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Accelerating Spirocyclic Polyketide Synthesis using Flow Chemistry**

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Abstract: *Over the past decade, the integration of synthetic chemistry with flow processing has resulted in a powerful platform for molecular assembly that is making an impact throughout the chemical community. Herein, we demonstrate the extension of these tools to encompass complex natural product synthesis. We have developed a number of novel flow-through processes for reactions commonly encountered in natural product synthesis programs to achieve the first total synthesis of spirodienal A and the preparation of spirangien A methyl ester. Highlights of the synthetic route include an iridium-catalyzed hydrogenation, iterative Roush crotylations, gold-catalyzed spiroketalization and a late-stage cis-selective reduction.*

Natural products provide constant inspiration for the academic community with their fascinating structures and potent biological activities.[1] Many effective batch-mode techniques for their preparation exist, however, a successful total synthesis programme still requires monumental research effort. Each synthetic step requires intensive optimization and repetitive experimentation. Today, given the plethora of synthetic methods at our disposal, the challenges go beyond one of molecular complexity to encompass more convergent, atom/step efficient and sustainable processes.[2] These principals are important in any synthetic endeavour but in our resource limited environment, the management of our labour intensive, energy and solvent inefficient practices need to change. As flow chemistry[3] continues to advance through the on-going development of equipment and software, it is our view that the next step is to expand the scope of flow protocols to encompass the sensitive and asymmetric transformations required to make natural products. Flow chemistry could streamline natural product synthesis, addressing some of the issues encountered in batch-mode.[4] At the same time, the challenging structures of natural products could be used to elevate flow chemistry to a new level of discovery.

In recent times, our group has focused on developing flow technologies and procedures to facilitate chemical processes through the use of inline analytical tools for seamless reaction analysis,[5] polymer-supported reagents to minimize downstream processing[6] and computational software to facilitate multistep sequences.[7] Here we describe how the application of these methods expedited the syntheses of two related spirocyclic polyketide natural products, spirangien A methyl ester (**2**) and spirodienal A (**3**) (Figure 1).[8]

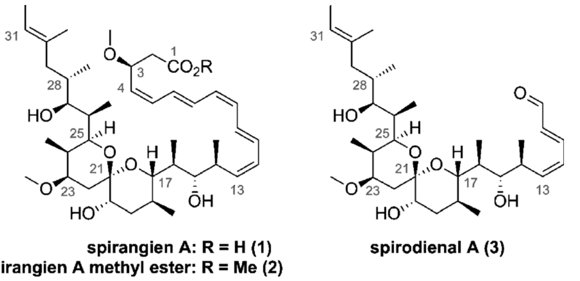

Figure 1. Spirocyclic polyketides isolated from *Sorangium cellulosum*.

Spirangien A (**1**) was isolated by Höfle in 2005 from the myxobacterium *Sorangium cellulosum* So ce90.[9] In 2008, Paterson et al. reported the first total synthesis of **1** together with its structurally more stable methyl ester **2**, confirming the structure and absolute stereochemistry.[10] This was followed by a number of fragment-based syntheses which focused on the spiroketal motif.[11] In 2009, Ahn isolated a related natural product from *Sorangium cellulosum* KM0141, spirodienal A (**3**),[12] the absolute configuration of which was unknown until this work.

The synthesis began with 2,3-butane diacetal protected aldehyde **4**, the flow synthesis of which we have previously described.[13] A functionalized triphenylphosphine monolith[14] was then used to perform a Wittig reaction in flow. The resultant triphenylphosphine oxide was immobilized on the monolith, delivering α,β-unsaturated methyl ester **5** without further purification (Scheme 1) which was then subjected to an asymmetric hydrogenation reaction in flow using Pfaltz's catalyst (*R*,*R*)-**6**[15] and a bespoke tube-in-tube reactor to facilitate gas–liquid contact.[16] This reactor enables pressurized gases to be used safely in the laboratory and significantly reduces the volume of gas required relative to batch-mode hydrogenations. A protecting group switch was then performed on the vicinal diol to prepare acetonide **8**. Polymer-supported benzylamine (QP-BZA) and basic aluminium oxide scavenged the acetic acid and ferric chloride respectively so that solvent removal was the only necessary manual handling required to isolate the product.

