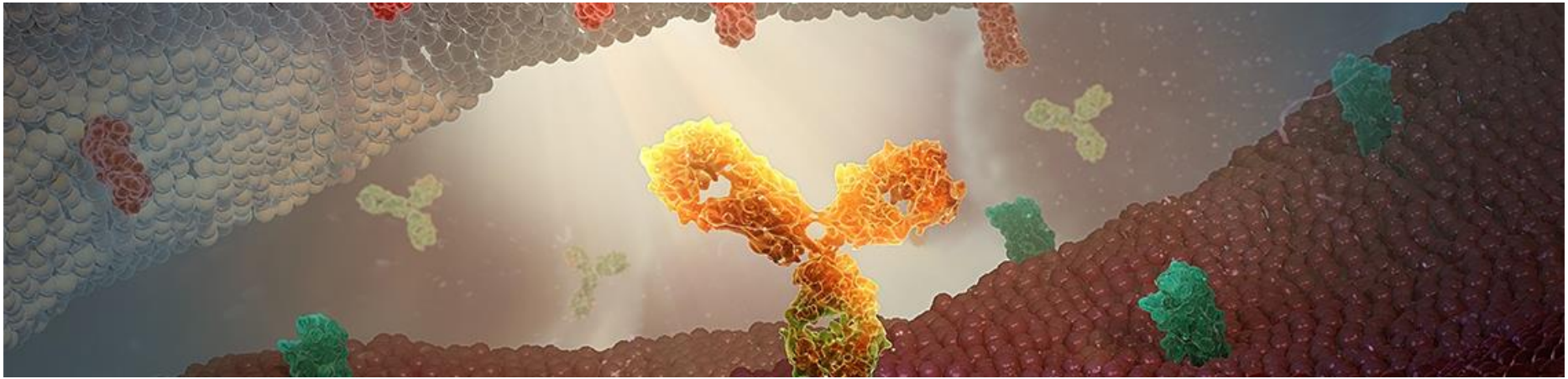
Filling the Armoury
Making Antibody-Drug Conjugate Payloads

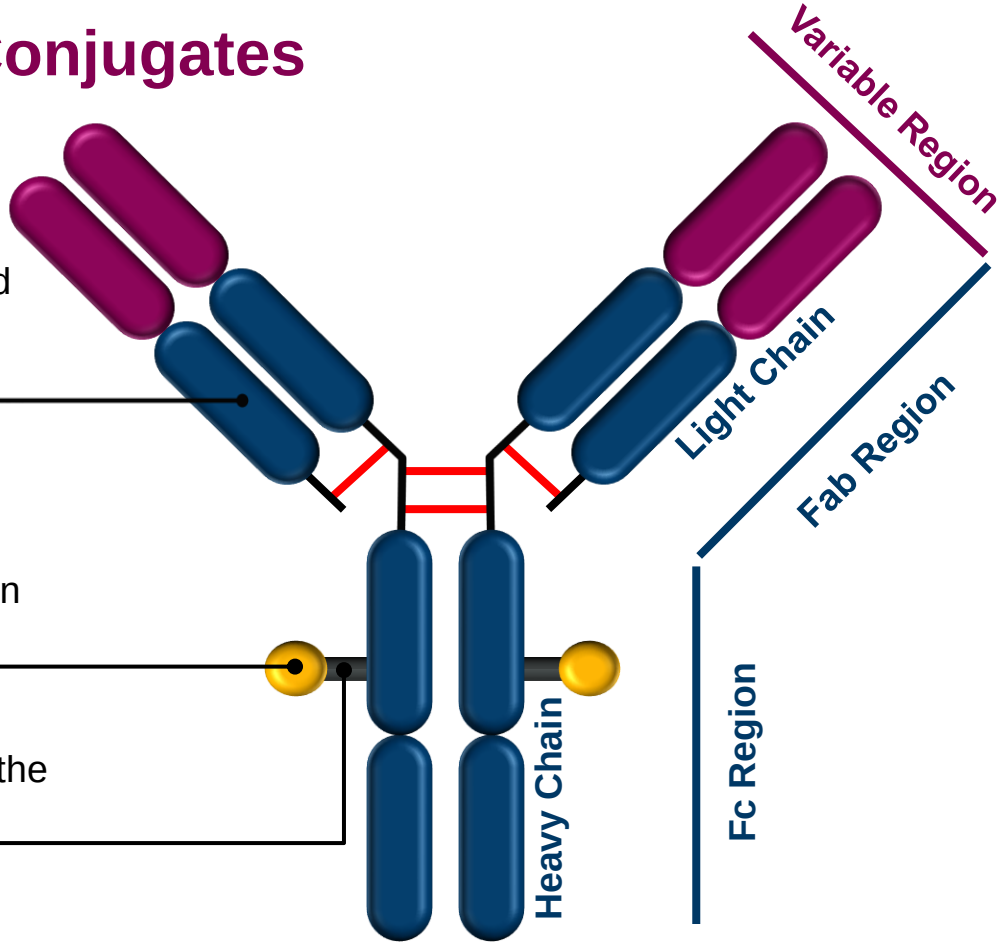
Jeremy Parker, Executive Director, Head of Early Chemical Development

Nordic-Irish Process Chemistry Forum 2023

07 June 23



Antibody Drug Conjugates



Antibody
Specific for a tumour-associated antigen that has restricted expression on normal cells

