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Progress toward the Synthesis of the Basiliolides and Transtaganolides: An Intramolecular Pyrone Diels–Alder Entry into a Novel Class of Natural Products

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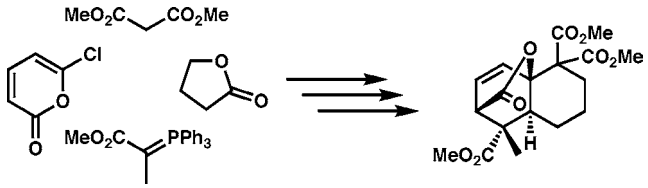
ABSTRACT



Efforts directed toward the synthesis of a basiliolide/transtaganolide model system are disclosed. A highly endo-selective intramolecular pyrone Diels–Alder (IMPDA) cycloaddition rapidly constructs the tricyclic core of the basiliolides and transtaganolides.

Thapsia garganica L., an herb native to Mediterranean countries, has a long history as a medicinal plant. Its roots have been used for the treatment of pulmonary diseases, catarrh, and rheumatoid arthritis.[1] Thapsigargin (TG)(**1**), the principle chemical component of *T. garganica* L., is a powerful histamine liberator and a non-TPA-type tumor promoter.[2,3] However, TG is best known as a selective and potent microsomal SERCA-ATPase inhibitor and is widely used as a chemical tool for cell physiological studies.[4] Because of its high cost[5] and variable concentration in *T. garganica* L., several groups have attempted to isolate TG analogues from *T. garganica* L., as well as from other members of the genus. Recent efforts have led to the isolation of six new compounds (Figure 1, **2**−**7**).[6] Strikingly, despite a lack of structural similarity to TG (cf. **1** to **4**−**7**), compounds **4**−**7** display an ability to regulate Ca^{2+} homeostasis in vivo, the primary action of SERCA-ATPase inhibitors such as TG (**1**).[7]

In addition to their interesting biological activity, we were drawn to the densely functionalized, yet compact, frameworks present in these natural products. In particular, the metabolites isolated from *T. garganica* L. and *T. transtagana* (**4**−**7**) contain an interesting tetracyclic core featuring a bicyclic lactone. Furthermore, the 7-methoxy-4,5-dihydro-3*H*-oxepin-2-one ring (C-ring) common to all six of the metabolites is unprecedented.

As an entry into this class of natural products, we chose to target basiliolide B (**6**).[8] Its densely functionalized ring

(1) Accounts of *T. garganica* L.'s medicinal qualities were first reported by Hippocrates in 400 B.C.; see: (a) Christensen, S. B.; Ramussen, U. *Tetrahedron Lett.* **1980**, *21*, 3829−3830. (b) Christensen, S. B.; Andersen, A.; Smitt, U. W. *Prog. Chem. Org. Nat. Prod.* **1997**, *71*, 130−167.

(2) Christensen, S. B.; Larsen, I. K.; Rasmussen, U.; Christophersen, C. *J. Org. Chem.* **1982**, *47*, 649−652.

(3) Perchellet, E. M.; Gali, H. U.; Gao, X. M.; Perchellet, J.-P. *Int. J. Cancer* **1993**, *55*, 1036−1043.

(4) Lytton, J.; Westlin, M.; Hanley, M. R. *J. Biol. Chem.* **1991**, *266*, 17067−17071.

(5) At the time of this publication, Sigma-Aldrich lists TG at $62.80 per 0.5 mg. However, there has recently been an improvement made to TG's isolation procedure; see: Pagani, A.; Pollastro, F.; Spera, S.; Ballero, M.; Sterner, O.; Appendino, G. *Nat. Prod. Commun.* **2007**, *2*, 637−642.

(6) (a) Saouf, A.; Guerra, F. M.; Rubal, J. J.; Moreno-Durado, F. J.; Akssira, M.; Mellouki, F.; López, M.; Pujadas, A. J.; Jorge, Z. D.; Massanet, G. M. *Org. Lett.* **2005**, *7*, 881−884. (b) Appendino, G.; Prosperini, S.; Valdivia, C.; Ballero, M.; Colombano, G.; Billington, R. A.; Genazzani, A. A.; Sterner, O. *J. Nat. Prod.* **2005**, *68*, 1213−1217.

(7) Navarette, C.; Sancho, R.; Caballero, F. J.; Pollastro, F.; Fiebich, B. L.; Sterner, O.; Appendino, G.; Muñoz, E. *J. Pharmacol. Exp. Ther.* **2006**, *319*, 422−430.

