Acid Catalysed Rearrangement of Fused Alkylideneoxetanols

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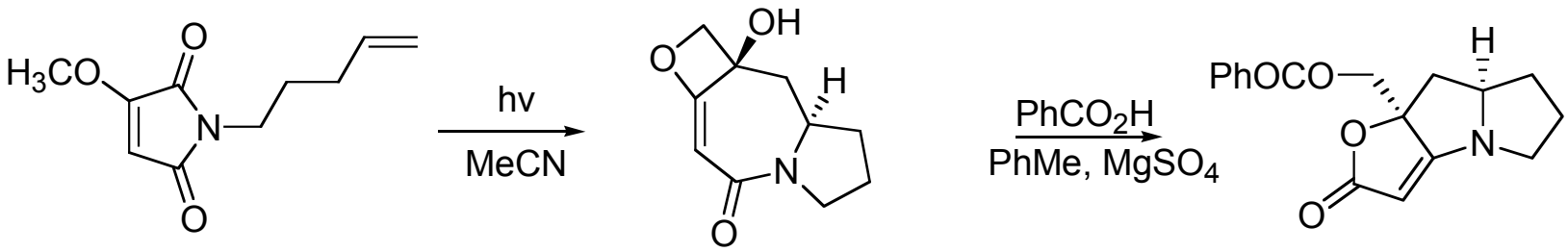
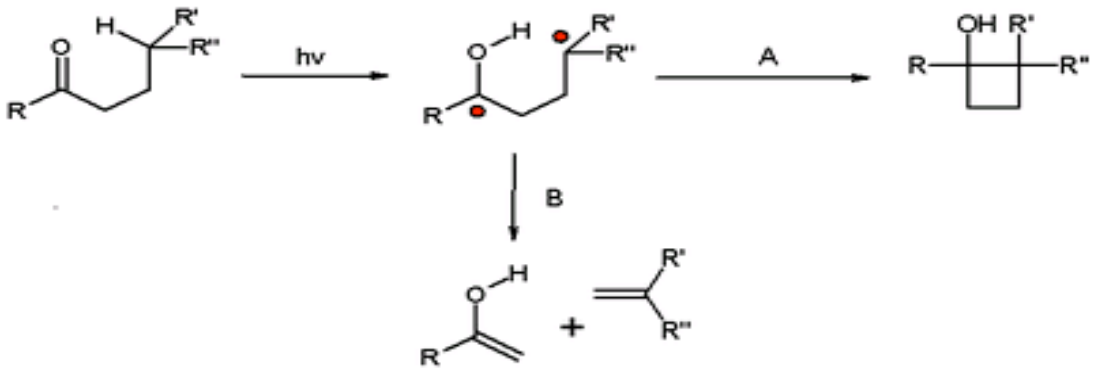
Abstract

- Synthesis of complex aza fused tricyclic lactones
  - Maleimide [5+2] cycloaddition/Norrish II cascade
  - Acid catalysed rearrangement of 3-oxetanol



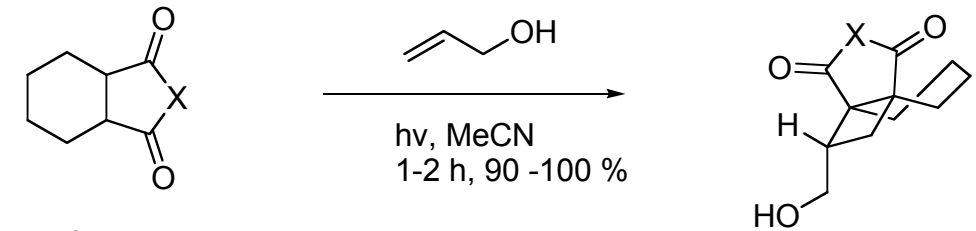
Norrish Type II

- Photochemical intramolecular abstraction of a γ-hydrogen by the excited carbonyl compound to produce a 1,4-biradical as a primary photoproduct
  - Intramolecular recombination – cyclobutanes
  - Fragmentation – enol and alkene



Initial Work

- Extensively studied intermolecular [2+2] reaction of tetrahydrophthalic anhydride (X = O) and imides (X = NH, NMe) with alkenols
  - Extremely efficient
  - High yielding
  - Excellent stereoselectivity



