An Integrated Flow and Batch-Based Approach for the Synthesis of *O*-Methyl Siphonazole

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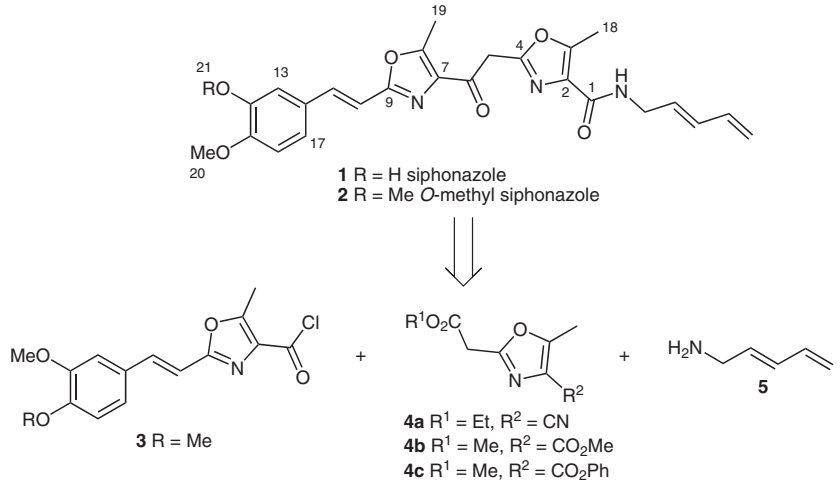
Abstract: The bisoxazole containing natural product *O*-methyl siphonazole was assembled using a suite of microreactors via a flow-based approach in concert with traditional batch methods. The use of a toolbox of solid-supported scavengers and reagents to aid purification afforded the natural product in a total of nine steps.

Key words: oxazoles, Claisen condensation, flow chemistry, microreactors, solid-supported reagents

As part of our ongoing interest in oxazole-containing natural products,[1] we have devised a synthetic route to the bisoxazole alkaloid *O*-methyl siphonazole (**2**), which was discovered by König and co-workers in 2006, along with the C-21-demethylated parent compound siphonazole (**1**, Scheme 1).[2] While Moody[3] and Ciufolini[4] reported the first syntheses of the siphonazoles in 2008 and 2009, a detailed biological profile of these metabolites of *Herpetosiphon sp.* has not been thoroughly established. Thus, a modular synthesis of the natural products **1** and **2**, flexible enough for the production of unnatural analogues, is of interest.

In this article we disclose our results on the preparation of *O*-methyl siphonazole (**2**) based on an integrated approach combining conventional batch and new flow chemistry methods. The application of flow techniques in organic synthesis as described by numerous laboratories[5] has transformed flow chemistry from an academic interest to a valuable enabling technology that overcomes several of the bottlenecks traditionally faced by synthetic chemists.[6] As such the generation and immediate use of hazardous, toxic, or unstable intermediates[7] has been reported as well as the possibility to more reliably perform reaction scale-up.[8] Furthermore, flow reactors can be transformed into automated platforms by the addition of liquid handling and fraction collector modules expanding the working capabilities of the units and allowing for 24/7 working regimes.[9] Finally, individual reactions can be telescoped into one continuous flow sequence, thus avoiding the iterative isolation, purification, and reprocessing of intermediates.[10] With these potential advantages in mind, we have orchestrated an improved total synthesis of *O*-methyl siphonazole by making use of flow techniques in order to expedite certain steps in the synthesis. Our first synthetic target was the oxazole carboxylic acid **10** which we intended to access from commercially available dimethoxycinnamic acid (**6**, Scheme 2).

In order to process this material quickly we decided to employ the Vapourtec R2+/R4 flow system[11] where two small HPLC pumps deliver streams of starting materials which are subsequently mixed at either a T-piece or within a microchip. The resulting stream can then be introduced into a tubular convection flow coil (CFC) which is