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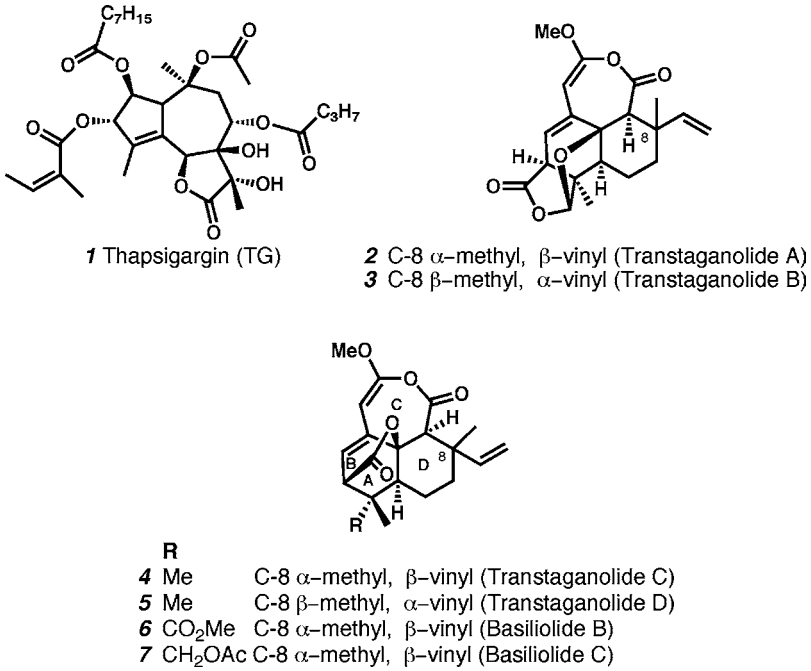


Figure 1. Basiliolides, transtaganolides, and thapsigargin.

system and six contiguous stereocenters posed considerable synthetic challenges. We envisioned that an intramolecular pyrone Diels−Alder cycloaddition (IMPDA) would allow for significant retrosynthetic simplification of basiliolide B (Scheme 1a). In a single step, the IMPDA forms four of the six stereocenters and three of the four rings. Furthermore, we reasoned that the IMPDA would need to precede the formation of the **C** ring, as construction of the oxepinone ring prior to the IMPDA would lead to incorrect relative stereochemistry (Scheme 1b).[9] Mindful of these considerations, we initiated model studies directed toward the synthesis of pyrones **13a** and **13b** to probe the capacity of either to undergo IMPDA under thermal or Lewis acidic conditions (Scheme 1c).

The preparation of **13a** began with the partial reduction of γ-butyrolactone (**15**) to the corresponding lactol, which was immediately treated with stabilized ylide **16**[10] to afford hydroxy enoate **17** (Scheme 2a). Alcohol **17** was converted to iodide **18** by treatment with iodine, imidazole, and PPh_3. In parallel, pyrone **21** was assembled by displacement of chloride **19** with the anion of dimethyl malonate (**20**). Coupling of pyrone **21** to alkyl iodide **18** furnished the IMPDA substrate **13a** in 83% yield.

Unfortunately, upon exposure of pyrone **13a** to thermal or Lewis acid catalyzed reaction conditions, we were unable to obtain the IMPDA product **14a** in good yield.[11] In accord with literature precedent,[12] we found that higher temperatures were required to obtain noticeable production of the Diels−Alder adduct. Furthermore, at these temperatures (≥120 °C), the decarboxylated product (**22**) is formed as the predominant product in 62% yield.

Given the lack of desired reactivity in our model compound **13a**, we turned our attention toward brominated derivative **13b**. Posner and others have demonstrated that halogen substitution at the 3- and/or 5-position of pyrone rings activates them toward electron-poor dienophiles, allowing for lower temperature non-decarboxylative cycloadditions.[13] Although direct monobromination of **13a** proved challenging due to competing bromination of the enoate moiety, we were delighted to find that treatment of pyrone **21** with bromine yielded bromopyrone **23** and dibrominated pyrone **24** in 48% and 32% yield, respectively (Scheme 3). Additionally, dibromide **24** could be smoothly monodehalogenated by exposure to Zn dust and acetic acid providing bromopyrone **23** in an overall 74% yield from pyrone **21**. The alkylative coupling of **23** with **18** was achieved using a carbonate base

(8) Although no published reports toward the synthesis of the basiliolides and transtaganolides have appeared, there are two abstracts relevant to such efforts; see: (a) Kozytska, M. V.; Dudley, G. B. *Abstracts of Papers*, 234th National Meeting of the American Chemical Society, Boston, MA, Aug 19−23, 2007; American Chemical Society; Washington, DC, 2007; ORGN 1012. (b) Kozytska, M. V.; Dudley, G. B. *Abstracts of Papers*, 58th Southeast Regional Meeting of the American Chemical Society, Augusta, GA, Nov 1−4, 2006; American Chemical Society; Washington, DC, 2006; SRM06 011.