A telescoped reduction–crotylation protocol was then used to convert methyl ester **8** directly into homoallylic

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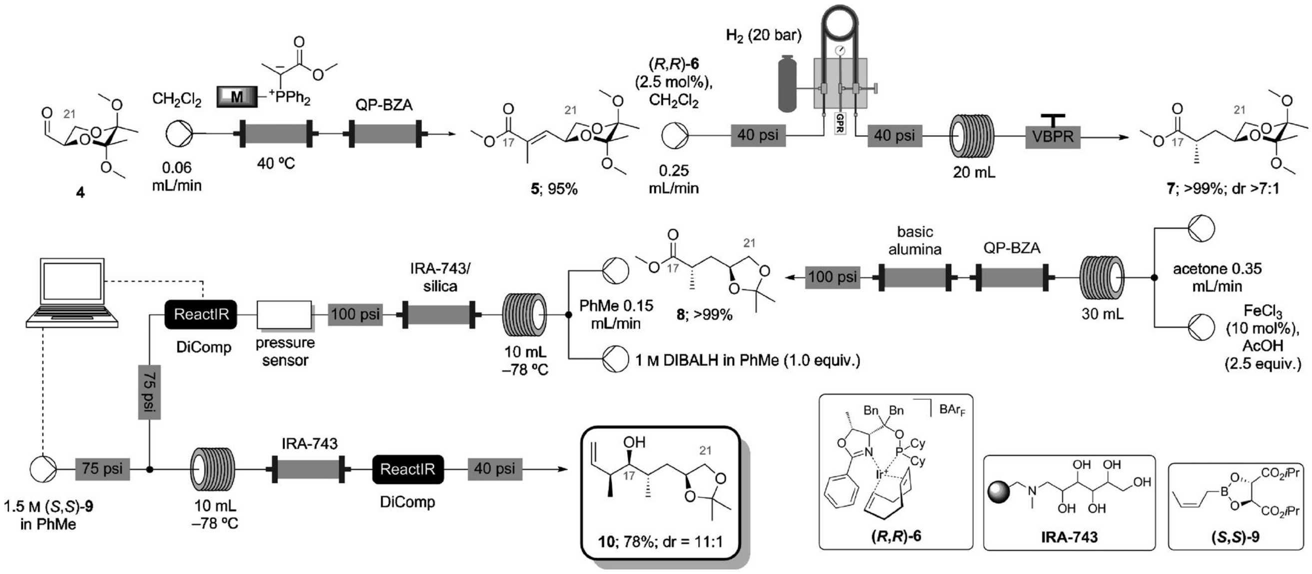


Scheme 1. Flow synthesis of homoallylic alcohol **10**. M = monolith; QP = QuadraPure; BZA = benzylamine; psi = pounds per square inch; VBPR = variable back pressure regulator; DIBALH = diisobutylaluminium hydride; Bn = benzyl; Cy = cyclohexyl; BAr$_F$ = tetrakis(pentafluorophenyl)-borate.

alcohol **10**.[17] Taking advantage of the superior temperature control in flow, methyl ester **8** was selectively and reproducibly reduced to the aldehyde. In real time, the concentration of the aldehyde intermediate was measured using a FlowIR cell.[18] This data was exported and converted into a flow rate for a third pump that dispensed crotylating reagent (*S*,*S*)-**9**. This reagent is therefore automatically dispensed as a function of the concentration of the aldehyde intermediate, maintaining stoichiometry along a flowing stream of varying concentration.