X = O, NH, NMe

- Natural progression of methodology – intramolecular variant

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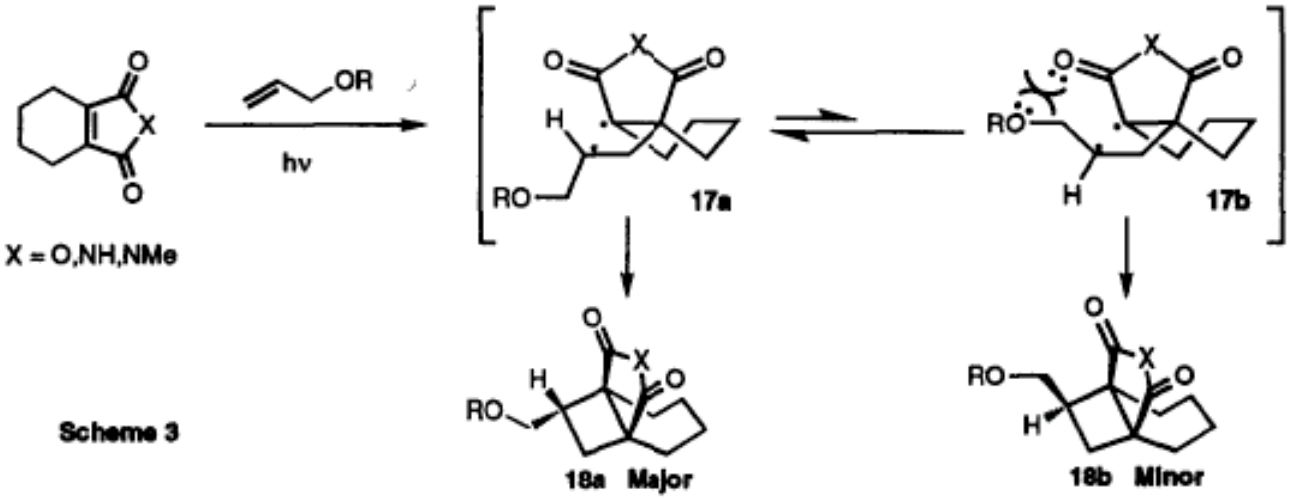
High-Stereoselectivity - Explained

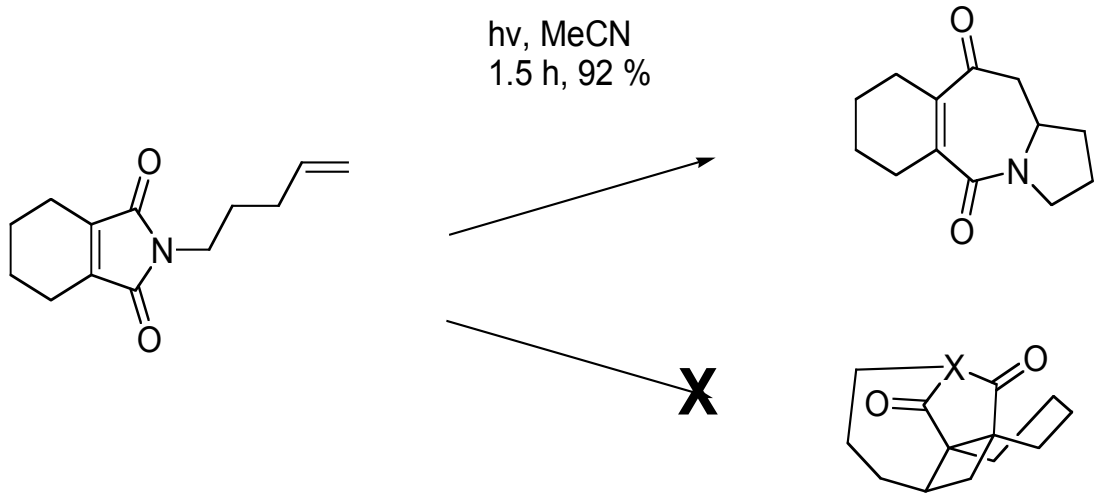


Scheme 3

- High Stereoselectivity in favour of exo-isomer
- Formation of 1,4 biradical adduct
  - Exsist as two conformers (17 a and 17 b)
  - Interconverable by free rotation
  - Electrostatic replusion of oxygen lone pairs in 17 b favours 17 a
- Exo isomer – major product

Initial Work

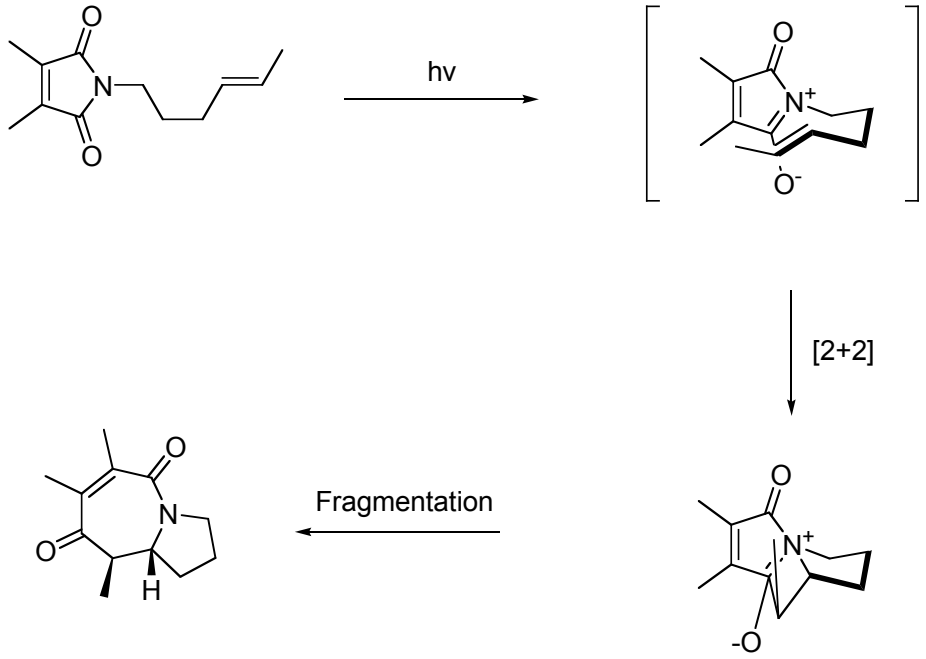
- Exclusive formation of tricyclic azepine



