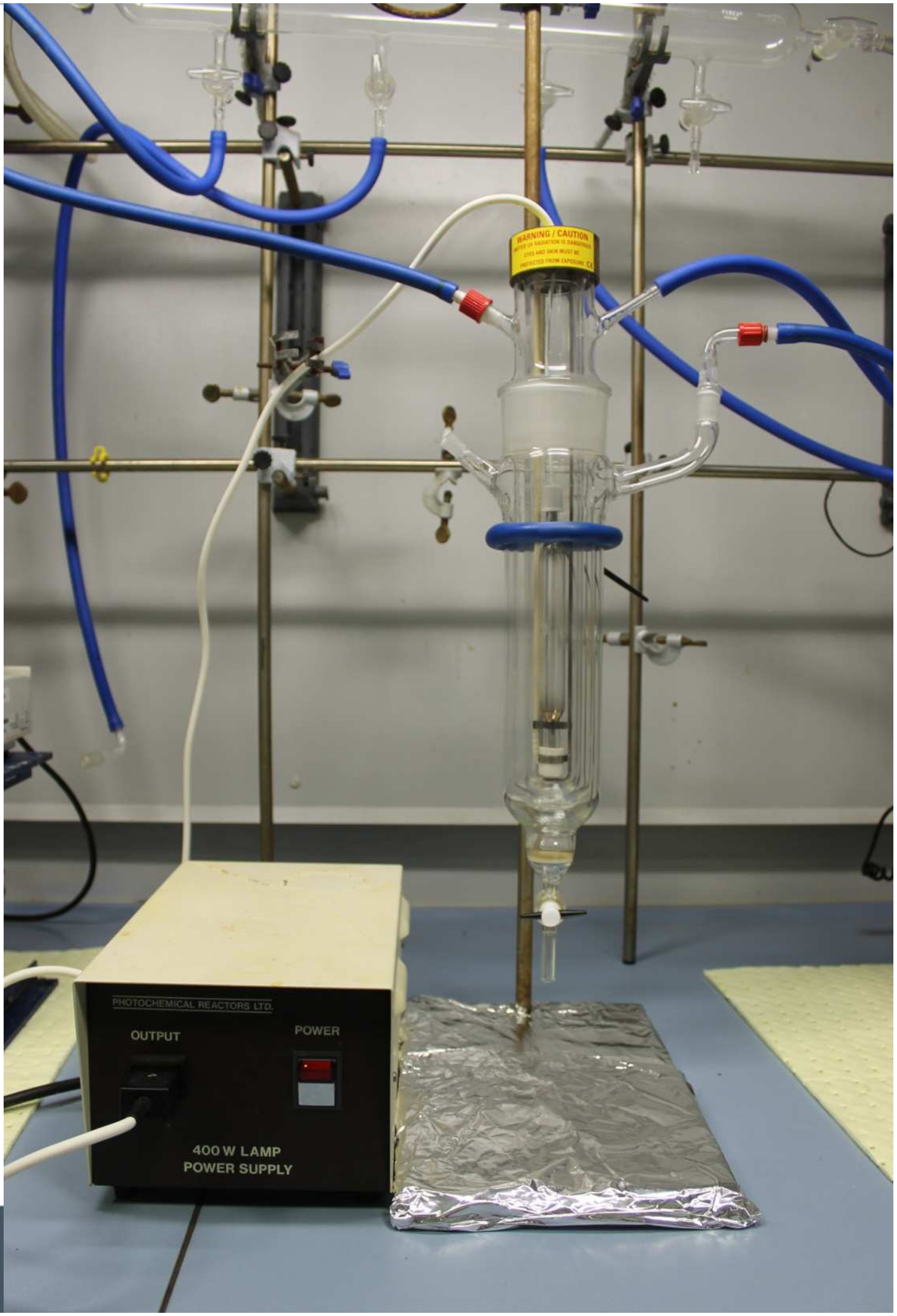


Visible Light Studies



Immersion Well Reactor

- Photochemical reactors Ltd
- 400 W Medium pressure mercury lamp
- 250 mL and a 2 L reactor vessel



Lab Reactor Components

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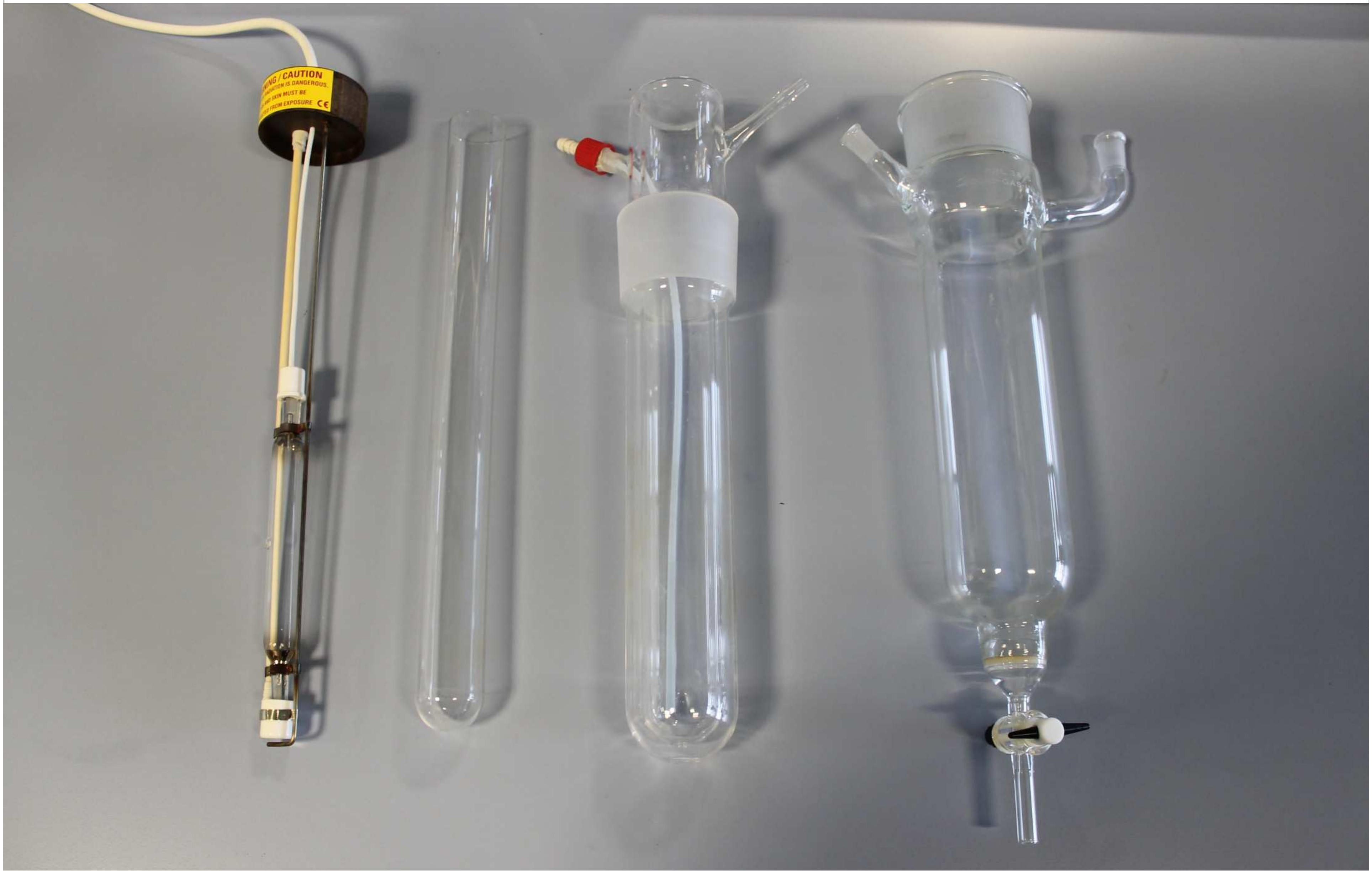
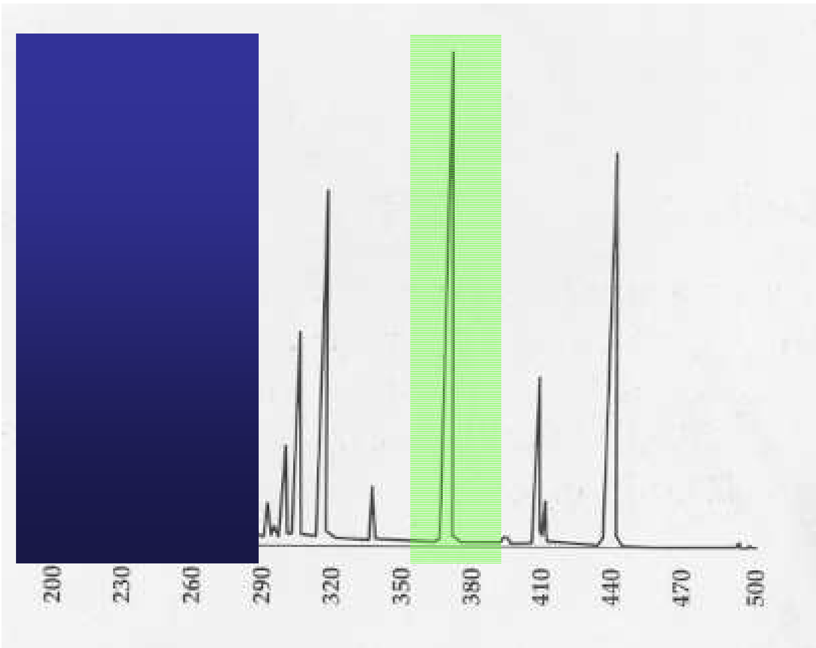
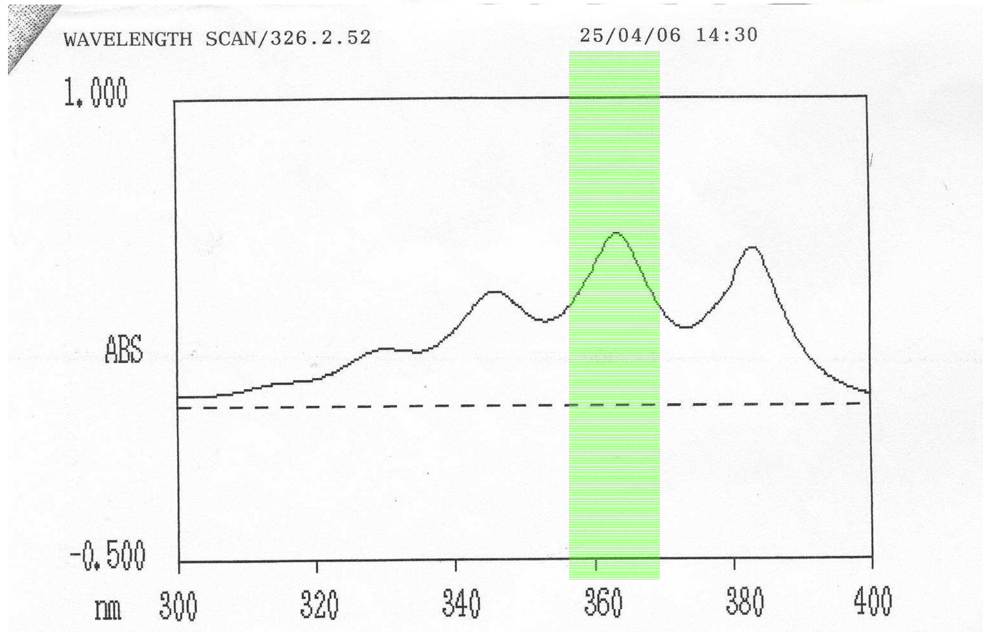


