



Progress toward the synthesis of the transtaganolide/basiliolide natural products: an Ireland–Claisen approach

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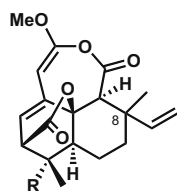
ABSTRACT

Efforts toward the synthesis of the transtaganolide natural product family are described. A highly efficient Ireland–Claisen/Diels–Alder approach has been developed, which rapidly constructs the highly oxygenated and stereochemically rich core of these natural products.

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Since their isolation,¹ the transtaganolide and basiliolide natural products have received considerable attention from the synthetic community. Initial reports from the groups of Stoltz,² Dudley,³ and Chi-Sing⁴ have demonstrated the utility of an intramolecular Diels–Alder cycloaddition in the construction of the tricyclic core of these molecules (Fig. 2a–c). However, these reports do not address the construction of the fully substituted C(8) carbon that is present in several members of the family (Fig. 1, 1–4).

Johansson and co-workers have recently reported an elegant biomimetic approach toward the transtaganolide natural products which installs the C(8) fully substituted carbon via an Ireland–Claisen rearrangement of an achiral precursor such as ester **11** (Fig. 2d).^{5,6} Independently, our group has been pursuing an analogous route to these natural products.⁷ In light of our ongoing interest in these molecules and the recent Johansson report,⁵ we deemed it necessary to disclose our synthetic results at this juncture (Scheme 1). Although we desire to establish our independent



- R**
- 1 Me C-8 α -methyl, β -vinyl (Transtaganolide C)
 - 2 Me C-8 β -methyl, α -vinyl (Transtaganolide D)
 - 3 CO₂Me C-8 α -methyl, β -vinyl (Basiliolide B)
 - 4 CH₂OAc C-8 α -methyl, β -vinyl (Basiliolide C)

Figure 1.

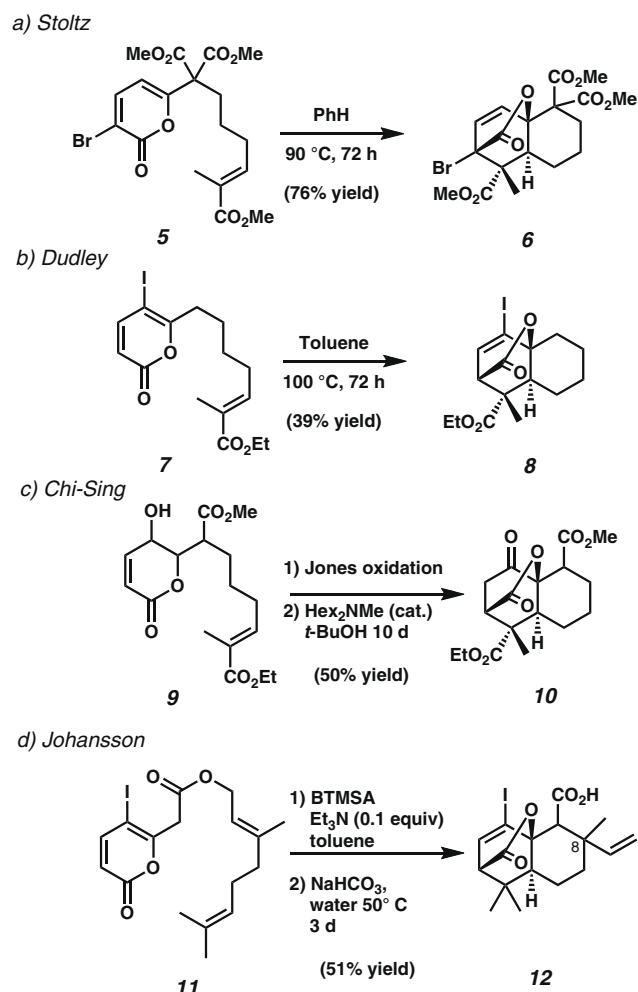
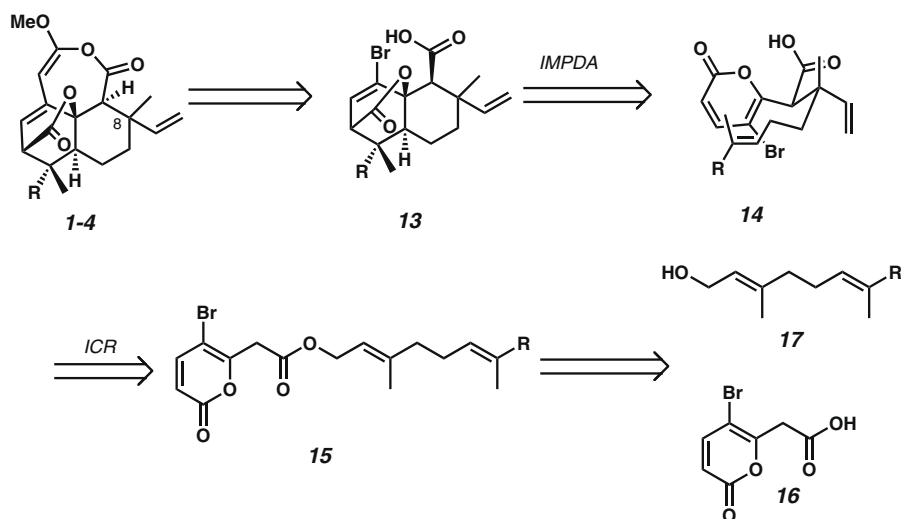
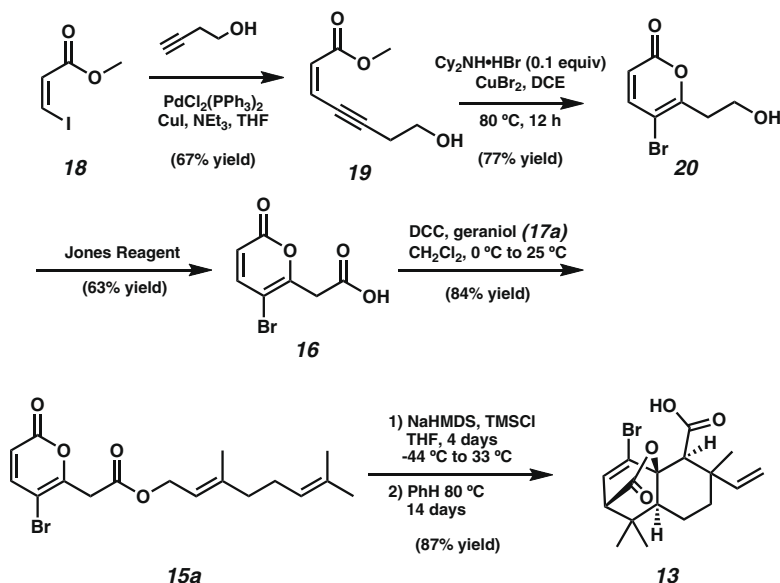