Scheme 1 Siphonazole (**1**) and its building blocks **3**–**5**

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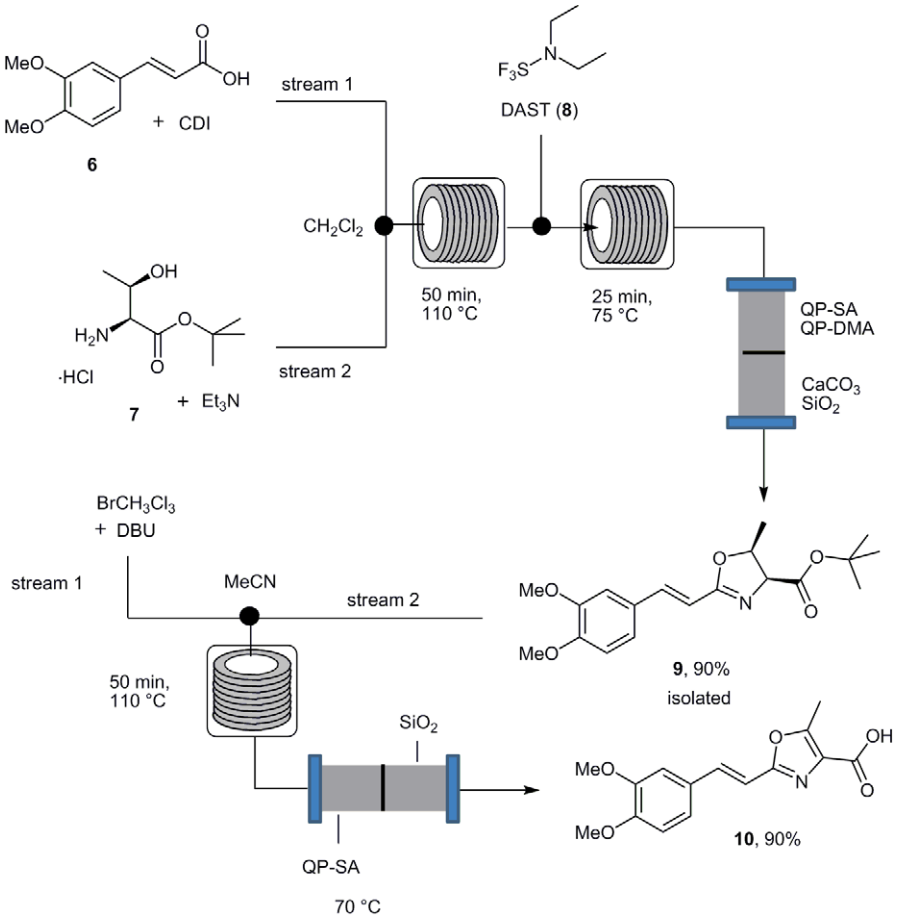


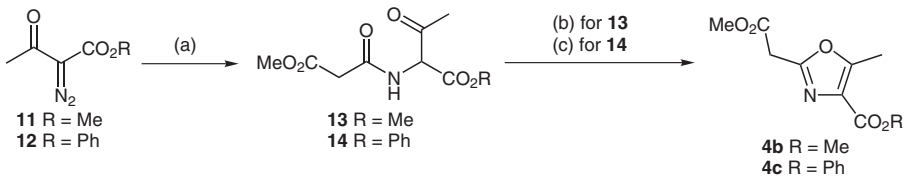
Scheme 2 Flow synthesis of oxazole carboxylic acid **10**

heated or cooled to a desired temperature. The reaction stream is then subjected to in-line purification using solid-supported quenching and scavenger resins prior to the product being collected or relayed directly into the next step of the synthesis sequence. Using this flow configuration we established conditions for converting dimethoxycinnamic acid (**6**) into oxazoline derivative **9** as shown in Scheme 2. The carboxylic acid was activated with CDI and coupled with threonine *tert*-butyl ester hydrochloride (**7**) in situ before adding a third stream containing diethylaminosulfur trifluoride (DAST)[12] to accomplish the cyclodehydration of the intermediate amide. A set of heterogeneous scavengers such as a sulfonic acid (QP-SA,[13] to remove Et_3N, imidazole and residual threonine *tert*-butyl ester), a tertiary amine (QP-DMA,[13] to remove residual acid), and plugs of $CaCO_3$ and SiO_2 (to quench and trap DAST and HF) were used in glass columns affording oxazoline **9** in greater than 95% purity. In a second step this oxazoline was then oxidized to the corresponding oxazole using a mixture of $BrCCl_3$ and DBU[14] followed by cleavage of the *tert*-butyl ester using the previous mentioned QP-SA scavenger resin placed in a heated glass column.