Spectroscopic Properties



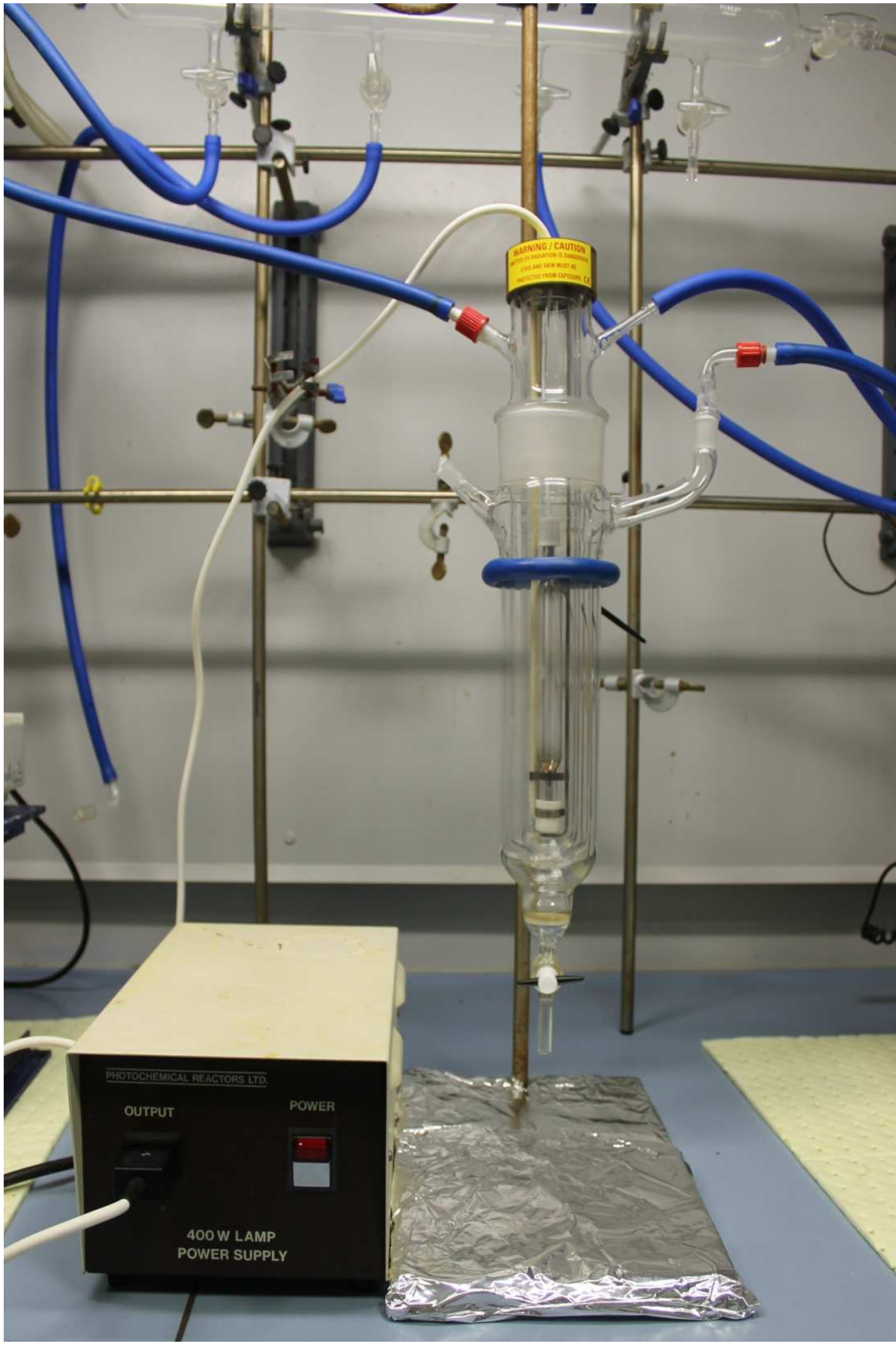


WAVELENGTH SCAN/326.2.52 25/04/06 14:31

NO.	PEAK nm	PEAK ABS	VALLEY nm	VALLEY ABS
1	383.0	0.514	373.6	0.252
2	363.4	0.562	353.2	0.277
3	346.2	0.374	334.2	0.179
4	330.4	0.190	304.0	0.038
5	303.4	0.040	302.4	0.038

