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Biomimetic Synthesis toward the Transtaganolides/Basiliolides

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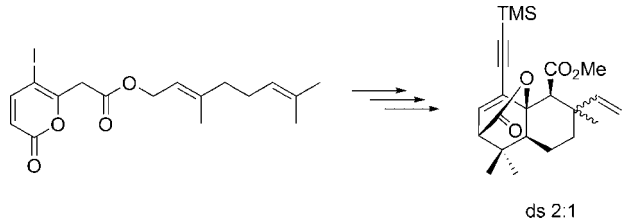
ABSTRACT



A concise biomimetic approach toward transtaganolides C and D involving an Ireland−Claisen rearrangement/intramolecular Diels−Alder reaction sequence suggesting the involvement of pericyclic reactions in the biosynthesis of these biologically active plant metabolites is presented. A final coupling reaction establishes the carbon framework of the transtaganolides.

The mediterranen plant *Thapsia garganica* is one the oldest medicinal plants known.[1] So far, the great interest in this plant stems from the fact that it is the natural source of thapsigargin (**1**), a potent inhibitor of calcium mobilization through irreversible inhibition of the Sarco/Endoplasmic Reticulum Ca^{2+}-ATPase pump (SERCA).[2] Compound **1** has consequently been used as an important pharmacological tool and is also under investigation as an apoptotic prostate cancer drug.[3] Due to its complex and highly oxygenated carbon framework, it has also posed as a chemical challenge for synthetic chemists.[4]

Recently, two groups independently isolated a series of C-19 terpenolides (e.g., **2**−**5**) from *T. transtagana*[5] and *T. garganica*.[6] The transtaganolides contain a unique 7-methoxy-4,5-dihydro-3*H*-oxepin-2-one ring and differ mainly in the oxygenation of the *gem*-dimethyl group (Figure 1). Intriguingly, transtaganolides C and D (**2** and **3**) and basiolide B (**4**) were shown to have SERCA-inhibiting properties despite the lack of structural similarity with thapsigargin (**1**).[7]

The biosynthetic origin of the transtaganolides is yet unknown. Initial suggestions pointed toward a "classical" terpenoid biosynthesis where the C-4 and C-8 *gem*-substituted decalin portion of the ring system originated from cyclization of farnesyl pyrophosphate.[6]

However, a more direct and fascinating origin starting from a prenylated coumarin (i.e., **6**, reported from *T. garganica*[8]) and involving an intramolecular Diels−Alder reaction yielding the natural product was also suggested.[6] The transtaganolides may biosynthetically be derived from **6** by the epoxidation of the aromatic 6,7-bond followed by a series of pericyclic reactions. This suggestion was further strengthened by the isolation of the novel prenylated pyran-

(1) (a) Rasmussen, U.; Christensen, S. B.; Sandberg, F. *Acta. Chem. Suec.* **1978**, *15*, 133. (b) Christensen, S. B.; Andersen, A.; Smitt, U. *Prog. Chem. Nat. Prod.* **1997**, *71*, 129.

(2) Thastrup, O.; Cullen, P. J.; Drøbak, B. K.; Hanley, M. R.; Dawson, M. P. *Proc. Natl. Acad. Sci. U.S.A.* **1990**, *87*, 2466.

(3) Furuya, Y.; Lundmo, P.; Short, A. D.; Gill, G. D.; Isaacs, J. T. *Cancer Res.* **1994**, *54*, 6167.

(4) Ley, S. V.; Antonello, A.; Balskus, E. P.; Booth, D. T.; Christensen, S. B.; Cleator, E.; Gold, H.; Högenauer, K.; Hünger, U.; Myers, R. M.; Oliver, S. F.; Simic, O.; Smith, M. D.; Søhoel, H.; Woolford, A. J. A. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 12073.

(5) Saouf, A.; Guerra, F. M.; Rubal, J. J.; Moreno-Dorado, F. J.; Akssira, M.; Mellouki, F.; López, M.; Pujadas, A. J.; Jorge, Z. D.; Massanet, G. M. *Org. Lett.* **2005**, *7*, 881–884.

(6) Appendino, G.; Prosperini, S.; Valdiva, 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. Pharm. Exp. Ther.* **2006**, *319*, 422–430.