- First example of formal [5+2] cycloaddition reaction of non-aryl imides
  - Could be used in rapid construction of perhydroazaazules

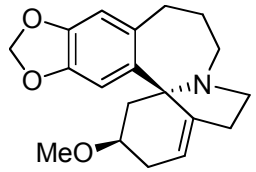
Mechanism

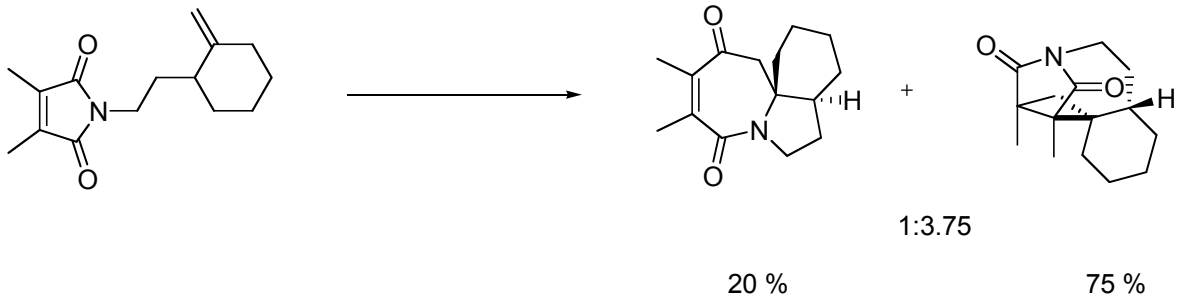
- Direct [2+2] onto excited amide resonance structure to give a zwitterionic intermediate
- Spontaneous fragmentation to yield the product
  - Alkene geometry supports this mechanism
  - stepwise process would allow bond rotations and give epimeric products