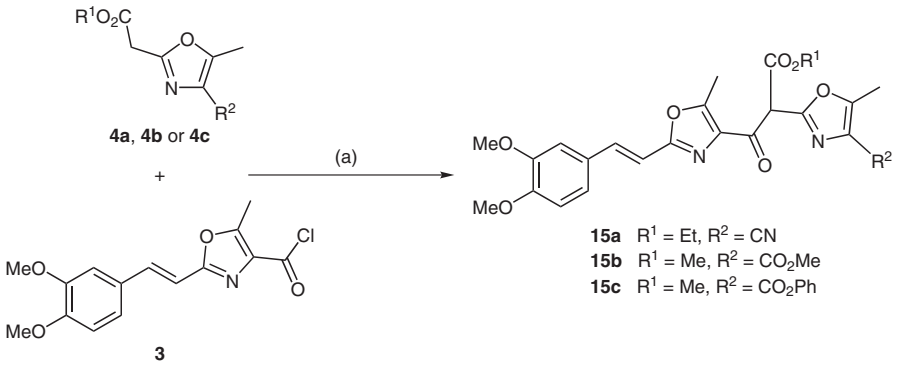
Using this flow sequence we achieved rapid access to pure carboxylic acid **10** as a white, bench-stable solid in multigram quantities without the need to perform any traditional workup or purification steps. This material could then be quantitatively converted into acyl chloride **3** using oxalyl chloride in the presence of catalytic amounts of DMF by a standard batch method.

Having accomplished an efficient synthesis of the left-hand fragment **10**, we next focused on the preparation of a suitable coupling partner. As the central carbon–carbon bond C5–C6 can be formed by a formal acylation, we synthesized several acetyl oxazoles **4a–c**. Whilst oxazole nitrile **4a** is a known compound,[15] oxazole diester building blocks **4b** and **4c** were prepared in two steps from diazo esters **11** and **12**[16] as described in Scheme 3. An NH insertion of the rhodium carbenoid derived from **11** and **12** with methyl malonate monoamide[17] led to keto amides **13** and **14**, which cyclized to oxazoles **4b** and **4c** under Wipf's conditions.[18] As this sequence involved the slow addition of methyl malonate monoamide, the use of a standard syringe pump gave the best results. This was followed by cyclodehydration of intermediates **13** and **14** where again all steps were performed by convenient batch methods (Scheme 3).

In order to progress the synthesis, acid chloride **3** was coupled by a Claisen condensation with the oxazole esters **4a–c** (Scheme 4). It was observed that the diesters **4b** and **4c** were prone to self-condensation upon treatment with NaHMDS, therefore the base (2.3 equiv) was added, via a syringe pump to the mixture of acid chloride **3** (1.3 equiv) and oxazole esters **4a–c** in THF (1.0 equiv each) at –78



Scheme 3 Preparation of oxazoles **4b** and **4c**. *Reagents and conditions*: (a) methyl malonate monoamide, $Rh_2(OAc)_4$ (2 mol%), CH_2Cl_2, reflux, syringe pump addition, 84% for **13**, 56% for **14**; (b) I_2, Ph_3P, Et_3N, CH_2Cl_2, r.t., 55%; (c) I_2, Ph_3P, *i*-Pr_2NEt, PhMe, 80 °C, 71%.

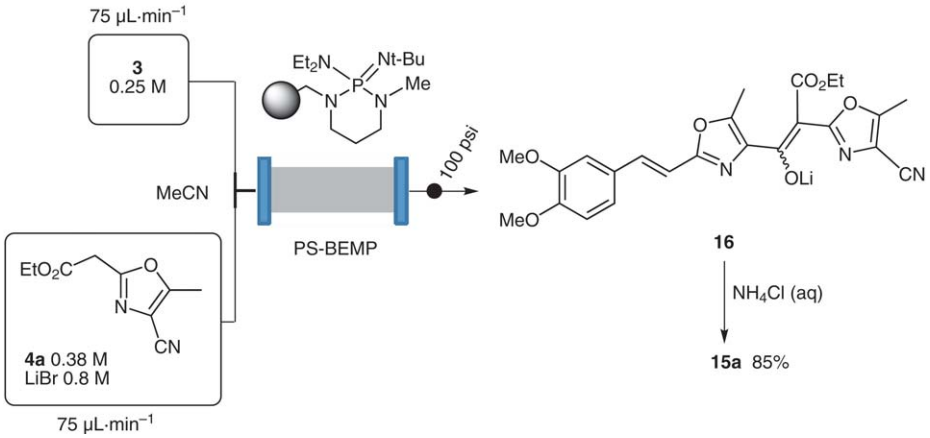


Scheme 4 Claisen condensation of acid chloride **3** with oxazoles **4a**–**c**. *Reagents and conditions*: (a) NaHMDS (2.3 equiv) added at –78 °C, via a syringe pump, to **3** (1.3 equiv) and **4a**–**c** (1.0 equiv) in THF.

