Natural Product Synthesis

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A General Approach to the Basiliolide/Transtaganolide Natural Products: Total Syntheses of Basiliolide B, *epi*-8-Basiliolide B, Transtaganolide C, and Transtaganolide D**

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Dedicated to Dr. Ahamindra Jain

The transtaganolides and basiliolides (**1**–**3**) are members of a growing family of natural products isolated from plants belonging to the genus *Thapsia*.[1,2] Compounds within this group (e.g., **1a**, **1b**, and **3a**; Figure 1) have been shown to induce rapid mobilization of intracellular Ca^{2+} stores.[3] This activity has been attributed to the inhibition of calcium ATPases residing within the sarco/endoplasmic reticulum (SERCA-ATPases).[4] Interestingly, *Thapsia sp.* are also the plant source of the commonly employed and structurally unrelated SERCA-ATPase inhibitor, thapsigargin (**4**).[5] Furthermore, Oikawa and co-workers have proposed a structure–function relationship to the widely utilized anti-malarial agent artemisinin (**5**),[6,7] which has also been proposed to act through ATPase inhibition.[8,9] Structurally, the transtaganolide/basiliolide molecules possess a dense array of functionalization and a polycyclic ring system comprised of *trans*-decalin framework, a bridging lactone (see **1a** rings A and B) and an unprecedented cyclic acyl ketene acetal (ring C).

Owing to the interesting biological activity and striking architectures, the transtaganolides (**1** and **2**) and basiliolides (**3**) have inspired significant interest from the synthetic community. Initial synthetic efforts from our own group,[10] as well as those of Dudley[11] and Lee[12] have utilized an intramolecular pyrone Diels–Alder cycloaddition to construct the oxabicyclo[2.2.2]octene moiety constituting the ABD ring system of **1** and **3**. Furthermore, our studies[13] and those of

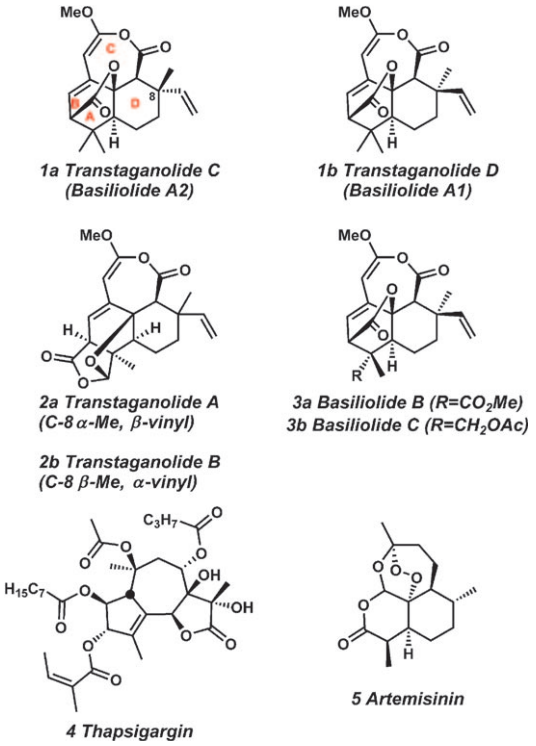
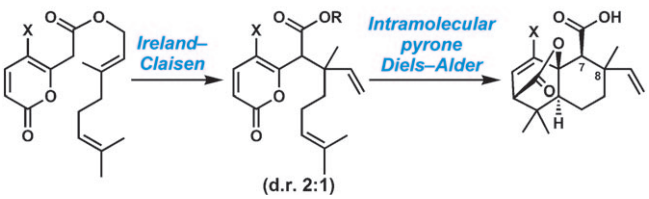


Figure 1. Transtaganolides (**1** and **2**), basiliolides (**3**), thapsigargin (**4**) and artemisinin (**5**).

Johansson[14] have independently demonstrated a rapid and diastereoselective construction of the tricyclic core from a simple ester precursor by sequential Ireland–Claisen rearrangement/intramolecular pyrone Diels–Alder cycloaddition (Scheme 1). This sequence, initially reported by both groups as a two-step procedure, smoothly installs the C(8) quaternary carbon as a 2:1 mixture of diastereomers with all other



Scheme 1. Ireland–Claisen/intramolecular pyrone Diels–Alder sequence.[13,14]

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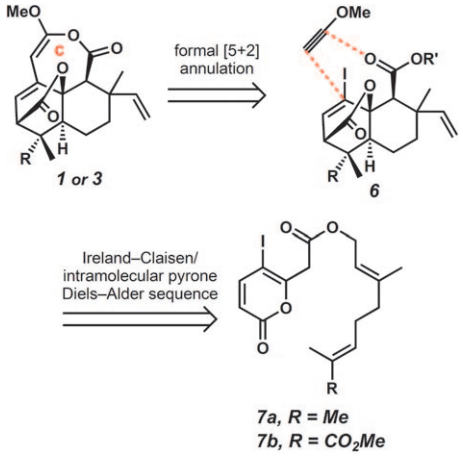
configurations being controlled by the C(7) ester configuration. Despite these early developments by multiple research groups and the disclosure of these advanced intermediates, no total syntheses of any transtaganolides or basiliolides have been reported to date. Here, we disclose the synthesis of transtaganolides C and D (**1a**, **1b**), basiliolide B (**3a**), and *epi*-8-basiliolide B, representing the first total syntheses of any members of this class.