(8) Larsen, P. K.; Sandberg, F. *Acta. Scand. Chem.* **1970**, *24*, 1113.

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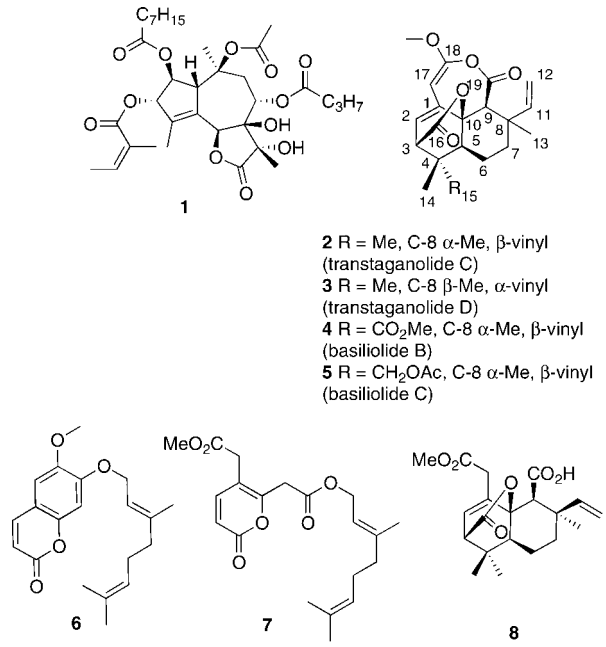


Figure 1. Structures of thapsigargin, transtaganolides C and D, basiliolides B and C, and proposed biosynthetic precursors of the transtaganolides and basiliolides.

2-one **7** from *T. transtagana*, which is proposed to be a precursor of the transtaganolides.[9]

The unique structures of the transtaganolides, as well as their biological activities, has attracted strong interest from synthetic chemists, and several groups have recently and independently reported progress toward the synthesis of members of this class of natural products via intramolecular Diels−Alder reactions.[10] These reports prompt us to present our own progress toward the synthesis of transtaganolides C and D. Our previous interest in the area of naturally occurring pericyclic reactions[11] made us focus on a biomimetic route toward the target compound that could also explain the observed stereochemistry of the basiliolides (i.e., the diastereomeric relationship between optically pure transtaganolides C and D, **2** and **3**, that differ only in the stereochemistry on C-8).

The likely instability of the oxepine ring prompted us to design a route that allowed the construction of this ring at the final stages of the proposed synthesis (Scheme 1). Selective *O*-acylation of the methyl ester **8** would yield this unique structural feature. Disconnecting the C−C bond of the methyl ester group in **8** at this stage was deemed favorable for two reasons; first, a successful synthesis would be more amendable to analogue synthesis by introducing a vinyl halide (**9**) as a functional handle, and second, a 3-halogenated 2(2*H*)-pyranone would be more reactive in a Diels−Alder reaction. The successful use of 3- (and 5)-halogenated 2(2*H*)-pyranones has previously been demonstrated[12] and is a key feature in the Stolz synthesis toward this compound class.[10a]

The 3-vinyl carboxyl moiety of intermediate **10** is the obvious product of an Ireland−Claisen rearrangement. The involvement of an Ireland−Claisen rearrangement would also nicely explain the observed stereochemical relationships in the transtaganolides (i.e., between **2** and **3**).

Synthetic asymmetric Ireland−Claisen rearrangements of geranyl esters have been shown to proceed with high enantioselectivity but with only modest diastereoselectivity.[13] Also, the carboxyl group would be prone to enolization due to the additional electron-withdrawing properties of the 2-pyranone ring, hopefully excluding the need for the use a strong base to generate the required enolate for the rearrangement. Mild conditions for this type of reaction would also be in line with a possible biosynthetic route, even though the involvement of naturally occurring Ireland−Claisen rearrangements have not been described.

