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Tetrahedron Letters 49 (2008) 2899–2901
Tetrahedron Letters

On the intramolecular pyrone Diels–Alder approach to basiliolide B

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Received 15 February 2008; accepted 5 March 2008
Available online 10 March 2008

Abstract

A unified synthetic approach to the basiliolides/transtaganolides is outlined herein, along with studies illustrating the feasibility of the strategy with respect to the total synthesis of basiliolide B. This work lays the foundation for chemical synthesis of an emerging family of *Thapsia* metabolites.

The basiliolides[1] and transtaganolides[2] recently joined thapsigargin (THG)[3] as the known bioactive metabolites from plants of the *Thapsia* genus, the medicinal value of which has been appreciated as far back as Hippocrates.[4] Despite no obvious structural homology, both the basiliolides[5] and THG are produced by *Thapsia garganica* L. and inhibit SERCA-ATPase activity.

The initial report on the biological activity of the basiliolides[1] highlighted similarities with THG, but subsequent studies revealed important distinctions.[6] THG, an irreversible SERCA (Ca^{2+}) pump inhibitor, induces apoptosis through endoplasmic reticulum stress.[7] In contrast, the basiliolides appear to inhibit SERCA *reversibly*; reversible inhibition of SERCA leads not to apoptosis but rather is associated with cell homeostasis. These new data point to potential roles for the basiliolides (transtaganolides) in the treatment of degenerative diseases.

A unified strategy that can allow access to the various basiliolides would be most attractive. Entry into the basiliolides through chemical synthesis requires that several challenges be addressed, including installation of three distinct ester/lactone linkages, six stereogenic centers,[8] two quaternary carbon atoms, and an unprecedented cyclic *O*-acyl ketene acetal moiety within the tetracyclic framework.

The retrosynthetic analysis shown in Figure 2[9] calls for an intramolecular pyrone Diels–Alder (IMPDA) reaction of **3**, which features an ambipihilic 5-iodo-2-pyrone[10] diene, to construct tricycle **2**. Halogen substitution on 2-pyrones[11] increases their reactivity in both normal and inverse electron-demand Diels–Alder reactions, thereby providing the flexibility needed to prepare other basiliolides (Fig. 1). Installation of the *O*-acyl ketene acetal is deferred until the late stages of the synthesis, at which point conformational biases of the rigid framework are expected to stabilize this otherwise labile structural element.[12]

Nelson and Stoltz recently reported progress toward the synthesis of the basiliolides and transtaganolides,[13] including an encouraging IMPDA reaction of a 3-bromo-2-pyrone. However, their system lacks an appropriate handle

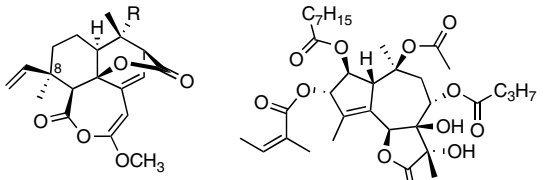

Fig. 1. Basiliolides/transtaganolides and thapsigargin.

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doi:10.1016/j.tetlet.2008.03.031

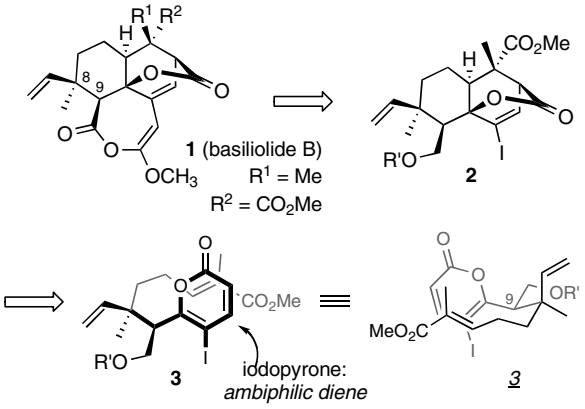


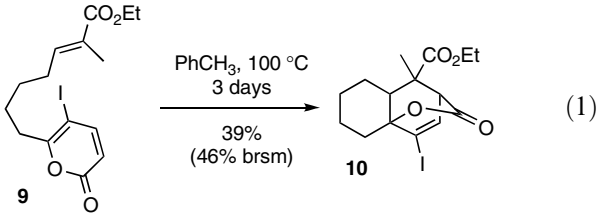
Fig. 2. Retrosynthetic analysis on basiliolide B based on a key intramolecular Diels–Alder reaction of iodopyrone **3**.

at the 5-position of the pyrone for further elaboration, and the bromine atom inserted late in the sequence to activate the key IMPDA reaction had to be removed in a subsequent step.

Herein, we share observations on new IMPDA reactions relevant to our approach to basiliolide B.[9] These studies provide data specific to the challenges of the basiliolides, and, in general terms, provide insight into the application of IMPDA reactions in natural products synthesis. In particular, we establish that halogen substitution at the 5-position of the pyrone (cf. **3**) is suitable for the IMPDA reaction that is central to our synthetic design.

To establish the feasibility of the IMPDA approach to the basiliolides using 5-halo-2-pyrones,[14] two main concerns must be addressed: (1) reactivity with respect to cycloaddition versus carbon dioxide (CO_2) cycloreversion[11] and (2) diastereoselectivity. Toward this end, two model studies were undertaken. The first addresses the feasibility of the IMPDA reaction in simplest terms, establishing that the desired cycloadducts of 5-iodo-2-pyrones can be obtained free from cycloreversion products (Eq. 1). The second study focuses on the diastereoselectivity of a strategic IMPDA reaction of a readily available and chiral 5-iodo-2-pyrone (**13**, Scheme 3).

