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]\(^3\) 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]\(^8\) 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 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 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

\[\text{Figure 1. Transtaganolides (1 and 2), basiliolides (3), thapsigargin (4) and artemisinin (5).}\]

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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 tricycle 6 (Scheme 2) to natural products 1–3 lies in the formation of the unusual 7-methoxy-4,5-dihydrooxepin-2(3H)-one ring (ring 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 LiNEt3, 1,1-dimethoxy-2-chloro-acetaldehyde (8) was transformed 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 TBSCI and imidazole (Scheme 4).[22] Exposure of silyl ester 6b and
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 \(\text{H}_2\text{O}\) resulted in the production and isolation of basiliolide B (6c, 13\%) and epi-8-basiliolide B (6d, 14\%) yields, respectively (6\% and 12\% with \([\text{Pd}(\text{PPh}_3)_4]\)).

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

Unpublished studies utilizing derivatives of commercially available ethoxyacyetylene confirmed the effectiveness of analogous Stille couplings, while Negishi or Sonogashira-type couplings were non-productive in our hands.


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%.


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 consumption of 10 and the formation of oligomeric products.

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.


These conditions are a variation of those previously disclosed by Larsson and co-workers; see ref. [14]. We found that lowering the concentration of the ester in the reaction allowed for the Diels–Alder cycloaddition to occur in the same pot. Alternatively, microwave irradiation of the intermediate acid in CH2Cl2 in a sealed vial at 165 °C for 48 h also smoothly produces the Diels–Alder product.

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