°C. This procedure cleanly generated the desired adducts **15a**–**c**, which were employed without purification in the subsequent decarboxylation step.

The use of a polymer-supported base for the Claisen condensation of acid chloride **3** with oxazole esters **4a**–**c** was also examined. As illustrated in Scheme 5, stock solutions of **3** and **4a** in MeCN were mixed in a microreactor, followed by elution through a cartridge[19] containing PS-BEMP.[20] Unfortunately this procedure did not deliver the expected coupled material. Ultimately, it was found that both the product and excess starting material **4a** were retained as the corresponding enolates by the immobilized base. This was potentially very problematic because applying any standard release protocol involving displacement of the product from the column by treatment with an acidic solution would also liberate the excess starting material and acid via hydrolysis of the acyl chloride **3**. As a result additional processing through subsequent in-line scavenging or column chromatography of the crude product would be required. However, pleasingly it was discovered that when LiBr was added to the stock solution of ester **4a**, the desired product **15a** could then be obtained cleanly in 85% yield after aqueous quenching. It is proposed that the addition of the LiBr leads to the formation of the strongly chelated and highly soluble lithium enolate adduct **16**. This therefore enables flow processing of the reaction with the advantage that the major potential contaminants of excess **4a** and hydrolyzed carboxylic acid of **3** are more strongly bound on the polymeric support and so removed from the product stream of enolate **16**.

Next the decarboxylation of Claisen adducts **15a**–**c** was studied in detail (Table 1). Adduct **15a** cleanly underwent decarboxylation in the presence of excess NaCl (20 equiv) in wet DMSO, to produce bisoxazole nitrile **17a** in 73% overall yield (two steps from **4a**). When the corresponding bismethylester **15b** was reacted under identical condi-

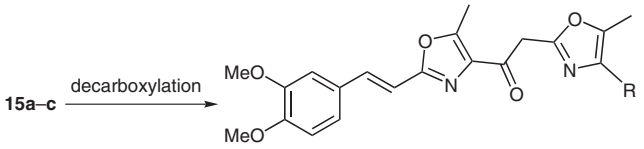


Scheme 5 Claisen reaction of oxazole **3** and **4a** induced by PS-BEMP as polymer-supported base in the presence of LiBr

tions, surprisingly, no easily identified products could be obtained, and recovery of the starting material after chromatographic separation was poor. However, decarboxylation of **15b** in the absence of NaCl did allow for the isolation of product **17b** albeit in very low yield (7%). The salt-free decarboxylation of adduct **15c**, bearing a phenyl ester group at C-2 (instead of the methyl ester) on the other hand produced bisoxazole ester **17c** in a correspondingly higher 40% overall yield from **4c**.

These results suggest that in the case of substrate **15b**, with a methyl ester in the 2-position, both the $B_{AL}2$ and $B_{AC}2$ cleavage mechanisms operate with almost the same efficiency. This is supported by the observation that although both pathways might be possible in the presence of chloride ions, presumably only the latter mechanism is possible when water is the sole nucleophile.[21] However, the disappointingly low yield of bisoxazole **17b** (7%) from the salt-free reaction indicates that the C-2 methyl ester is highly reactive towards hydrolysis at elevated temperatures, and so it was not possible to tune the reactivity by switching the external nucleophile from chloride to water. Furthermore, it would appear that the free C-2 carboxylate generated from **15b** is highly unstable and prone to thermal decarboxylation, followed by a further decomposition of the resulting C-2 carbanion precluding this as a viable synthetic route. Compared to substrate **15b**, the alternative diester substrate **15c** demonstrated improved stability, as the $B_{AL}2$ mechanism cannot operate at the site of the C-2 phenyl ester. Thus, it was possible to isolate the decarboxylation product **17c** in 40% yield. This was lower than the 73% yield of the C-2 cyano compound **17a**, due to partial hydrolysis of the phenyl ester of **15c** via the $B_{AC}2$ mechanism.