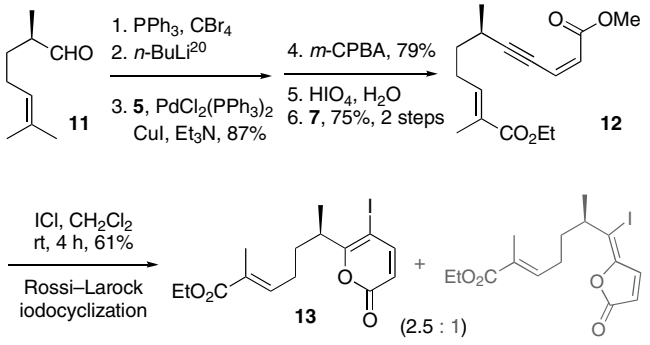
The first test substrate, 5-iodo-2-pyrone **9**, was synthesized as shown in Scheme 1. Heptynoic acid (**4**) was reduced to heptyn-7-ol following the known procedure[16] and coupled with iodide **5** under Sonogashira conditions to give alcohol **6**. Homologation of alcohol **6** was achieved using the Swern oxidation and Wittig olefination to furnish dienyne **8**. Finally, Rossi–Larock iodocyclization[17,18] employing Larock's protocol[18] provided iodopyrone **9**.



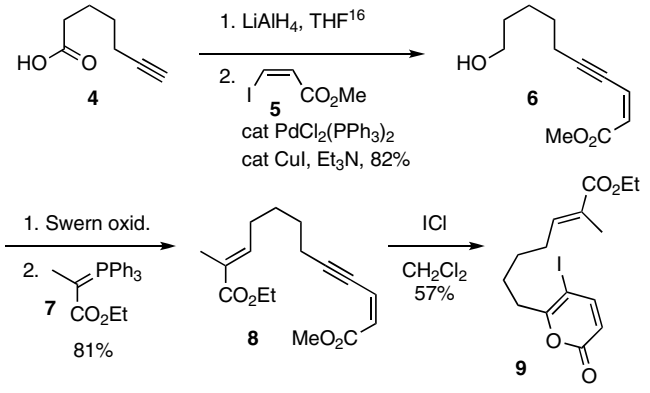
(1)

5-Iodo-2-pyrone **9** provides insight into cycloaddition reactivity vis-à-vis decarboxylation (Eq. 1). Heating **9** at 100 °C for three days provided cycloadduct **10** as a single diastereomer and free from cycloreversion products. Extrusion of CO_2 becomes dominant at higher temperatures, illustrating the delicate balance of pyrone Diels–Alder reactions.

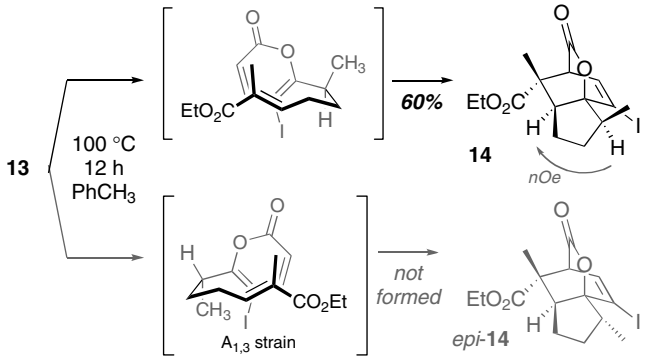
This model system (**9**) demonstrates the utility of 5-halo-2-pyrones in IMPDA chemistry despite the lack of Thorpe–Ingold conformational biases that are expected to assist in the assembly of the basiliolides (cf. **3**). A second IMPDA substrate (**13**, Scheme 2) better mimics the entropic biases of the key step[19] and includes a stereogenic center to influence the diastereoselectivity of the reaction.



Scheme 2. Synthesis of IMPDA substrate **13**.[15]



Scheme 1. Synthesis of 5-iodo-2-pyrone **9**.[15]



Scheme 3. IMPDA reactivity of **13**.[15]

Scheme 2 illustrates the synthesis of IMPDA substrate **13**. Corey–Fuchs homologation of citronellal (**6**),[20] Sonogashira coupling with iodide **5**, chemoselective epoxidation, hydration to the diol, cleavage with periodic acid, and Wittig olefination provided enyne **12** (15% yield from **11**). Iodocyclization provided iodopyrone **13** along with the iodobutenolide product of 5-*exo* cyclization in a 2.5:1 ratio.

The IMPDA reaction of pyrone **13** (**13→14**, Scheme 3) was much faster than that of pyrone **9** with the four-methylene tether and no Thorpe–Ingold assistance (**9→10**, Eq. 1): complete conversion of **13** occurred within 12 h at 100 °C. Furthermore, the desired cycloadduct *formed as a single diastereomer* along with a minor by-product (⩽9%) arising from decarboxylation.[15]

The cycloaddition reactions of **9** and **13** illustrate the utility of 5-iodo-2-pyrones in intramolecular Diels–Alder reactions, building on promising initial data from related *inter* molecular processes.[10d] It is worth noting that similar IMPDA reactions are completely intractable in the absence of halogen activation.[13]

These initial studies provide a solid foundation for the synthesis of the basiliolides and transtaganolides. Importantly, this work afforded preliminary experimental support—in the form of a diastereoselective IMPDA reaction (**13→14**, Scheme 3) controlled by a stereogenic center on the tether—for the hypothesis that the C9 stereochemistry can be used to impart diastereocontrol over the construction of the basiliolides and transtaganolides (Fig. 2). What remains is to prepare, following the general approach outlined in Scheme 1, an IMPDA substrate (cf. **3**) with appropriate functional group handles for further elaboration. Efforts toward the chemical synthesis of basiliolide B and other members of the family are on-going and will be reported in due course.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.03.031.

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