# The Flow-Assisted Total Synthesis of Spirodienal A

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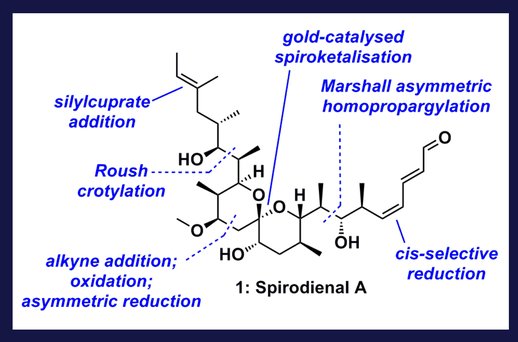
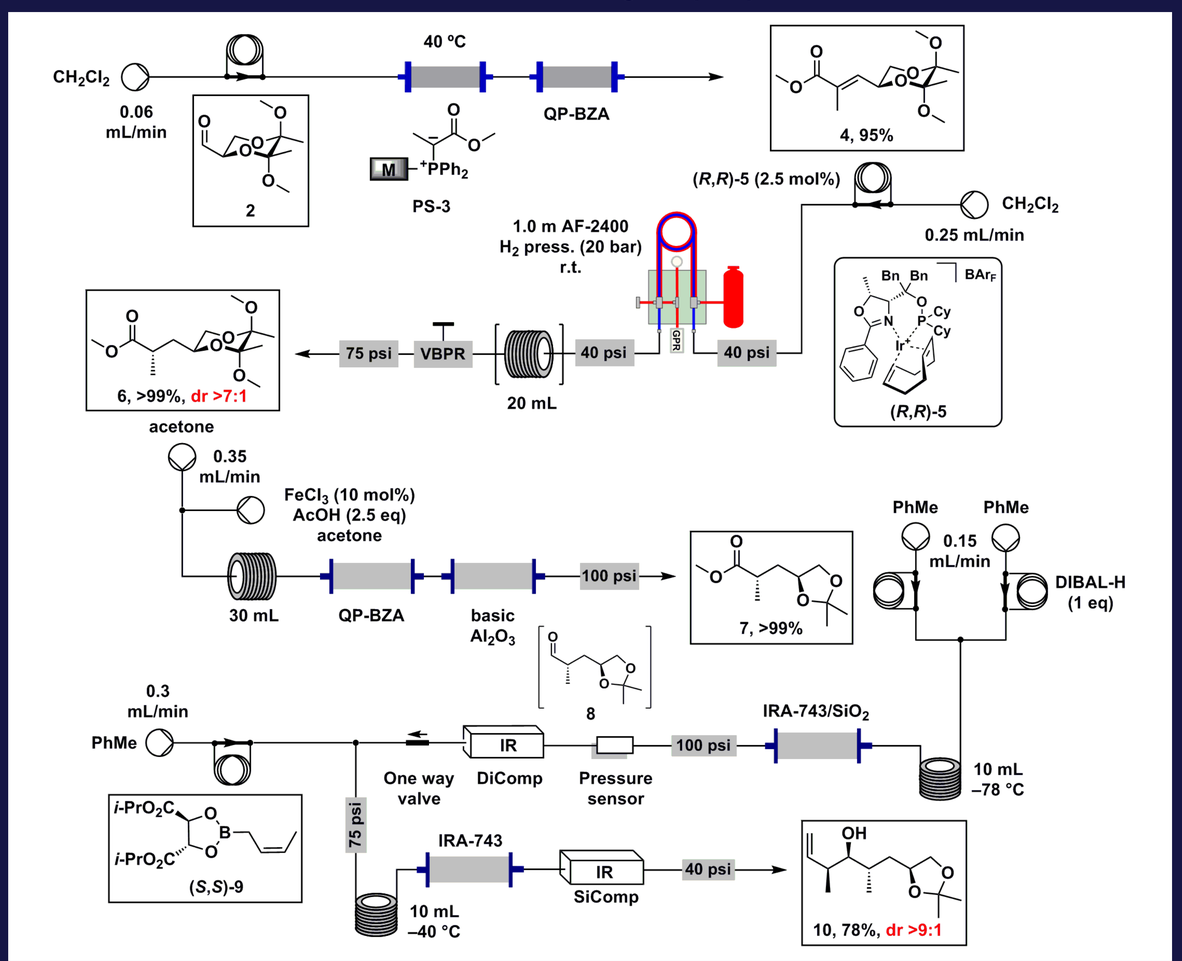
## Background and Synthetic Strategy