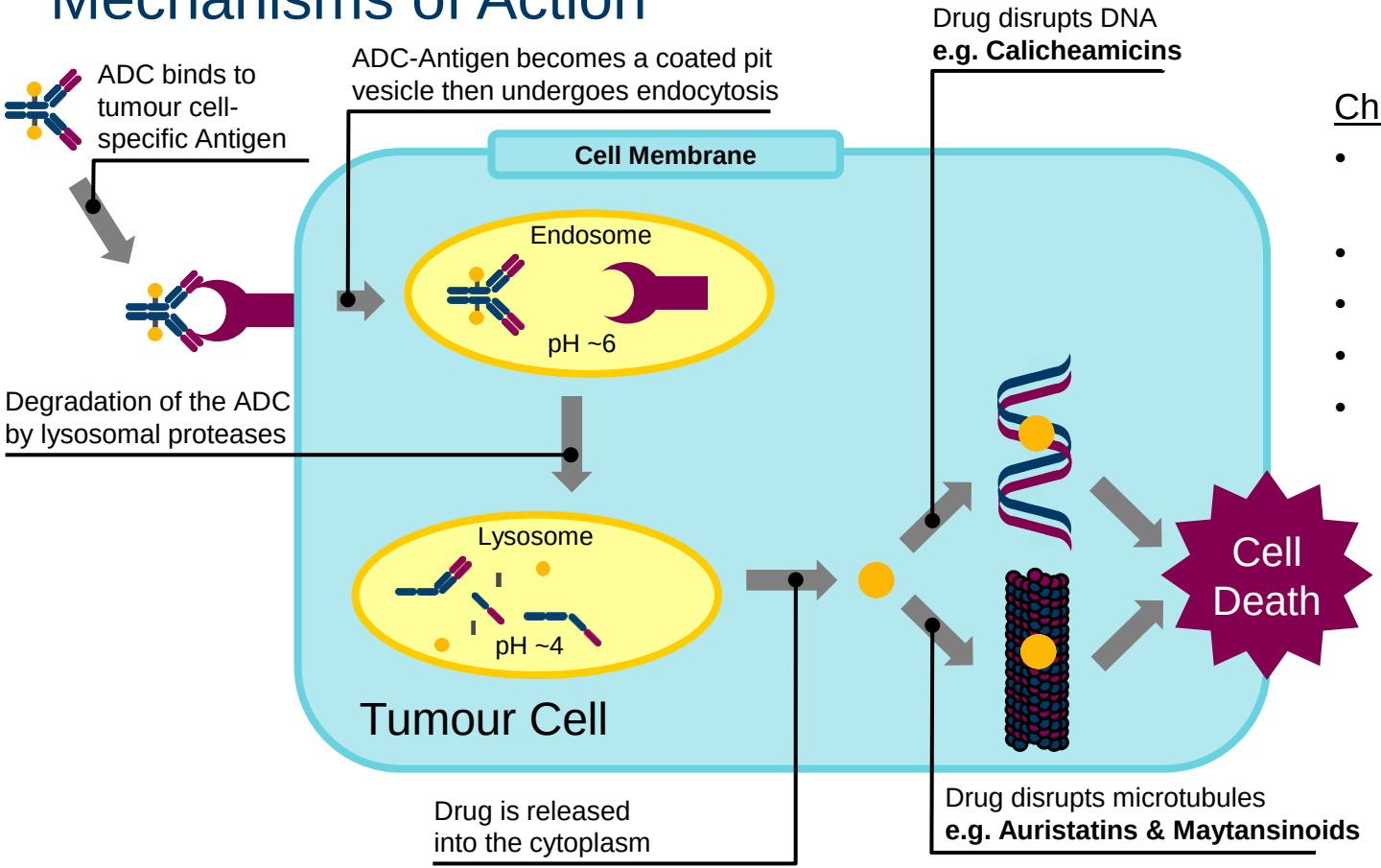
Cytotoxic Agent
Designed to kill target cells when internalised and released

Linker
Attaches the cytotoxic agent to the antibody

A Beck, L Goetsch, C Dumontet, N Corvaia *Nat. Rev. Drug Discov.* **2017**, *16*, 315

ADC Payloads

Mechanisms of Action

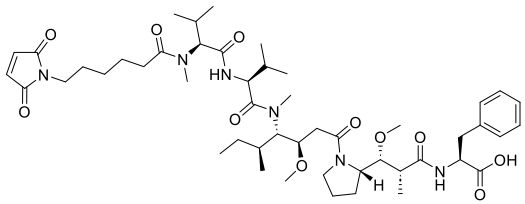


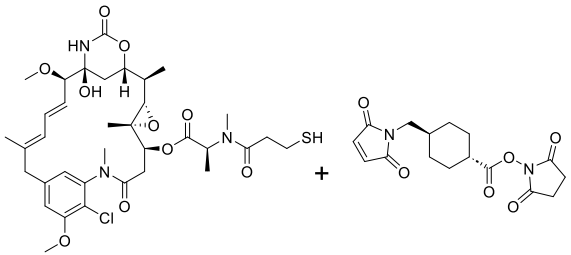
Chemotherapy Approaches:

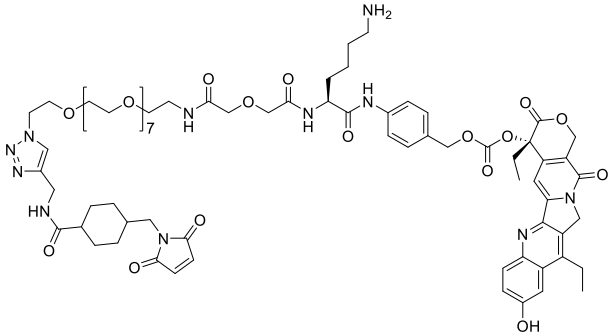
- Alkylating antineoplastic agents
- Antimetabolites
- Anti-microtubule agents
- Topoisomerase inhibitors
- Kinase Inhibitors

