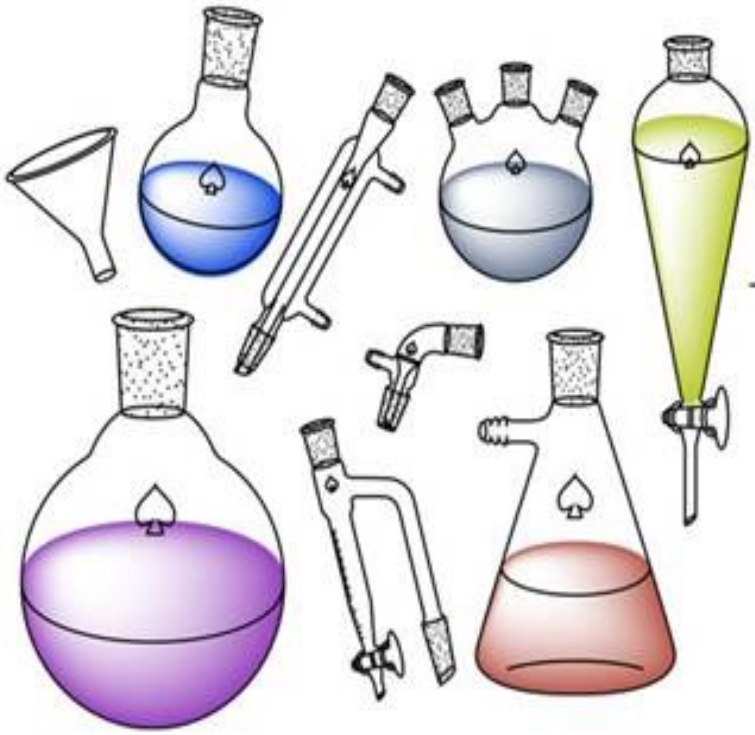
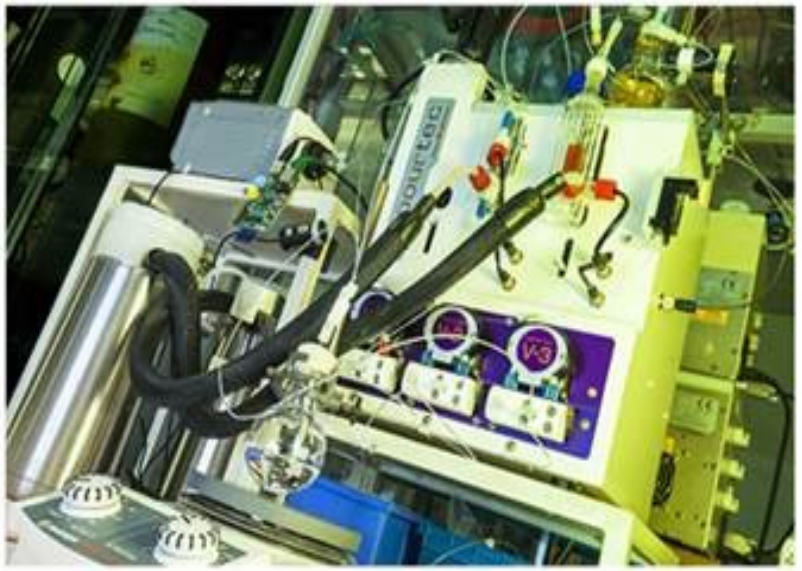
On the development of new tools for molecule makers

April 2024

Steven V. Ley
Yusuf Hamied Department of Chemistry
University of Cambridge
http://www.leygroup.ch.cam.ac.uk

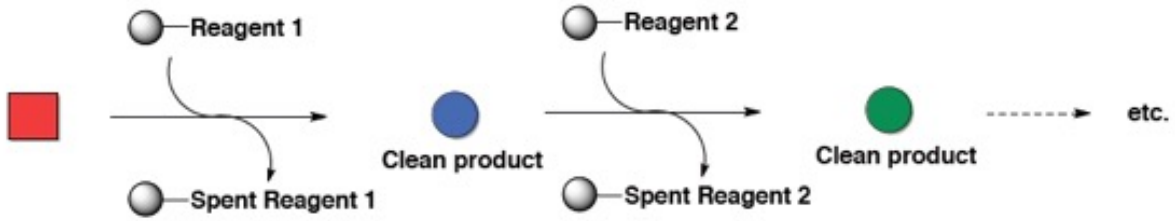
From Flasks to Machines





Polymer-supported Reagents: Concepts

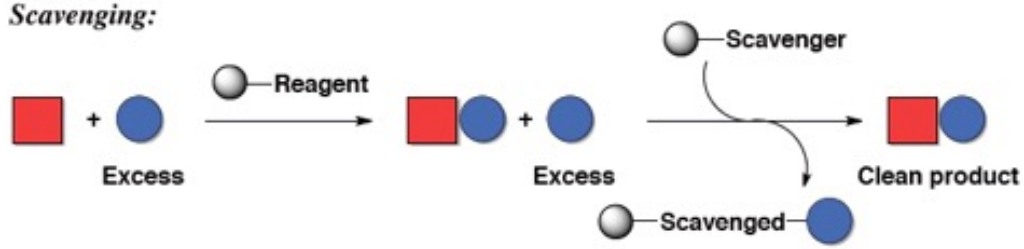
Multistep:

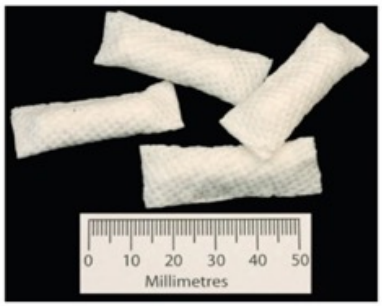


No need for:

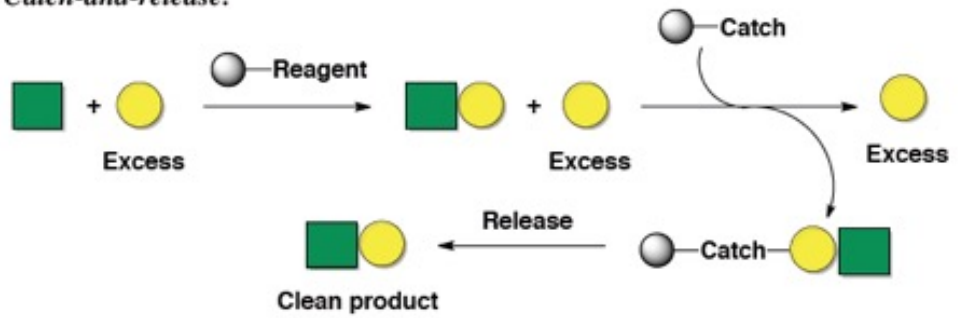
- Chromatography
- Crystallisation
- Distillation
- Water washes/ reaction quenching

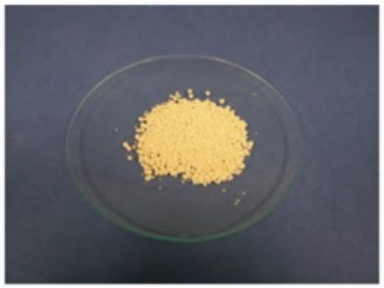
Scavenging:





Catch-and-release:



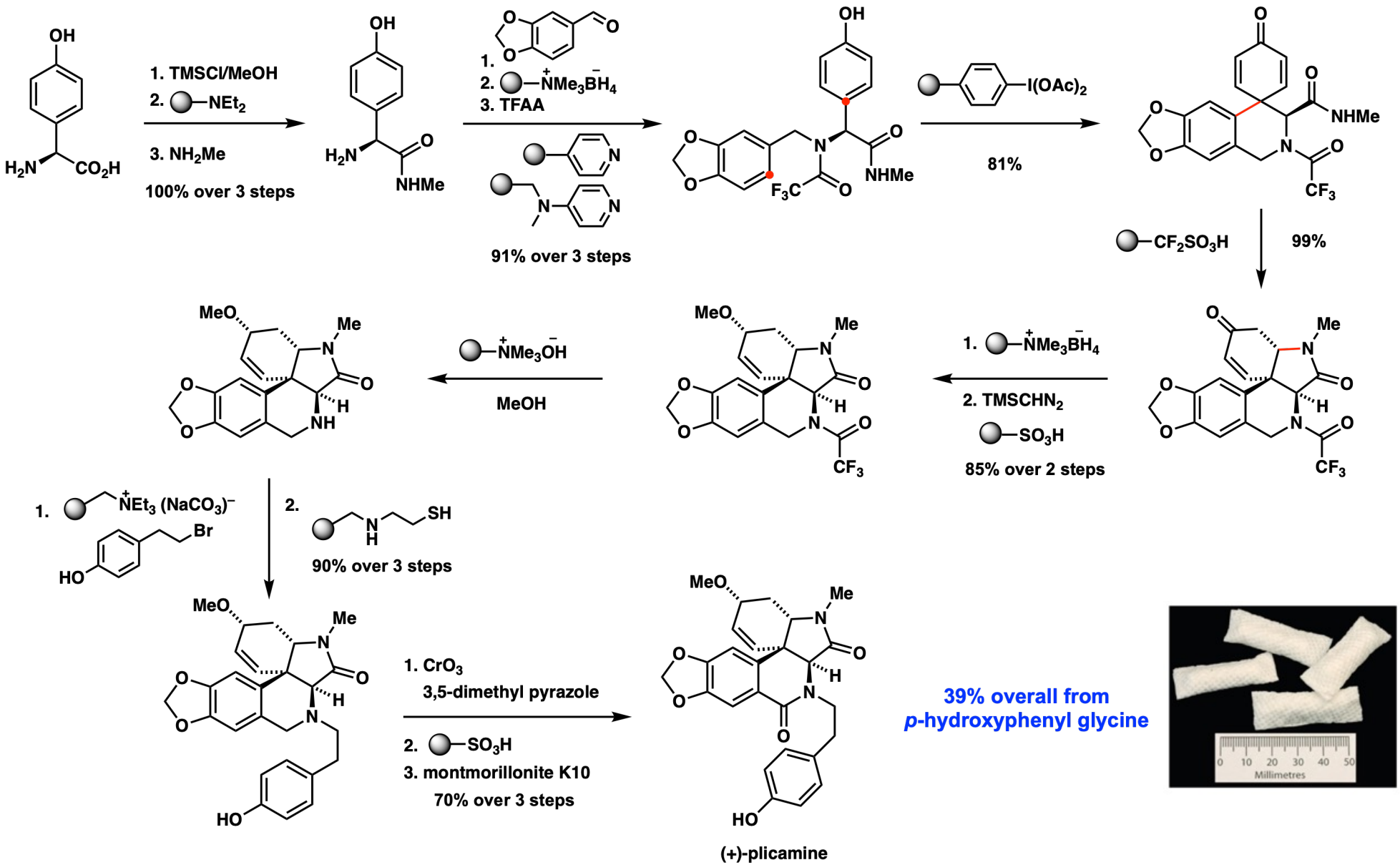


Multistep Organic Synthesis using Solid Supported Reagents and Scavengers: S.V. Ley, I.R. Baxendale, R.N. Bream, P.S. Jackson, A.G. Leach, D.A. Longbottom, M. Nesi, J.S. Scott, R.I. Storer and S.J. Taylor *J. Chem. Soc., Perkin Trans. 1*, **2000**, 3815.

New Tools and Concepts in Modern Organic Synthesis

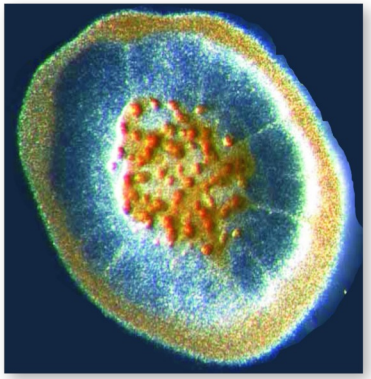
S.V. Ley and I.R. Baxendale, *Nature Reviews*, **2002**, *1*, 573.

Synthesis of Plicamine: Tea-Bag Approach

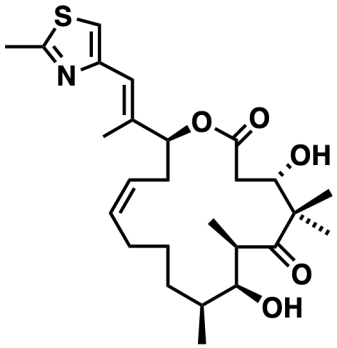


I.R. Baxendale, S.V. Ley and C. Piutti, *Angew. Chem. Int. Edn*. **2002**, *41*, 2194-2197.