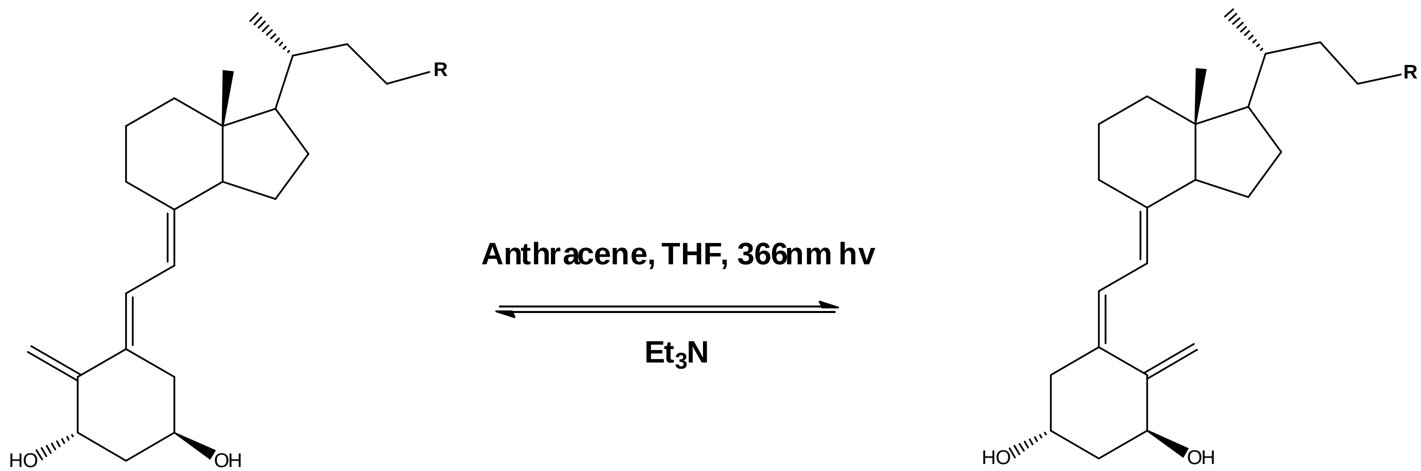
- UV emission spectrum of lamp

- UV absorption spectrum of sensitizer

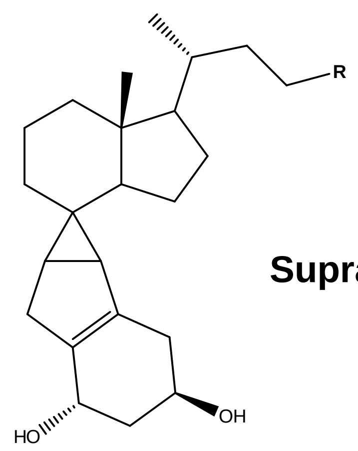

WARNING / CAUTION
PHOTOCHEMICAL REACTORS LTD.
OUTPUT
POWER
400 W LAMP
POWER SUPPLY

WARNING / CAUTION
MITTED UV RADIATION IS DANGEROUS
EYES AND SKIN MUST BE
PROTECTED FROM EXPOSURE
CE

The First UV Trials

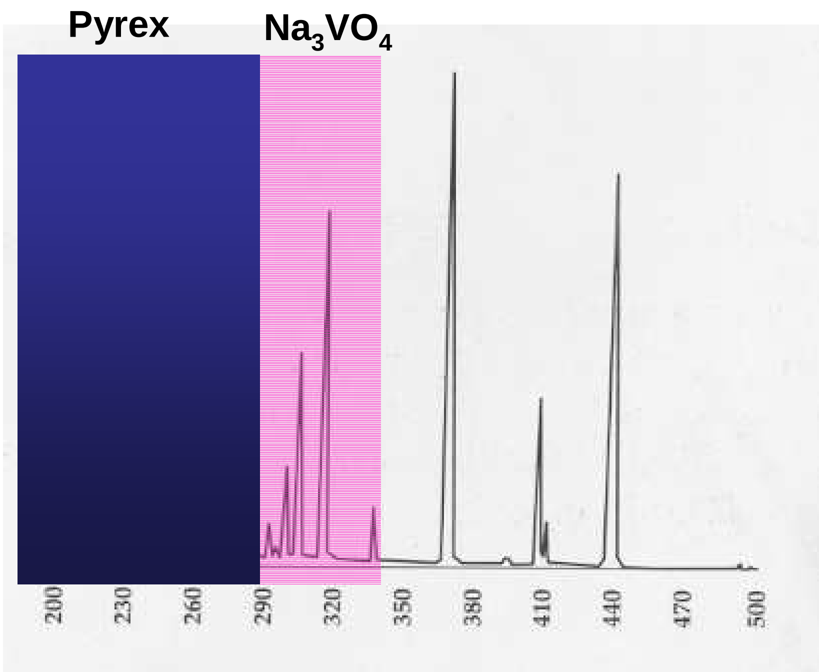


No Product Formed



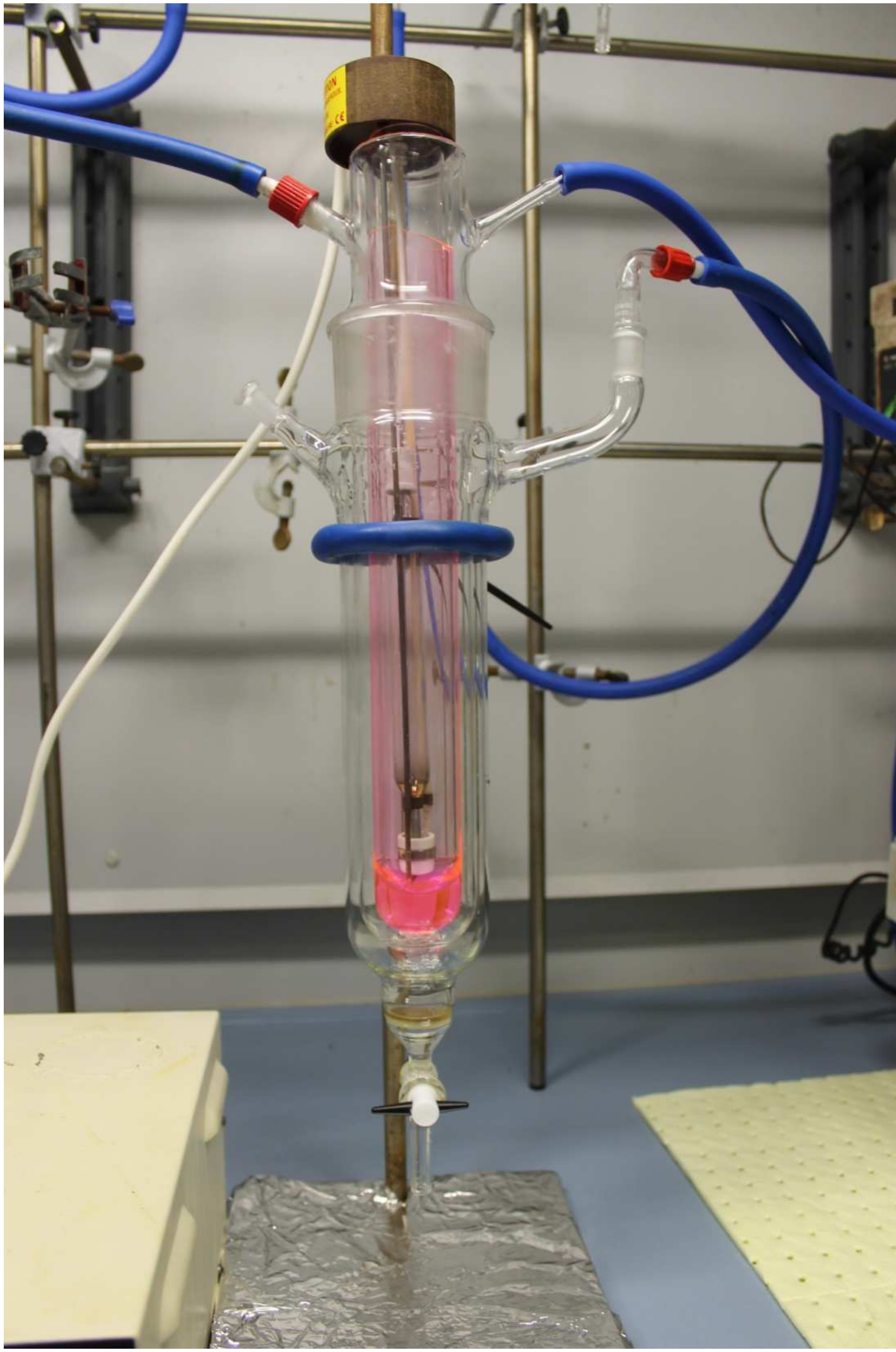
Suprasterol

The Suprasterol Problem

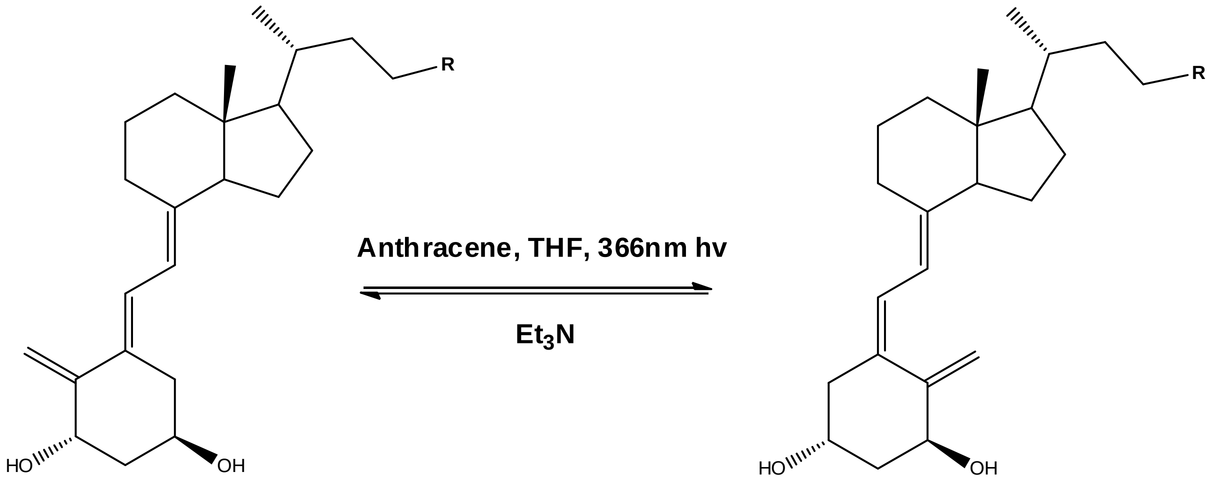


- UV emission spectrum of lamp

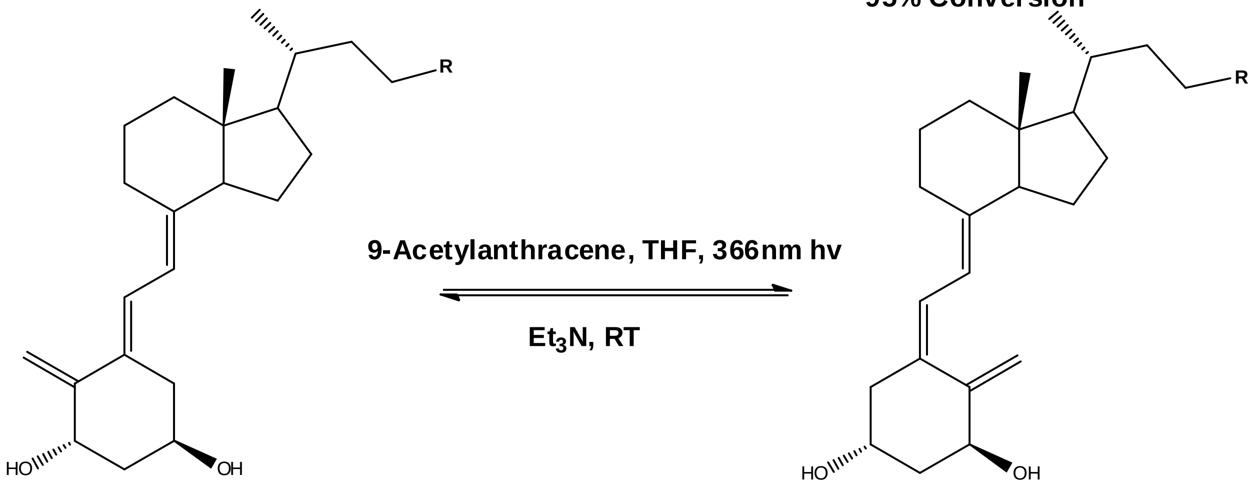
- Suprasterol formation occurs ~300-310 nm
- Pyrex filter cuts off below 290 nm
- Several Hg emission lines - 290-320nm
- Need additional filter but doped glass filters were expensive and on long lead times
- Liquid filter chosen
- 2M Aqueous solution of Na_3VO_4
- Placed between pyrex and quartz walls



Filtered UV Trials

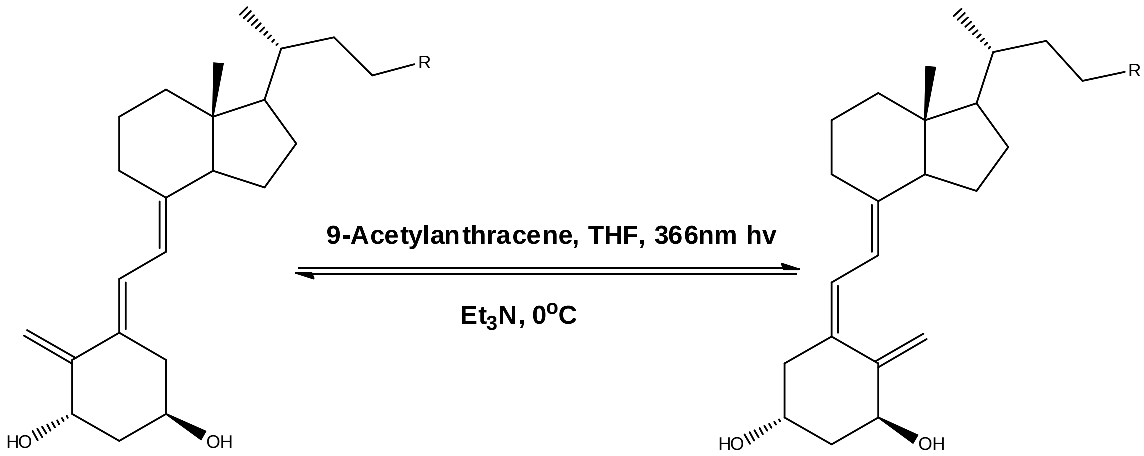


95% Conversion



98% Conversion

The Optimised Lab Process



99% Conversion

Parameter screen results

- 9-Acetylanthracene is the best sensitiser – highest conversion at equilibrium – 98%
- Solvent and substrate concentration have little effect – mainly solubility issues – THF best
- Solvent volumes are scaled to the equipment rather than batch size
- Temperature has a slight but significant effect – 0ºC gave >99% conversion
- Goal of lab PRD achieved

- Further work to support scale up and GMP reactor design

The Sensitiser Concentration

Effect of sensitiser concentration

• During initial trials 5 mol% loading was used
• Path length of lab reactor is 1cm – distance from immersion well to outer glass wall
• Extinction coefficient of 9-acetylanthracene at 366nm is 6722 mol^{-1} cm^{-1}

Beer-Lambert law **$A = \varepsilon cL$**

ε = extinction coefficient, c is conc in mol dm^{-3} and L is path length in cm

$A = -\log_{10}(I/I_0)$

I = Intensity of light and I_0 = Initial intensity of light

so when A = 2 then I/I_0 is 0.01 or 99% absorbed

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How far does the light penetrate when 5 mol% is used?