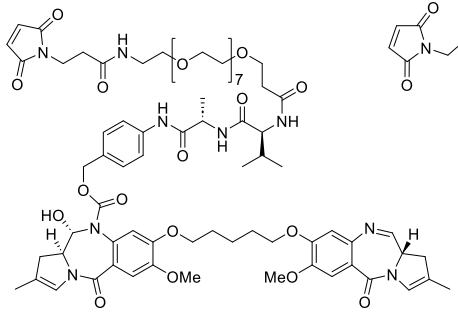
ADC Payloads

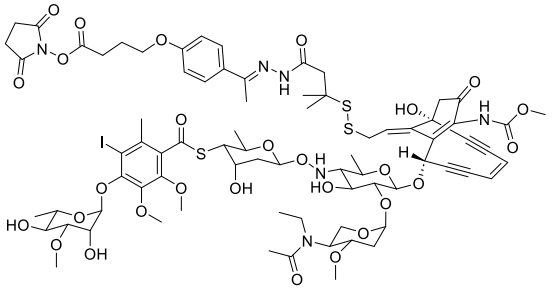
Marketed Drugs

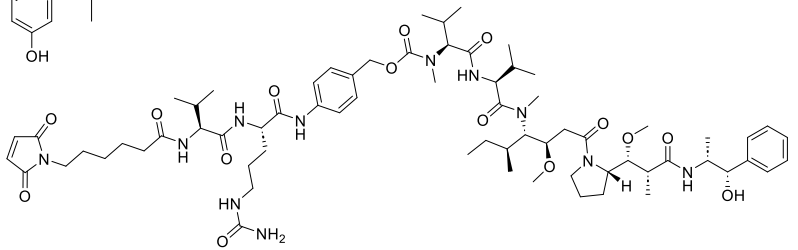


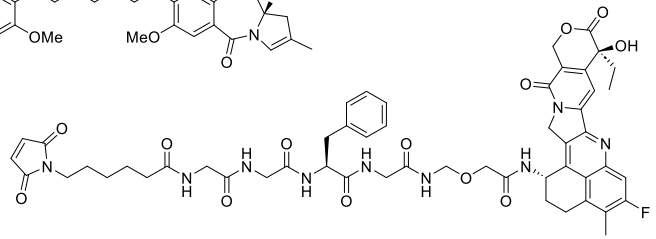












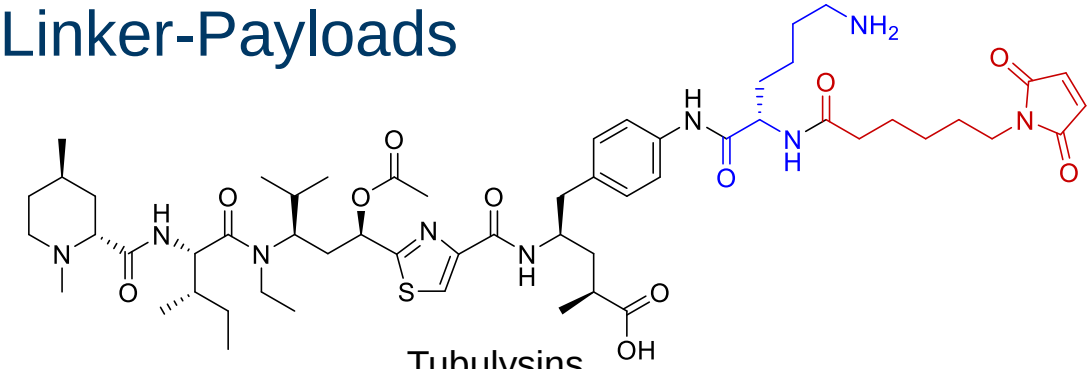
- Key Challenges
  - Highly synthetic complexity/long routes
  - High containment facilities required for final stages
- Key Opportunities
  - Only small amounts required (vs potency)

W Goundry, J Parker *Org. Process Res. Dev.* **2022**, *26*, 2121

Early Payloads within Early Chemical Development at AstraZeneca

ADC Payloads

AstraZeneca Proprietary Linker-Payloads



Tubulysins

- Developed by AstraZeneca
- Inhibitors of Tubulin Polymerization

D Toader, F Wang, L Gingipalli, M Vasbinder *et al*
J. Med. Chem. **2016**, *59*, 10781

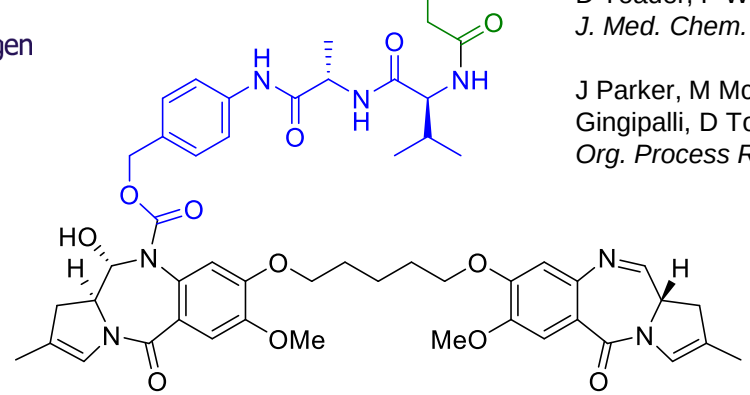
J Parker, M McCormick, D Anderson, B Maltman, L Gingipalli, D Toader
Org. Process Res. Dev. **2017**, *21*, 1602

PBDs

- Developed by Spirogen
- Minor-grove DNA binders

A Tiberghien, J-N Levy, L Masterson *et al*
ACS Med. Chem. Lett. **2016**, *7*, 983

A Tiberghien, C von Bulow, C Barry, H Ge, C Noti, F Collet Leiris, M McCormick, P Howard, J Parker
Org. Process Res. Dev. **2018**, *22*, 1241