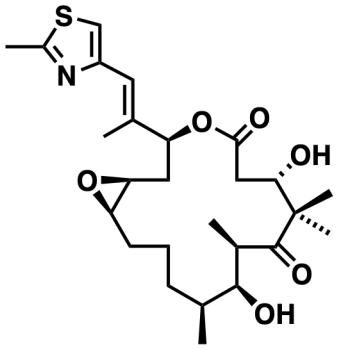
The Epothilones



Sorangium cellulosum



Epothilone C



Epothilone A



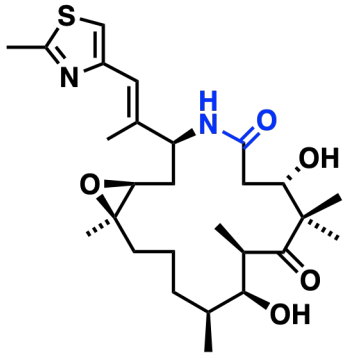
Biological Profile

•Isolated from a myxobacterium, *Sorangium cellulosum*.

•New generation of microtubule-stabilizing agents sharing the same mechanism of action as the taxanes.

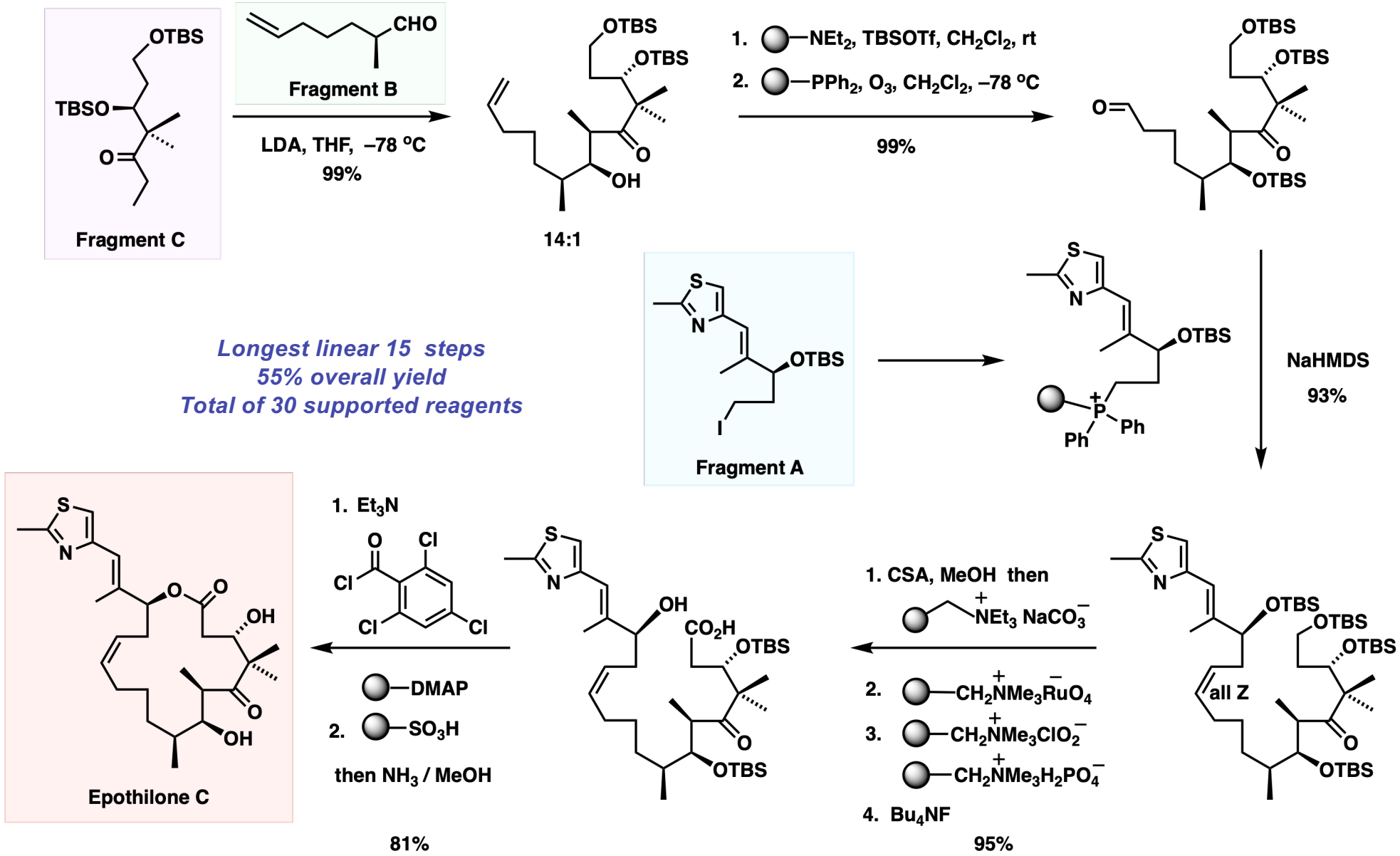
•*In vitro*, new drugs promote tubulin polymerization and stabilise the microtubules thus created.

•Epothilones are potent inhibitors of cell growth and have cytotoxic activity on cells over-expressing P-glycoprotein. It is this characteristic that distinguishes the epothilones from the taxanes.



Ixabepilone

Epothilone C: The Final Steps



M. Baumann, I.R. Baxendale, S.V. Ley, C.D. Smith and G.K. Tranmer, *Org. Lett.* **2006**, *8*, 5231-5234

Moving to Flow

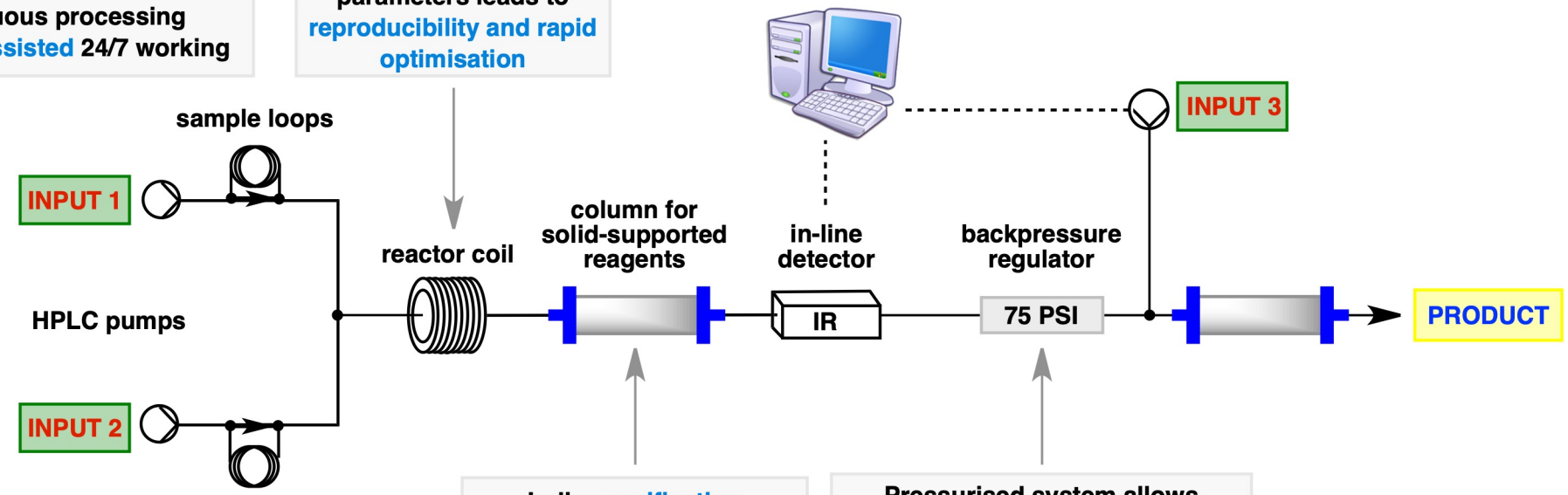
Increased process safety through containment of hazardous or malodorous substances

Continuous processing machine-assisted 24/7 working

Control over reaction parameters leads to reproducibility and rapid optimisation

real-time diagnostics

Ability to carry out multistep sequences, many unit operations saved



In-line purification methods minimise manual handling and lessens waste

Pressurised system allows superheating of solvents, superior reaction profiles

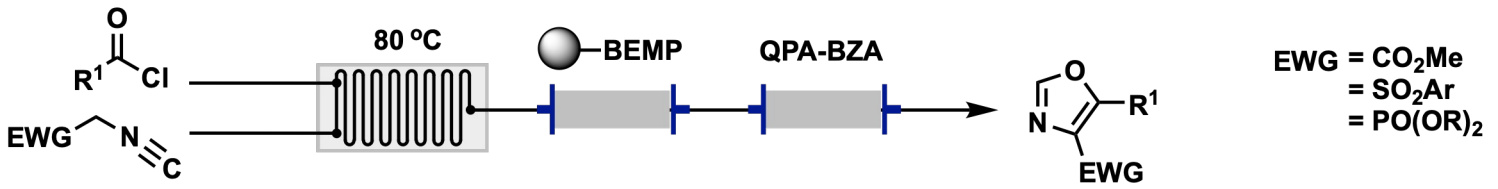


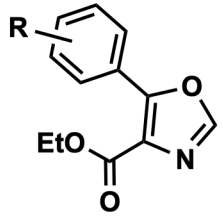


March of the Machines, S.V. Ley, D.E. Fitzpatrick, R. J. Ingham, R.M. Myers, *Angew. Chem. Int. Edn*. **2015**, *54*, 3449.

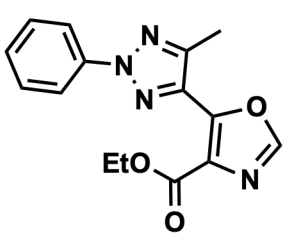
Machine-Assisted Organic Synthesis, S.V. Ley, D.E. Fitzpatrick, R.M. Myers, C. Battilocchio, R. J. Ingham, *Angew. Chem. Int. Edn*. **2015**, *54*, 10122

Flow Synthesis of Oxazoles

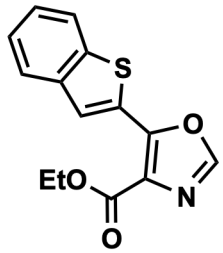




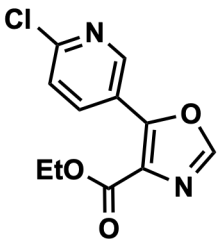
4-Br, 88%
4-I, 88%
3-Br, 85%
2-Cl, 98%
4-NO_2, 83%
3-NO_2, 91%
4-F, 94%
2-CF_3, 98%
4-CF_3, 95%
4-CN, 83%
2,6-F, 94%
3,4-OMe 83%



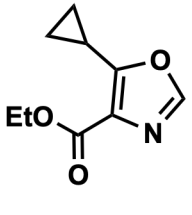
93%



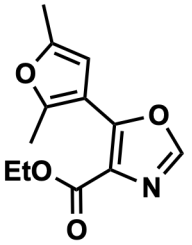
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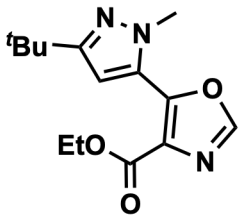
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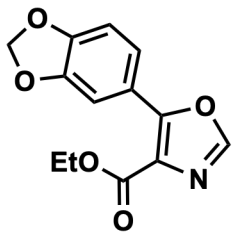
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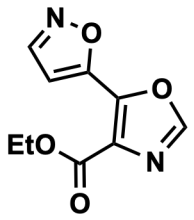
99%



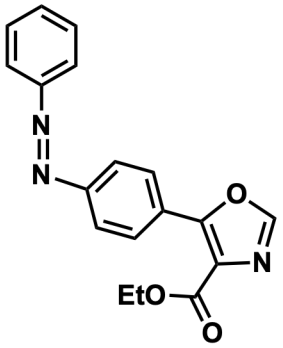
86%



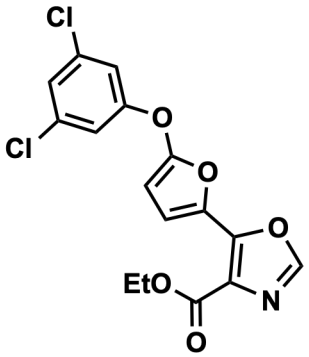
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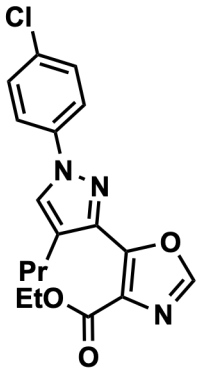
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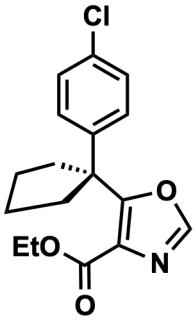
88%