Example: 10 g batch in 200mL THF – MW of substrate approx. 500

20 mmol batch size

5 mol% sensitiser = 1 mmol in 200 mL or 5 mM concentration

L = A/εc or 2/(6722x0.005) = 0.6 mm

99% of the light is absorbed in the first 6% of its way through the reaction mixture

All reaction takes place in thin layer active zone against the lamp vessel wall

Optimised Sensitiser Concentration

- To avoid mass transfer problems on scale up, we needed to reduce the sensitiser concentration
- Also needed uniform irradiation of the mass flow in order to move to a flow-through regime
- Reduce concentration by factor of 10
- The light now penetrates 10x further through the mixture
- The same number of molecules of sensitiser are activated but they are now uniformly distributed
- Diffusion of substrate and mixing are no longer as important

Optimised Sensitiser Concentration

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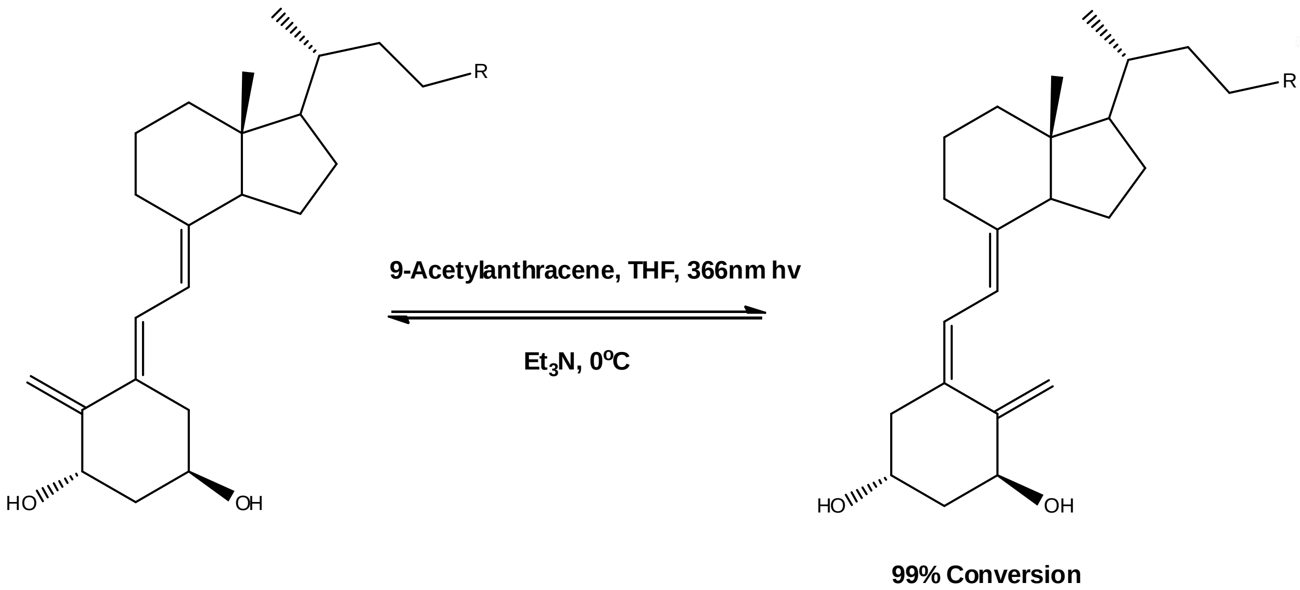
Consequences

- The optimum concentration is related only to L (reactor optical path length)
- Amount of sensitiser used is independent of the batch size
- Scaling from lab to plant equipment the concentration used goes down
- In finalised process: a 2 kg batch required only 0.5 g of sensitiser; results in a faster reaction than using more!

Reaction Kinetics



Reactions followed by sampling and conversions determined by NMR

- 400 W lab reactor used
- 10 g batch shows 60% conversion in 30 min and full conversion in 1 h
- 20 g batch shows 75% conversion after 1 h and full conversion in 2 h (~30 mmol per hour)

- Light is a reagent in this reaction and its addition is rate limiting!
- What is the rate at which the lamp emits photons at 366 nm?
- What is the quantum yield of reaction Φ ?
- Both of these numbers will determine power requirement for full scale equipment

Photochemical Definitions

Photon Flux – photons per second

Quantum Yield Φ – No. of molecules converted per photon absorbed

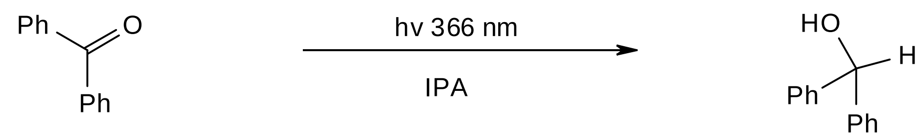
Measures efficiency of a photochemical process – usually < 1

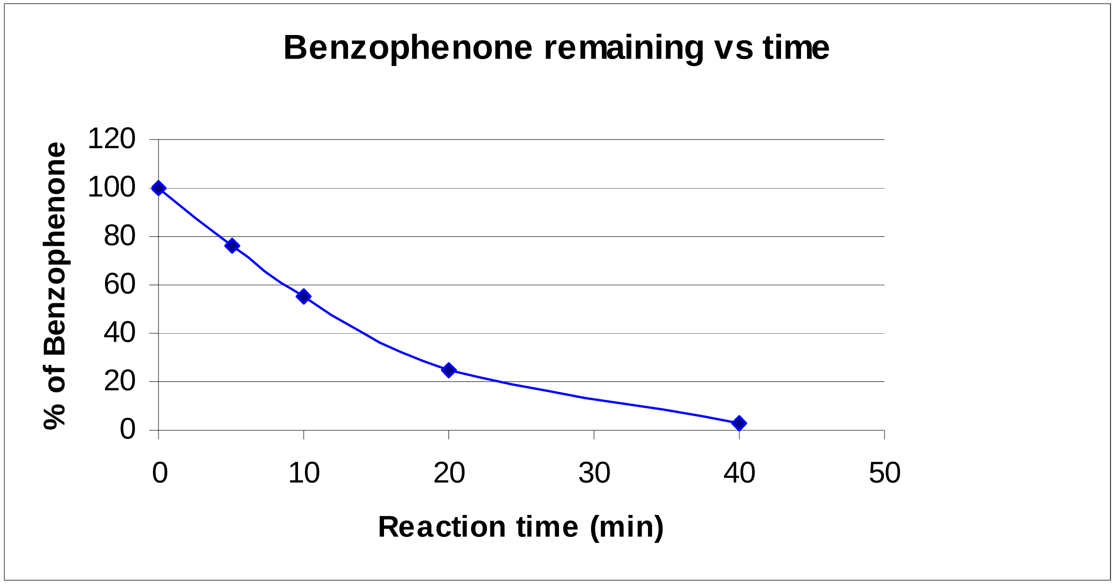
Actinometry – measurement of photon flux from the yield of a chemical reaction

Requires knowledge of the quantum yield at the wavelength of interest

Titration of light

Actinometry Studies





Quantum yield (fraction of absorbed photons that lead to product)

Benzophenone photoreduction is known to go in quantum yield of 0.8

From measurement of reaction rate during the first 10% conversion allows us to know photon output

Our 400 W medium pressure Hg lamp emits 6.9×10^{18} photons per second at 366 nm

Moles of Light

- One mole of photons (6.022×10^{23}) = one Einstein
- 400 W lamp emits 6.9×10^{18} photons per second at 366 nm
- Equivalent to 2.48×10^{22} photons per hour = 41 mmol of light per hour
- From conversion rates measured for the photoisomerisation the quantum yield = 0.58
- To process a 2 kg batch using lab equipment would therefore take ~170 hr

Reactor Design

- To process a 2 kg batch in a useful time we want to increase lamp power x10
- 5 KW Medium pressure Hg lamp chosen for GMP Reactor
- Want to perform 2 kg batch in 25 vol THF with possibility of using larger batches in future
- Reactor needs to be ~ 100 L.
- Reactor dimensions are constrained by the lamp design
- Need to move towards a flow through operation mode