Application of Methodology to Total Synthesis - I

- Model Studies towards homoerythrinan alkaloids eg robustine

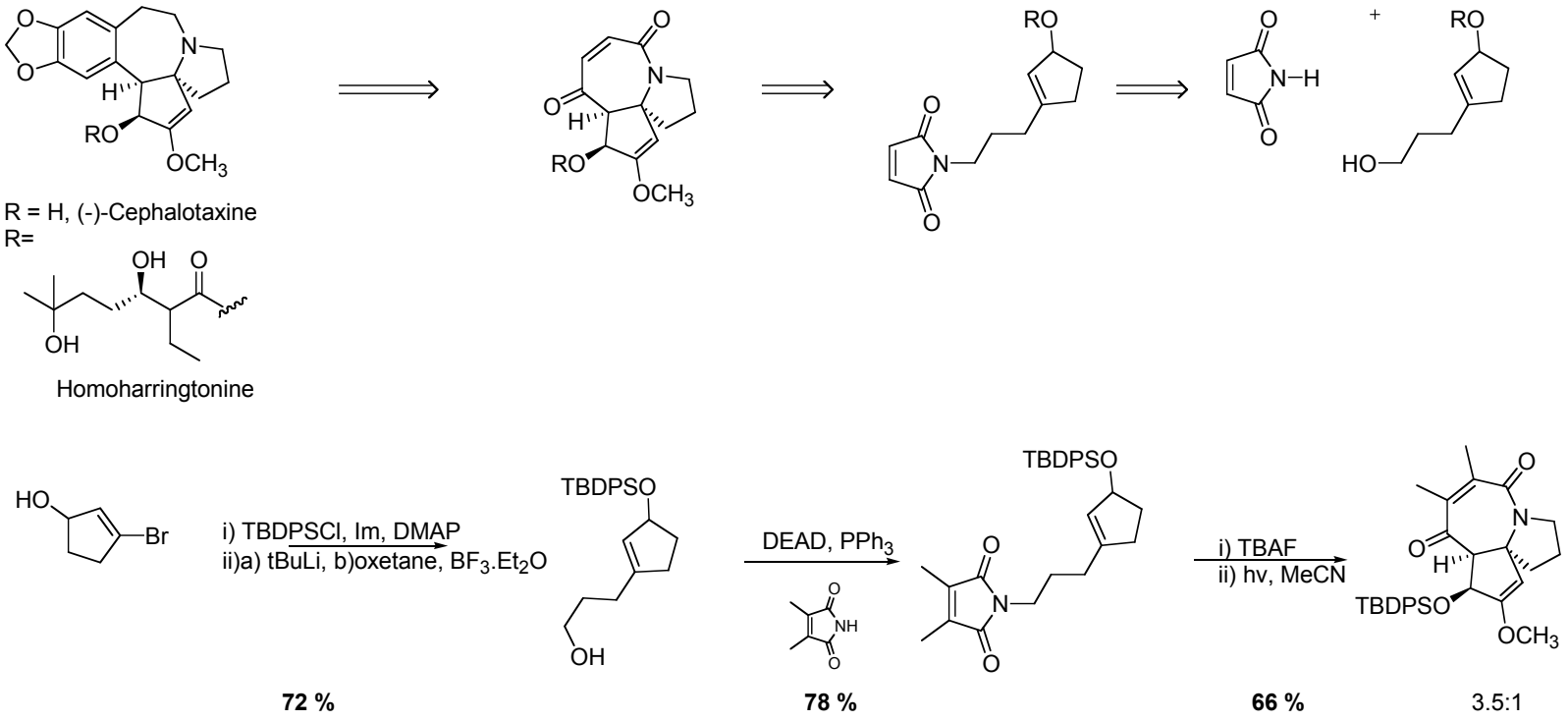




- Unexpected result – favours [2+2] addition
  - [5+2] TS less favourable
  - Require molecular modelling to help elucidate factors controlling the switch in mode of cycloaddition

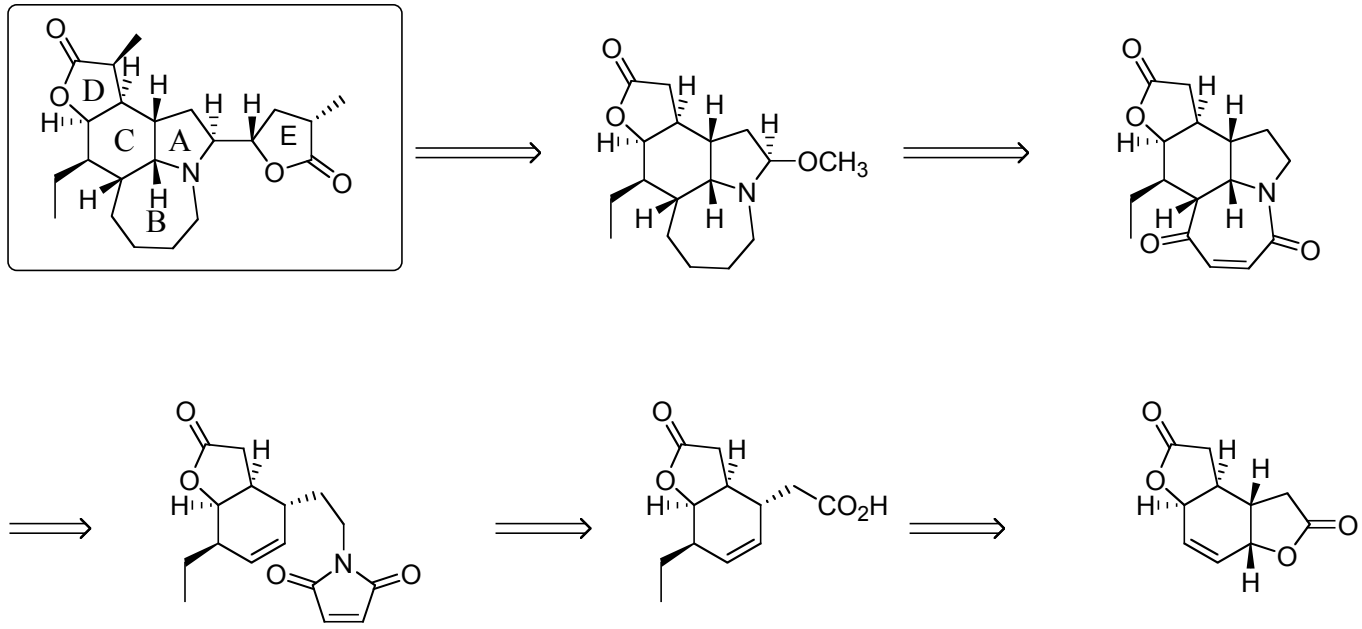
Application of Methodology to Total Synthesis - II

- Synthesis of CDE skeleton of (-)-Cephalotaxine
- Derivatives in Phase III for treatment of chronic myelogenous leukaemia
- Formal [5+2] maleimide photocycloaddition sequence