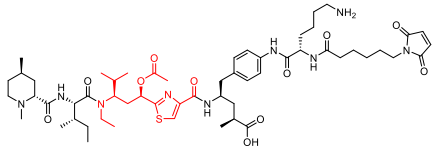


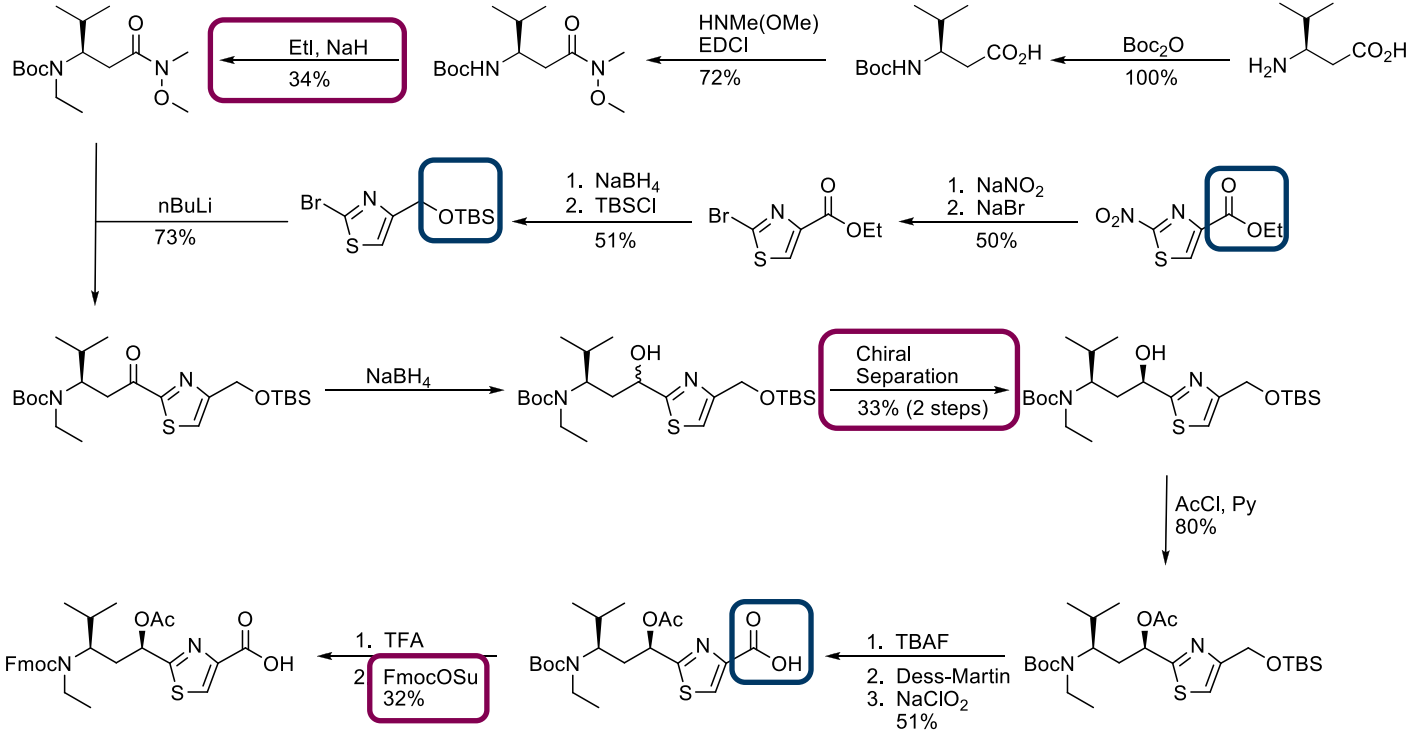
Trigger
Spacer
Linker

Classic Route Design

Classic Route Design

Tubuvaline Synthesis

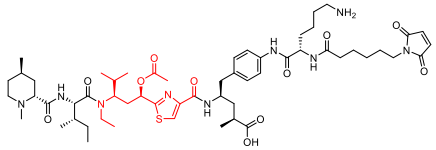


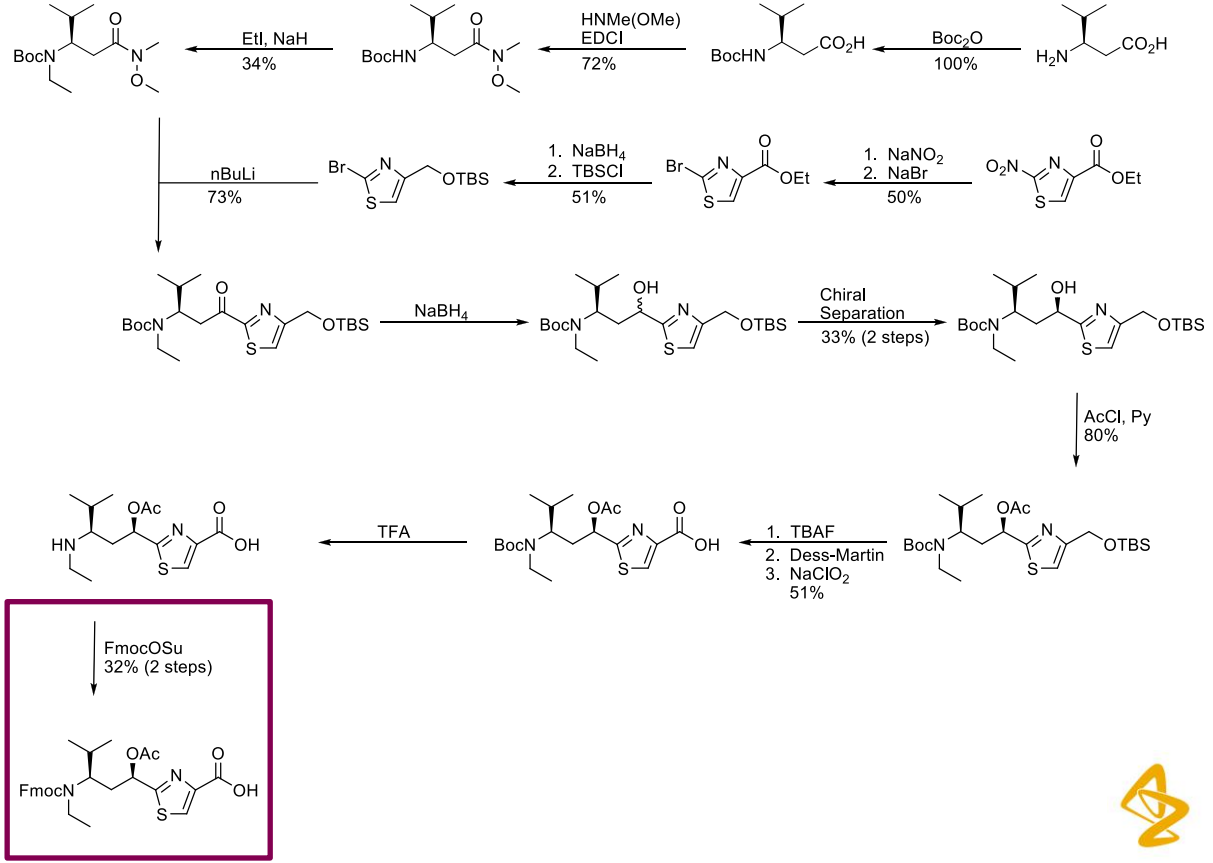


R Fecik *et al* *J. Med. Chem.* **2008**, *9*, 1530; P Wipf, Z Wang *Org. Lett.* **2007**, *9*, 1605