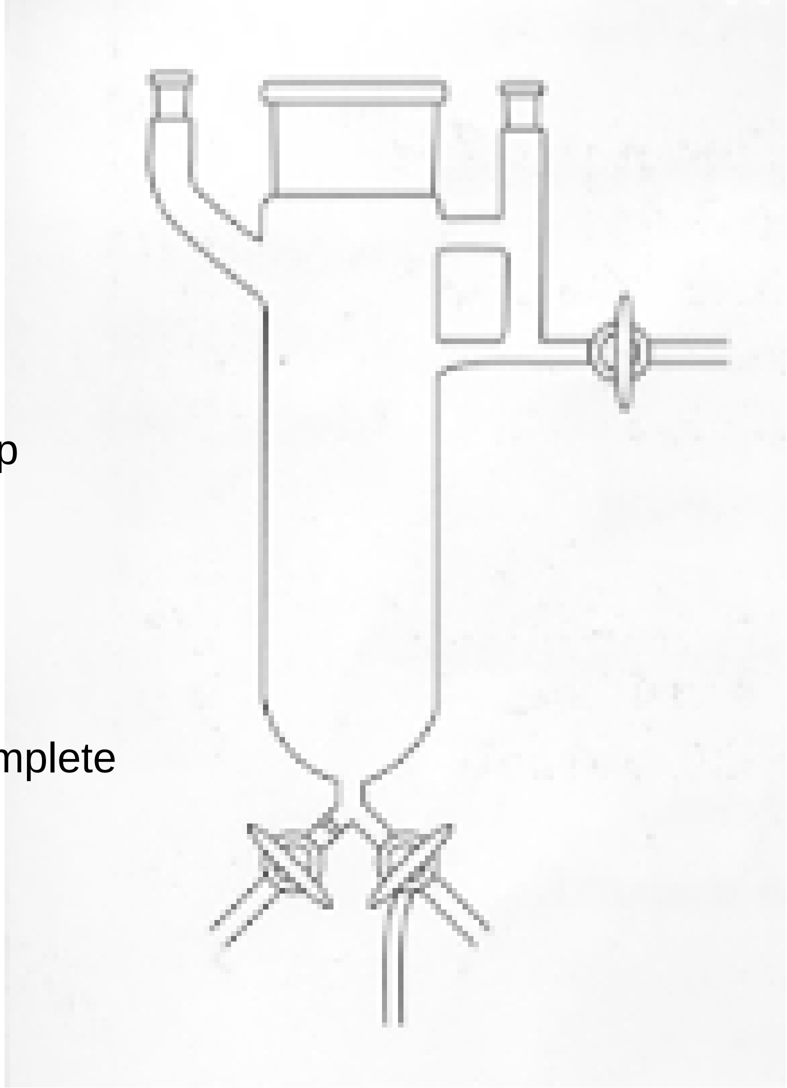
Flow Photochemistry

Lab Trial – 200mL Flow flask

700 mL solution
circulated through reaction
flask at 50 $mLmin^{-1}$ using peristaltic pump

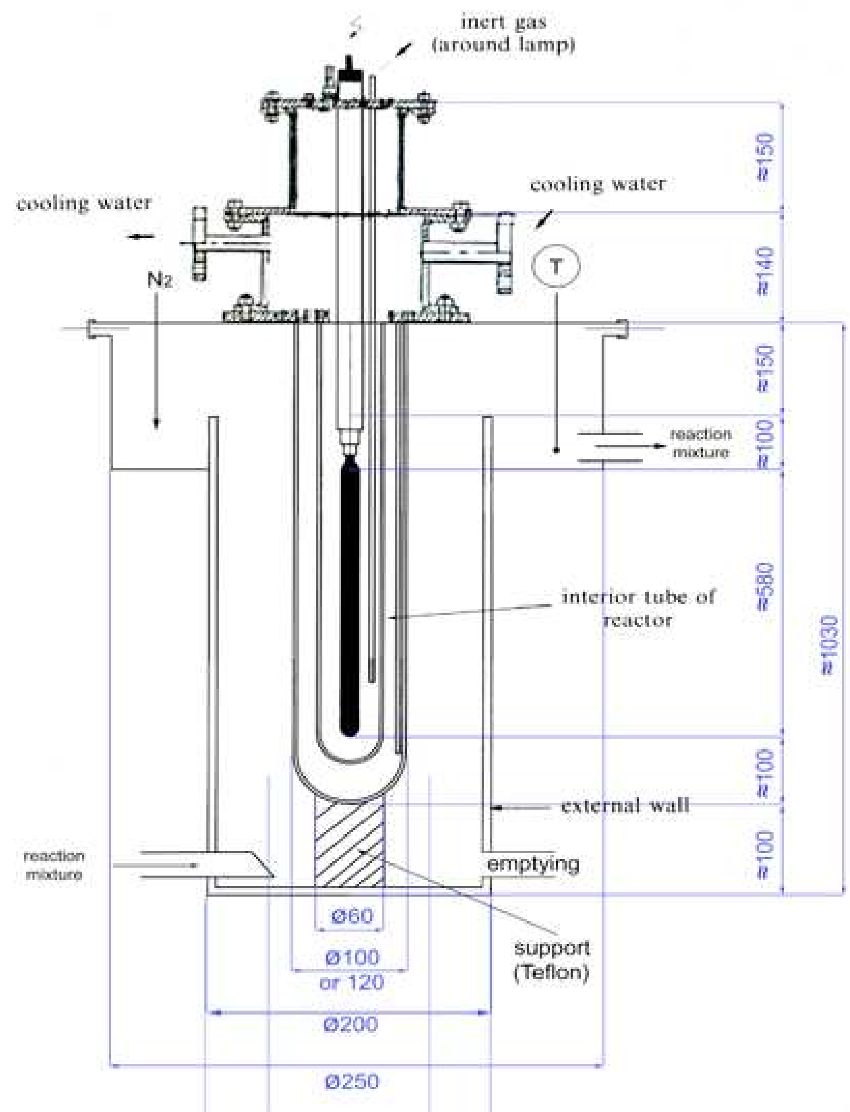
1/3 of batch resides in lamp vessel
2/3 in reservoir at any given time

Operated in semi-continuous flow mode
Recirculation continues until reaction complete
Reaction time = 3 x 200 mL batches



Semi-continuous Flow Photoreactor

- Inner area for lamp
  - 5 kW Mercury medium pressure lamp
  - Adjustable current to control light output
- Middle area for coolant/filter medium
  - Rated to 0-135ºC
  - Connected to Huber unit
- Outer area for reactants
  - 14 L around lamp, 70 L vessel
  - Adjustable flow speed 0-50Lts/min
  - Temperature controlled via secondary reactor



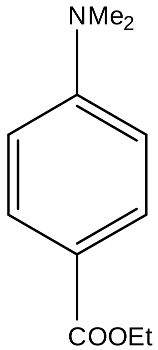
Filter for Production

Problem

- 2M Na_3VO_4 solution used in lab trials as wavelength filter
- Performance degrades over time and multiple batches
- Filter performance is a critical quality attribute
- If filter is located in lamp cavity then inaccessible for easy replacement