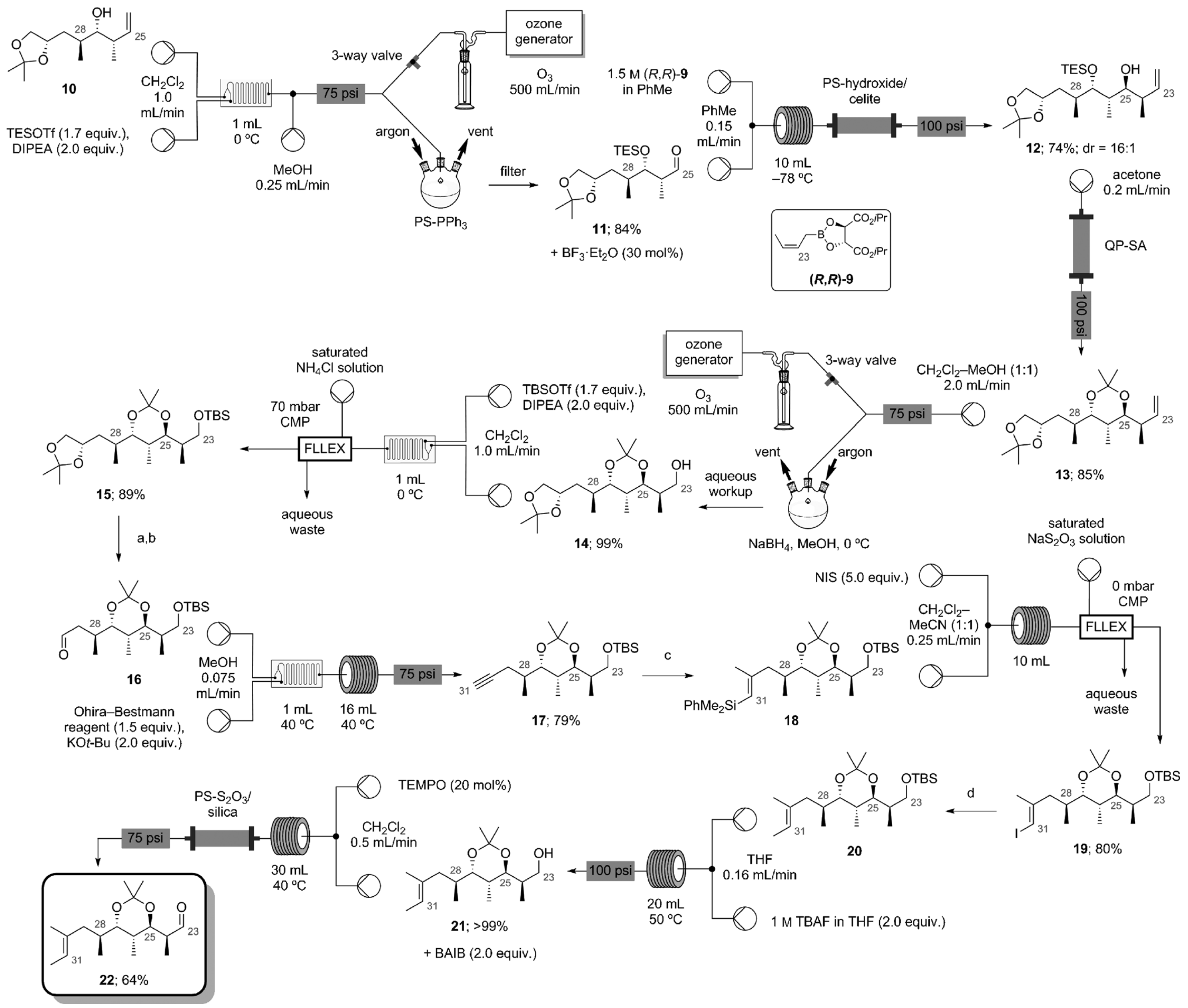
Homoallylic alcohol **10** was used to prepare two advanced fragments, aldehyde **22** (Scheme 2) and bis-alkyne **31** (Scheme 3), which contain the same three contiguous stereocenters. This high yielding four step flow sequence from readily available aldehyde **4** enabled useful quantities of this key olefin to be prepared repeatedly on demand, which was essential to support the synthesis in its latter stages.