(9) Closure of the C ring prior to an IMDA has previously been included in a proposed biosynthesis; see ref 6b.

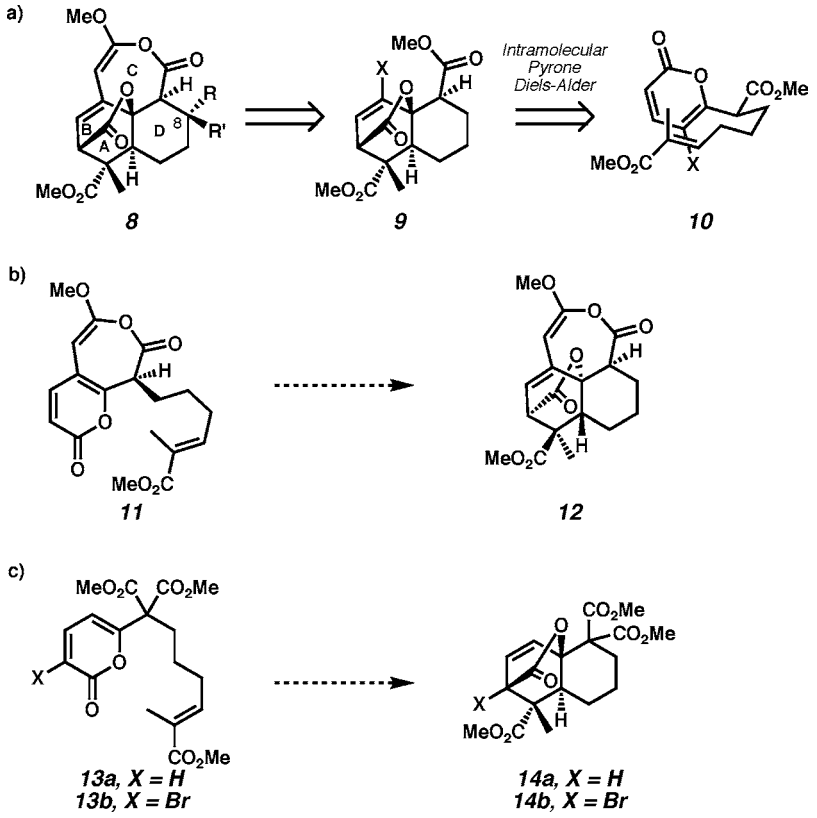
(10) Werkhoven, T. M.; van Nipsen, R.; Lugtenburg, J. *Eur. J. Org. Chem.* **1999**, *1999*, 2909−2914.

(11) Treatment of **13a** with a number of Lewis acids did not afford observable convsersion to **14a**. Furthermore, heating of **13a** to 90 °C for 86 h led to minimal conversion to **14a**. See the Supporting Information for details.

(12) For a review of the subject, see: Afarinkia, K.; Vinader, V.; Nelson, T. D.; Posner, G. H. *Tetrahedron* **1992**, *48*, 9111−9171.

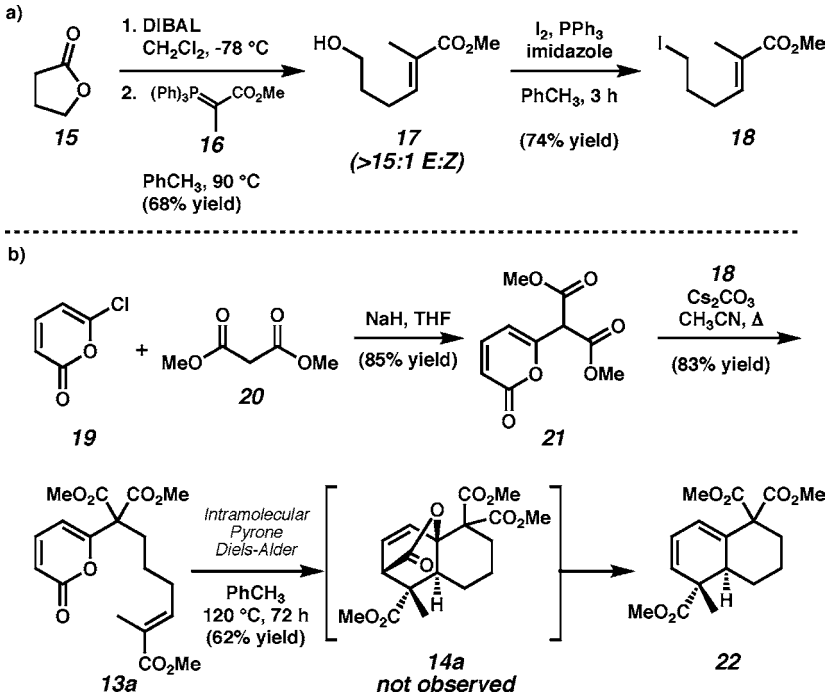
(13) (a) Posner, G. H.; Nelson, T. D.; Kinter, C. M.; Afarinkia, K. *Tetrahedron Lett.* **1991**, *32*, 5295−5298. (b) Posner, G. H.; Dai, H.; Afarinkia, K.; Murthy, N. N.; Guyton, K. Z.; Kensler, T. W. *J. Org. Chem.* **1993**, *58*, 7209−7215. (c) For a theoretical discussion and computational models, see: Afarinkia, K; Bearpark, M. J.; Ndibwami, A. *J. Org. Chem.* **2005**, *70*, 1122−1133.