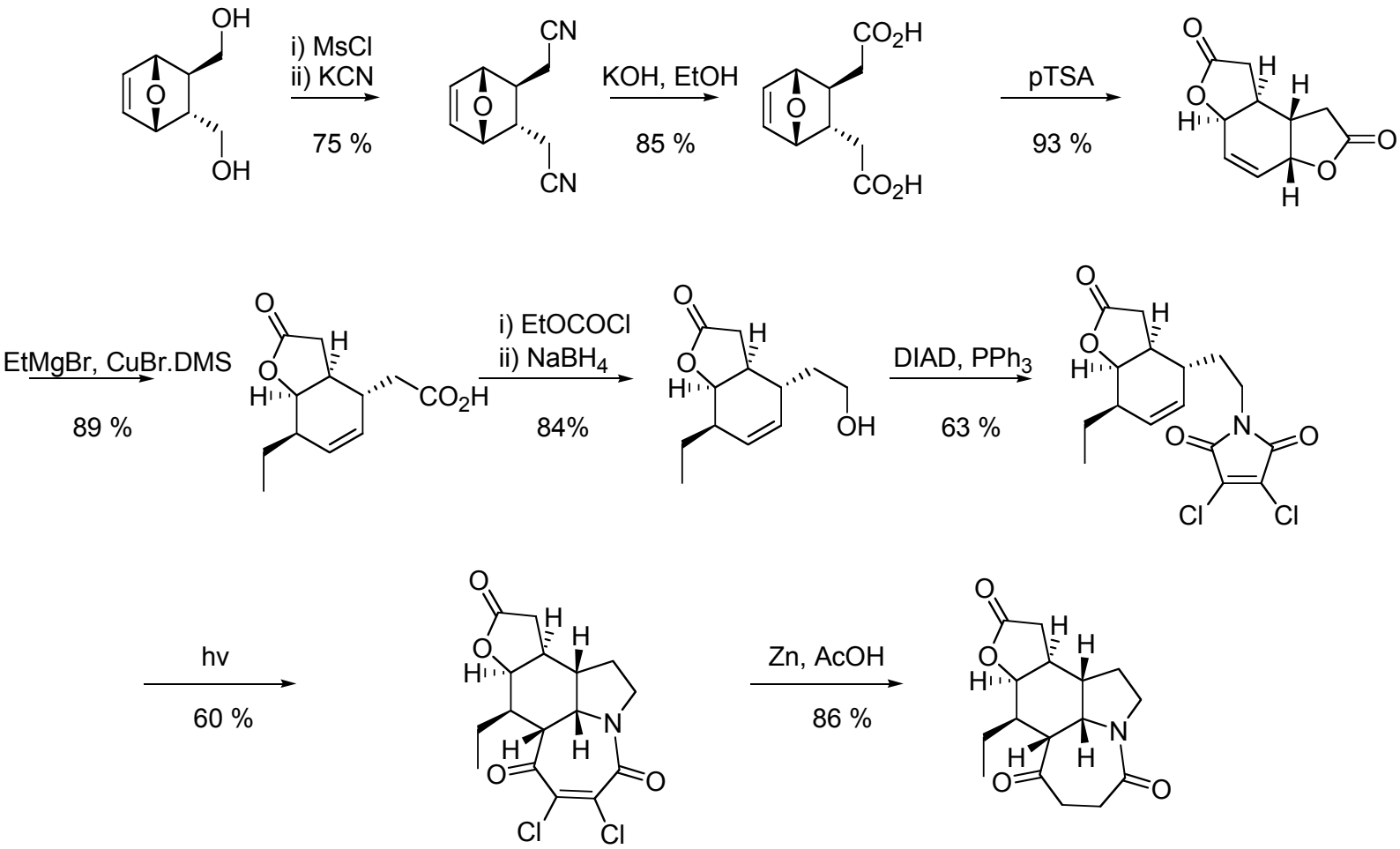
Application of Methodology to Total Synthesis

- ABCD Tetracyclic Core of Neotuberostemonine
  - Human cough remedies and antihelminthics
  - [5+2] cycloaddition as key step to synthesise ABC ring system