- Spirodienal A was isolated by Ahn in 2009 from the myxobacterium *Sorangium cellulosum* KM0141[1]
- No reported total syntheses of spirodienal A
- The aim of the project was to utilise newly-developed flow technologies and polymer-supported reagents to assist in the synthesis of this complex natural product
- The route employs Roush crotylation, asymmetric hydrogenation, silylcupration addition and gold-catalysed spiroketalisation chemistries as the key steps



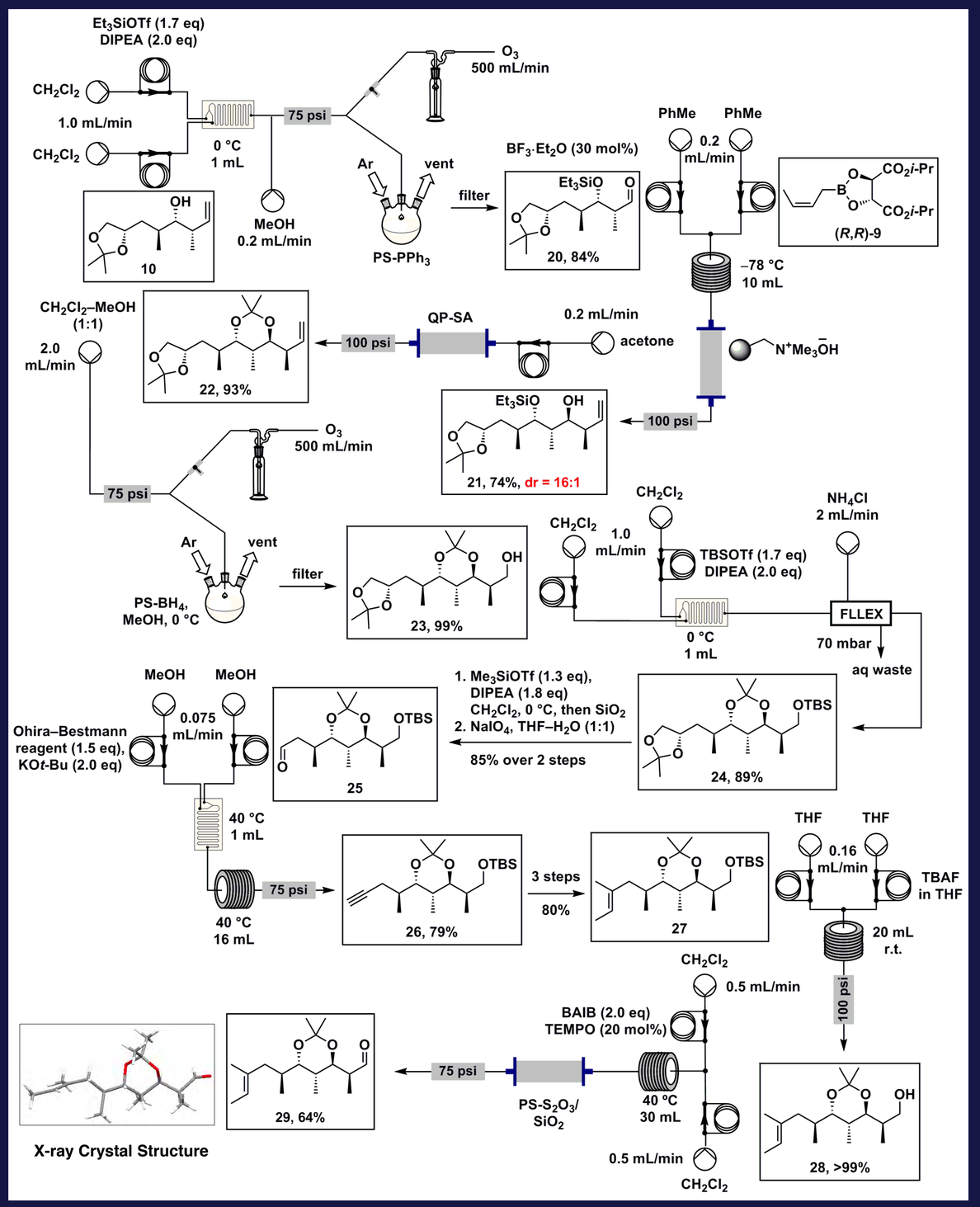

## Flow Synthesis of Homoallylic Olefin **10**

- The synthesis of homoallylic olefin **10** was completed in 5 flow steps
- A novel tube-in-tube reactor was used in the asymmetric hydrogenation of **4**[2]
- The ester reduction and Roush crotylation reactions were performed in a single operation using the ReacIR™ in conjunction with LabVIEW software to facilitate the automated addition of the boronate reagent **(*S*,*S*)-9**[3,4]