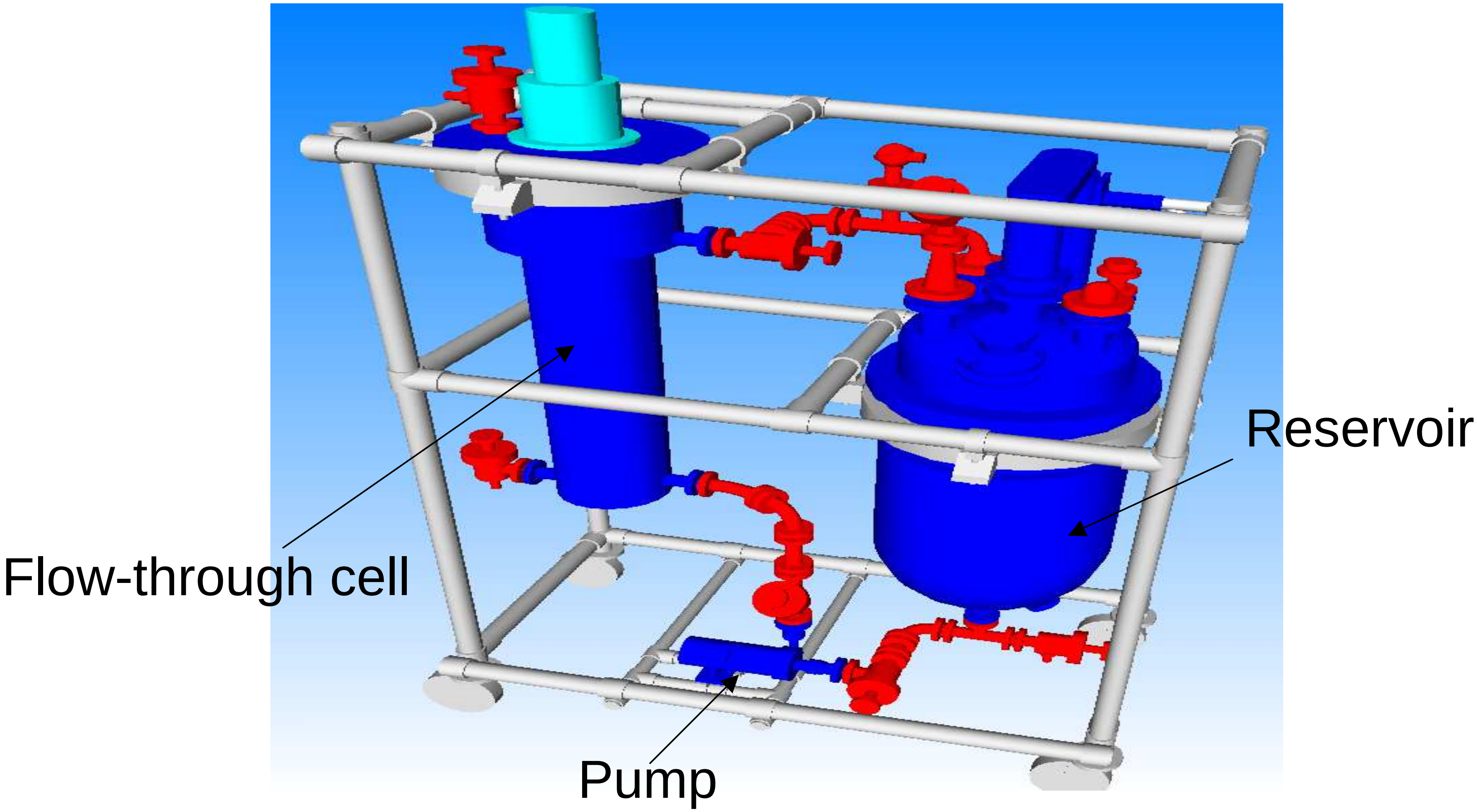
Solution

- Use the filter solution as the cooling fluid – circulated by Huber unit and easily changed
- But, Na_3VO_4 is not soluble in ethylene glycol solutions
- Need an organic filter that absorbs at much lower concentrations

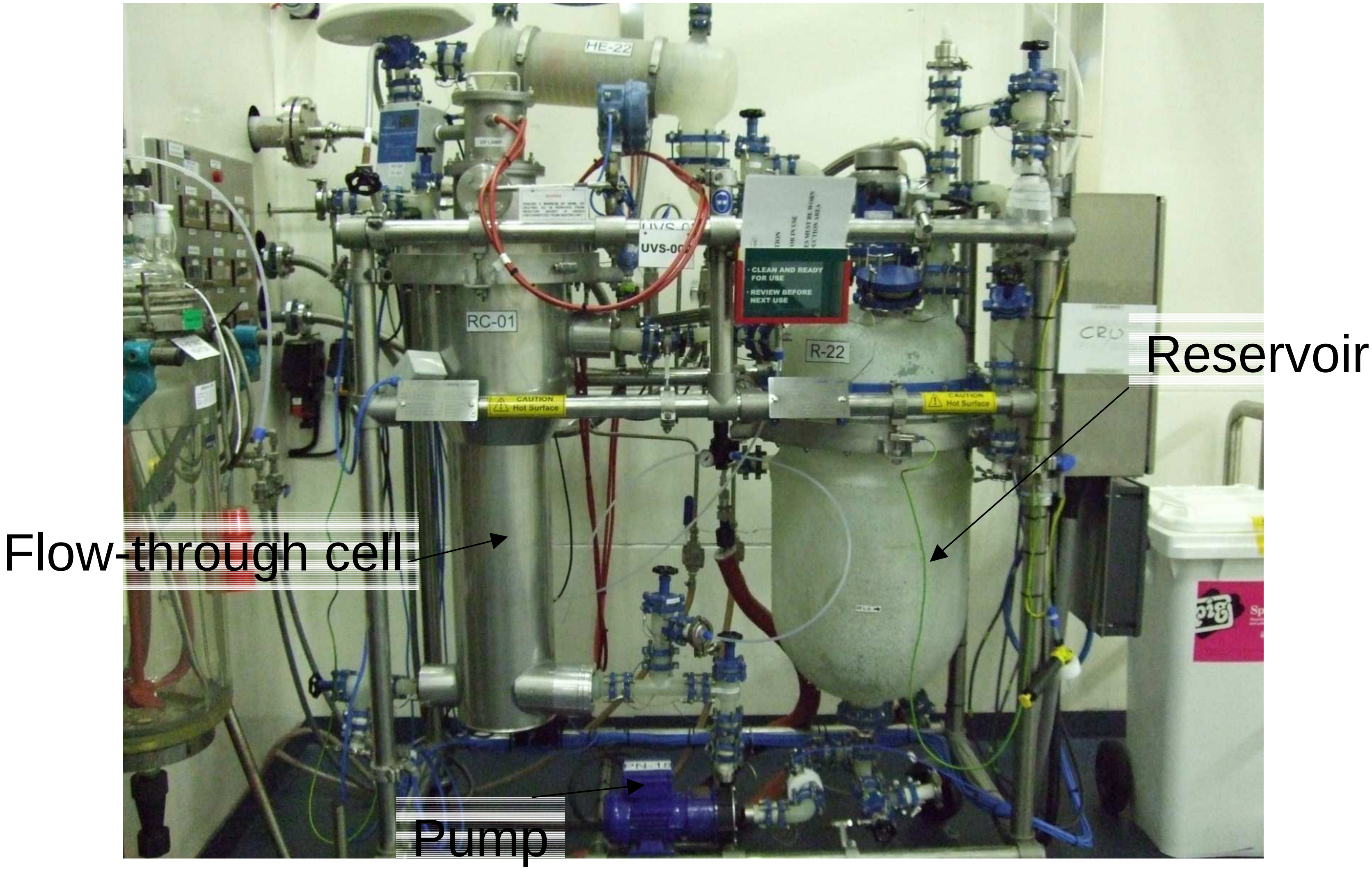


0.5% w/w solution in ethylene glycol
Inexpensive
Absorbs strongly at 290-320 nm and is stable for multiple runs
Does not crystallise out with temperature changes