Scheme 1

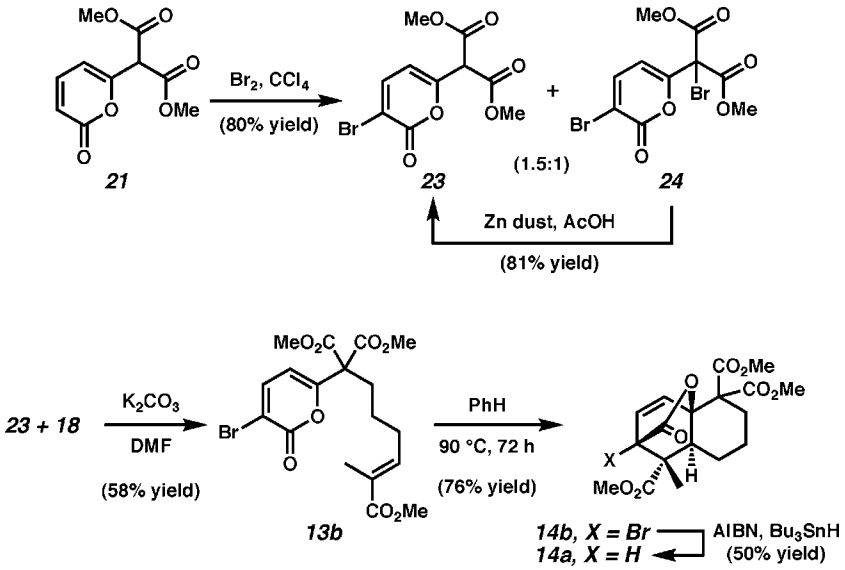


to provide IMPDA substrate **13b** in 58% yield. Importantly, upon heating bromide **13b** in a sealed tube at 90 °C, smooth cycloaddition occurred to produce tricycle **14b** as a single diastereomer in 76% yield.[14] The structure and relative stereochemistry of endo Diels−Alder adduct **14b** was unambiguously established by single-crystal X-ray crystal-

Scheme 2



Scheme 3



lography (Figure 2).[15] Treatment of the IMPDA product **14b** with tributyltin hydride and AIBN allowed for removal of the bridgehead bromine to provide **14a** in 50% yield.[13b]

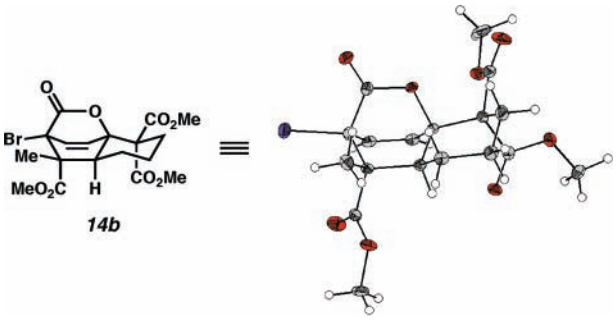


Figure 2. X-ray crystal structure of **14b**.

In conclusion, we have demonstrated that an intramolecular pyrone Diels−Alder cycloaddition can be used to construct the core of basiliolide B and other related natural products. Furthermore, we have developed a rapid, stereoselective route to highly substituted *trans*-decalin systems that may be useful for other applications. This technology is currently being utilized in the synthesis of basiliolide B and other members of this interesting family of natural products.

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Supporting Information Available: Full experimental details and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) The Diels−Alder product **14b** can be directly isolated from the alkylation reaction (i.e., **22** + **18** → **14b**). However, better yields are obtained if **13b** is purified prior to cycloaddition.

(15) Crystallographic data have been deposited at the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, and copies can be obtained on request, free of charge, by quoting the publication citation and the deposition number 656115.