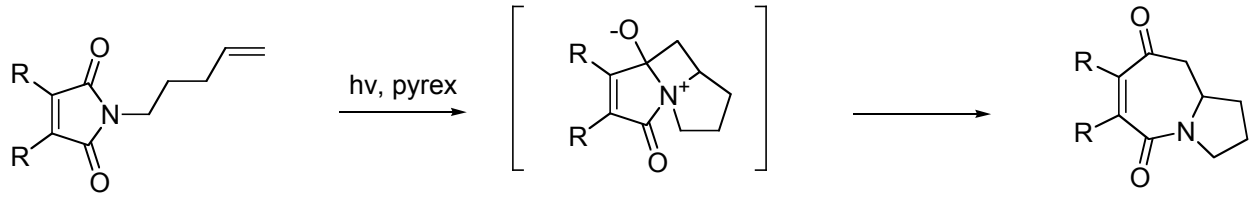


Booker-Milburn *et al ACIE*, **2003**, *42*, 1642

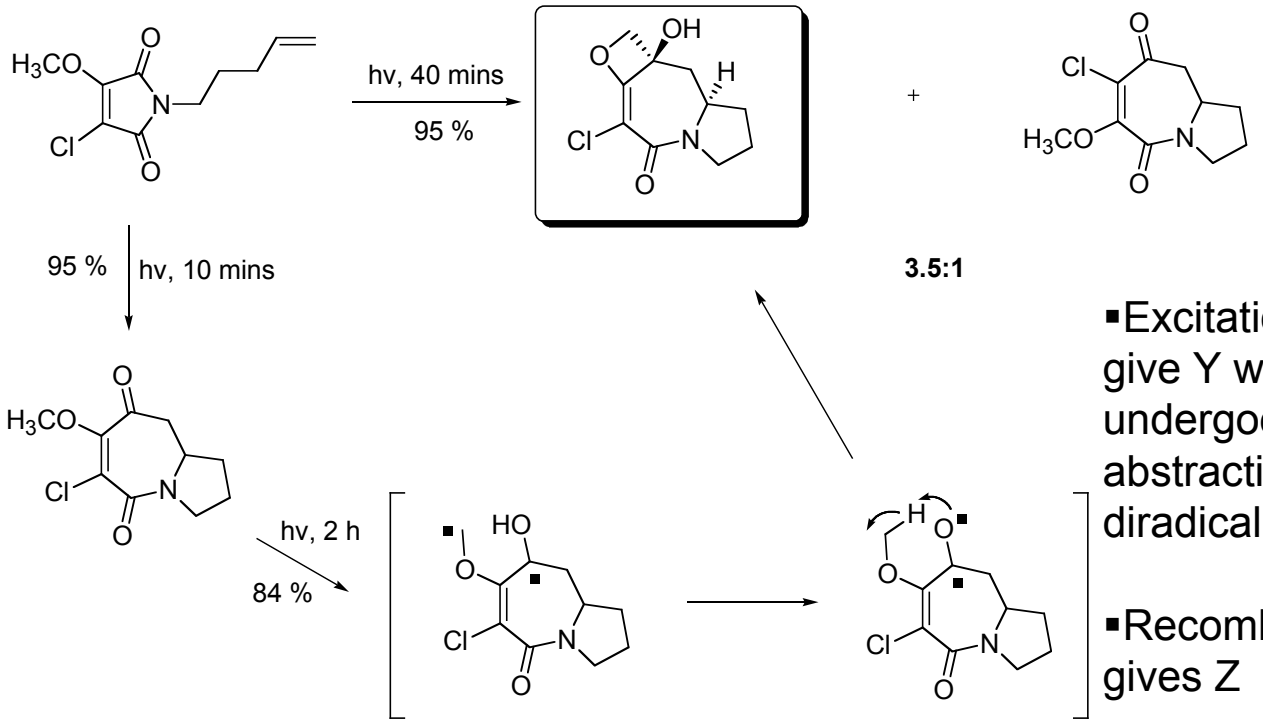
Application of Methodology to Total Synthesis



Second Iteration – Substituted Maleimides



- Methoxymaleimide [5+2]/Norrish II Cascade

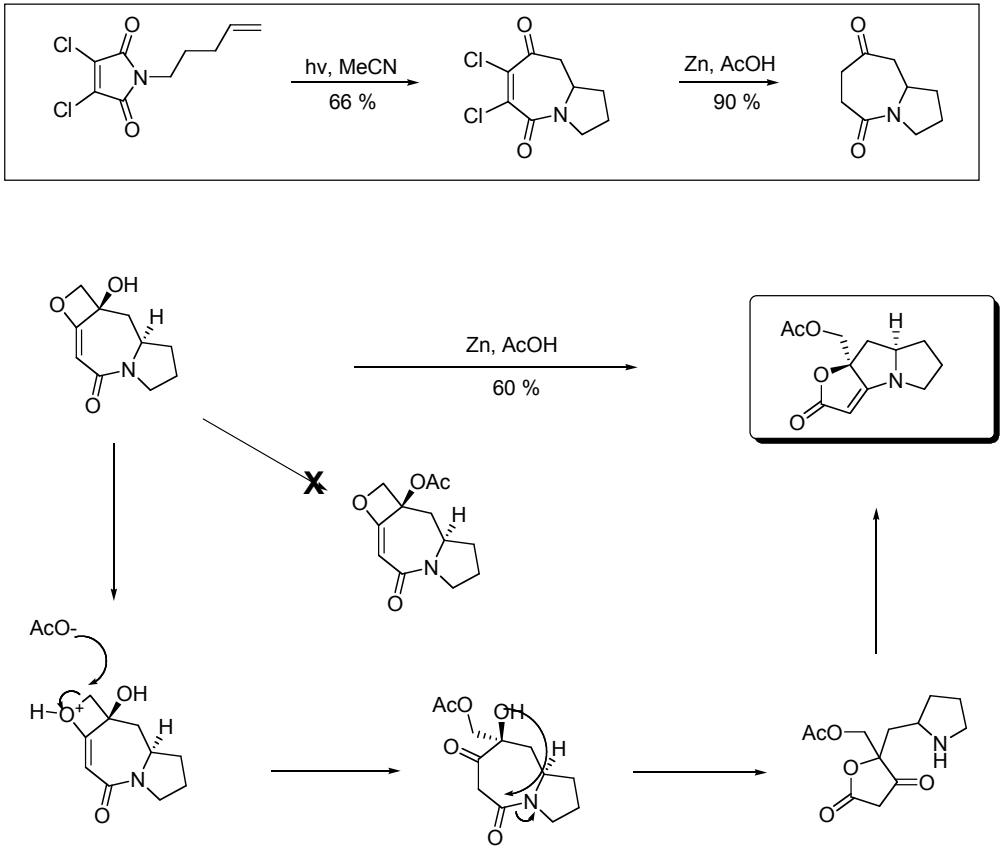


Recombination of the radicals occurs form the least hindered, CONVEX face of the azelene system – very stereoselective