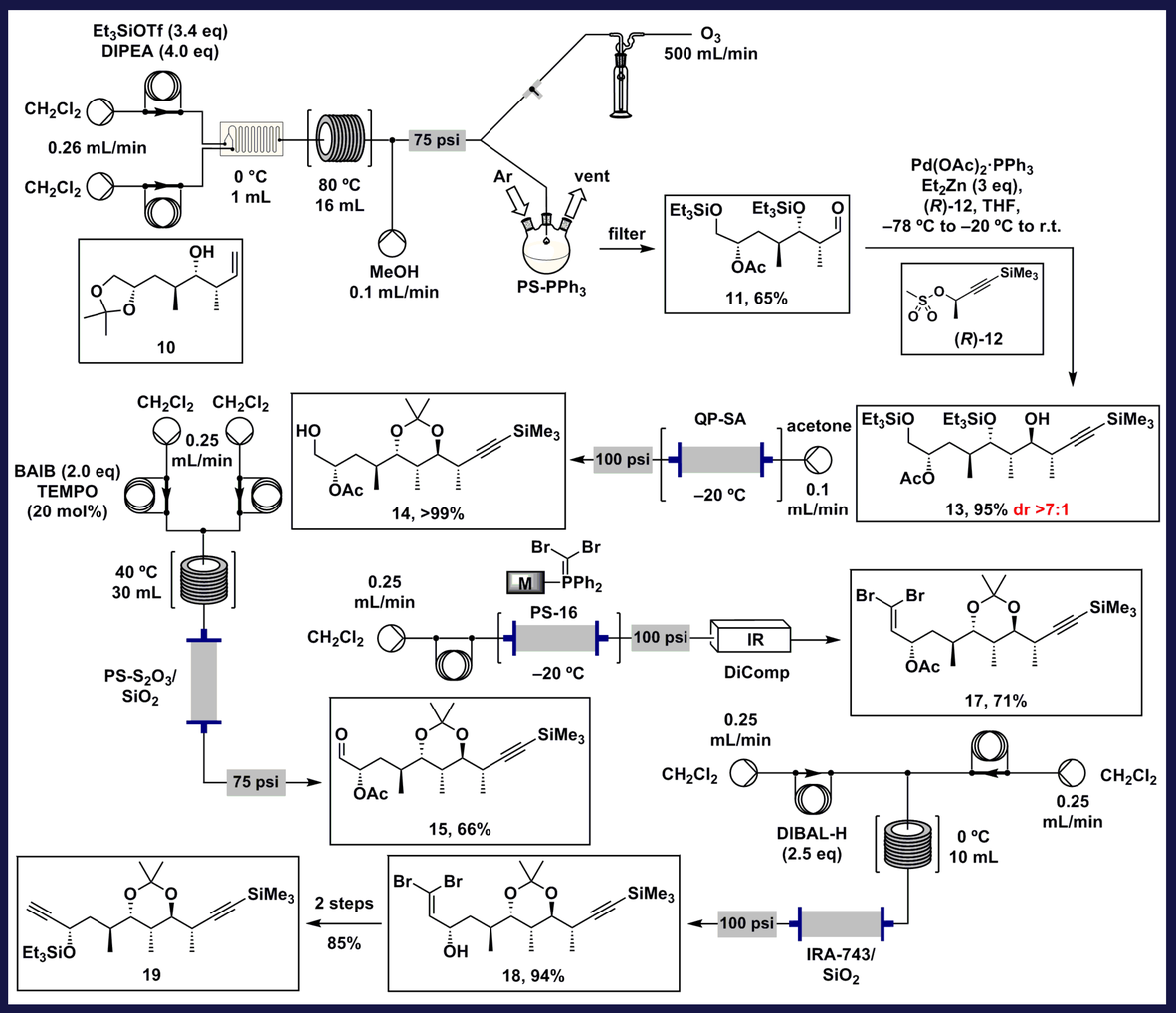

## Flow-Assisted Synthesis of Aldehyde **29**

- Aldehyde **29** was prepared in 8 flow steps and 6 batch from olefin **10**
- The use of PS-reagents minimised the number of chromatographic purifications
- Several steps were telescoped into a single flow sequence
- The absolute configuration of **29** was confirmed by X-ray crystallography analysis