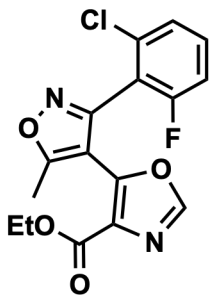
90%



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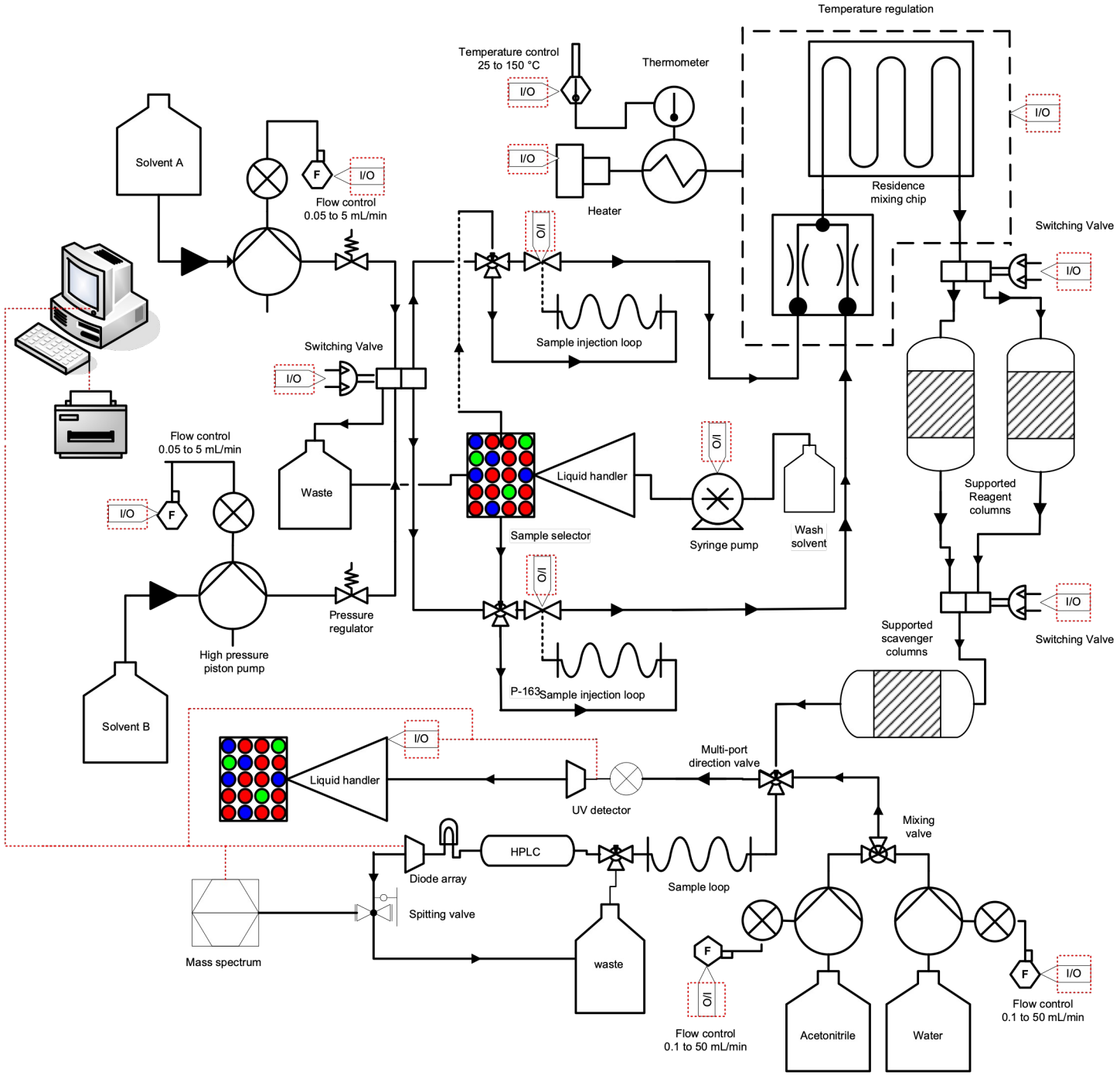
83%

