Progress towards the Total synthesis of Frondosin D lab report

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Progress toward the Total synthesis of Frondosin D

Introduction:

Organic synthesis has allowed humans to synthesize molecules beneficial to their existence. Over the years, more complex methods have been developed. This includes the Diels-Alder Reactions that was recognized with the Nobel Prize in Chemistry in 1950\(^1\). The increase in the complexity of Organic Chemistry provided more tools for synthesizing natural compounds with important medicinal properties but whose isolation was complicated and, in some cases, even unfeasible.\(^2\)

Natural products are the basis of the pharmaceutical industry.

Marine sponges are a source of various biologically active compounds with interesting medicinal applications. In 1997, the Frondosin family of marine-derived meroterpenoid natural products was first isolated from the marine sponge from Micronesia, *Dysidea frondos*\(^3\). The extracts showed an affinity towards the receptor CX-CLR1/2 of the cytokine interleukin-8 (IL-8). This inhibits the binding of the cytokine interleukin-8 (IL-8) to its receptor. Studies of the extract revealed a family of five sesquiterpene hydroquinones was responsible for the observed inhibitory activity\(^3\). Based on their bicyclo[5.4.0]undecene core, Frondosins are a fascinating group of chemical compounds. In addition to their affinity to IL-8, the frondosins have been shown to inhibit protein kinase C (PKC).\(^4\)
Many chronic and acute illnesses have been linked to the IL-8 signaling pathway. These include sepsis syndrome, psoriasis, rheumatoid arthritis, gout, and asthma. Further experiments studying inflammation in animals have shown that IL-8 is the key leukocyte chemotactic factor. It directs neutrophil recruitment, and activation at the inflammatory focus. As a result of this, Frondosins have increasingly attracted attention as potential IL8 receptor antagonists. This has led to a possibility of new pharmacological agents against autoimmune hyperactivity. Also, neutrophil activation plays a key role in malignant tumor progression and metastasis in certain cancers. This has further made Frondosins a promising candidate for oncology studies. Furthermore, preliminary anti-HIV assays have revealed that Frondosins A and D exhibit HIV-inhibitory activity at the low micromolar level. With a host of biological implications for IL-8 inhibition, Frondosins became a popular target for total synthesis.

Frondosins B, C, D, and E have a common structural feature: a bicyclo[5.4.0]undecane sesquiterpene core structure. The difference is in the structure C and D rings (Figure 1). All the members of the Frondosin family except Frondosin A have a tetracyclic core structure. Frondosin A has a tricyclic structure rather than a tetracyclic structure. Synthesis of Frondosin A, B, and C has been achieved via 5-Exo cyclization-Claisen rearrangements (Figure 2). Despite these achievements in synthesizing Frondosin A to C, Frondosins have proven to have a difficult synthetic route, with the synthesis of Frondosin D yet to happen. Overall, the above-mentioned facts make Frondosin D an exciting synthetic target. The cyclization/Claisen rearrangement sequence will be applied for the synthesis of Frondosin D through a strategy that allows the simultaneous assembly of three of the requisite rings with the seven-membered ring at the core. The sequence would also generate a ketone carbonyl group in the seven-membered ring, for further functionalization of the advanced intermediate.
In this paper, we report the approach used by the Ovaska research group to synthesize the molecular scaffold of frondosins D. The studied synthetic approach for the synthesis of Frondosin D designed by the Ovaska group involves the cyclization/Claisen rearrangement sequence that allows the assembly of the seven-membered ring in the Frondosin D core structure.