The preparation of aldehyde fragment **22** from homoallylic alcohol **10** commenced with a telescoped silylation-ozonolysis sequence. Olefin **10** was firstly reacted with a stream of TESOTf and DIPEA (Scheme 2). The reaction was complete in 30 seconds, taking advantage of the enhanced mixing in the 1 mL chip. The output was then diluted with methanol and subjected to a rapid flow of ozone.[19] The resulting ozonide was collected in a flask containing polymer-supported triphenylphosphine to generate aldehyde **11**. This setup avoids significant ozonide build up as it is instantaneously quenched. The fast flow rates used for this sequence established a high throughput of 12 mmol h^{-1} of aldehyde **11** from olefin **10**.

The next two stereocenters were also installed using a flow-Roush crotylation, this time with (*R*,*R*)-**9**. Chain elongation reactions are key to natural product assembly and the development of this flow protocol has been described elsewhere.[17] In this sterically demanding case, boron trifluoride was required to improve the conversion and diastereoselectivity of the reaction. Advanced olefin **12** was then dissolved in acetone and passed through a column containing polymer-supported sulfonic acid (QP-SA) to concomitantly cleave the silyl ether and protect the 1,3-diol as an acetonide **13**. This was then subjected to a second ozonolysis in flow to afford primary alcohol **14** following a reductive workup. The same silyl protection procedure was then used, this time with TBSOTf. However, in this case, the output from the 1 mL chip was mixed with a stream of aqueous ammonium chloride solution and directed through a commercially available flow liquid-liquid extractor (FLLEX)[20] to remove the salts in situ and furnish silyl ether **15**. The FLLEX unit offers an alternative to polymer-supported reagents for inline work-up procedures.

A two step batch-mode sequence was required to synthesize aldehyde **16**. Selective cleavage of the external acetonide to furnish the vicinal diol[21] was followed by oxidative cleavage under standard conditions. These steps required long reaction times and were not suitable for a flow protocol. Aldehyde **16** was converted into alkyne **17** in flow using the Ohira–Bestmann reagent.[22]