M. Baumann, I.R. Baxendale, S.V. Ley, C.D. Smith and G.K. Tranmer, *Org. Lett.* **2006**, *8*, 5231-5234

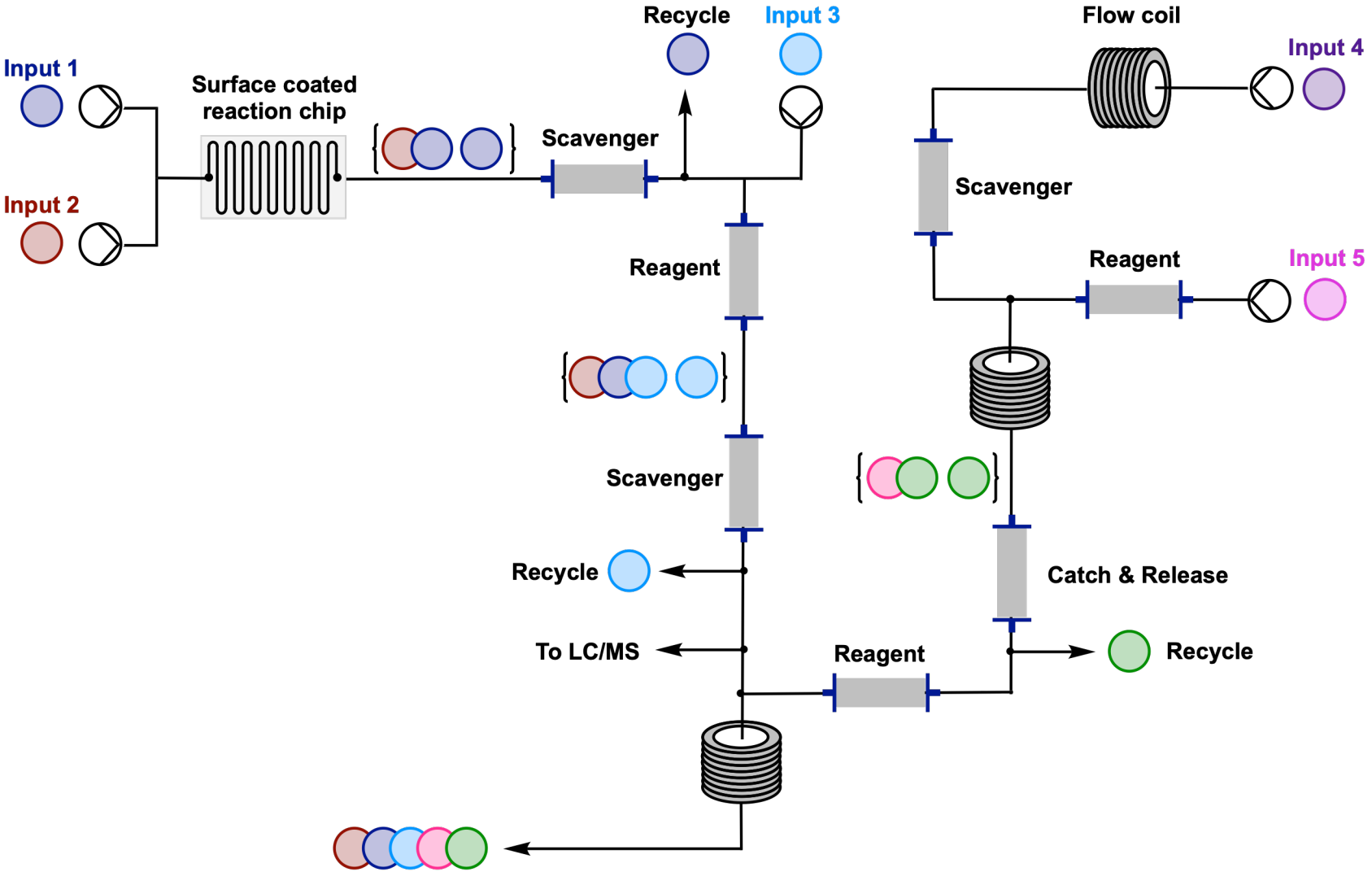
Flow Synthesis of Oxazoles



Flow Synthesis of Oxazoles

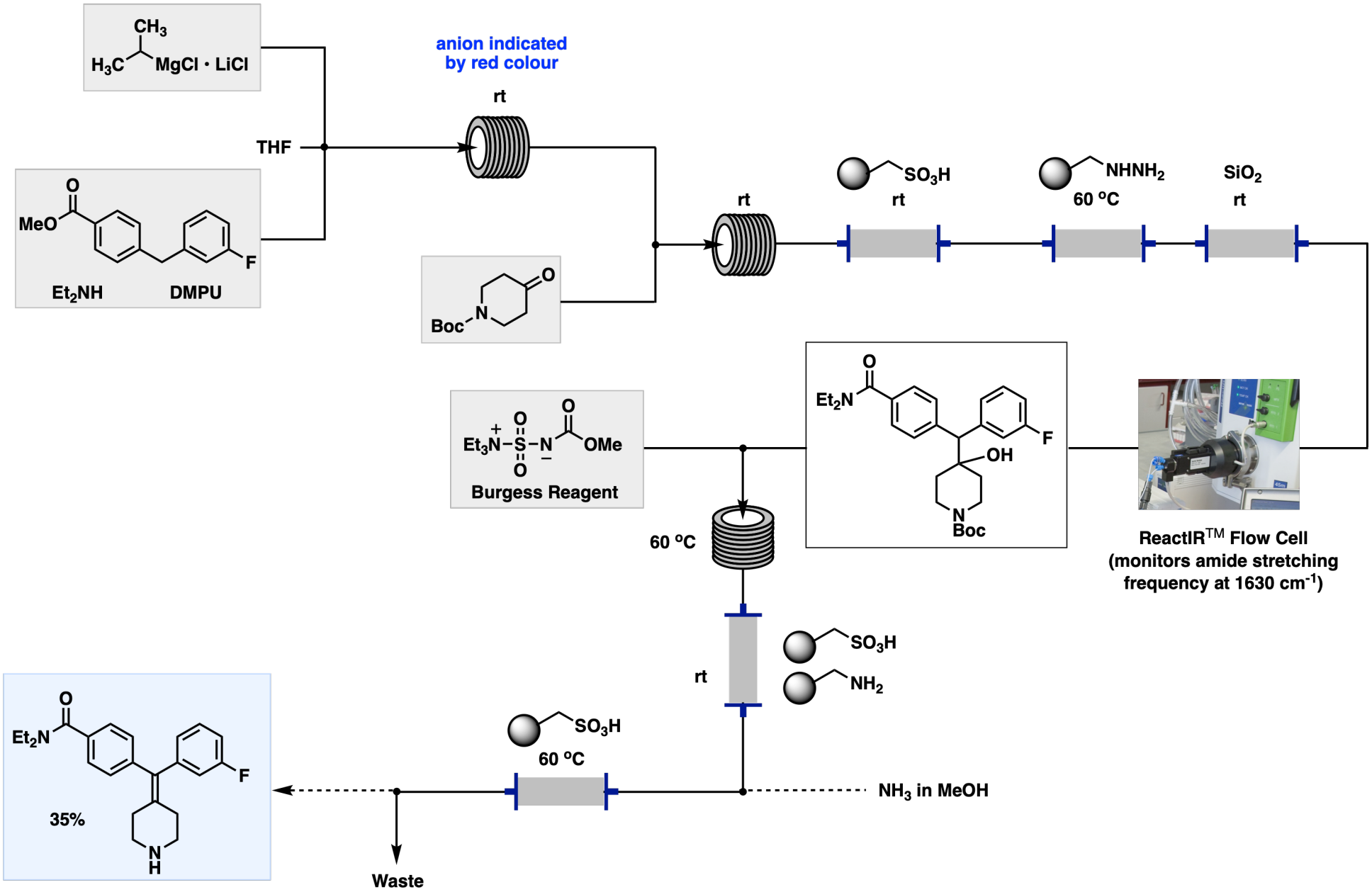


Flow Reactor Configuration: More Advanced Systems



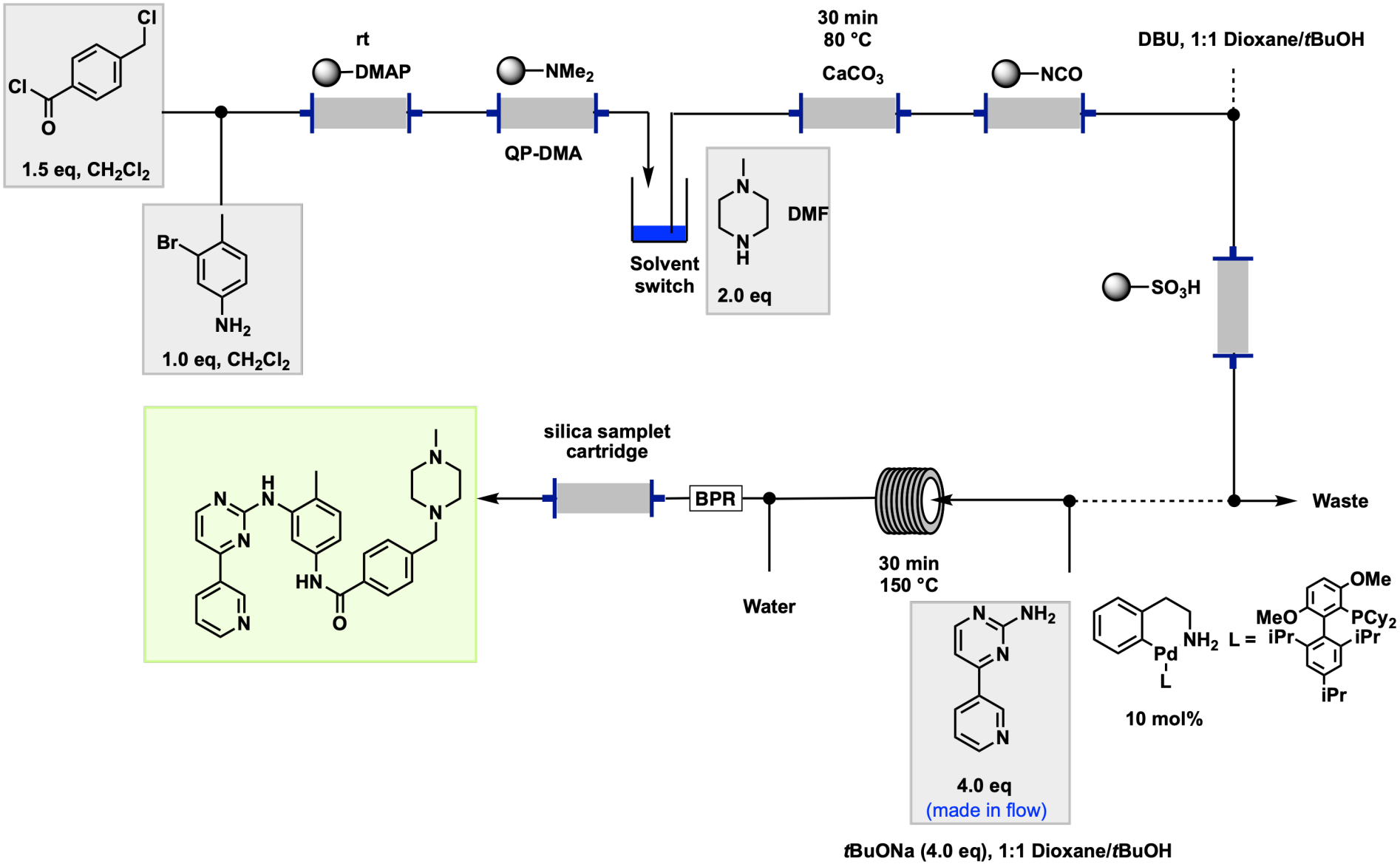
WO 99/58475: S.V. Ley , M. Bolli, B. Hinzen, A.-G. Gervois, B. Hall, J. Habermann, J. Scott

Flow Synthesis of δ-Opioid Receptor Agonist



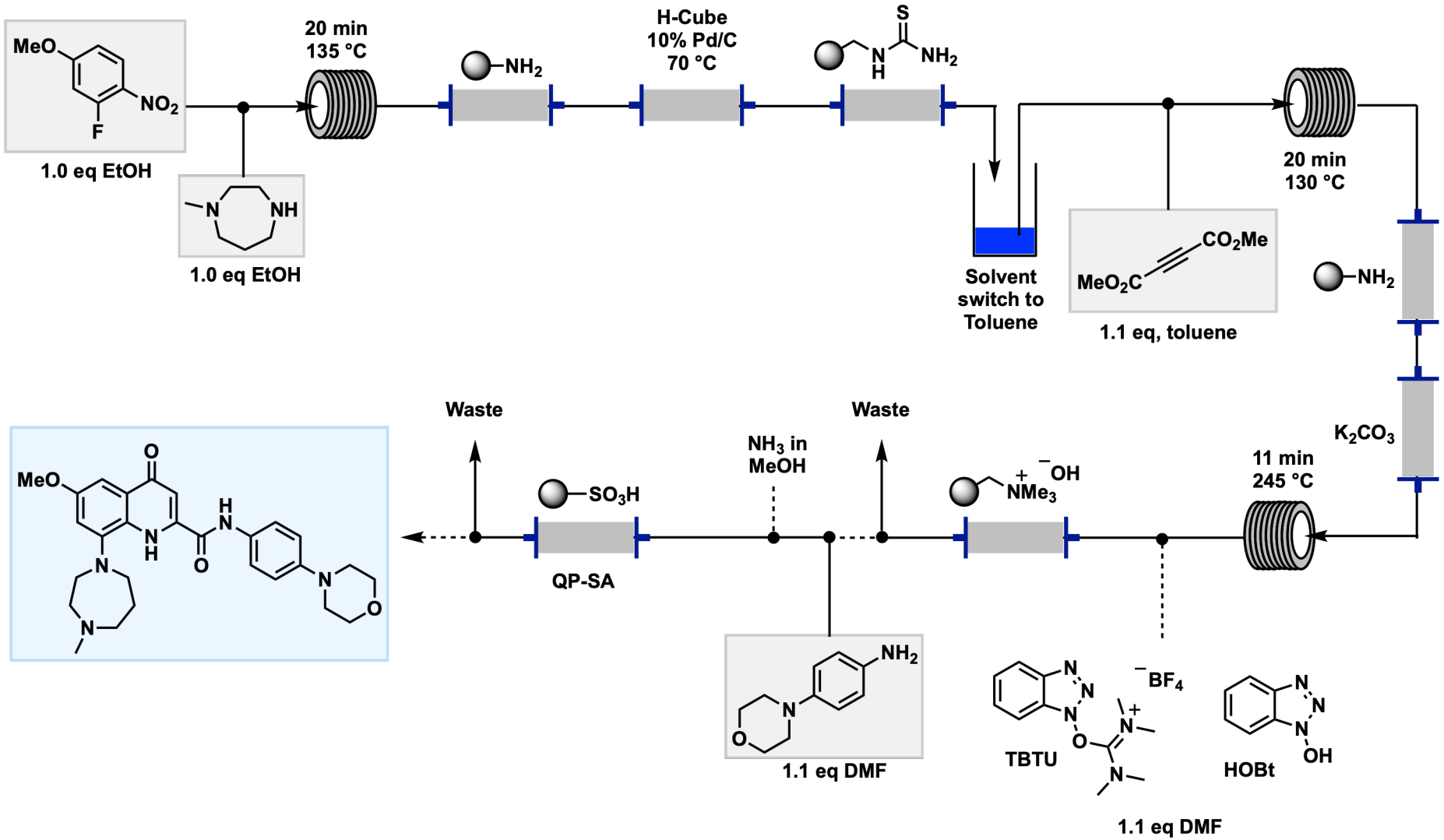
Z. Qian, I.R. Baxendale, S.V. Ley, *Chem. Eur. J.* **2010**, *16*, 12342

Flow Synthesis of Imatanib Mesylate (Gleevec)



M.D. Hopkin, I.R. Baxendale and S.V. Ley, *J.C.S. Chem. Commun.*, **2010**, *46*, 2450-2452.

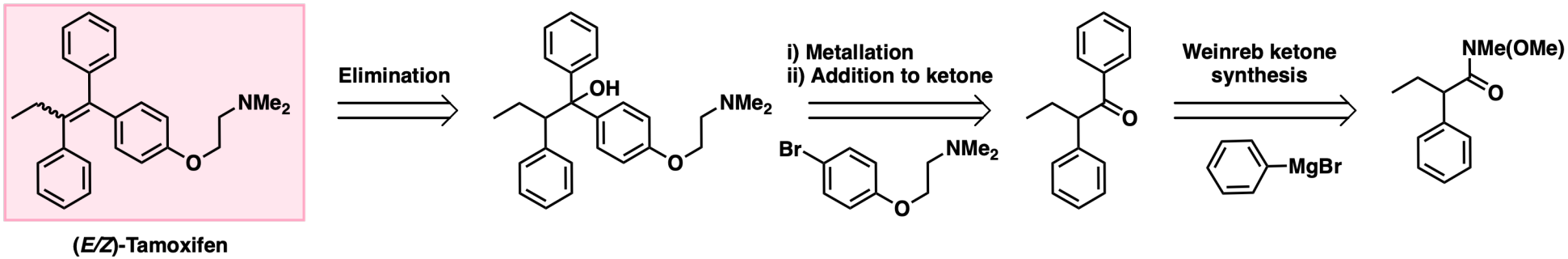
Flow Synthesis of a 5HT1B Antagonist



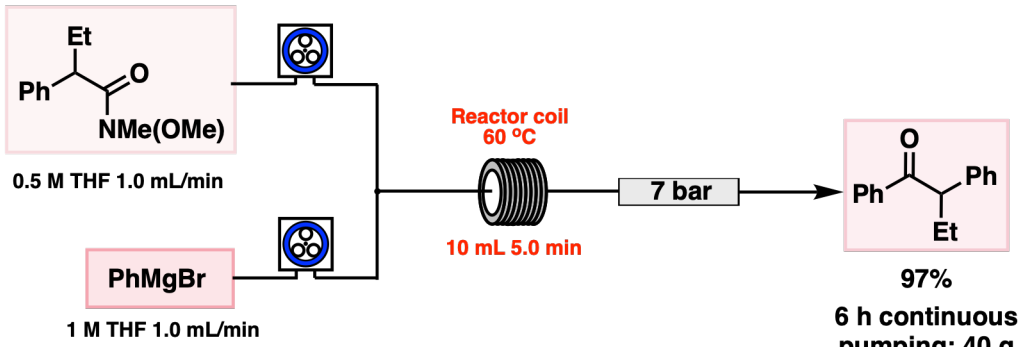
Z. Qian, I. R. Baxendale and S.V. Ley, *Synlett*, **2010**, 505-508

Telescoped Flow Synthesis of (*E*/*Z*)-Tamoxifen

Synthesis plan:



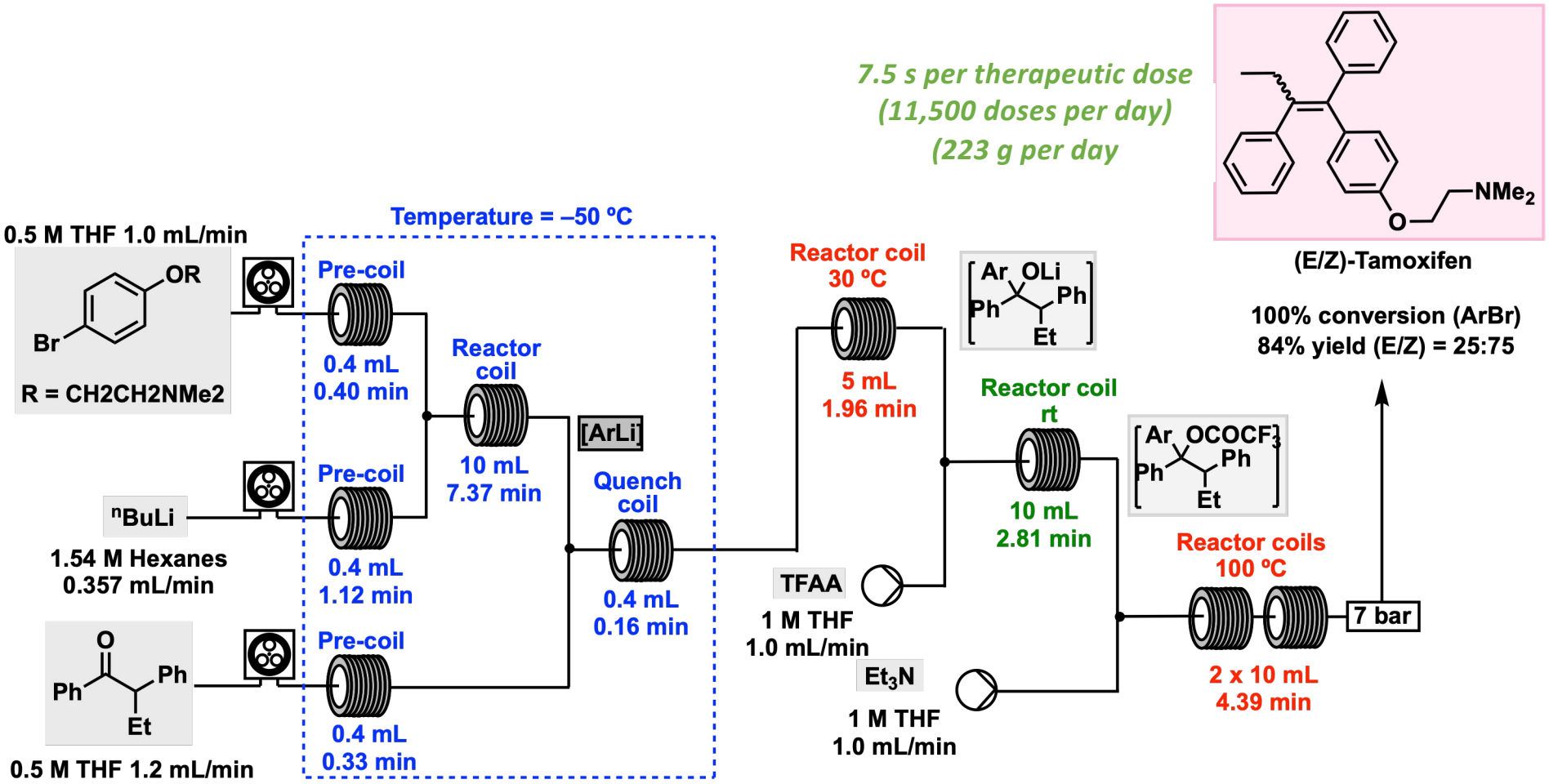
Continuous flow Weinreb synthesis:





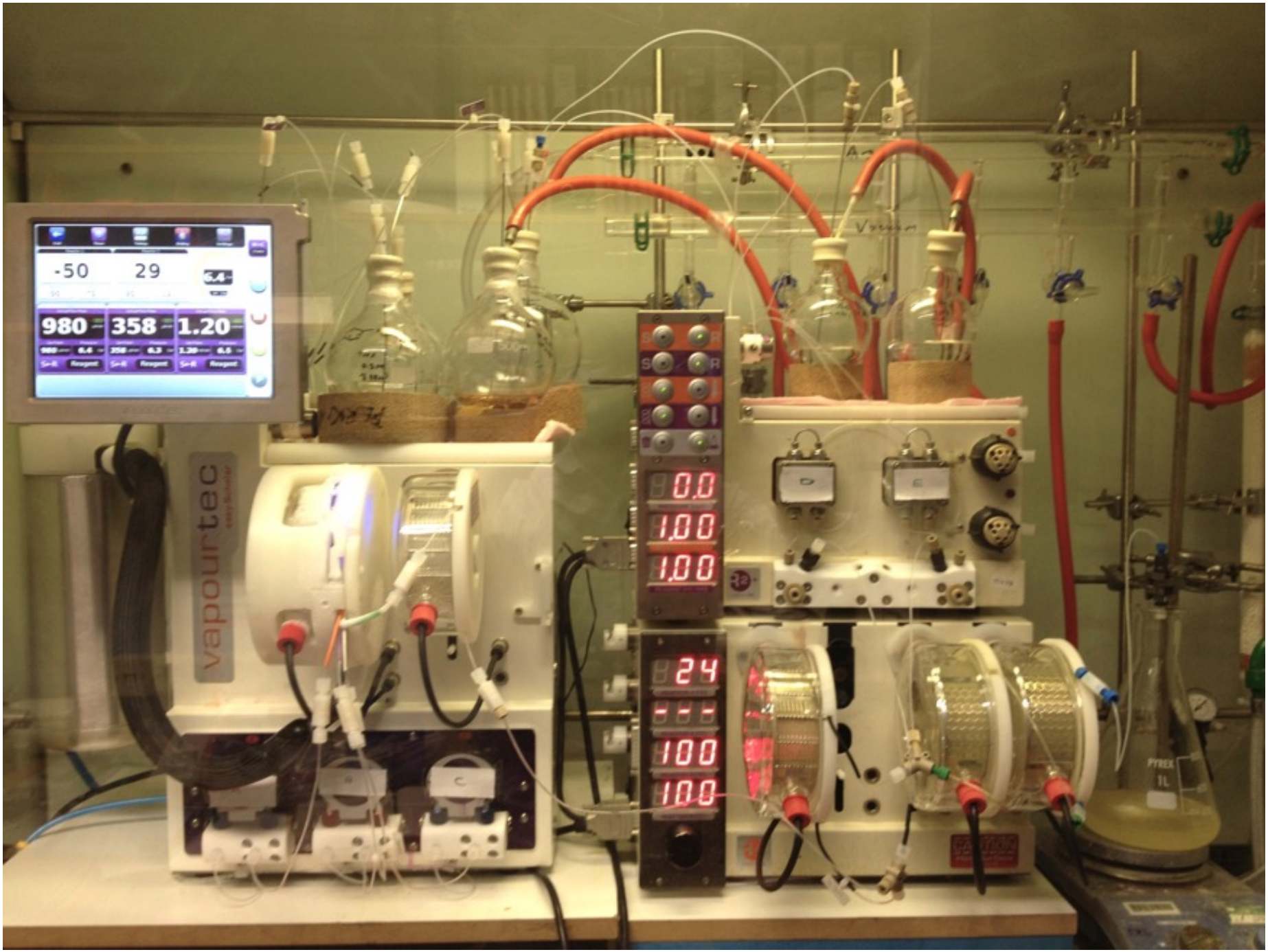


Telescoped Flow Synthesis of (*E*/*Z*)-Tamoxifen

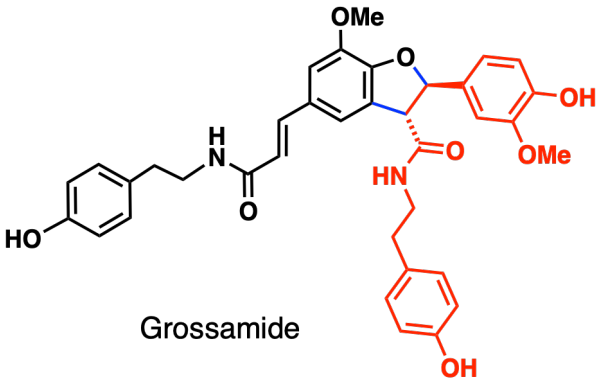


P.R.D. Murray, D.L. Browne, J.C. Pastre, C. Butters, D. Guthrie, S.V. Ley, *Org. Proc. Res. Dev*. **2013**, *17*, 1192-1208

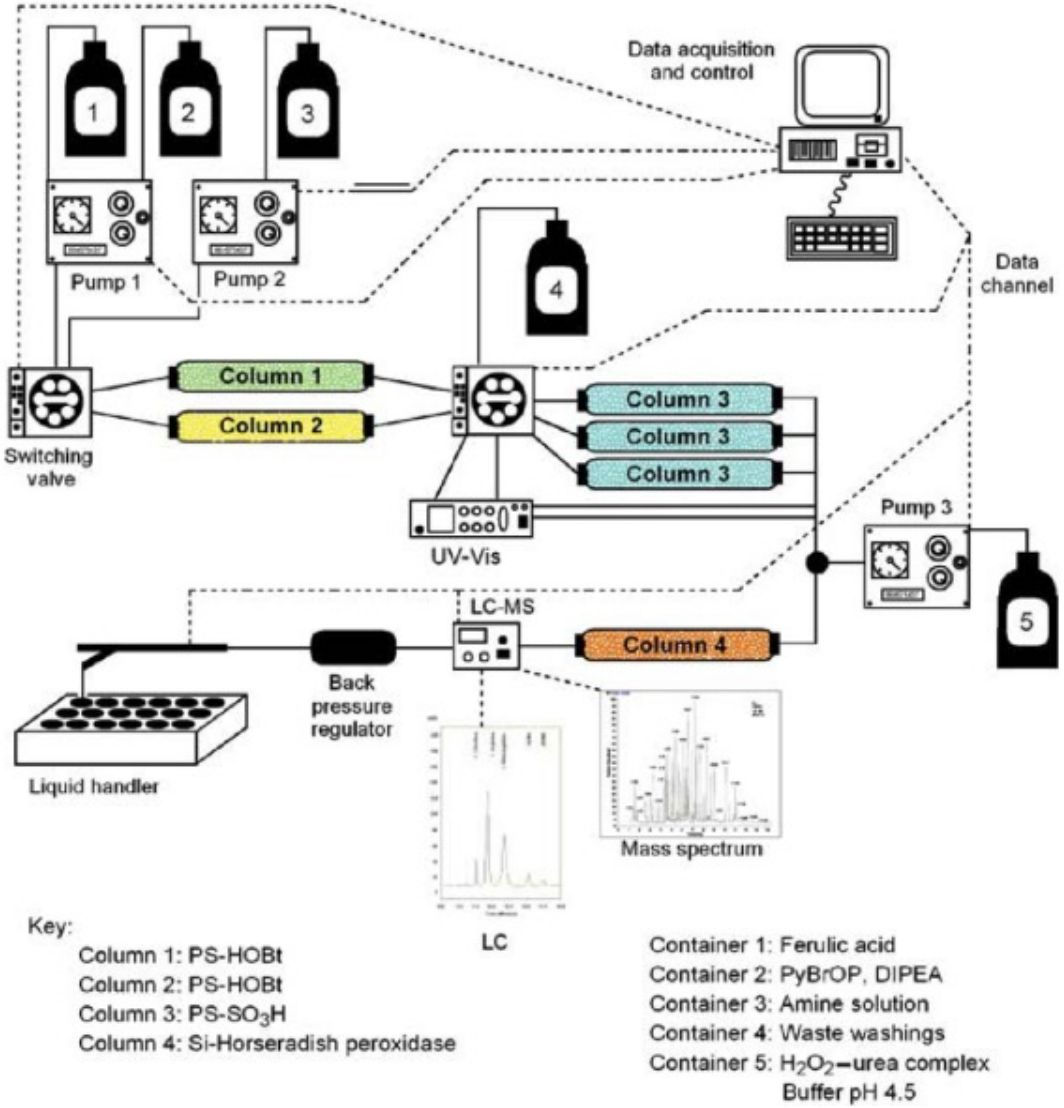
Telescoped Flow Synthesis of (*E*/*Z*)-Tamoxifen



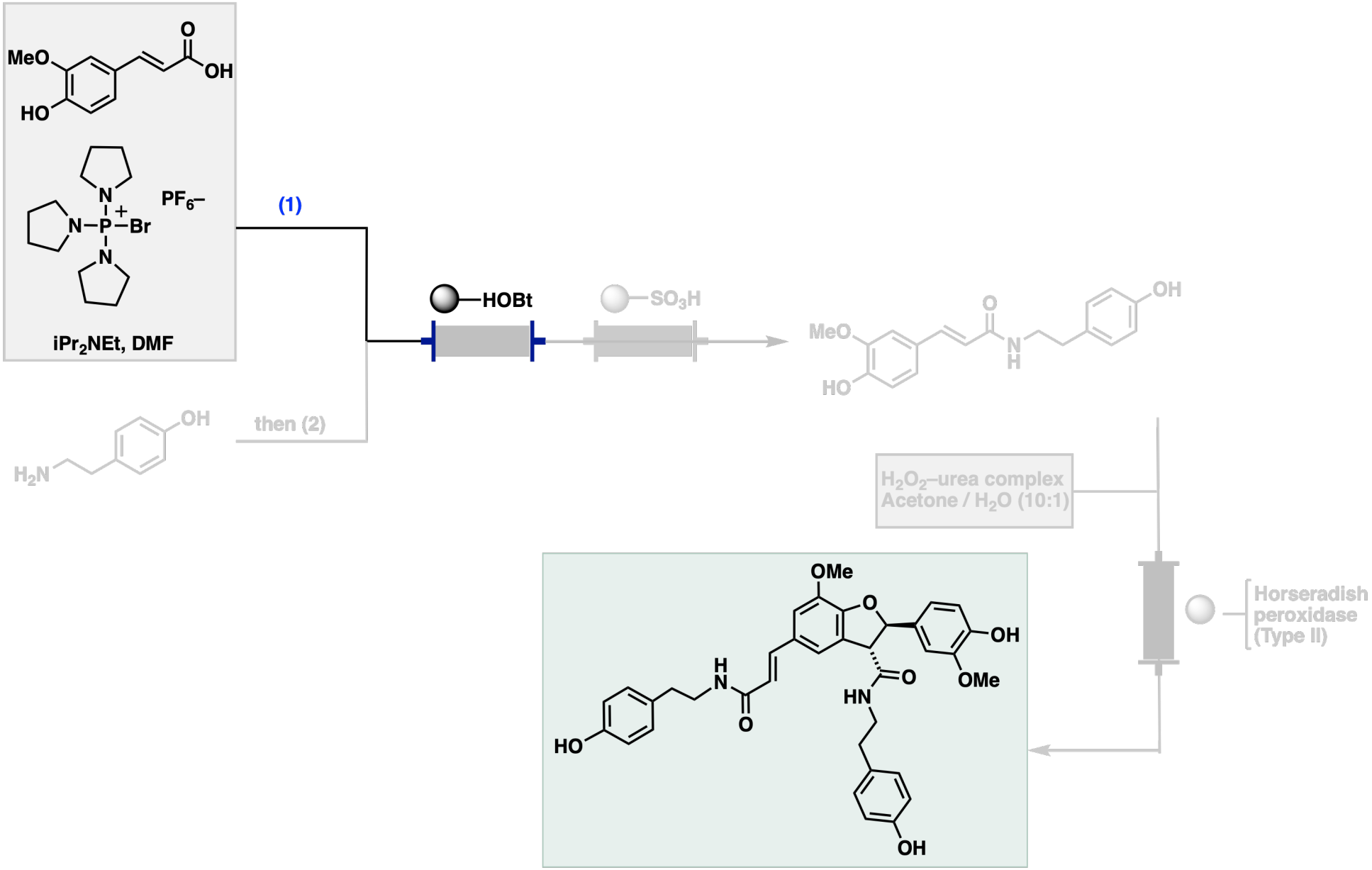
Flow Synthesis of Grossamide Using Immobilised Enzymes