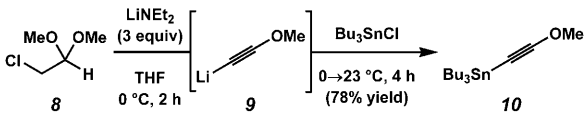
The challenge in advancing intermediates akin to tricyle **6** (Scheme 2) to natural products **1**–**3** lies in the formation of the unusual 7-methoxy-4,5-dihydrooxepin-2(3*H*)-one ring (ring



Scheme 2. Retrosynthetic analysis.

C).[15] Embedded within this ring is an acyl ketene acetal that is potentially labile to both acid and base, as evidenced by the co-isolation of seco acid derivatives of **1**–**3** from *Thapsia sp.*[1] Retrosynthetically, we envisioned that the C ring could be prepared by a formal [5+2] annulation process of advanced tricycle **6** and methoxyacetylene, or a suitable derivative, leading directly to the natural products (Scheme 2). Tricycle **6** would be prepared from the tandem Claisen/Diels–Alder sequence of ester **7**. Importantly, with an available late-stage construction of ring C, variants of this ester (e.g., **7a** and **7b**) prepared from geraniol derivatives could provide rapid access to a number of basiliolide and transtaganolide natural products.

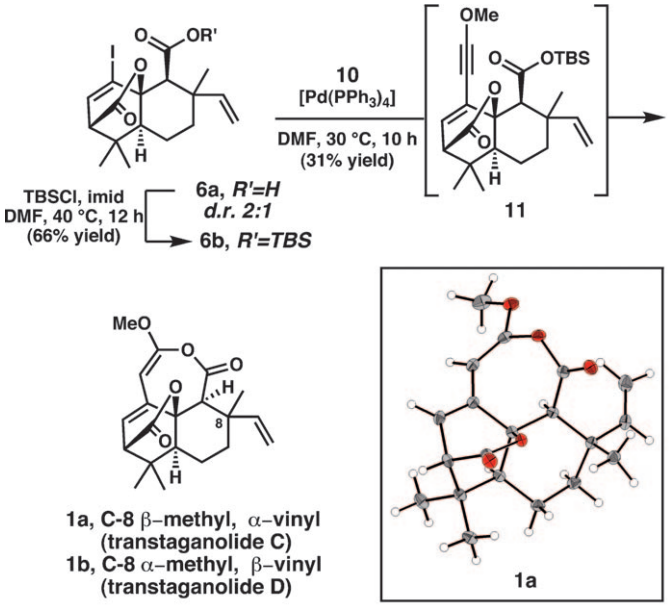
At the outset of our studies to build the C ring, we attempted a variety of inter- and intramolecular annulation strategies but were unable to affect formation of the daunting C ring. Having few remaining options, we turned our attention to approaches involving palladium-mediated cross-coupling reactions.[16] In addition to the possible steric hindrance of vinyl halide **6**, no successful cross-coupling reactions of methoxyacetylene or derivatives thereof have been reported to any vinyl or aryl halide. Nonetheless, limited reports of tin and zinc derivatives of commercial ethoxyacetylene in palladium-catalyzed cross-couplings have been published and provided some precedent for the coupling.[17,18] Hence, efforts turned to the preparation of stannane **10** (Scheme 3). We were pleased to find, that when exposed to $LiNEt_2$, 1,1-dimethoxy-2-chloro-acetaldehyde (**8**) was trans-



Scheme 3. Synthesis of stannane **10**.

formed into lithium acetylide **9**,[19] which could be quenched with tributyltin chloride to safely[20] afford stannane **10** in 78% yield in a single operation.

Attempts to directly couple stannane **10** to iodoacid **6a** (prepared from **7a**)[13,14] were unsuccessful under standard cross-coupling conditions. We attributed the lack of desired reactivity to acid-mediated decomposition of stannane **10**.[20b] Therefore, extensive efforts were undertaken to devise a suitable protecting group strategy for the carboxylic acid moiety. Ultimately, acid **6a** was transformed into *tert*-butyl dimethylsilyl ester **6b**[21] by treatment with TBSCl and imidazole (Scheme 4).[22] Exposure of silyl ester **6b** and



Scheme 4. Syntheses of transtaganolide C (**1a**) and transtaganolide D (**1b**) and X-ray crystal structure of transtaganolide C (**1a**).