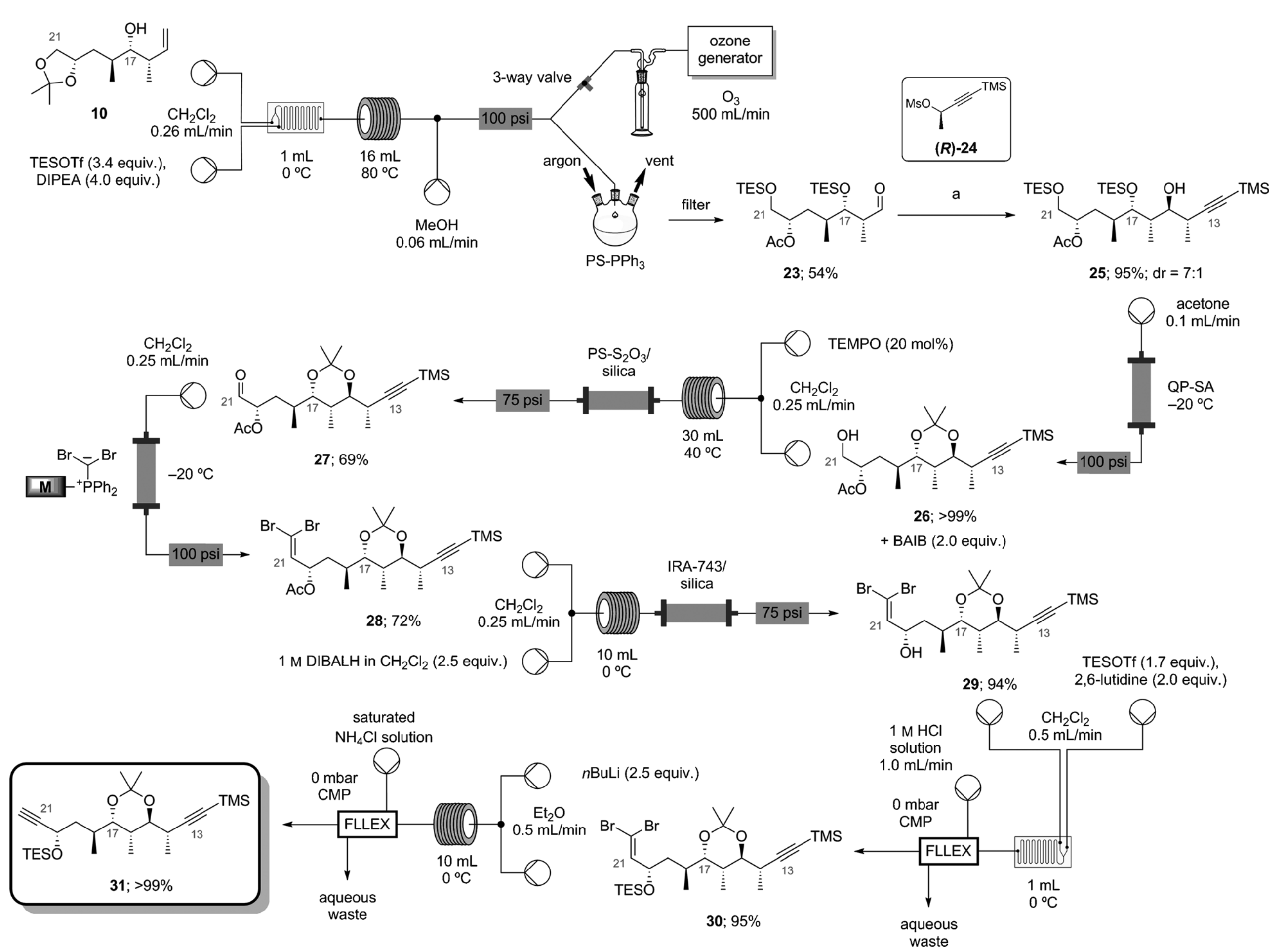
With alkyne **17** in hand, we then investigated methods to install the two methyl groups of the terminal trisubstituted double bond. This was eventually achieved through a silylcupration reaction wherein the transient vinyl cuprate species was quenched with iodomethane to generate vinylsilane **18** with the required *syn* relationship.[23] Vinyl iodide **19** was prepared in flow by combining vinyl silane **18** with a solution of *N*-iodosuccinimide. Excess reagent was efficiently removed inline by washing with an aqueous thiosulfate solution. The final methyl group of the trisubstituted double bond was installed through a Negishi cross-coupling reaction between vinyl iodide **19** and dimethylzinc in batch-mode (Scheme 2). The last two steps to provide the advanced aldehyde fragment **22** were a silyl deprotection in flow, using an elevated reaction temperature to reduce the reaction time from 16 h to 1 h,



Scheme 2. Flow synthesis of aldehyde **22**. Reagents and conditions a) TMSOTf, DIPEA, CH_2Cl_2, 0 °C→RT, 89 %; b) $NaIO_4$, THF-H_2O (1:1), RT, 95 %; c) CuCN, $PhMe_2SiLi$, THF, 0 °C, then MeI, 0 °C, 90 %; d) $PdCl_2(PPh_3)_2$ (20 mol %), Me_2Zn, THF, RT, 82 %. TESOTf = triethylsilyl trifluoromethanesulfonate; DIPEA = *N*,*N*-diisopropylethylamine; PS = polymer-supported; SA = sulfonic acid; TBS = *tert*-butyldimethylsilyl; FLLEX = flow liquid-liquid extractor; CMP = cross membrane pressure; NIS = *N*-iodosuccinimide; TBAF = tetrabutylammonium fluoride; BAIB = bis(acetoxy)iodobenzene; TEMPO = 2,2,6,6-tetramethylpiperidine 1-oxyl.

followed by a TEMPO-mediated oxidation, again in flow.[24] It was found that a plug of silica gel was sufficient to separate any trace of unreacted alcohol **21** from the desired product whereas the iodine by-products were removed with a polymer-supported thiosulfate.