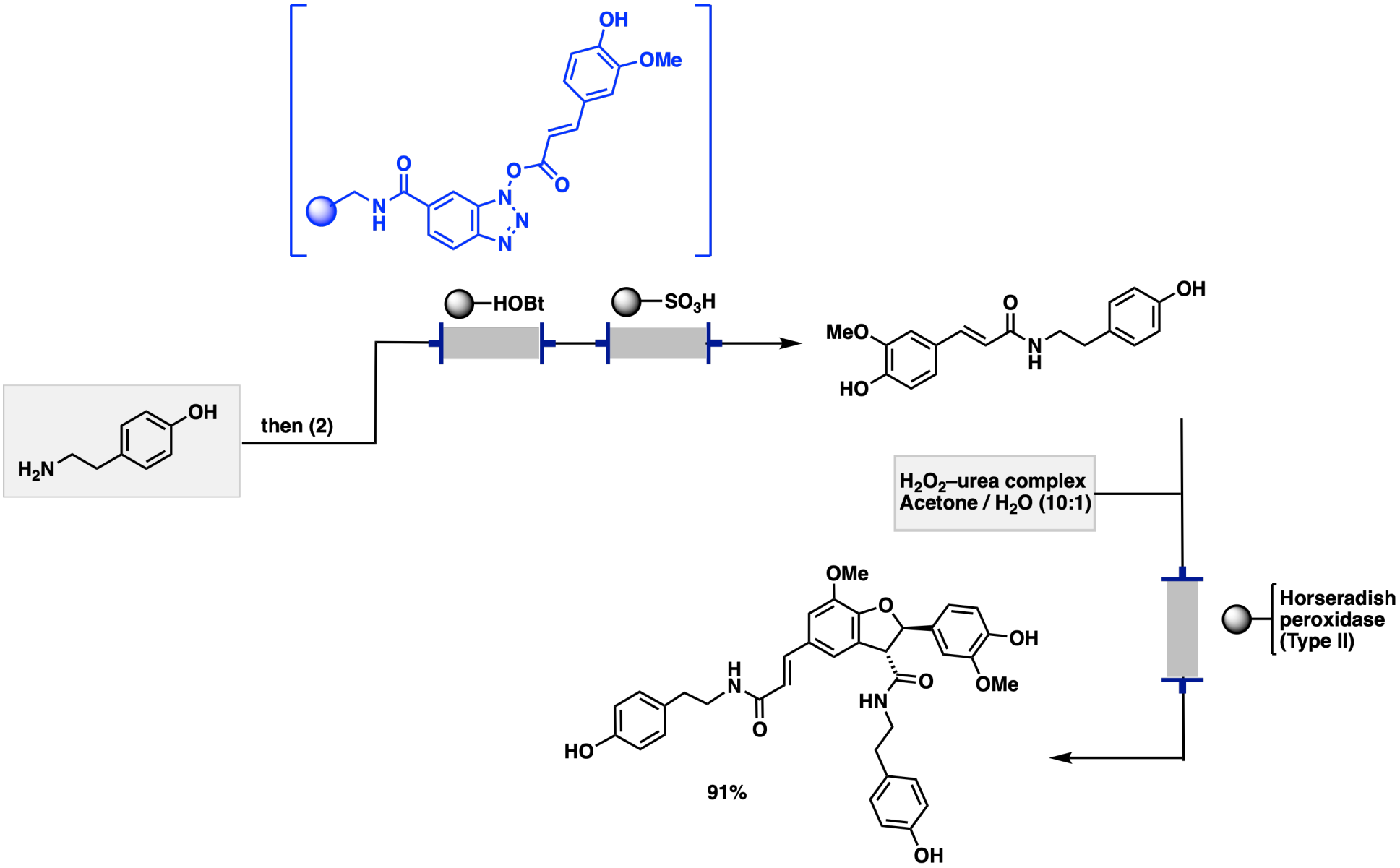
Grossamide



Flow Synthesis of Grossamide Using Immobilised Enzymes

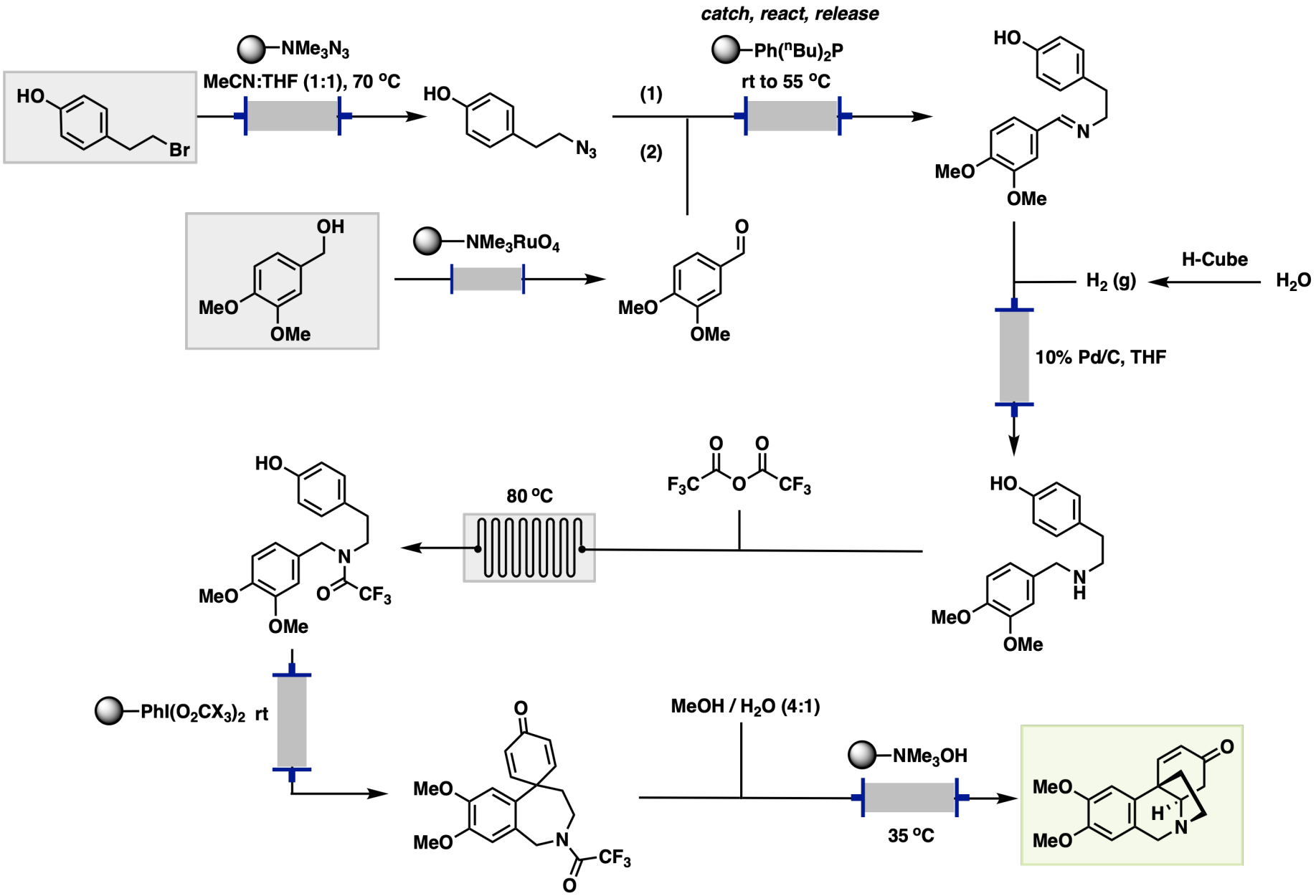


Flow Synthesis of Grossamide Using Immobilised Enzymes



I.R. Baxendale, C.M. Griffiths-Jones, S.V. Ley and G.K. Tranmer, *Synlett*, **2006**, 427-430

Flow Synthesis of Oxomaritidine



I.R. Baxendale, J. Deeley, C.M. Griffiths-Jones, S.V. Ley, S. Saaby and G. Tranmer, *J. Chem. Soc., Chem. Commun*. **2006**, 2566-2568

Flow Synthesis of Spirodienal & Spirangiens

Spirangiens

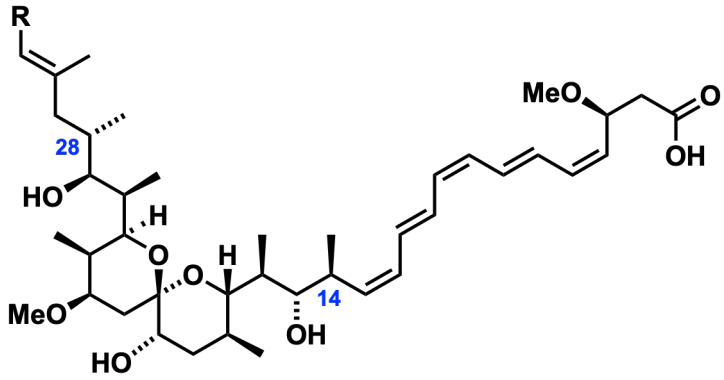
Isolated from *Sorangium cellulosum* So ce90 in 2005.

Antifungal properties and cytotoxic activity (IC50 = 0.7 ng/mL mouse fibroblast, L929)

Absolute stereochemistry proposed by analysis of gene cluster and later confirmed by total synthesis of spirangien A

Three published syntheses containing the functionalised

C14-C28 spiroketal core.



Spirangiens A and B
R = CH_3 or CH_2CH_3

Isolation: Höfle *et al. Eur. J. Org. Chem.* **2005**, *70*, 5013

Previous synthesis studies

Paterson et al. *Angew. Chem. Int. Ed*. 2007, *46*, 6699

Kalesse *et al. Org. Lett*. 2008, *10*, 4371

Cossy *et al. J. Org. Chem*. 2010, *75*, 5151

Rizzacasa *et al*. *Org.Lett*. 2013,*15*, 516

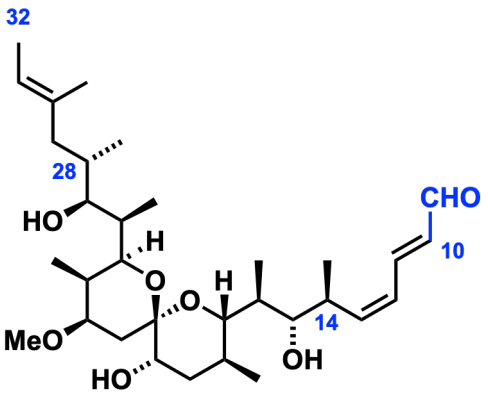
Spirodienal

Spirodienal A isolated from *Sorangium cellulosum* KM0141.

Exhibits antifungal activity against Botrytis cinerea but no activity against S. aureus or E. coli.

Relative configuration of core and double bond geometries based on 2D-NMR and ROESY correlations.

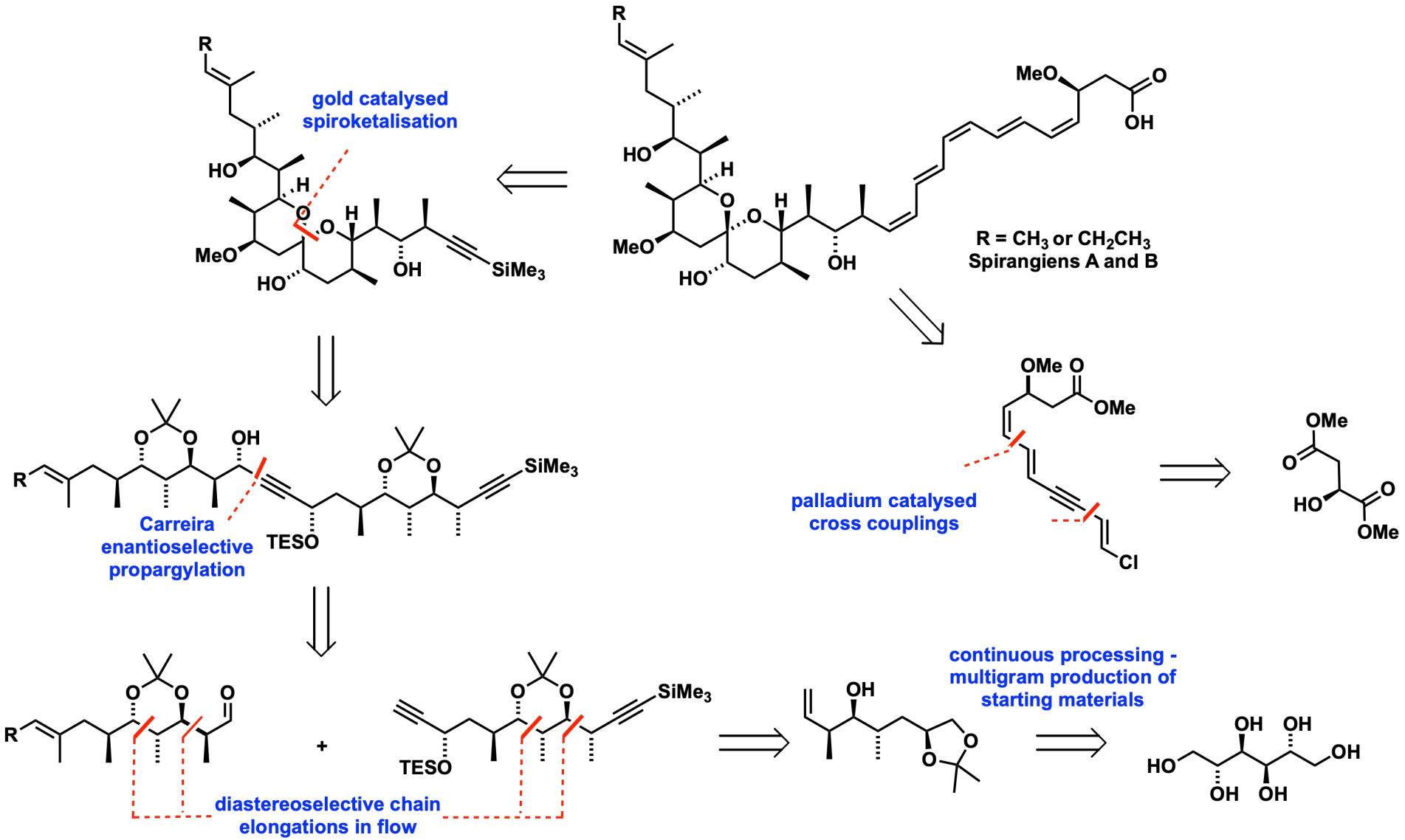
Structurally similar to the spirangien molecules.



