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A Short Multistep Flow Synthesis of a Potential Spirocyclic Fragrance Component

The search for novel chemical architectures displaying improved biological properties is a never-ending synthetic challenge. In this context many new test structures are often conceived by selecting and replicating specific design elements from naturally occurring molecules and displaying them in an alternative format by way of a new chemical assembly. Constructing these newly designed compounds can be a timely and expensive process especially when a large quantity of the target material is required for physiochemical and property testing. To permit easier scale-up and safer working practice, many chemical researchers are employing flow chemistry approaches to aid in their synthesis challenges. The preparation of a key spirocyclic lactone using flow-based reaction processing techniques is reported.

Keywords: Baylis-Hillman reaction, Diels-Alder reaction, Flow synthesis, Meso reactor

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Supporting Information available online

1 Introduction

Within the flavors and fragrance industries terpenoid structures dominate the chemical portfolios of most supply houses. The *gem*-dimethylcyclohexene unit is particularly prevalent as occurring in the carotenoids (retinal, vitamin A, β-carotene) and many bench mark fragrance classes such as the ionones and damascones (Fig. 1) [1, 2]. As part of a collaboration exploring new fragrance components we were recently challenged to formulate a scalable synthesis to the target 2-oxaspiro [4.5]decan-1-one, molecule **1**, which had been identified as a compound of interest from biological isolation. The crude extraction containing the proposed structure **1** had shown modest antimicrobial activity and promising indicators as a base fragrance note.

2 Retrosynthesis

The synthetic approach aimed to make use of the inherent symmetry invested in the core structure which we perceived could be assembled from a Diels-Alder cycloaddition reaction (Scheme 1). A survey of the literature indicated that elimination from an appropriately functionalized allylic system **4** could be used to in situ generate the necessary diene component **3** [3]. Correspondingly, a Baylis-Hillman reaction between the low-cost starting materials isobutyraldehyde (**5**) and acrylonitrile (**6**) would furnish the target allylic system which could be activated to induce elimination using various mediators. Indeed, a similar tactic had previously been used in the preparation of a related but simplified structure mikanecic acid [4, 5]. Encouraged by this, we set out to devise a flow-based synthesis to the target structure [6–15]. The experimental procedures can be found in the Supporting Information.

3 Synthesis

The Baylis-Hillman reaction is a very versatile and powerful bond-forming reaction; however, it is normally associated with prolonged reaction times of up to seven days [16]. In order to provide sufficient residence time to achieve high conversions, we elected to progress the reaction through a set of continuous-flow stirred tank reactors (6×CFSTR) operated in series, each of 100 mL internal volume. The reactors were stirred at a constant 280 rpm and isothermally incubated at 65 °C. The residence-time distribution (RTD) of the reactor was not determined, instead chemical optimization was performed based upon conversion measurements taken between the reactors using a non-invasive ReactIR sampling method. Flow rates were adjusted to give > 90 % conversion by the exit of the 5th reactor [17]. Two feed lines were prepared as stock solutions; solution 1: 6 M isobutyraldehyde (**5**) containing 15 mol % 1,4-diazabicyclo[2.2.2]octane (DABCO) and solution 2: 6.6 M solution of acrylonitrile (**6**). A mixed solvent system of 2-methyl tetrahydrofuran and trifluoroethanol (15:2 volumetric ratio) served as the makeup solvent. The presence of hydrogen donor solvents has been shown to significantly improve the kinetics of the Baylis-Hillman reaction [18–21]. Although water or MeOH are often employed, the use of the more acidic trifluoroethanol was found to be particularly beneficial for this transformation.

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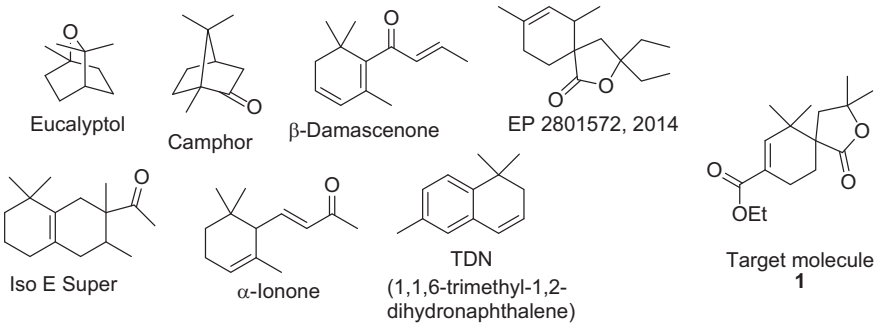


Figure 1. Common structural motifs in fragrances and flavors.