Figure 1. Structure of Frondosins A-E
Results and discussion:

The Ovaska lab has explored two different approaches towards the synthesis of Frondosin D in the past. These are A-D-B-C and D-C-A-B approach. The approaches differ from one another in the order that each ring of the core structure of frondosin D is assembled. The first approach, A-D-B-C approach (Scheme 1), the ring C is synthesized in the last step, after the seven-membered ring B which is constructed through tandem cyclization/Claisen rearrangement. The second approach, called D-C-B-A approach (scheme 2), ring D is present in the starting material and ring A is synthesized last, after rings C and B are assembled. Here, retrosynthesis starts with a tertiary alcohol 30. This is then cyclized through cyclization/Claisen rearrangement sequence to yield the tricyclic cycloheptanoid intermediate 29. Then, the double bond in ring B is isomerized into the same position as seen in the frondosin D ring system. This yields ketone 28. Specifically, the synthetic route for the synthesis of the tricyclic intermediate was explored. The resulting ketone can then be alkylated with methyl lithium and the appropriate alkyl iodide to form ketone 27 that can undergo a triflation in the alpha position to the carbonyl to yield triflate 26. The Heck reaction can then be applied for the assembling of the last ring in the system to form 25. The terminal double bond attached to ring A can be selectively dehydroxylated and then ketone 24 can be formed through the 1,2-diol oxidative cleavage protocol. The gem-dimethylated intermediate can be synthesized from 24 by the utilization of a variation of the Reetz conditions that has been designed by Trauner et al.14 At this point, the TBS

Figure 2: Applications of the 5-exo cyclization-Claisen rearrangements in the total synthesis of Frondosin B, A, and C.11,12,13
group can be removed with TBAF to form intermediate 2, which can be subsequently oxidized by hypervalent iodide oxidation to yield frondosin D.

In this independent study we explored the synthetic route for the synthesis of the tricyclic intermediate presented in Scheme 3.

Scheme 1: A-D-B-C Retrosynthetic Approach for frondosin D
Scheme 2: D-C-B-A Retrosynthetic Approach for frondosin D
The synthesis begins with the synthesis of ketone 3 from commercially available 2-hydroxy-5-methoxy benzaldehyde 1 and methyl vinyl ketone 2 through an intermolecular Baylis-Hillman reaction. The triple bond in 4-pentyn-1-ol is then protected with a -TMS group to yield
alcohol 5 that can be converted to iodide an 6 in an Appel reaction. Iodide 6 is coupled with ketone 3 through n-BuLi coupling to yield compound 8 as a crude product. The crude product from the coupling reaction was then used for direct TBAF deprotection. According to previous studies in the Ovaska lab, this resulted in higher yields and reduced time and material input in the synthesis of cyclization precursor 9. This precursor then has to undergo a tandem cyclization/Claisen rearrangement sequence to yield the tricyclic intermediate 10. The reaction to obtain product 10 was not done in this independent study due to time constraints and challenges observed in synthesizing precursor 6. Precursor 6 had to be redistilled to purify it. When this proved to be challenging redistillation was done on precursor 5, the alcohol to purify it and proceed with the synthesis.

**Conclusion:**

The synthesis of Frondosin D has not yet been achieved. In the independent study, we explored the synthesis tricyclic intermediate that is the part of the core of the Frondosin D. Though there were challenges observed in this synthesis, specifically during the synthesis of precursor 6. The Ovaska group, through future studies, hopes to explore this work further to fully synthesize the tricyclic intermediate of the Frondosin D.

**Reference:**

1) Koehn, F. E.; Newman, D. J. Drug discovery from natural products, 2009
2) Marcus Vinicius Pinto Pereira Junior. Progress towards the total synthesis of Frondosin D. Department of Chemistry, Connecticut College, New London, CT, May 2020


10) Kye-Simeon Masters and Bernard L. Flynn The Journal of Organic Chemistry 2008 73 (20), 8081-8084


Experimental Details:

General Experimental

The synthesized compounds were analyzed using $^1$H and $^{13}$C NMR acquired with a Varian INOVA NMR 500 MHz spectrophotometer and with deuterated chloroform as solvent. The chemical shifts observed are reported as parts per million (ppm), with tetramethylsilane as the primary reference at $\delta = 0.00$ ppm. Moreover, the coupling constants $J$ are reported in hertz (Hz). The synthesized compounds were purified by column chromatography, flash chromatography in Biotage Isolera One purification system, simple distillation, or fractional distillation. All the starting materials used were purchased from Aldrich, Acros or Strem. Diethyl ether, dichloromethane, tetrahydrofuran, and dimethylformamide were purchased from Fisher and VWR and were dried and deoxygenated via a PureSolv solvent purification system. Trimethylsilyl chloride, phenetole, acetonitrile and triethylamine were freshly distilled from calcium hydride. Furthermore, all glassware was flame-dried under nitrogen atmosphere and all reactions were performed under dry nitrogen atmosphere conditions.
Experimental Details