Figure 2.

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Scheme 1.



Scheme 2.

development of the Ireland–Claisen approach, the primary motivation for this document is one of support for a substantial development in the field.

At the outset of our synthetic endeavor, we envisioned that transtaganolide C (**1**), transtaganolide D (**2**), basiliolide B (**3**), and basiliolide C (**4**) could be prepared in the laboratory via an Ireland–Claisen rearrangement (ICR)/ intramolecular pyrone Diels–Alder (IMPDA) sequence (Scheme 1).⁷ We proposed that intermediate **13** could arise from pyrone **14** via an IMPDA. Furthermore, we reasoned that IMPDA substrate **14** could be derived from the Ireland–Claisen rearrangement of pyrone ester **15**. The ICR substrate (**15**) was to arise from the coupling of geraniol (**17**) to pyrone acid **16**.

The synthesis began with the palladium-catalyzed coupling of known (*Z*)-methyl iodoacrylate **18**⁸ with commercially available 3-buten-1-ol to provide methylester **19** in good yield (Scheme 2). Heating of ester **19** with CuBr_2 in the presence of a catalytic amount of dicyclohexylamine hydrobromide led to the formation of bromopyrone **20**.⁹ Jones oxidation of the resulting primary alco-

hol (**20**) yielded the desired pyrone acid **16** in moderate yield. Direct DCC coupling of the pyrone acid (**16**) to geraniol cleanly provided Ireland–Claisen substrate **15a**. We were delighted to find that a slow addition of a NaHMDS solution to a cold mixture of pyrone ester **15a** and TMSCl promoted a high yielding Ireland–Claisen rearrangement. After removal of volatiles from the crude ICR reaction,¹⁰ prolonged heating in a sealed tube charged with benzene and argon smoothly afforded the IMPDA product **13** in 87% yield as a mixture of C(8) diastereomers (~2:1 dr).

In conclusion, we have developed a brief and practical synthesis of the core the basiliolide/transtaganolide natural products. Efforts toward the synthesis of completed **1-4** continue.

Acknowledgments

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References and notes

1. (a) Abderrahmane, A.; Guerra, F. M.; Rubal, J. J.; Moreno Durado, F. J.; Akssira, M.; Mellouki, F.; Lopez, M.; Pujadas, A. J.; Jorge, Z. D.; Massanet, G. M. *Org. Lett.* **2005**, *5*, 881–884; (b) Appendino, G.; Properini, S.; Valdivia, C.; Ballero, M.; Colombano, G.; Billington, R. A.; Genazzani, A. A.; Sterner, O. *J. Nat. Prod.* **2005**, *68*, 1213–1217.
2. Nelson, H. M.; Stoltz, B. M. *Org. Lett.* **2008**, *10*, 25–28.
3. Kozytska, M. V.; Dudley, G. B. *Tetrahedron Lett.* **2008**, *49*, 2899–2901.
4. Xiongfei, Z.; Wanqing, W.; Xiaozu, L.; Chi-Sing, L. *Org. Lett.* **2008**, *10*, 5525–5528.
5. Larsson, R.; Sterner, O.; Johansson, M. *Org. Lett.* **2009**, doi:10.1021/ol802760z.
6. Ireland, R. E.; Mueller, R. H. *J. Am. Chem. Soc.* **1972**, *94*, 5897–5898.
7. Nelson, H. M. Progress Toward the Synthesis of the Transtaganolide Natural Products. Ph.D. Candidacy Report, California Institute of Technology, Pasadena, CA Mar 2008.
8. Batsanov, A. S.; Knowles, J. P.; Whiting, A. J. *Org. Chem.* **2007**, *72*, 2525–2532.
9. Liang, Y.; Xie, Y.-X.; Li, J.-H. *Synthesis* **2007**, 400–406.
10. As discussed by Johansson and co-workers, the immediate product of the Ireland–Claisen rearrangement is prone to thermal decomposition via a decarboxylative pathway. Use of the crude Ireland–Claisen product (presumably the silyl ester) under rigorously dry conditions allows for direct thermal cycloaddition. See Ref. 5.