- Excitation of X to give Y which undergoes 1, 5 H abstraction to give diradical
- Recombination gives Z

Title Paper – Unexpected Rearrangements

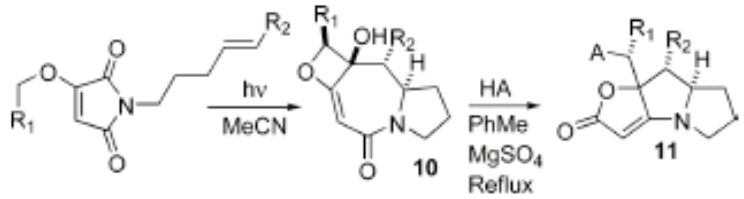
- Investigating further reactivity of oxetane dervatives
  - Unusual behaviour observed
- Reduction/dechlorination can be carried out with Zn/AcOH
  - OAc ester initially proposed
  - coupling constants
    - oxetanol J = 6Hz
    - Product J = 12 Hz
  - Acid cat. Rearrangement
- Nucleophillic ring opening of oxetane ring
  - Followed by transannular amide cleavage
  - Rationalised by Relief of ring strain



Reaction Scope

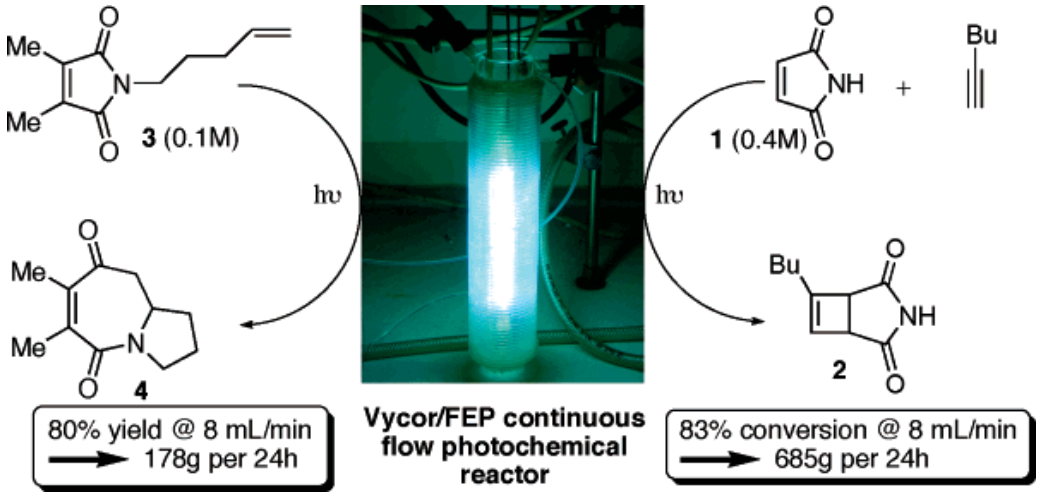
- Continuous flow reactor
  - Gram quantities of oxetanes to be obtained
- Initial ring opening occurs mainly by SN2 (minor diastereomer from competing SN1 pathway)
- Inversion of stereochemistry of reacting centre (confirmed by X-ray crystallography of 11)
- pTSA gave incorporation of OTs

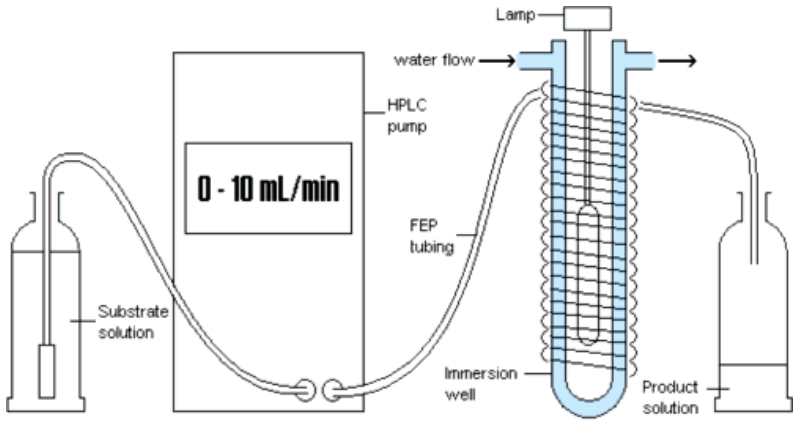
Table 1. Rearrangement of Oxetanes[a]

