The increasing use of Flow Synthesis applied to complex structures

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Accelerating Spiro cyclic Polyketide Synthesis using Flow Chemistry

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What is Flow Chemistry?

Flow Chemistry Applied to Peptide Synthesis

- Synthesized DARPin pE59 and Barnase (130 and 113 residues respectively)
- 3 minutes/ residue as opposed 1 hr and 2-6 weeks per peptide

Flow Chemistry Applied to Difficult Reactions

Flow Chemistry Total Synthesis

Grossamide

Synthesis of Spirangien A methyl ester and Spirodienal A

Spirangien A methyl ester

Spirodienal A

Synthesized by Paterson group (18 steps, 2% overall)

Absolute configuration unknown

Goal: Use benefits of flow chemistry to expedite the syntheses of the two spirocyclic polyketide natural products
Retrosynthetic Approach

Spirangien A \rightleftharpoons \text{Spirodienal A} \rightleftharpoons \text{Hypothetical Intermediate} \rightleftharpoons \text{Final Product}

Prepared using primarily flow chemistry
Synthesis of Key Homoallylic Alcohol

PPh₃ functionalized monolith

Tube-in-tube reactor

Real-time concentration monitoring
Synthesis of the Aldehyde fragment

30 sec
12 mmol/hr
Synthesis of Aldehyde Fragment (Con’t)

13 steps, 11.6%
(9 flow 4 batch)
Synthesis of bis-alkyne fragment

3 protecting groups
2 oxidations
1 step in flow

8 steps, 22% (7 flow, 1 batch)
1.) Oxidation
2.) Reduction
3.) Methylate
4.) Deprotect

All batch mode
Conclusion

• Flow chemistry with silylations, crotylations, ozonolysis, olefinations, and oxidations.
• Ability to make large amounts of compound in flow of the early, complex, intermediates.
• Higher yields, improved safety, faster
Discussion

• Is it worth the trouble?
• Will it ever be reasonable to do a synthesis with only flow?
• Questions?