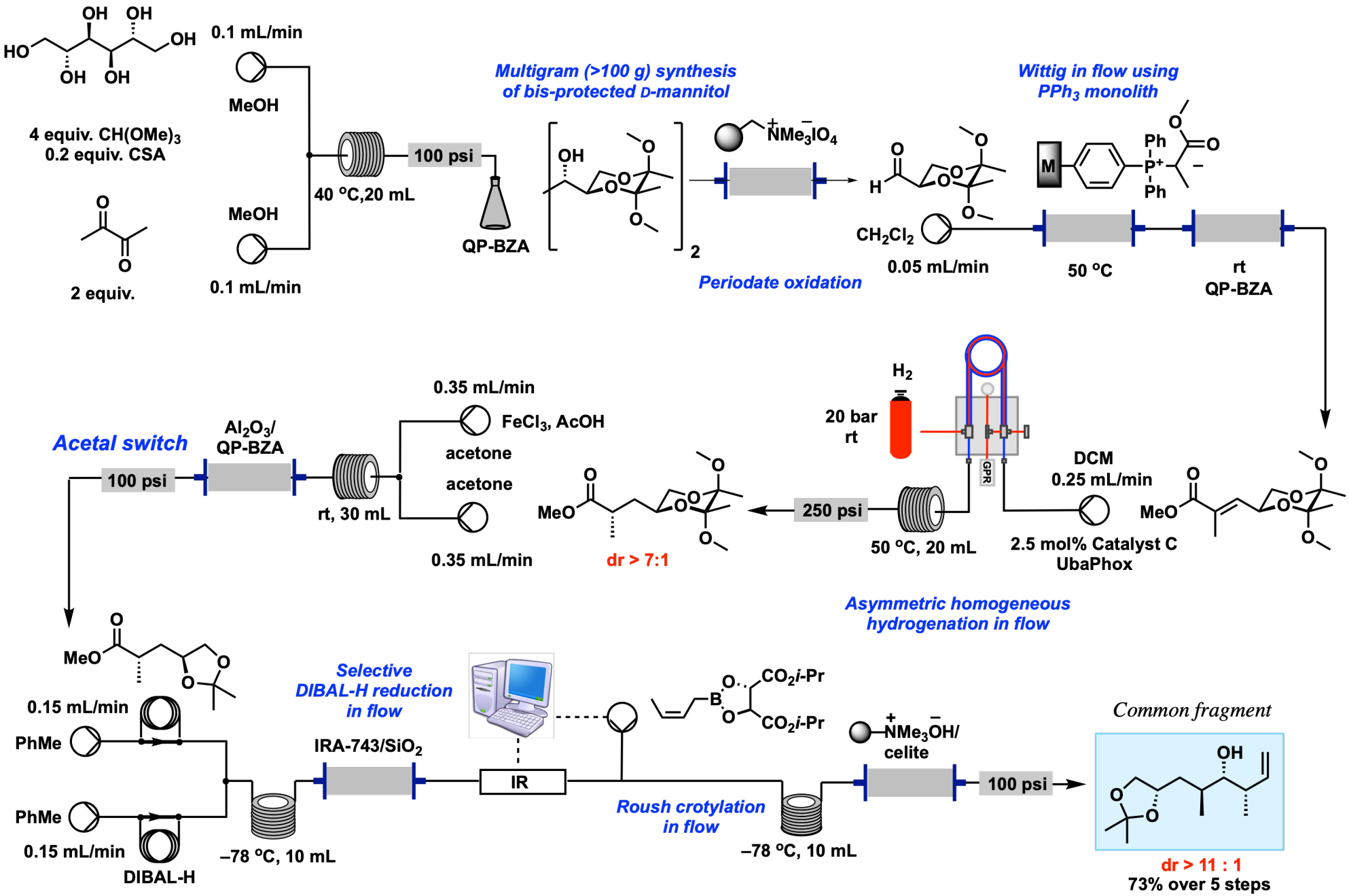
Spirodienal
Degradation product (C10-C32) retains biological activity (IC_{50} = 7 ng/mL)

Isolation: J.-W. Ahn *Bull. Korean Chem. Soc.* **2009**, *30*, 742

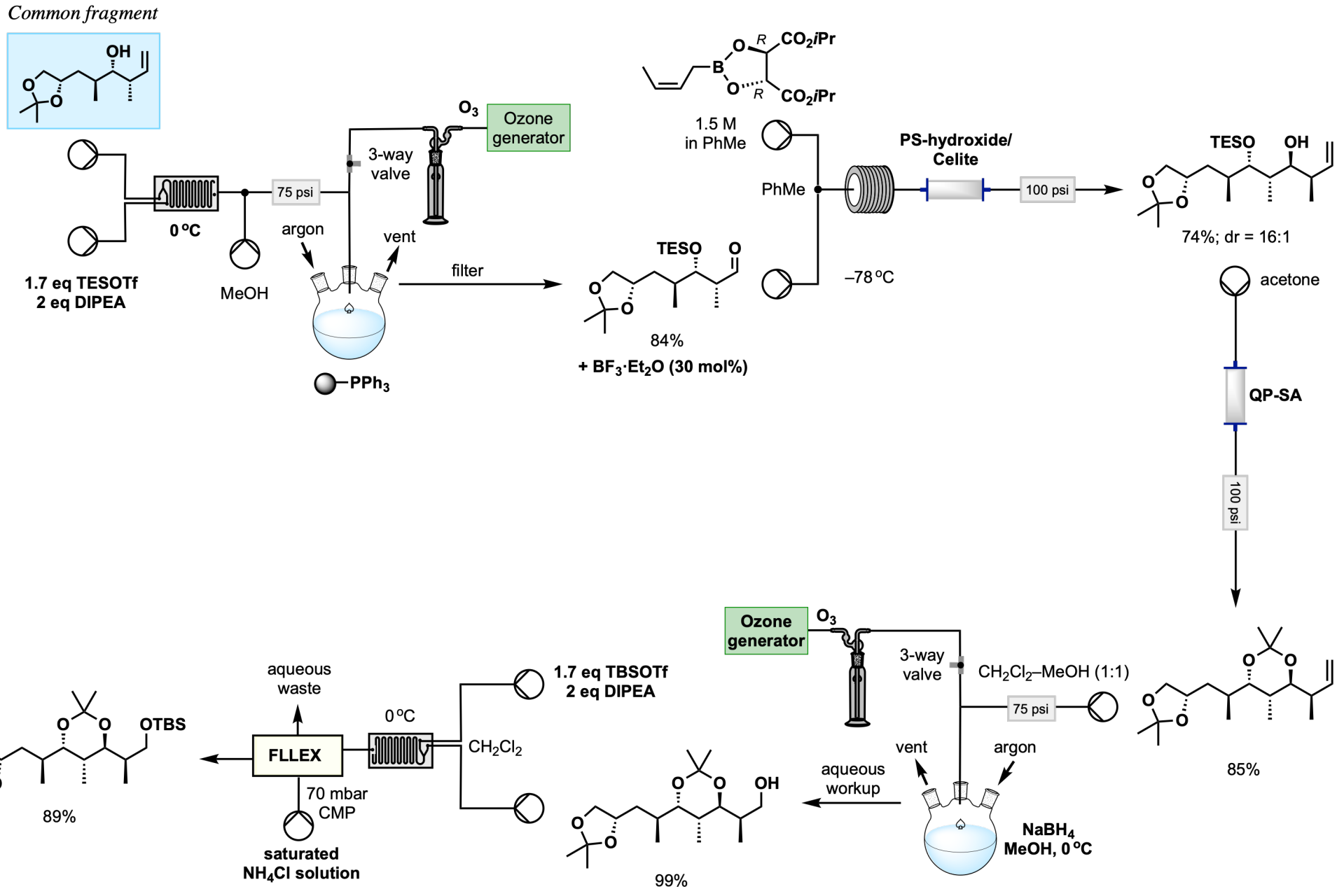
Retrosynthesis of Spirangien: First Thoughts



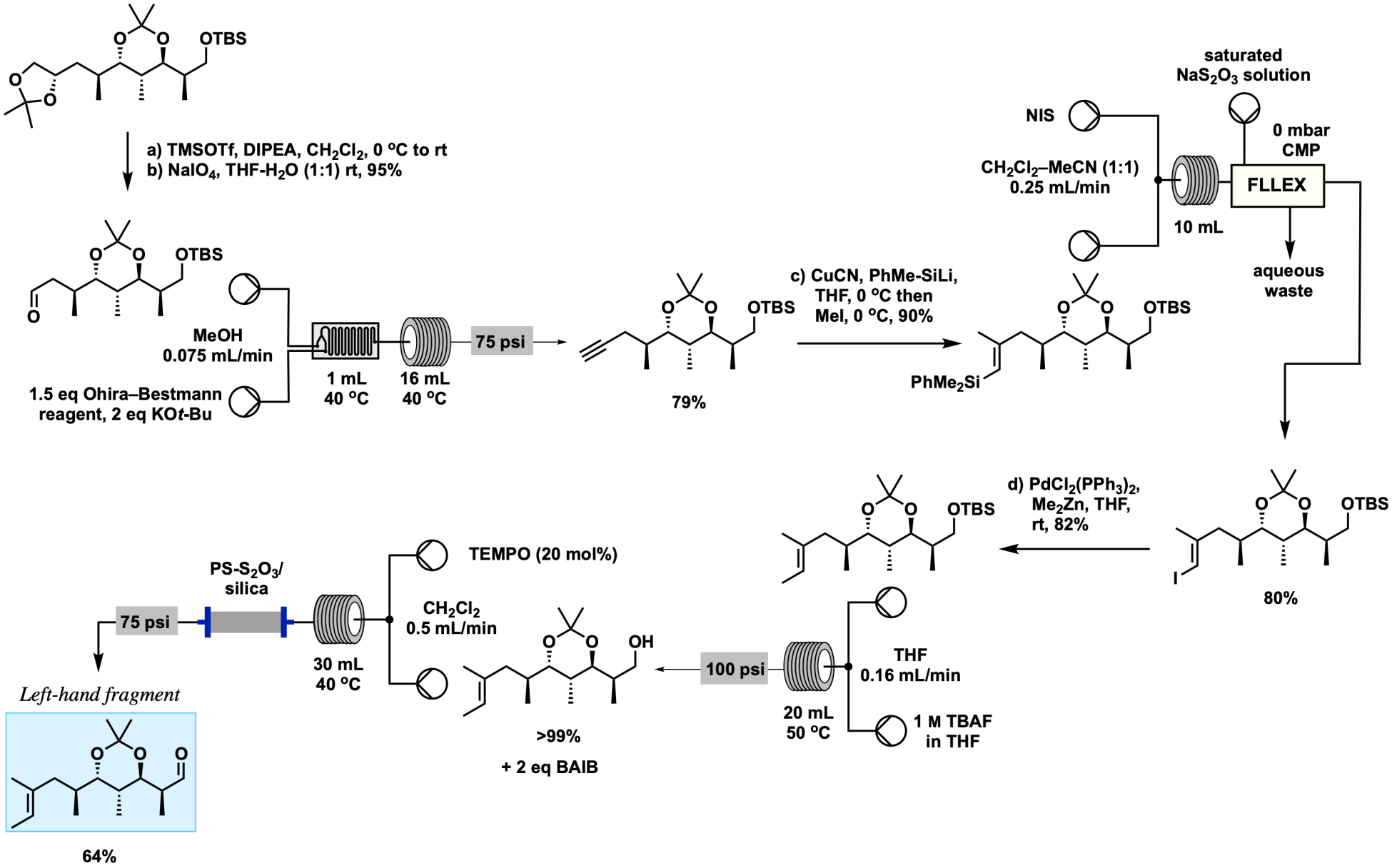
Flow Synthesis of the Spirangiens: Common Fragment