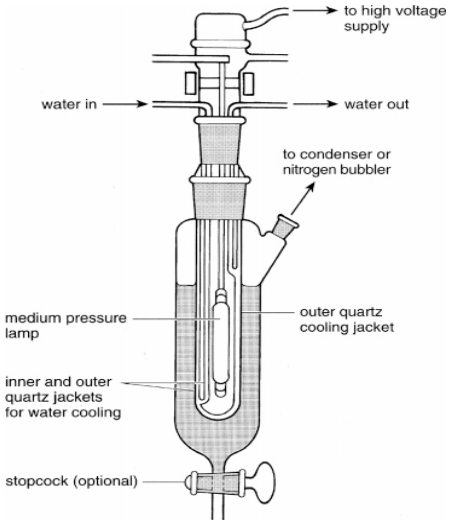


entry	R_1	R_2	**10** yield [%]	acid (HA)	**11** yield [%]	dr[b]
1	H	H	76[c]	AcOH	59	1:0
2	H	H		$PhCO_2H$	54	1:0
3	H	H		$PhCH_2CO_2H$	69	1:0
4	H	H		m-$NO_2C_6H_4CO_2H$	52	1:0
5	H	H		TsOH	47	1:0
6	H	Me	71[c]	AcOH	59	1:0
7	H	Me		$PhCO_2H$	41	1:0
8	Me	H	55[d]	AcOH	47	4:1
9	Me	H		$PhCO_2H$	38	3.5:1
10	Me	H		m-$NO_2C_6H_4CO_2H$	56	3.6:1
11	Me	Me	46[d]	AcOH	34	2.1:1[e]
12	Me	Me		$PhCO_2H$	0	–

[a] Rearrangements typically on a 50-mg scale. [b] Determined by ^1H NMR analysis. [c] Isolated yields by column chromatography. [d] Recrystallized yields of a single diastereomer. [e] Only two diastereomers observed (at the R_1 stereogenic center).


Me
Me
N
O
O
3 (0.1M)
hυ
Me
Me
N
O
O
4
80% yield @ 8 mL/min
178g per 24h
Vycor/FEP continuous flow photochemical reactor
O
NH
O
1 (0.4M)
+
Bu
hυ
Bu
O
NH
O
2
83% conversion @ 8 mL/min
685g per 24h

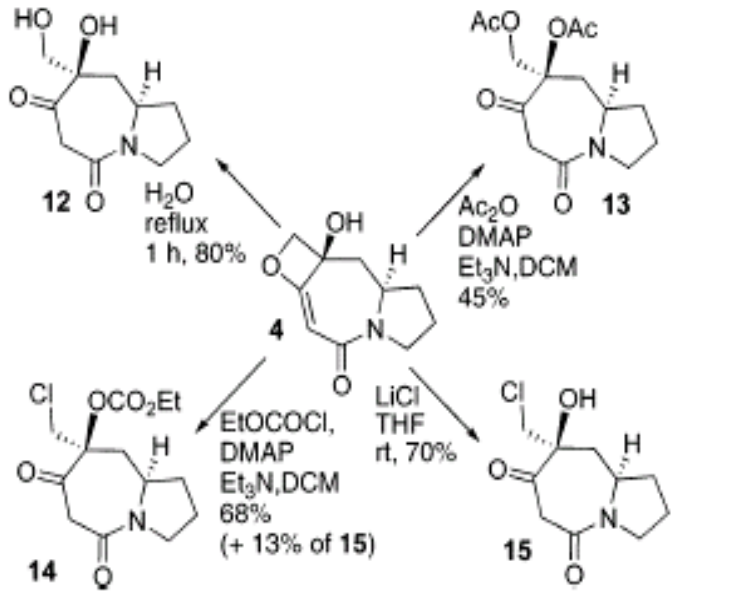

Lamp
water flow
HPLC pump
0 - 10 mL/min
FEP tubing
Substrate solution
Immersion well
Product solution


to high voltage supply
water in
water out
to condenser or nitrogen bubbler
medium pressure lamp
outer quartz cooling jacket
inner and outer quartz jackets for water cooling
stopcock (optional)

Ring Opening of Oxetanes

- Alternative nucleophiles
  - Enabled isolation of initial oxetane ring opened product to aid mechanism and structure elucidation
- Cl anion from LiCl sufficiently nucleophilic for ring opening
- 2-substituted (R = CH_3) oxetanes do not undergo ring opening reactions (cf with acid cat. opening)
  - Nucleophilic attack at 2Y oxetane centre is severely restricted –SN2 mechanism under non-acidic conditions

Scheme 3. Ring-Opening of Oxetanes under Nonacidic Conditions



Summary

- Concerted [5+2]/Norrish II photocycloaddition sequence of simple alkoxy maleimide derivatives to provide oxetane/azepine fused system
  - Excellent yields and stereoselctivity

- Novel acid catalysed rearrangement of oxetane-fused azepines to complex lactone fused azatricycles