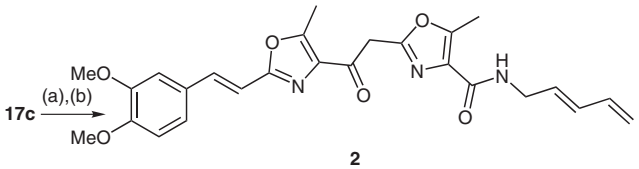
Table 1 Decarboxylation of Keto Esters **15a–c** to Bisoxazole Ketones **15a–c**



17a–c

R	Conditions	Yield from **4a–c** (%)	
CN	NaCl, DMSO, H_2O MW, 160 °C, 1 h	**17a**	73
CO_2Me	NaCl, DMSO, H_2O MW, 160 °C, 1 h	**17b**	0
CO_2Me	DMSO, H_2O MW, 150 °C, 1 h	**17b**	7
CO_2Ph	DMSO, H_2O MW, 150 °C, 1 h	**17c**	40

Nevertheless, the bisoxazole nitrile **17a** was not a suitable precursor to the natural product **2** as the cyano group at C-2 resisted all attempts at hydrolysis to the carboxylic acid. Even strongly acidic or basic conditions only led to the corresponding carboxamide in low yields, accompanied by significant demethylation of the C-20 methoxy group. Pleasingly, however, bisoxazole phenyl ester **17c** readily hydrolyzed when treated with barium hydroxide generating the corresponding acid, which was obtained in 1:1 mixture with phenol. Purification and isolation of the acid was possible, however, it was found that the crude material could be coupled with pentadienyl amine **5**[22] directly even in the presence of the phenol (Scheme 6). When the acid was activated with TBTU[23] (1.5 equiv), and amine **5** (2.2 equiv) was added to the mixture after 15 minutes incubation, no product derived from phenol addition was observed, with *O*-methyl siphonazole (**2**)[24] being formed exclusively, and enabling isolation in 47% combined yield over the two steps.



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Scheme 6 Conversion of bisoxazole ester **17c** into *O*-methyl siphonazole **2**. *Reagents and conditions*: (a) $BaOH_2{\cdot}8H_2O$, THF–H_2O, r.t.; (b) TBTU (1.5 equiv), **5** (2.2 equiv), DMF, r.t., 47% (2 steps).

The outcome of our efforts presented in this article shows that the synthesis of the natural product *O*-methyl siphonazole (**2**) from oxazole units **3** and **4c**, and amine **5** was accomplished via a short sequence including a Claisen condensation and Krapcho decarboxylation as key steps. Furthermore, the use of flow techniques in concert with immobilized reagents and scavengers greatly improved the overall efficiency of the synthesis by circumventing unnecessary isolation and purification steps. In summary, this work exemplifies the benefit of an integrated approach combining traditional batch procedures with appropriate enabling techniques such as flow chemistry. This strategy afforded *O*-methyl siphonazole in nine steps.

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(24) **NMR Data**
^{1}H NMR (600 MHz, $CDCl_3$): δ = 2.64, 2.67 (2 s, 2 × 3 H, 18-H, 19-H), 3.92, 3.93 (2 s, 2 × 3 H, 20-H, 21-H), 4.03 (*t*, *J* = 5.8 Hz, 2 H, 1′-H), 4.41 (s, 2 H, 5-H), 5.06 (d, *J* = 10.3 Hz, 1 H, 5′-H), 5.18 (d, *J* = 17.0 Hz, 1 H, 5′-H), 5.73 (td, *J* = 5.8, 15.0 Hz, 1 H, 2′-H), 6.22 (dd, *J* = 10.3, 15.0 Hz, 1 H,

3′-H), 6.31 (td, *J* = 10.3, 17.0 Hz, 1 H, 4′-H), 6.75 (d, *J* = 16.4, 1 H, 10-H), 6.88 (d, *J* = 8.2 Hz, 1 H, 16-H), 7.00 (t, *J* = 5.8 Hz, 1 H, NH), 7.07 (d, *J* = 1.6 Hz, 1 H, 13-H), 7.09 (dd, *J* = 1.6, 8.2 Hz, 1 H, 17-H), 7.44 (d, *J* = 16.4 Hz, 1 H, 11-H) ppm. ^{13}C NMR (150 MHz): δ = 11.7, 12.4 (2 q, C-18, C-19), 39.4 (t, C-5), 40.3 (t, C-1′), 55.9, 56.0 (2 q, C-20, C-21), 108.9 (d, C-13), 110.8 (d, C-10), 111.2 (d, C-16), 117.4 (t, C-5′), 121.5 (d, C-17), 128.1 (s, C-12), 129.45, 129.49 (2 d, C-2′, C-3′), 132.8 (s, C-2), 134.5 (s, C-7), 136.1 (d, C-4′), 137.3 (d, C-11), 149.3, 150.6 (2 s, C-14, C-15), 153.8 (s, C-3), 155.3 (s, C-8), 155.6 (s, C-4), 159.1 (s, C-9), 161.7 (s, C-1), 189.4 (s, C-6) ppm.