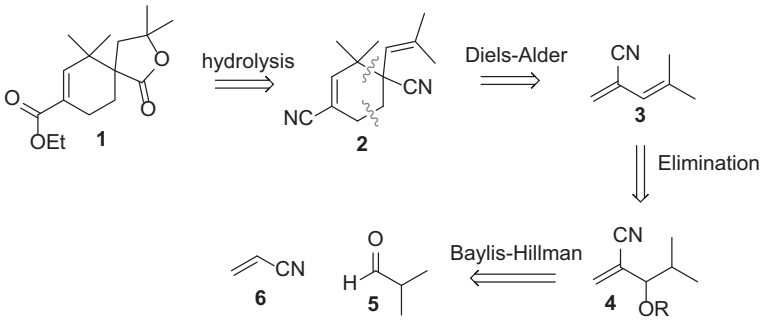
Equal flow rates of 0.3 mL min^{-1} were utilized for dispensing each feed line. The output flow from the sixth consecutive CFSTR yielded > 95 % conversion (^{1}H NMR analysis) running at steady state (20.2 h as determined by GC analysis). This crude output was directly coupled with an additional feed of neat acetic anhydride (10.6 M, 1.1 equiv., 0.17 mL min^{-1}) and directed into a second-stage reactor group comprising of three sequentially linked Polar bear plus reactors (3 × 52 mL) (Fig. 2) [22].

The reactors were maintained at 135 °C providing a combined residence time of approximately 202 min. During solution progression through this second reactor group the Baylis-Hillman adduct was first acylated (**4** R=OH → **5** R=Ac) and then underwent a thermally promoted elimination to furnish the butadiene species **3** [23]. This material was relatively short-lived at the elevated working temperature and was seen to rapidly convert via a Diels-Alder cycloaddition to the desired cyclohexene derivative **2** (residence time 202 min). The process was easily monitored by GC-MS sampling (Fig. 3).

Isolation of compound **2** was readily affected by direct evaporation of the reactor output. The residual brown oil then upon standing crystallized to yield large orange/brown crystals as displayed in Fig. 4. The material could be readily recrystallized from ethanol to give a colorless transparent crystal. However, the purity of the crude solid was sufficient to progress through the later stages of the sequence. The process to this stage running at steady state gave a throughput of ~ 23 g h^{-1} and proved very robust being run as an uninterrupted sequence for 6.5 days generating over 3.58 kg of isolated material **2**.

Having successfully devised a flow route to key intermediate **2**, next attention turned to the transformations for the subsequent esterification and lactonization (**2** → **1**). As nitriles are normally more easily hydrolyzed under basic conditions, first aqueous NaOH was used to generate the corresponding carboxylates which we anticipated would under a pH switch, to acidic conditions in the presence of ethanol, generate the desired final product **1**. However, initial attempts applying a range of basic conditions gave only partial hydrolysis resulting in exclusive formation of compound **7** upon acidification albeit in very high isolated yields and purity (> 90 % conversion, > 95 % purity ^{1}H NMR). For example, an ethanolic stock solution of intermediate **2** (2 M) was pumped (0.5 mL min^{-1}) to mix with a 4 M solution of NaOH (0.5 mL min^{-1}) before passing into a heated reactor coil (2 × 52 mL, residence time 104 min) maintained at 125 °C. The reactor output was collected and the ethanol evaporated under reduced pressure. The mixture was acidified with aqueous hydrochloric acid (2 M, pH 2) which resulted in the precipitation of a white solid which was filtered, washed with cold water, cold EtOH and dried under vacuum to yield compound **7** (91 % isolated yield).