Flow Synthesis of the Spirangiens: Left Hand Fragment

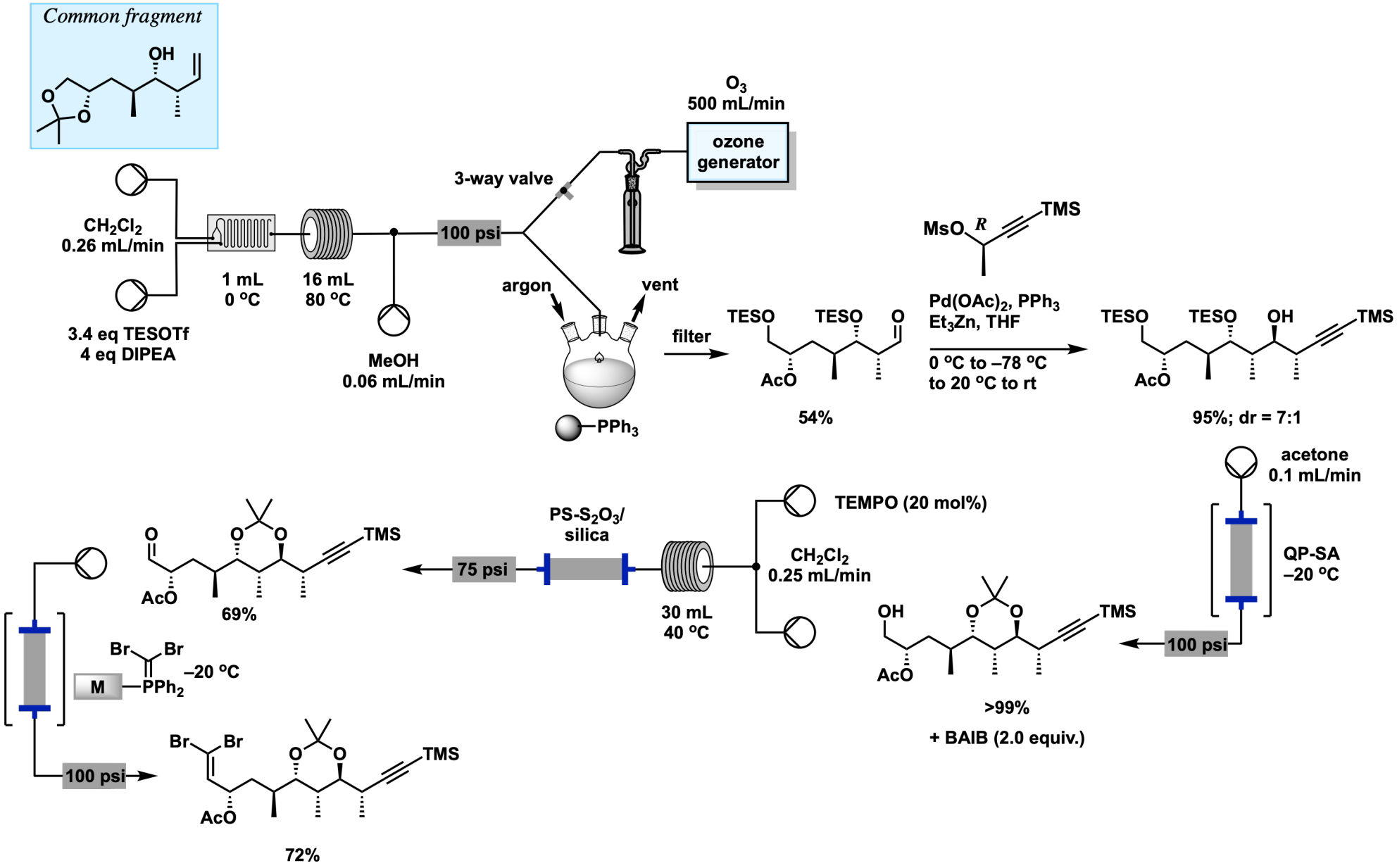


Flow Synthesis of the Spirangiens: Left Hand Fragment



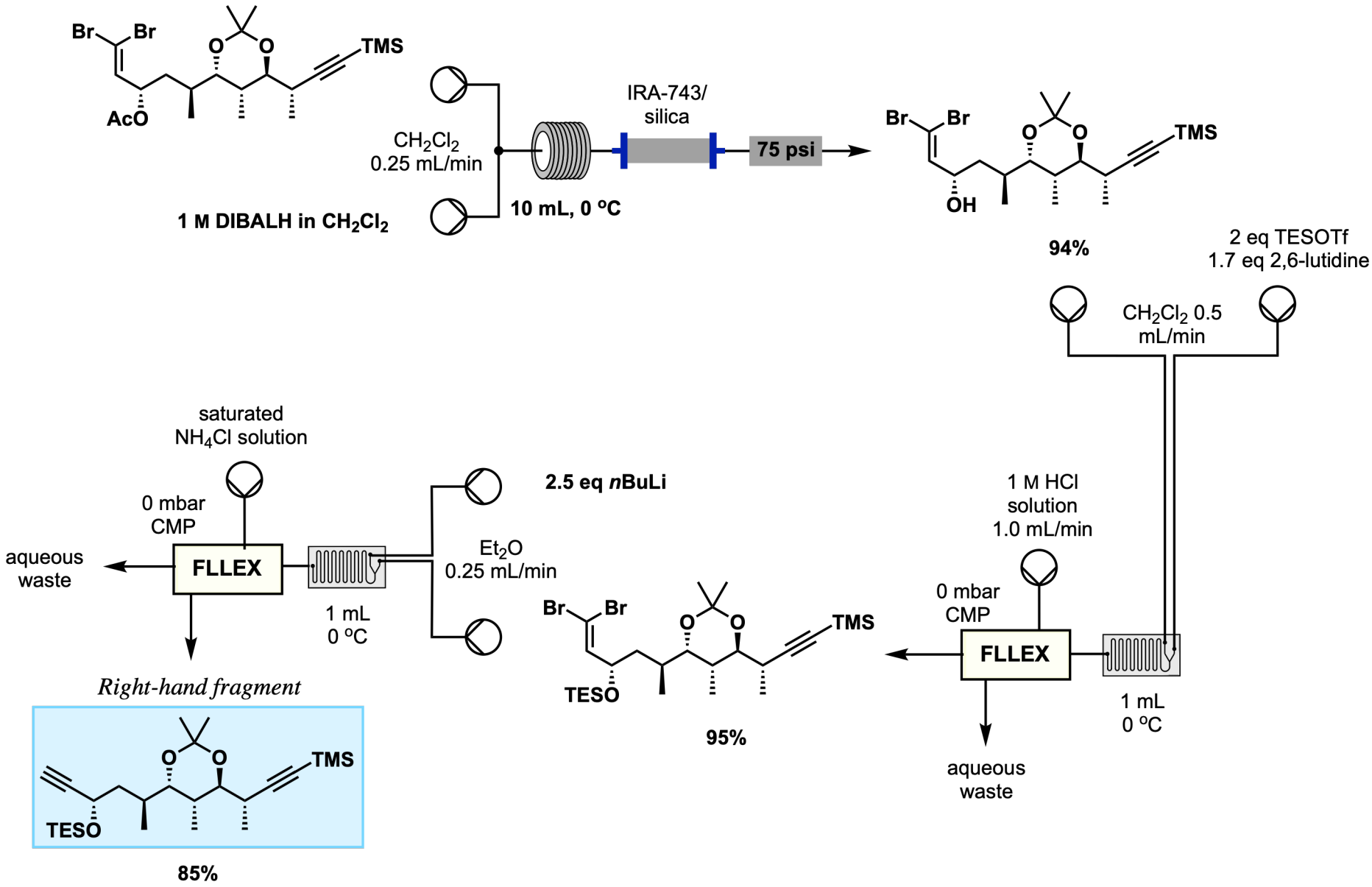
S. Newton, C.F. Carter, C.M. Pearson, L.C. Alves, H. Lange, P. Thansandote, S.V. Ley, *Angew. Chem. Int. Edn.* **2014**, *53*, 4915-4920

Flow Synthesis of the Spirangiens: Right Hand Fragment



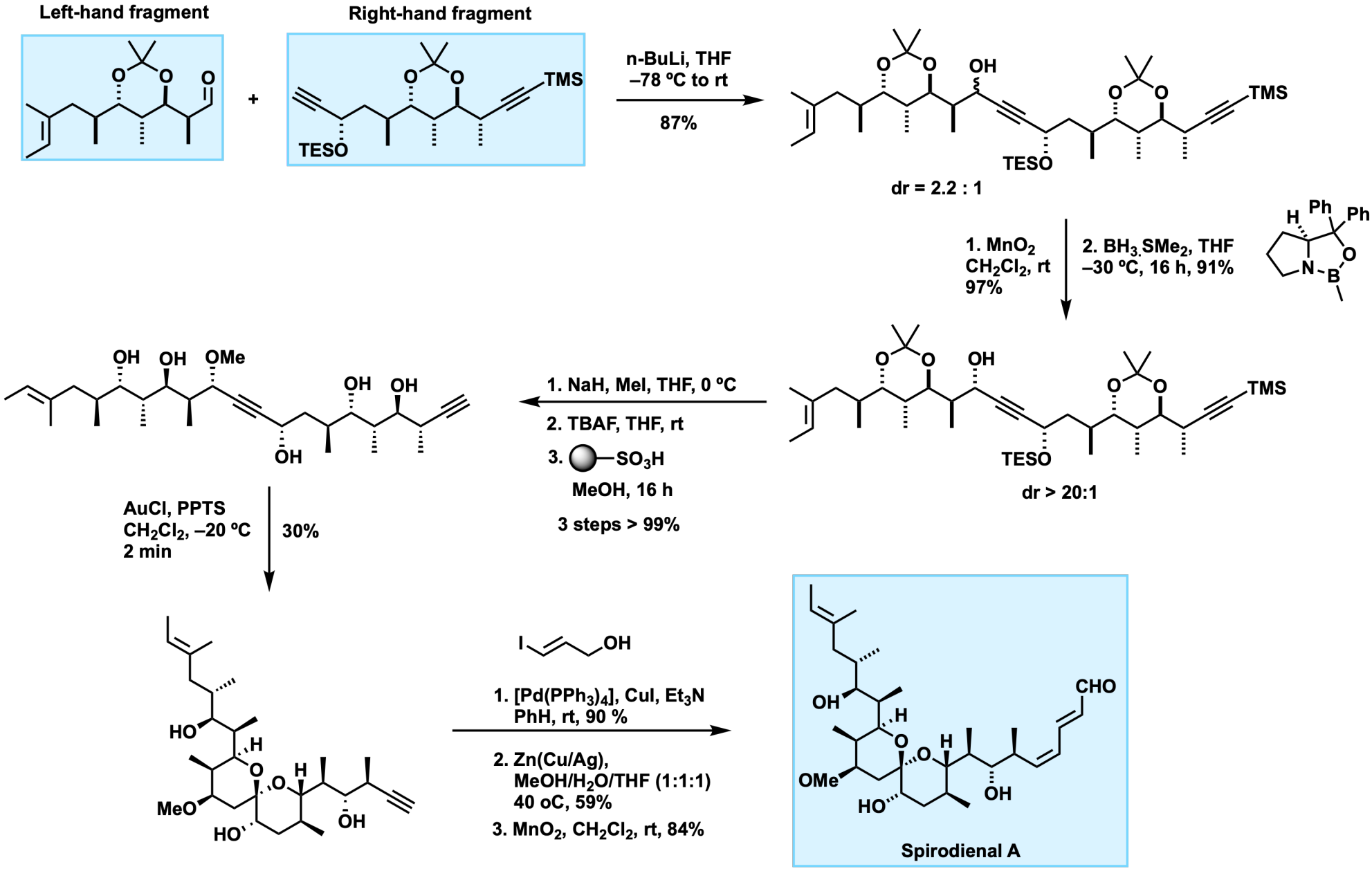
S. Newton, C.F. Carter, C.M. Pearson, L.C. Alves, H. Lange, P. Thansandote, S.V. Ley, *Angew. Chem. Int. Edn.* **2014**, *53*, 4915-4920

Flow Synthesis of the Spirangiens: Right Hand Fragment



S. Newton, C.F. Carter, C.M. Pearson, L.C. Alves, H. Lange, P. Thansandote, S.V. Ley, *Angew. Chem. Int. Edn.* **2014**, *53*, 4915-4920

Flow Synthesis of the Spirangiens: Batch Fragment Coupling



S. Newton, C.F. Carter, C.M. Pearson, L.C. Alves, H. Lange, P. Thansandote, S.V. Ley, *Angew. Chem. Int. Edn.* **2014**, *53*, 4915-4920

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