Classic Route Design

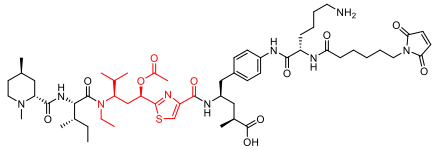
Tubuvaline Synthesis

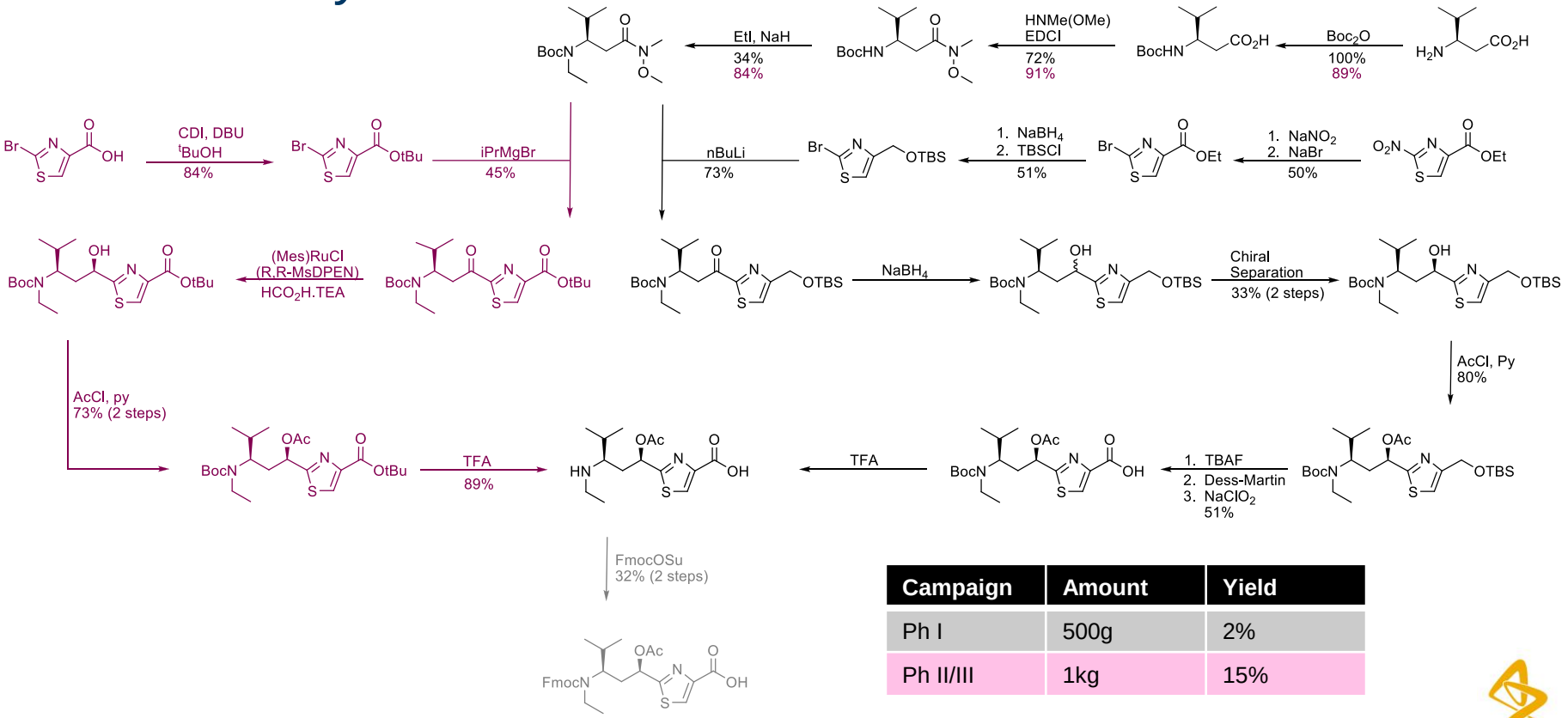




Classic Route Design

Tubuvaline Synthesis





Campaign	Amount	Yield
Ph I	500g	2%
Ph II/III	1kg	15%

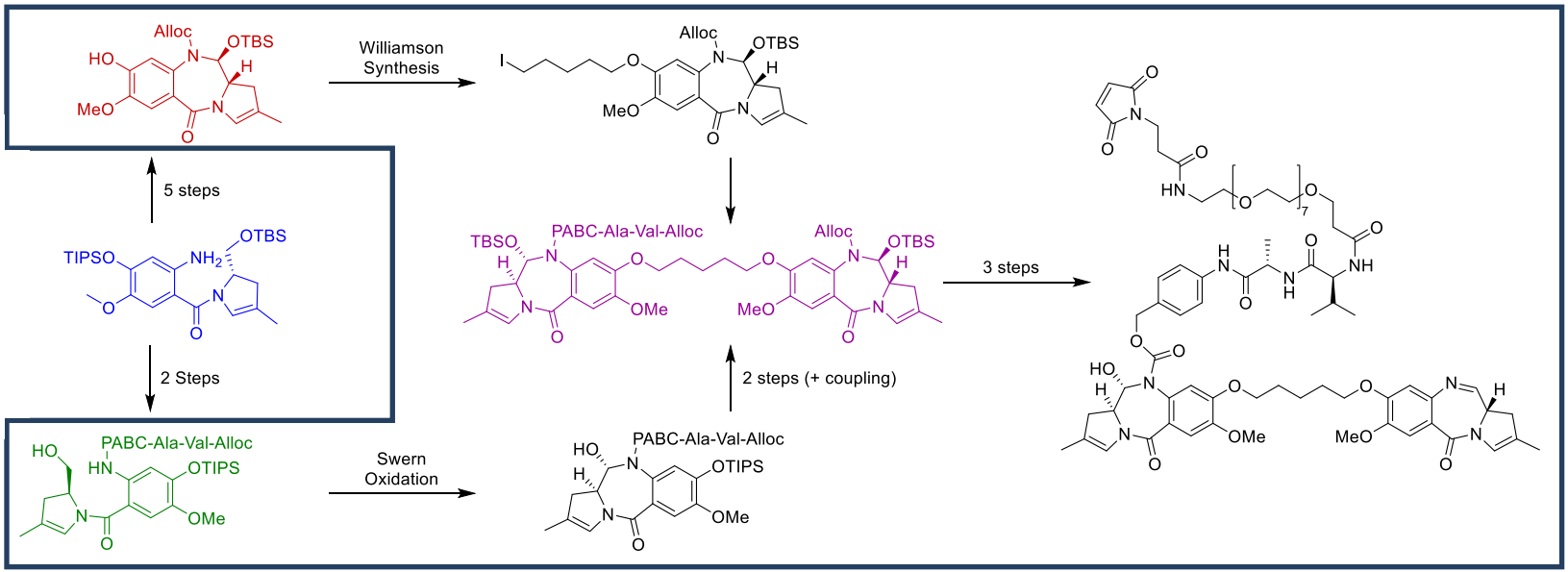
J Parker, M McCormick, D Anderson, B Maltman, L Gingipalli, D Toader *Org. Process Res. Dev.* **2017**, *21*, 1602

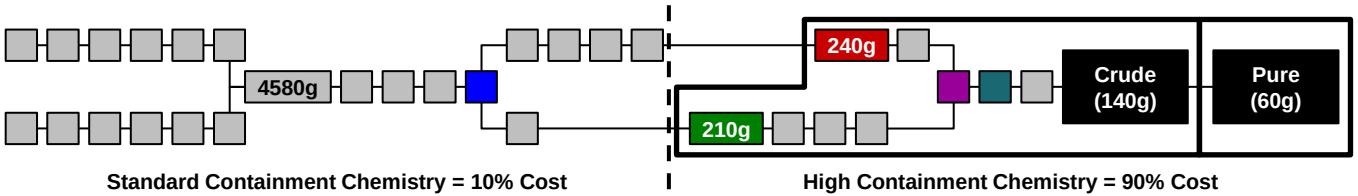
Route Design to Minimise High Containment

Route Design to Minimise High Containment

Tesirine (SG3249)