The quaternary cyano group of **2** being flanked by the *gem*-dimethyl and allyl group is highly stearically hindered and so proved resistant to hydrolysis. This was exemplified by the fact that even heating a 6 M NaOH solution of the dinitrile **2** (0.1 M in 10 % v/v EtOH) for seven days at 120 °C gave only the mono acid derivative **7**. By extension compound **7** was shown to be easily converted to the corresponding ethyl ester **8** under standard esterification conditions (batch: 1 M in EtOH, cat H_2SO_4, reflux 6 h). Therefore, it was concluded that the most promising approach would be to alterna-



Scheme 1. Retrosynthesis of the target 2-oxaspiro[4.5]decan-1-one.

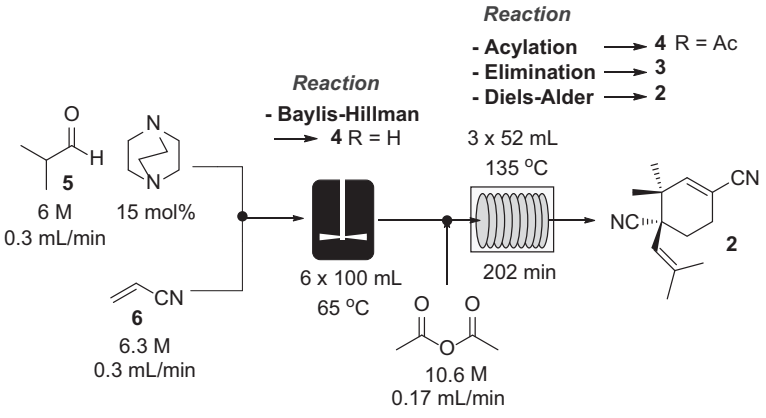


Figure 2. Reactor step-up for the dual stage formation of cycloadduct 2 (overall 89 % purity crude).

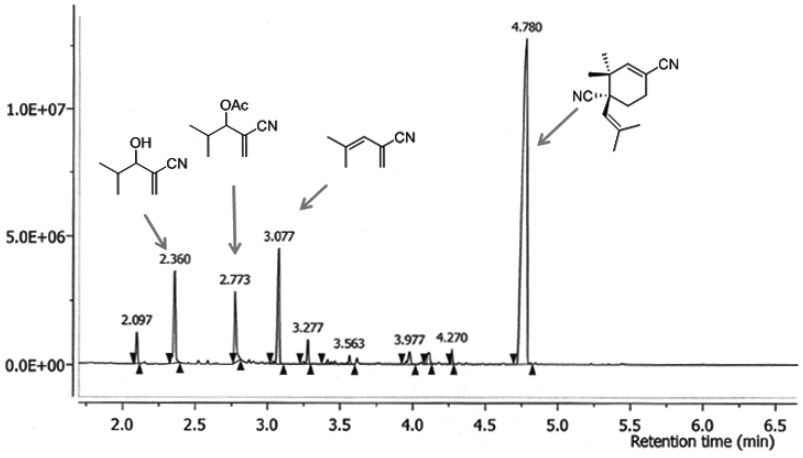


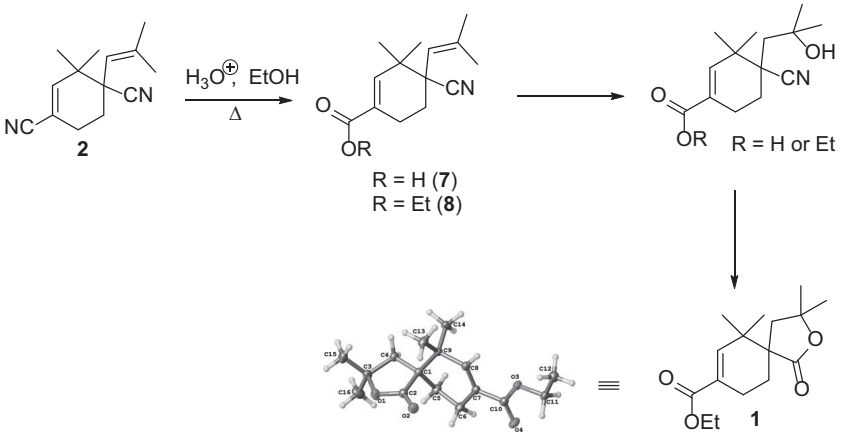
Figure 3. Representative reaction sampling and analysis via GC-MS TIC plot for the thermal Diels-Alder sequence **4** R=H → **2**.