The second advanced fragment bis-alkyne **31** was also prepared from homoallylic alcohol **10**. As with the previous fragment, the synthesis began with a telescoped silylation–ozonolysis protocol (Scheme 3). However, in this case, homoallylic alcohol **10** was treated with an excess of TESOTf to both protect the secondary alcohol and open the acetonide ring, preparing the primary silyl ether and secondary enol ether in situ.[21] The output stream was then diluted with methanol and subjected to a stream of ozone to oxidatively cleave the enol ether and terminal olefin. This single flow operation carries out three protecting group manipulations and two oxidations, resulting in the preparation of aldehyde **23** for the subsequent chain elongation step. The stereogenic relationship from C14–C16 was realized following the method developed by Marshall et al., using propargylic mesylate (*R*)-**24** to generate a chiral allenylzinc reagent in situ which reacts with aldehyde **23** through an S_E2' mechanism.[25] This furnished bis-silyl ether **25** in high yield and reasonable diastereoselectivity which was then passed through a column containing QP-SA held at low temperature to perform the silyl deprotection and 1,3-diol protection in a single step. The low temperature was necessary to avoid 1,2-acyl migration of the secondary acetate group, a major



Scheme 3. Flow synthesis of bis-alkyne **31**. Reagents and conditions a) (*R*)-**24**, Pd(OAc)$_2$ (10 mol%), PPh$_3$, Et$_2$Zn, THF, 0°C→−78°C→−20°C→RT, 95%. Ms = methanesulfonate; TMS = trimethylsilyl.

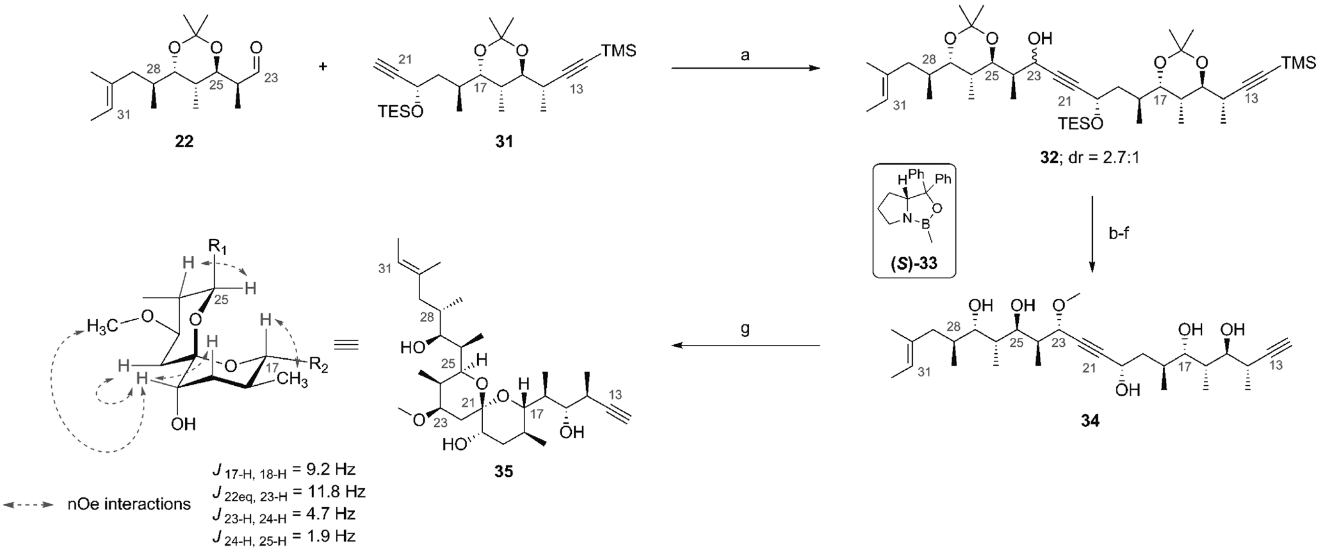
impurity formed during the corresponding batch protocol.[26] Primary alcohol **26** was oxidized to aldehyde **27** in flow using TEMPO, following the same procedure described above. Dibromoolefin **28** was then synthesized using a previously reported protocol from our group to effect the Ramirez olefination in flow using a monolithic ylid.[27]