[35] 4-(trimethylsilyl)but-3-yn-1-ol

\[
\text{HO} \quad \equiv \quad \text{TMS}
\]

\[\text{n-Butyllithium (1.6 M in hexane, 91.6ml, 146.6 mmol) was added dropwise to a stirring solution of but-3-yn-1-ol (6.02g, 70.57mmol) in tetrahydrofuran (70 ml) at } -78^\circ \text{C, and the resulting mixture was stirred for 1 h. Trimethylsilyl chloride (19.9 ml, 157.05 mmol) was then added dropwise and the reaction was warmed to } 0^\circ \text{C and stirred for 1 h. Then, 10\% hydrochloric acid (15 ml) was added and the reaction was stirred for 30 min at } 0^\circ \text{C. At this point, tetrahydrofuran was removed under reduced pressure, and diethyl ether (35 ml) and water (20 ml) were added to the mixture. The layers were separated, and the aqueous layer was rinsed with diethyl ether (3x 20 ml). The combined organic layers were dried over magnesium sulfate and concentrated under reduced pressure. The crude product was filtered through a pad of silica using hexane and compound 1 was obtained as a colorless liquid (9.32g, 93.6 \%). Compound 1 was previously reported.}^6
\]

[36] (4-iodobut-1-yn-1-yl)trimethylsilane

To a stirring solution of 35 (3.955 g, 27.8mmol) with triphenylphosphine (8.76g, 33.36 mmol) and imidazole (2.84g g, 41.68 mmol) in dichloromethane (100 ml) at 0°C, I\(_2\) (8.47 g, 33.36
mmol) was added. Then, the reaction mixture was allowed to stir at room temperature for 14 h before being quenched with saturated ammonium chloride (25 ml). At this point, the reaction mixture was diluted with dichloromethane (20 ml) and layers were separated. The aqueous layer was extracted with dichloromethane (2x 30 ml) and the resulting combined organic layers were dried over magnesium sulfate and concentrated under reduced pressure. Crude product was filtered through a pad of silica using hexane to yield 2 as a colorless liquid (5.983g, 85.4%). **1H NMR** (CDCl$_3$, 500 MHz): $\delta$ 3.22 (t, $J = 7.6$ Hz, 2H), 2.79 (t, $J = 7.6$ Hz, 2H), 0.16 (s, 9H) ppm. **13C NMR** (CDCl$_3$, 126 MHz): $\delta$ 105.2, 86.9, 25.2, 1.18, 0.08 ppm.

![Chemical structure of the product](image)

**[33]** 1-(6-methoxy-2H-chromen-3-yl)ethenone

Methyl vinyl ketone (1.99, 28.32 mmol) was added to a stirring mixture of 2-Hydroxy-5-methoxybenzaldehyde (3.92g, 28.32 mmol) and potassium carbonate (4.31g, 28.32 mmol) in methyl ethyl ketone (45 ml). The mixture was heated at 100°C for 10 h and then it was allowed to cool down to room temperature before being diluted with ethyl acetate (70 ml). The resulting mixture solution was filtered over celite and then mixed with water (50 ml). The aqueous layer was rinsed with ethyl acetate (4x 30 ml), and the combined organic layers were dried over magnesium sulfate and concentrated under reduced pressure. The crude product was purified by Biotage Isolera™ (SNAP Ultra, 25g, 2 to 20%, 10CV, ethyl acetate in hexane) to obtain 33 as a yellow solid (1.878g, 48.8 %). **1H NMR** (500 MHz, CDCl$_3$): $\delta$ 7.27 (s, 1H),
6.86–6.78 (m, 2H), 6.72 (d, J = 2.7 Hz, 1H), 4.95 (s, 2H), 3.78 (s, 3H), 2.41 (s, 3H) ppm; 

13CNMR (126 MHz, CDCl₃): δ 196.1, 154.4, 149.7, 134.1, 131.7, 121.5, 118.4, 117.1, 113.3, 64.3, 55.9, 25.2 ppm.