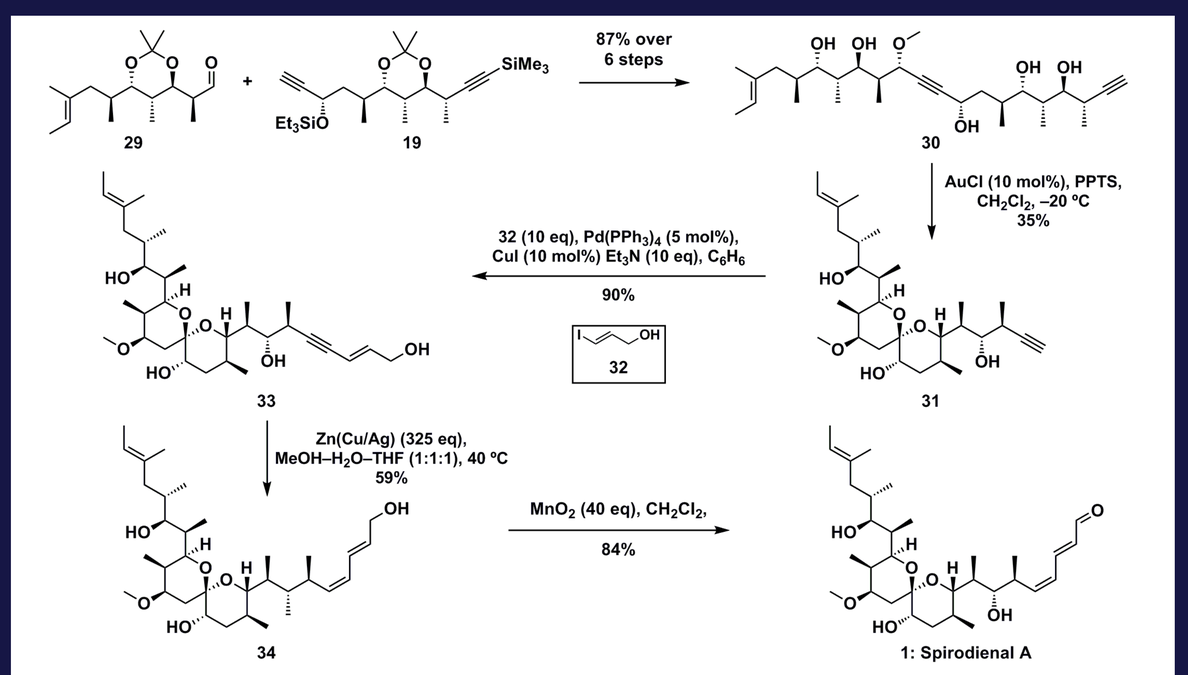

## Flow-Assisted Synthesis of Bis-Alkyne **19**

- Bis-alkyne **19** was completed in 5 flow steps and 3 batch from olefin **10**
- Silyl protection/ring-opening/ozonolysis of **10** were done in a single flow operation
- Desilylation of **13** in flow avoided 1,2-acyl migration observed in batch mode
- Dibromoolefination of **15** using **PS-16** negated chromatographic purification of **17**




## Completion of the Total Synthesis

- A gold-catalysed spiroketalisation reaction prepared spiroketal **31** in moderate yield
- A mixed-metal *cis*-selective reduction was used to prepare diene **34**
- Spirodienal A was prepared in 10 batch steps from coupling fragments **19** and **29**[5]




## Summary

- The first total synthesis of spirodienal A is described confirming the absolute structure
- The synthesis was completed in 37 steps (28 longest linear) and 0.37% overall yield
- Flow technologies and polymer-supported reagents are used in ~50% of the route
- Further studies aim to develop more flow steps and multistep sequences

## References and Acknowledgements

[1] Spirodienal, a New Spiroketal from Sorangium cellulosum: J.-W. Ahn, *Bull. Korean Chem. Soc.*, **2009**, *30*, 742-744; [2] Asymmetric Homogeneous Hydrogenation in Flow using a Tube-in-Tube Reactor: S. Newton, S. V. Ley, E. Casas Arcé and D. Grainger, *Adv. Synth. Catal.*, **2012**, *354*, 1805-1812; [3] Diastereoselective Chain-Elongation Reactions Using Microreactors for Applications in Complex Molecule Assembly: C. F. Carter, H. Lange, D. Sakai , I. R. Baxendale and S. V. Ley, *Chem. Eur. J.*, *17*, **2011**, 3398-3405; [4] A breakthrough method for the accurate addition of reagents in multi-step segmented flow processing: H. Lange, C. F. Carter, M. D. Hopkin, A. Burke, J. G. Goode, I. R. Baxendale and S. V. Ley, *Chem. Sci.*, *2*, **2011**, 765-769; [5] S. Newton, PhD thesis, University of Cambridge, **2013**, *unpublished results*.

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