Attempts to generate the bis-alkyne from dibromoolefin **28** failed, presumably due to the lability of the acetate protecting group. To progress the synthesis, the acetate group was cleaved by combining dibromoolefin **28** with a stream of DIBALH. The reaction was purified inline using a polyol resin (IRA-743), which effectively chelates aluminium residues, to afford secondary alcohol **29**, which was then reprotected using the previously described silylation procedure. Finally, bis-alkyne **31** was prepared through a Corey–Fuchs reaction in flow. The excess base was quenched inline using a stream of aqueous ammonium chloride solution.

In summary, synthesis of advanced aldehyde fragment **22** was completed in 13 steps (9 in flow and 4 in batch) and 11.6% overall yield from homoallylic alcohol **10** (Scheme 2).[28] The second advanced fragment, bis-alkyne **31**, was prepared in 8 steps (7 in flow and 1 in batch) and in 22% overall yield, also from homoallylic alcohol **10**. In terms of complexity, aldehyde **22** and bis-alkyne **31** are among the most advanced substrates prepared in flow to date.

Previous approaches prepared the spiroketal fragment via conventional acid-catalyzed spiroketalization in which the linear precursor was prepared from an aldol reaction.[29] Our approach involved a highly ambitious gold catalyzed spiroketalization from an internal alkyne and so the fragments were coupled by reacting the lithium acetylide of bis-alkyne **31** with aldehyde **22** to furnish ynol **32** as an inseparable epimeric mixture (d.r. = 2.7:1) at the C23 position (Scheme 4). This was subsequently oxidized to the ynone and reduced using the Corey–Bakshi–Shibata reagent (*S*)-**33** to give a single diastereoisomer[30] which was characterized via Mosher's method (see Supporting Information). The ynol was then methylated and the linear precursor globally deprotected to afford pentol **34** in preparation for the key spiroketalization step.

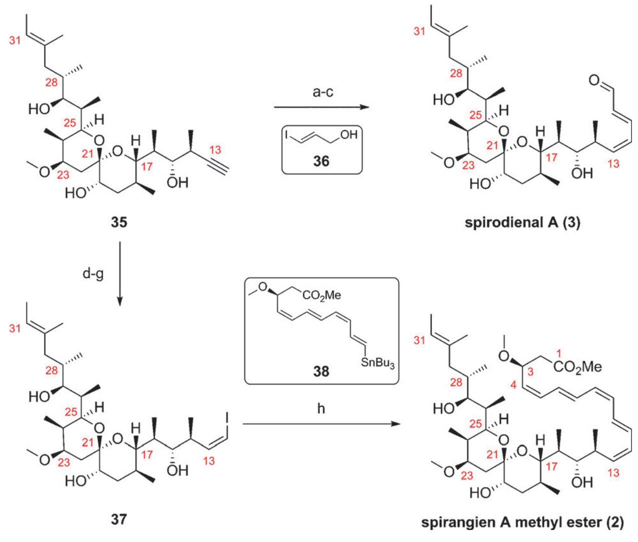
In recent years, gold-catalyzed reactions have been used in total synthesis programs to promote selective spiroketalization reactions.[31] After extensive screening, it was found that gold(I) chloride would promote the desired spiroketalization event and afford the key spiroketal intermediate **35** in moderate yield. Other spiroketal frameworks were isolated including a minor amount of a [4.6]-spiroketal generated by



Scheme 4. Reagents and conditions a) **31**, *n*BuLi, THF, −78 °C, then **22**, −78 °C→RT, 87 % (> 99 % brsm); b) MnO_2, CH_2Cl_2, RT, 97 %; c) (*S*)-**33**, $BH_3{\cdot}Me_2S$, THF, −30 °C, 91 %; d) NaH, MeI, THF, 0 °C→RT, 99 %; e) TBAF, THF, RT, > 99 %; f) QP-SA, MeOH, RT, > 99 %; g) AuCl (10 mol %), PPTS, CH_2Cl_2, −20 °C→RT, 30 %. PPTS = pyridinium *p*-toluenesulfonate.