Figure 4. Crystallization of crude intermediate compound **2** upon standing at room temperature for two days.

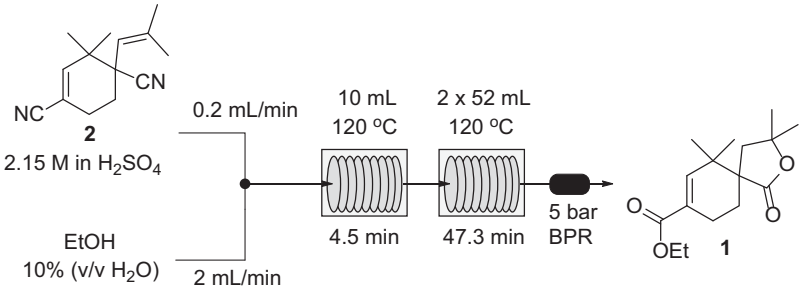
tively first induce hydration of the pendant alkene group. The rationale was to thus use the generated tertiary alcohol formed under Markovnikov conditions to subsequently assist in an intramolecular hydration of the adjacent nitrile as indicated in Scheme 2. In this scenario the proximity of the alcohol and presence of the double *gem*-dimethyl group would result in an enhanced Thorpe-Ingold effect [24–27] and would help promote the intramolecular attack onto the proximal nitrile. Additionally, although the molecule **2** contains two olefinic functionalities, the significant difference in their nucleophilic character should allow them to be chemically distinguished in an acid-catalyzed hydration.

Consequently, the acid-promoted direct lactonization and concurrent esterification was evaluated. Initial exploration using acidic ethanolic conditions (1 M in EtOH with 10 % 4 M HCl v/v, 102 °C) rapidly generated the ethyl ester **8** starting from either compound **7** or **2** but even after prolonged reaction times did not realize the required alkene hydration. Eventually it was determined that much stronger acidic conditions were required.

Therefore, compound **2** (or intermediate **7**) was dissolved in cold (0 °C) conc. H_2SO_4 to create a 2.15 M solution. As this mixture was relatively viscous, a peristaltic pumping unit (Vapourtec MedChem – E series [28]) was used to drive the fluidic flow (0.2 mL min^{-1}). This mixture was united with a flow stream of ethanol (10 % H_2O v/v) pumped via the second peristaltic pump (2 mL min^{-1}) to mix at a Teflon T-piece before passing into a heated (120 °C) FEP coil reactor (10 mL). The mixture was then progressed into a further residence time flow coil also maintained at 120 °C (104 mL; 2×52 mL FEP conjoined coils). System pressure was ensured using a 5 bar back pressure regulator which was placed just before the exit of the system as indicated in Scheme 3. The output flow was collected as batches (528 mL; 4 h processing time) and further processed by evaporation of the volatiles and extraction of the residue with 3×150 mL dichloromethane. This process was performed manually at larger scales but could be conducted using an in-line membrane extraction procedure at smaller scale; currently scale-up is being investigated. This allowed the final product **1** to be isolated by solvent evaporation. Note the dichloromethane was recycled for subsequent extractions. Upon standing, the pale yellow oil isolated started to crystallize, a small sample was removed, washed with ether, and dried. This material was recrystallized from hexane and used as seeding material for a future batch of the product. Following this procedure, a final yield of **1** derived from compound **2** or **7** was 72–74 %, respectively.



Scheme 2. Proposed hydration strategy to compound **1**.



Scheme 3. Reactor setup for conversion of compound **2** into **1**.

4 Conclusions

The application of flow chemistry to the scale-up synthesis of a previously identified target validation structure derived from a natural product screening campaign of new fragrance components has been demonstrated. The multistep sequence constructed was robust and easily scaled to allow the kilo production of the target material and its intermediates; 1.42 kg of compound **1** was eventually generated. Several options for improving the synthesis were determined though the course of the study based upon both reactor designs and chemical synthesis. The work demonstrates the potential value of flow chemistry as applied to target synthesis in the flavors and fragrance industries. Unfortunately, comparison to the original natural sample indicated the material did not match the synthesized compound 1. A reinvestigation of the original structural assignment of the isolated natural compound is currently underway.

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