stannane **10** to $[Pd(PPh_3)_4]$ or Fu's $[Pd(P\mathit{t}Bu_3)_2]$[23] led to transient formation of enyne **11**. While observable by mass spectrometry and ^1H NMR analysis, direct isolation of methoxyenyne **11** proved difficult. After optimization of the reaction conditions, we found that aqueous work-up effected in situ desilylation and cyclization to afford a separable mixture of transtaganolide C (**1a**) and transtaganolide D (**1b**) in 21% and 10% yield, respectively (19% and 10% with Fu's catalyst).[24] The relative stereochemistry of synthetic transtaganolide C (**1a**) was unambiguously confirmed by X-ray crystallography,[25] and synthetic transtaganolides C and D were spectroscopically indistinguishable from the naturally occurring isolates.[2]

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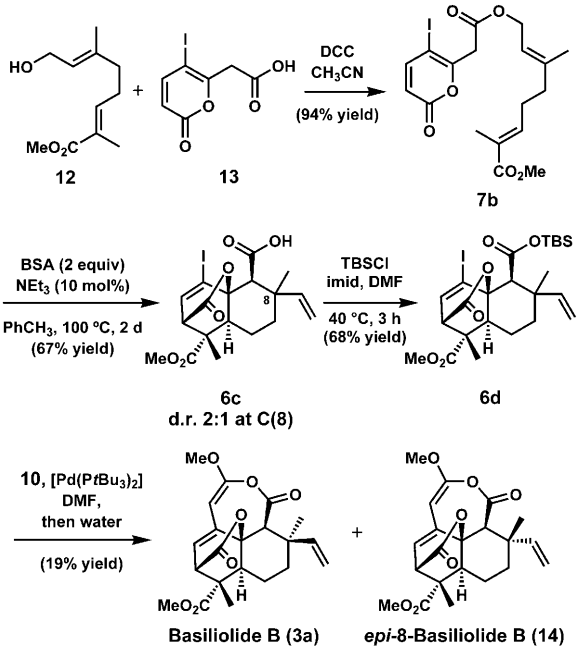
With the syntheses of transtaganolide C (**1a**) and transtaganolide D (**1b**) serving as a proof of concept, we sought to extend our approach to the rapid total synthesis of more complex members of this family. Our efforts to prepare basiliolide B (**3a**) were undertaken by preparation of known geraniol derivative **12** (available in 4 steps)[26] and coupling to iodopyrone acid **13**,[13,14] producing ester **7b** in excellent yield.

We were pleased to find that treatment of ester **7b** with *N*,*O*-bis(trimethylsilyl)acetamide (BSA) and triethylamine resulted in a Claisen/Diels–Alder cascade to yield the resulting acid **6c** in a single operation and in 67% yield as a 2:1 mixture of diastereomers (Scheme 5).[27] This represents



Scheme 5. Synthesis of basiliolide B and *epi*-8-basiliolide B.

an improvement over previous, two-step procedures that required isolation and/or manipulation of the Claisen products (see Scheme 1), and is the first example in this area that utilizes a more functionalized dienophile. Following silylation of the free acid (**6c**→**6d**),[22] the resulting silyl ester (**6d**) was exposed to our methoxyalkynylation conditions comprised of stannane **10** and $[Pd(PtBu_3)_2]$. Gratifyingly, cross-coupling and treatment of the crude product mixture with H_2O resulted in the production and isolation of basiliolide B (**3a**)[28] and previously unreported *epi*-8-basiliolide B (**14**) in 5% and 14% yields, respectively (6% and 12% with $[Pd(PPh_3)_4]$).

A rapid, modular and convergent strategy for the synthesis of the basiliolides and transtaganolides has been described. Basiliolide B (**3a**), *epi*-8-basiliolide B (**14**), transtaganolide C (**1a**), and transtaganolide D (**1b**) were each prepared in only seven steps (longest linear sequence) from commercially available materials. Critical to the success of this effort was the development of an effective preparation of, and cross-coupling protocol for, methoxyacetylide **10**. Remarkably, the disclosed end-game procedure transforms simple, monocyclic, achiral precursors to the stereochemically rich, tetracyclic natural products in three steps (e.g., **7b**→**3a**). Efforts to prepare other members of the family and to render these syntheses asymmetric are ongoing in our laboratories.

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[21] Silyl ester **6a** could be prepared directly from ester **6a** (X = I) under slightly modified reaction conditions, that is, using *N,O*-bis(*tert*-butyldimethylsilyl)acetimide. However, the yield over three steps was significantly lower; ca. 10%.

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[24] Hitherto, screening of reaction conditions has failed to improve the yields of transtaganolides **1a** and **1b**. The difficulty in achieving an efficient [5+2] annulation is attributed to several factors. We have found that methoxyenyne **11** is unstable under the reaction conditions: modest extension of the reaction time (24 h) leads to non-productive consumption of intermediate methoxyenyne **11**. Additionally, stannane **10** is itself unstable to Pd catalysis: addition of $[Pd(PPh_3)_4]$ to a solution of stannane **10** in DMF leads to comsumption of **10** and the formation of oligomeric products.

[25] CCDC 796908 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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[28] Synthetic basiliolide B was spectroscopically indistinguishable from the natural product isolated from *Thapsia sp.*, see ref. [4].

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