spiroketalization onto the C22 position, and an unsaturated spiroketal compound formed through elimination of the C23 methoxy group. However, the desired spiroketal **35** was isolated and the configuration confirmed via nOe analysis and proton-proton coupling constants.[9]

With spiroketal **35** in hand, the endgame strategies for both natural products were explored (Scheme 5). Spirodienal A (**3**) was prepared from alkyne **35** in a three step sequence. Firstly, a Sonogashira reaction with vinyl iodide **36**,[32] followed by a mixed-metal *cis*-selective reduction[33] of the C12–C13 internal alkyne and lastly an allylic oxidation to afford the dienal motif. The data for synthetic spirodienal A (**3**) matched the isolated natural product and signified a first total synthesis, confirming the absolute structure and stereochemistry of the natural product.



Scheme 5. Reagents and conditions a) **36**, $[Pd(PPh_3)_4]$ (5 mol %), CuI (10 mol %), Et_3N, PhH, RT, 90 %; b) Zn(Cu/Ag), MeOH-H_2O-THF (1:1:1), 40 °C, 59 %; c) MnO_2, CH_2Cl_2, RT, 84 %; d) TESOTf, 2,6-lutidine, CH_2Cl_2, −78 °C→0 °C, 59 %; e) NIS, $AgNO_3$, acetone-DMF (5:1), RT, 49 %; f) NBSH, Et_3N, *i*PrOH-THF (1:1), RT, 93 %; g) CSA, MeOH, RT, 91 %; h) **38**, $[Pd_2(dba)_3]$ (10 mol %), $AsPh_3$ (26 mol %), DMF-THF (4:1), RT, 43 %. NBSH = 2-nitrobenzenesulfonylhydrazide; CSA = (±)-camphor-10-sulfonic acid; dba = dibenzylideneacetone.

The synthesis of spirangien A methyl ester (**2**) required silyl protection of the hydroxy groups followed by iodination of the terminal alkyne. Following diimide reduction of the iodoalkyne and global desilylation, vinyl iodide **37** was prepared which represented a formal total synthesis.[10] Appendage of the stannane tetraene **38** reported by Paterson et al. then furnished spirangien A methyl ester (**2**). The spectroscopic data matched those previously reported.[10]

In conclusion, we have synthesized spirangien A methyl ester (**2**) and spirodienal A (**3**) with a divergent and conceptually new approach that integrates batch and flow chemistry. Our approach also gives access to other members of this family of natural products.[34] Both syntheses share a common building block, homoallylic alcohol **10**, which was readily available in multigram quantities via a short flow sequence. The highlight of this work is the significant use of flow technologies to prepare the two complex coupling fragments, aldehyde **22** and bis-alkyne **31**. Completing these syntheses in flow required the development of a number of new methods including automated reagent addition, silylations, crotylations, ozonolysis, olefinations and oxidations in flow all of which were used iteratively and dramatically accelerated the parallel synthesis of these two fragments.

Whilst complex and sensitive reactions using a flow based approach is certainly challenging, this work shows that once general protocols are in place the benefits are soon realized. In every case, the transformations developed in flow display an advantage over the corresponding batch reactions, whether it is a higher yield, an improved safety profile or simply a faster and more efficient process. As flow technologies continue to be developed and become more accessible, we hope to see more machine assisted applications in synthetic laboratories especially as enabling tools for natural product synthetic chemists.

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Keywords: flow chemistry · natural products · spirangien A · spirodienal A · total synthesis

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[28] Single-crystal X-ray analysis confirmed the absolute configuration of aldehyde **22** and hence the stereochemistry of homoallylic alcohol **10**.

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[34] Performing the late-stage Negishi cross-coupling reaction with diethylzinc instead of dimethylzinc en route to the synthesis of aldehyde **22** would access the first total syntheses of spirangien B and spirodienal B.