High Containment Steps





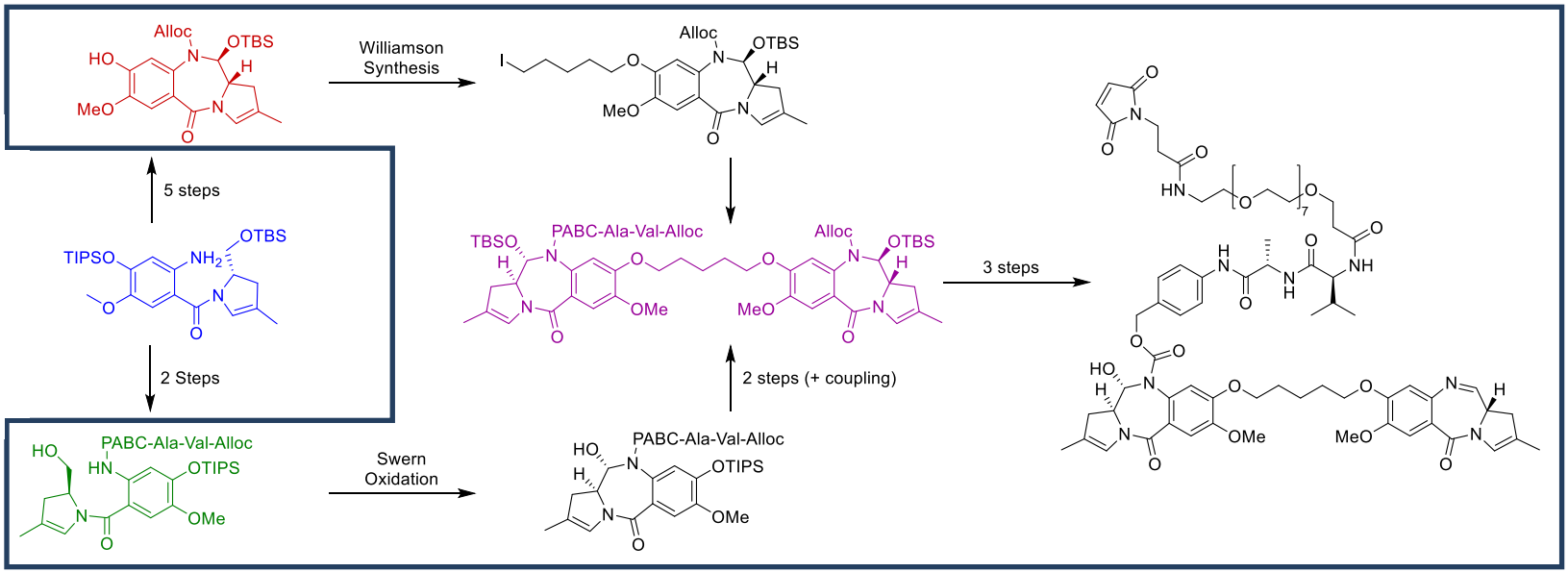
34 Step Route

A Tiberghien, C von Bulow, C Barry, H Ge, C Noti, F Collet Leiris, M McCormick, P Howard, J Parker *Org. Process Res. Dev.* **2018**, *22*, 1241

Route Design to Minimise High Containment

Tesirine (SG3249)

High Containment Steps

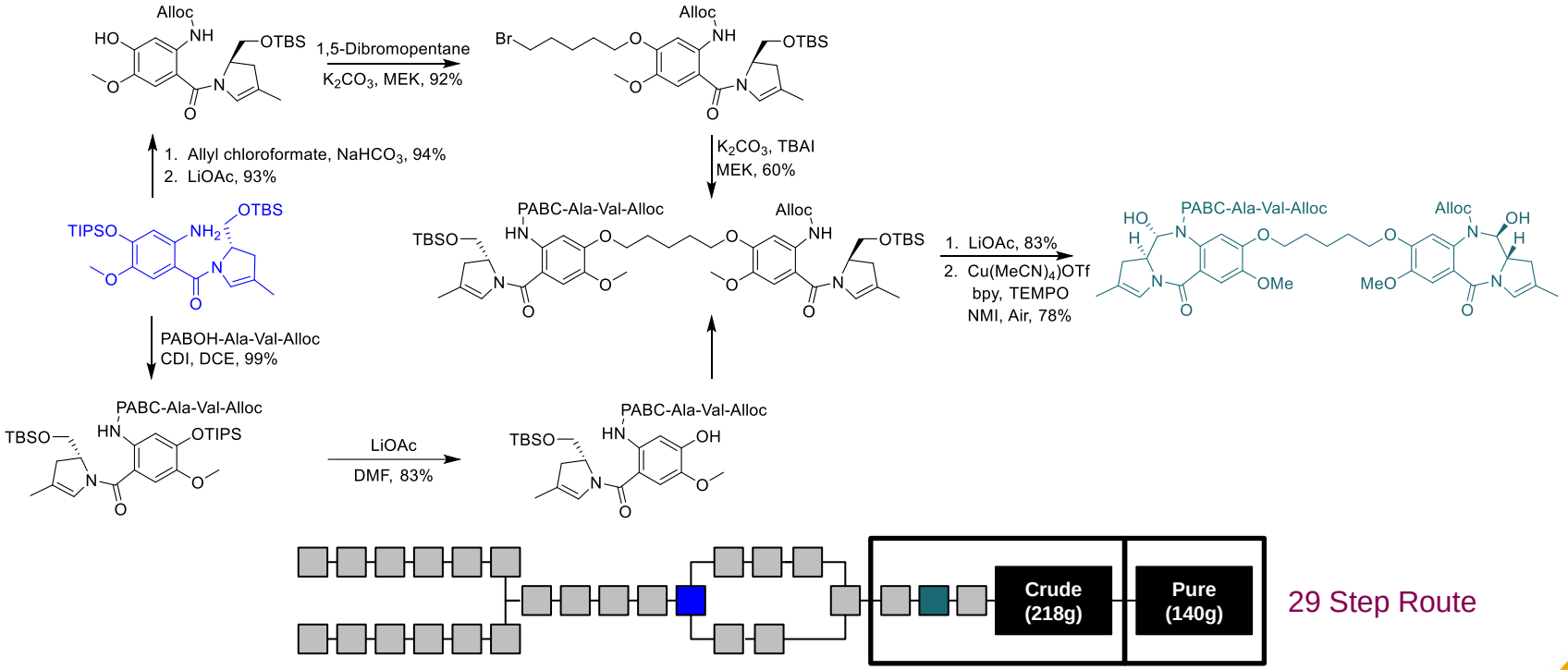


- Can we redesign the synthesis to reduce the number of High Containment steps?