amount to a stirring solution of the resulting crude product in tetrahydrofuran (18 ml) at 0°C. The reaction was allowed to stir for 1.5 h before being quenched with water (1 ml). Then, tetrahydrofuran was removed under reduced pressure, and the resulting mixture was diluted with diethyl ether (40 ml) and water (15 ml), and layers were separated. The aqueous layer was extracted with diethyl ether (2x 25 ml), and the resulting combined organic layers were dried over magnesium sulfate and concentrated [38] 2-(6-methoxy-2H-chromen-3-yl)hex-5-yn-2-ol

t-Butyllithium (1.9M in hexane, 5.31 mL, 12.87 mmol) was added dropwise to a stirring solution of iodide 36 (2.47g, 9.91 mmol) in diethyl ether (75 ml) at −78°C. Then, the ketone 33 (1.012g, 4.95 mmol) was dissolved in diethyl ether (40 ml) and slowly transferred via cannula to the reaction mixture. Then, the reaction mixture was stirred at −78°C for 1 h before being quenched with methanol (2 ml) and allowed to warm to room temperature. Water (40 ml) was added to the mixture and the aqueous layer was separated from the organic layer. The aqueous layer was then washed with diethyl ether (2x 30 ml), and the combined organic layers were dried over magnesium sulfate and concentrated under reduced pressure. At this point, tetra-n-butylammonium fluoride (1M in tetrahydrofuran, 0.2 mL) was added in catalytic under
reduced pressure. Crude product was purified by Biotage Isolera™ (SNAP Ultra, 25g, 5 to 40%, 10CV, ethyl acetate in hexane) to obtain 38 as a yellow liquid (0.357g, 27.5 %). 1HNMR (500 MHz, CDCl₃): δ 6.76 (d, J = 8.8 Hz, 1H), 6.67 (dd, J = 8.8, 3.0 Hz, 1H), 6.61 (d, J = 3.0 Hz, 1H), 6.44 (s, 1H), 4.64-4.67 (m, 2H), 3.76 (s, 3H), 2.20-2.35 (m, 2H), 2.07 (s, 1H), 1.98-2.00 (m, 1H), 1.89-1.90 (t, J = 7.6 Hz, 2H), 1.41 (s, 3H) ppm. 13CNMR (500 MHz, CDCl₃): δ 154.4, 147.2, 139.7, 123.6, 118.8, 116.1, 114.2, 112.1, 84.3, 73.8, 69.3, 65.5, 55.9, 38.8, 27.3, 13.7 ppm.

NMR SPECTRA
Sample Name: CN20100001
Data collected on: June 7 2019
Machine directory: ...
Sample directory: ...
FidFile: CN20100001
Pulse Sequence: CN20100001
Operator: abel
Data collected on: June 7 2019
Temp. 22.5 C / 72.1 K
Sample 511, Operator: students casa
Relax: delay 1.089 sec
Delay 1.089 sec
 nghi. time 1.089 sec
Chop: 1.2050.0 Hz
256 repetitions

MODE: 611, 219.6720.12 MHz
BO: 1.298748.08 MHz
Power: 48 dB
Dwell: 100 ms
MULTI-16 modulated

Sample: hydrogen
Line broadening 0.5 Hz
PY size 49500
Total time 6 min 46 sec
**KEILIN-HEIDEN 1,6-CYCLOHEXANE**

Sample Name: DC-8038
Data Collected on: 315-350-nm-PFGS
Archive directory: /home/relab/relab/relab/data/students_2020
Sample directory: dc-8038_202002012_01
file: pm11m_21

Pulse sequence: PROTON 60/20
Solvent: AB115
Date collected: 2020-02-01

Temp: 25.0 °C / 77.0 K
Sample ID: Operator: students_2020

Pulse: Relay 1.000 usec
Phase 60.0 degrees.
FID time 81.0 usec
ACQ time 16.0 usec
8 acquisition
CREATING: X2, 10760000/5 MHz
DATA PROCESS
FT axis 30724
Total time 5 min 24 sec