UV Photoreactor UVS-002



UV Photoreactor UVS-002



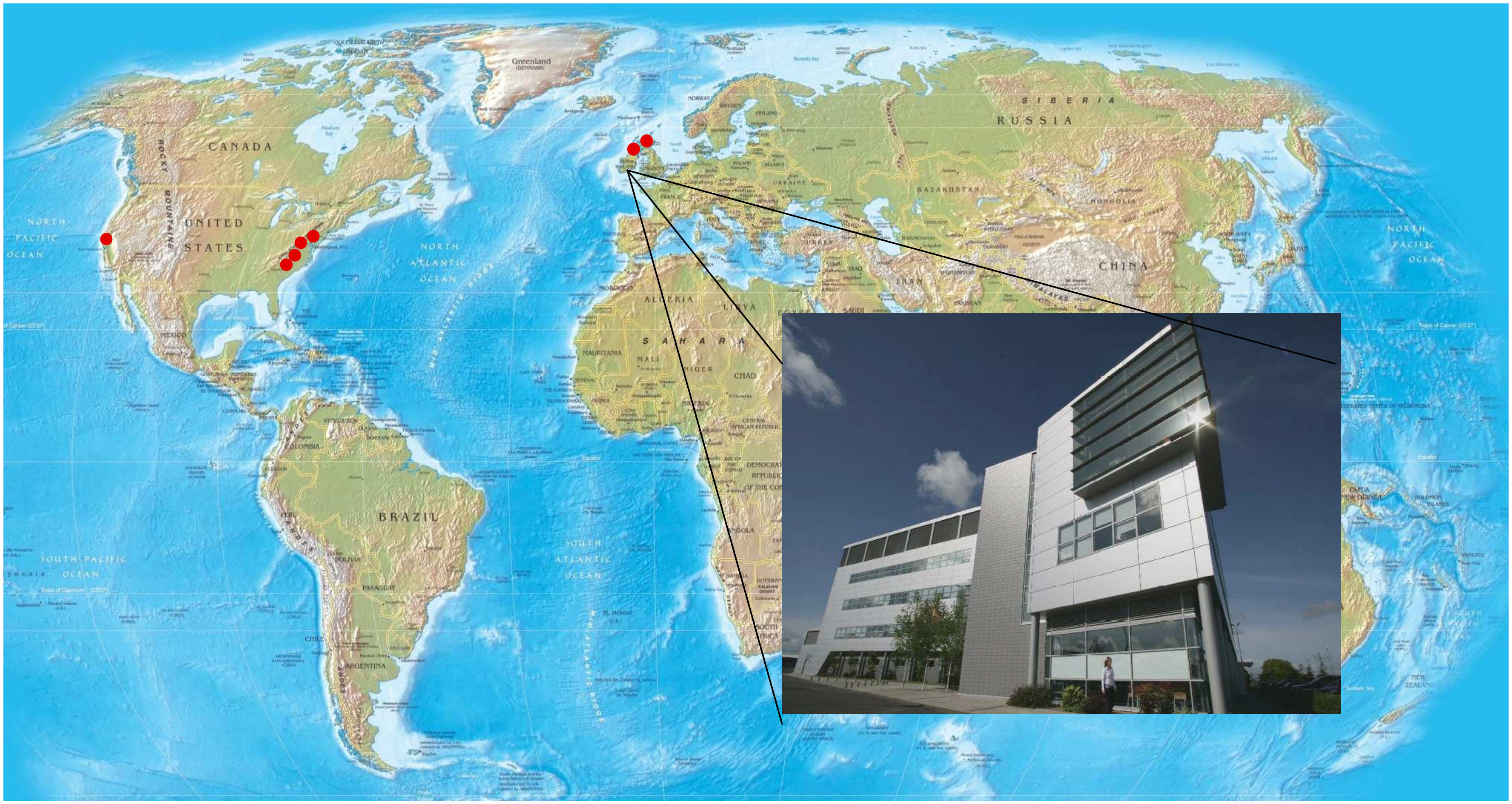
UV Photoreactor UVS-002

- The irradiated reactor volume chamber is approx 14 L
- The reaction chamber is fed from a stirred jacketed glass tank reservoir (70 L capacity), or alternatively could be connected to a larger reservoir system.
- The system uses a pump to circulate the flow of reactants in a multi-pass arrangement relative to the light source.
- Lamp type - Medium pressure mercury lamp although this can be exchanged to suit customer requirements of light wavelength and an additional filter applied if needed
  Lamp output – 5 KW (40% min output)
- The system has been designed for use within flammable atmospheres and is ATEX rated
- Multi-purpose capability - versatile enough to do other photochemistry

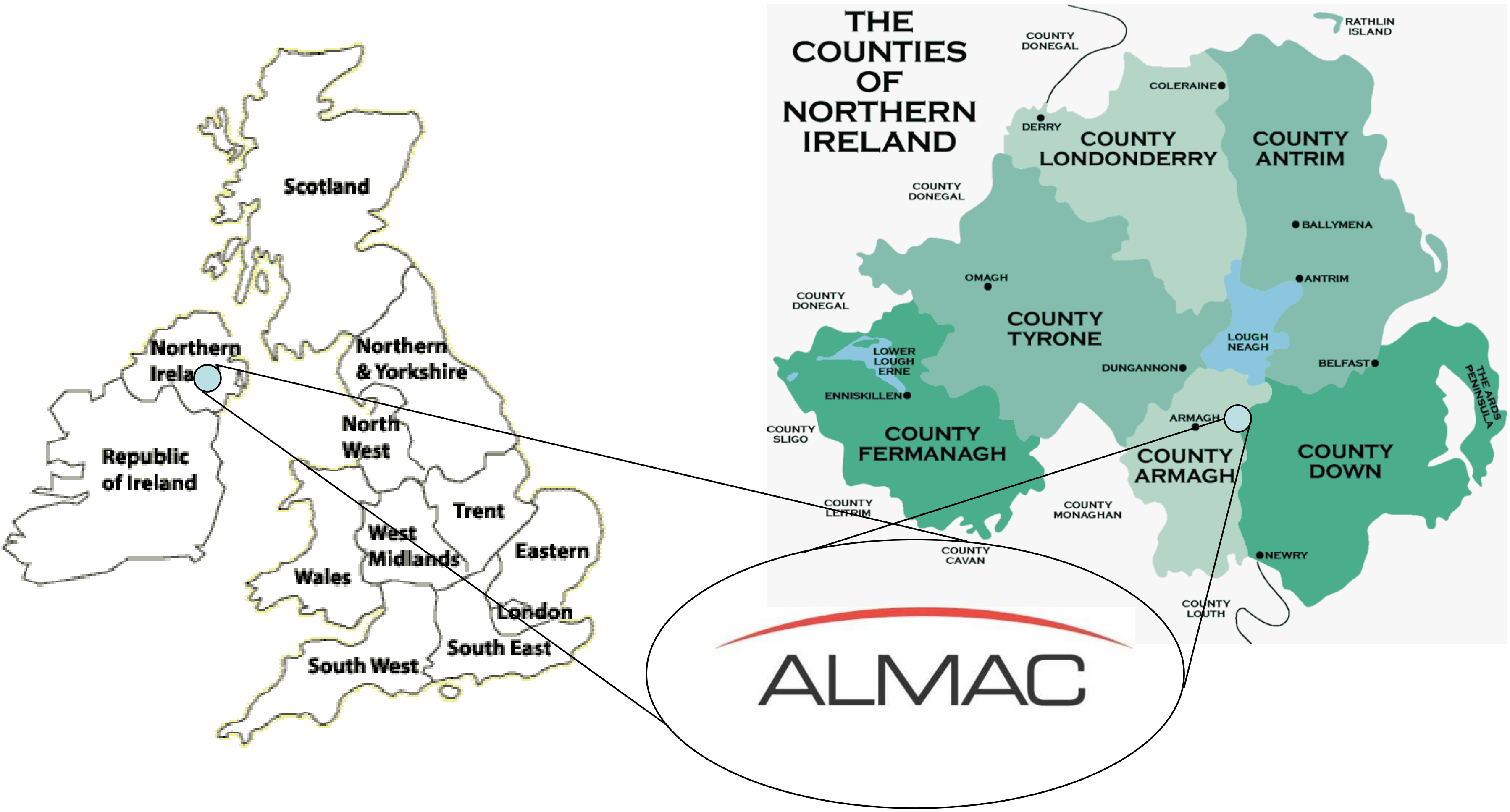
Summary

- Photoisomerisation scaled from mgs to kgs
- GMP Photoreactor designed, built and installed
- Three 0.5 kg validation batches successfully completed
- Process is versatile enough to produce any secosteroid analogue of this class
- Reactor is capable of performing most other types of photochemical transformations

Almac Facilities



Where we are:


Scotland
Northern Ireland
Northern & Yorkshire
Republic of Ireland
North West
Trent
West Midlands
Eastern
Wales
London
South East
South West
THE COUNTIES OF NORTHERN IRELAND
RATHLIN ISLAND
COUNTY DONEGAL
COLERAINE
DERRY
COUNTY LONDONDERRY
COUNTY ANTRIM
BALLYMENA
ANTRIM
OMAGH
COUNTY TYRONE
LOUGH NEAGH
LOWER LOUGH ERNE
DUNGANNON
BELFAST
THE ARDS PENINSULA
ENNISKILLEN
ARMAGH
COUNTY SLIGO
COUNTY FERMANAGH
COUNTY ARMAGH
COUNTY DOWN
COUNTY LEITRIM
COUNTY MONAGHAN
COUNTY CAVAN
NEWRY
COUNTY LOUTH
ALMAC

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PRD Group

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