A Tiberghien, C von Bulow, C Barry, H Ge, C Noti, F Collet Leiris, M McCormick, P Howard, J Parker *Org. Process Res. Dev.* **2018**, *22*, 1241

Route Design to Minimise High Containment

Tesirine (SG3249)



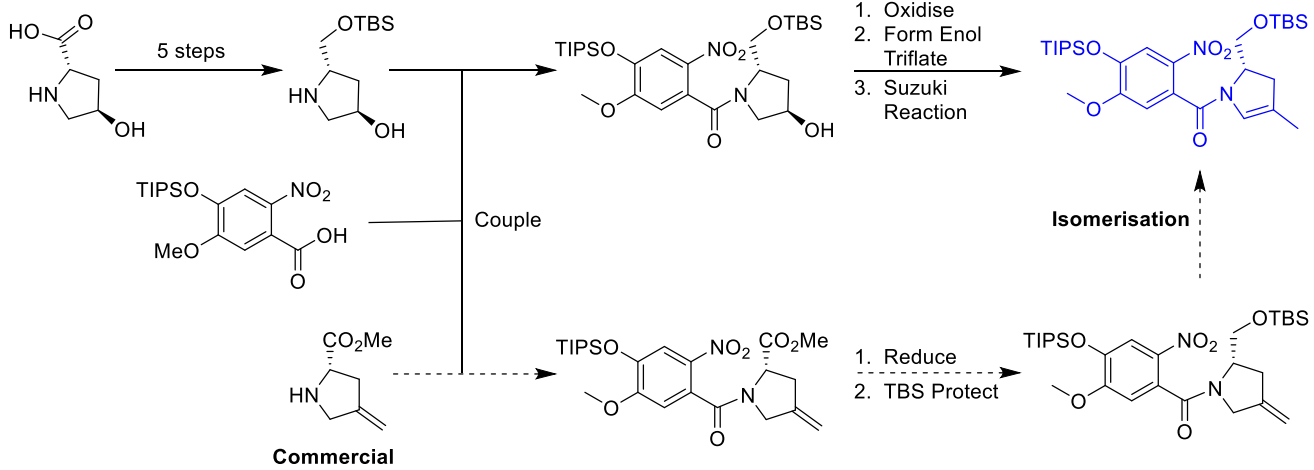
29 Step Route

A Tiberghien, P Howard, W Goundry, M McCormick, J Parker *J. Org. Chem.* **2019**, *84*, 4830

Route Design using New Methodology

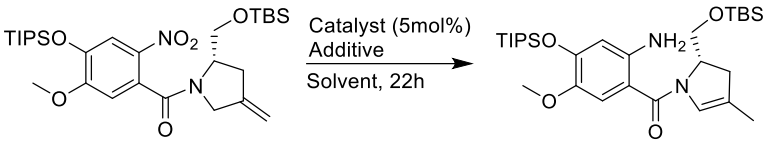
Route Design using New Methodology

Tesirine (SG3249)



Route Design using New Methodology

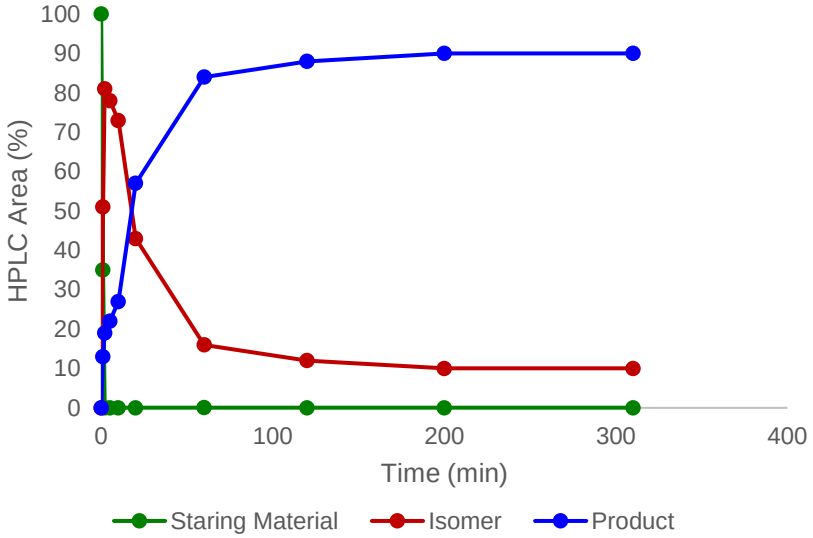
Tesirine (SG3249)

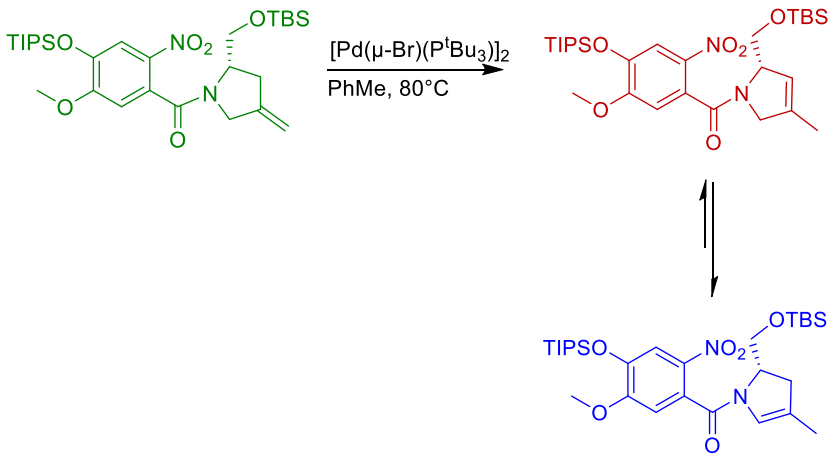


Entry	Catalyst	Additive	Additive eq.	Solvent (20 vols)	HPLC Area% (220nm)			
					Product	Isomer	Starting Material	Other Peaks
1	Grubbs I	none		PhMe	7.7	12.4	77.9	2.0
2	Grubbs I	Et_3SiH	1.00	PhMe	12.3	11.0	49.1	27.7
3	Grubbs II	none		PhMe	14.5	2.7	71.1	11.7
4	Grubbs II	none		MeOH	46.2	52.4	0.0	1.4
5	None	$Fe(CO)_5$	3.00	CPME	0.0	0.0	70.1	29.9
6	Crabtrees Catalyst	none		PhMe	12.1	0.5	78.8	8.6
7	Crabtrees Catalyst	none		IPA/PhMe	29.2	36.9	0.0	33.9
8	$Ru(H_2)(PPh_3)_4$	None		PhMe	0.0	0.0	95.2	4.8
9	$RuHCl(CO)PPh_3$	none		PhMe	26.4	68.6	0.0	5.0
10	cationic $CpRu(Pr_3)$	none		PhMe	25.2	71.4	0.0	3.3
11	$RhH(CO)PPh_3$	none		PhMe	6.3	38.6	50.3	4.8
12	$RhCl_3.H_2O$	none		nBuOH	0.0	0.0	0.0	100.0
13	$Rh(COD)_2BF_4$	BINAP	0.05	PhMe	25.1	56.6	0.0	18.3
14	Pd/C	none		PhMe	0.0	0.0	99.7	0.3
15	$\{Pd(\mu\text{-}Br)[P(tBu)_3]\}_2$	none		PhMe	89.5	5.7	0.0	4.8
16	$PdCl_2(dtbpf)$	Et_3SiH	0.10	PhMe	20.5	64.4	0.0	15.2
17	$Pd(MeCN)_2Cl_2$	none		PhMe	0.0	0.0	91.4	8.6
18	$Pd(OAc)_2/PhS(O)(CH_2)_2S(O)Ph$	none		PhMe	0.0	0.0	93.5	6.5

Route Design using New Methodology

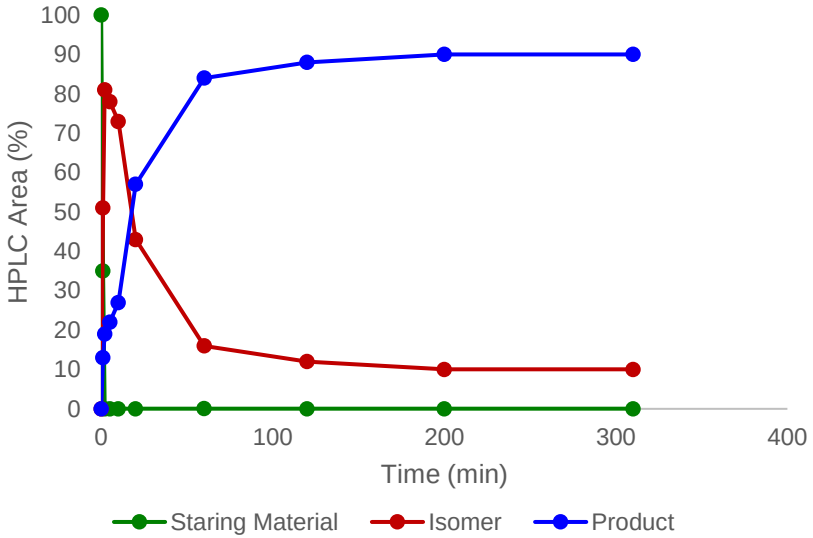
Tesirine (SG3249)

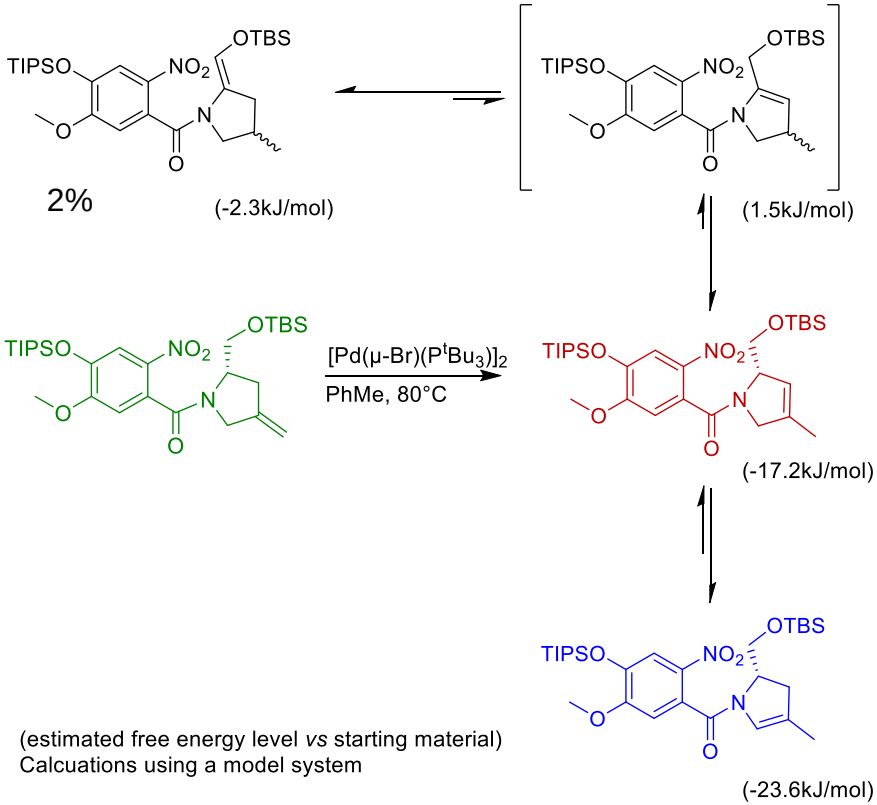




Route Design using New Methodology

Tesirine (SG3249)

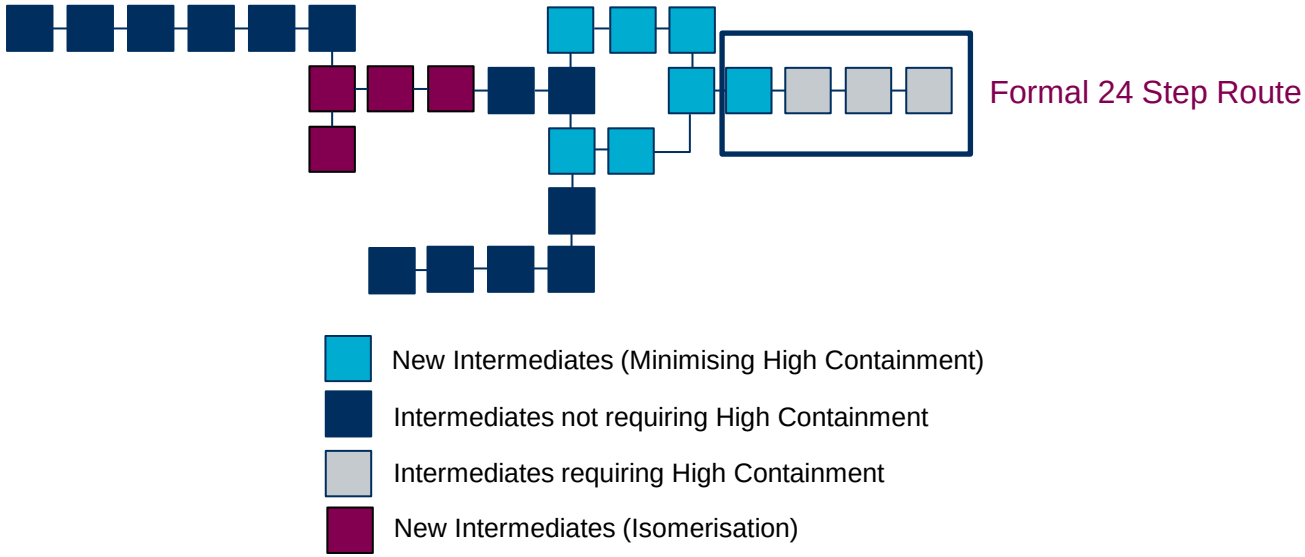




(estimated free energy level *vs* starting material)
Calcuations using a model system

Route Design using New Methodology

Tesirine (SG3249)



A Campbell, S Tomasi, A Tiberghien, J Parker *Org. Process Res. Dev.* **2019**, *23*, 2543

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