The required Ireland−Claisen precursor, the geranylated pyranone **11**, could be obtained from the corresponding acid **12** which in turn is the possible oxidation product of a primary alcohol. 6-Substituted 5-iodo-pyran-2-ones are readily available through iodine catalyzed electrophilic cyclizations from alkenynes such as **13**.[14]

The synthesis (Scheme 2) starts with a Sonogashira coupling of (*Z*)-methyl iodoacrylate **14**[15] with but-3-yn-1-ol to provide the cyclization precursor **13**. Treatment of **13** with ICl in CH_2Cl_2 gave a smooth cyclization to the desired 2-pyranone **15** as a solid.[13] The furanone product arising from a competing 5-exo cyclization was not detected. Treatment of alcohol **15** with H_5IO_6 in the presence of a catalytic amount of PCC provided the acid **12** in good yield.[16] The crude acid was directly coupled with geraniol to give the key geranylated intermediate **11**. With iodo compound **11** in hand, we turned our attention to the key Ireland−Claisen/Diels−Alder sequence.

Reasoning that the electron-poor 2-pyranone ring would further increase the acidity of the protons on the methylene position circumventing the need for the use of a strong base such as LDA to form the enolate, we looked for alternative procedures. Inspired by a report on the decarboxylative Ireland−Claisen reaction of sulfone esters,[17] we tried heating **11** in toluene in a microwave reactor in the presence

(9) Rubal, J. J.; Moreno-Dorado, F. J.; Guerra, F. M.; Jorge, Z. D.; Saouf, A.; Aksirra, M.; Mellouki, F.; Romero-Garrido, R.; Massanet, G. M. *Phytochemistry* **2007**, *68*, 2480.

(10) (a) Nelson, H. M.; Stoltz, B. M. *Org. Lett.* **2008**, *10*, 25. (b) Kozytska, M. V.; Dudley, G. B. *Tetrahedron Lett.* **2008**, *49*, 2899. (c) Xiongfei, Z.; Wanqing, W.; Xiaozu, L.; Chi-Sing, L. *Org. Lett.* **2008**, *10*, 5525.

(11) (a) Johansson, M.; Köpcke, B.; Anke, H.; Sterner, O. *Angew. Chem., Int. Ed.* **2002**, *41*, 2158. (b) Johansson, M.; Köpcke, B.; Anke, H.; SternerO., *Tetrahedron* **2002**, *58*, 2523.

(12) (a) Posner, G. H.; Dai, H.; Afarinkia, K.; Murthy, N. N.; Guyton, K. Z.; Kensler, T. W. *J. Org. Chem.* **1993**, *58*, 7209. (b) Afarinkia, K.; Bearpark, M. J.; Ndibwami, A. *J. Org. Chem.* **2005**, *70*, 1122.

(13) Corey, E. J.; Roberts, B. E.; Dixon, B. R. *J. Am. Chem. Soc.* **1995**, *117*, 193.

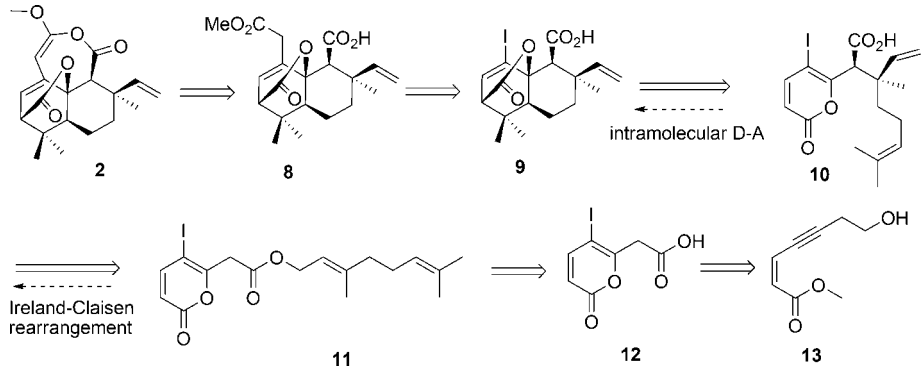
(14) (a) Yao, T.; Larock, R. C. *J. Org. Chem.* **2003**, *68*, 5936. (b) Biagetti, M.; Bellina, F.; Carpita, A.; Stabile, P.; Rossi, R. *Tetrahedron* **2002**, *58*, 5023.

(15) Batsanov, A. S.; Knowles, J. P.; Whiting, A. *J. Org. Chem.* **2007**, *72*, 2525.

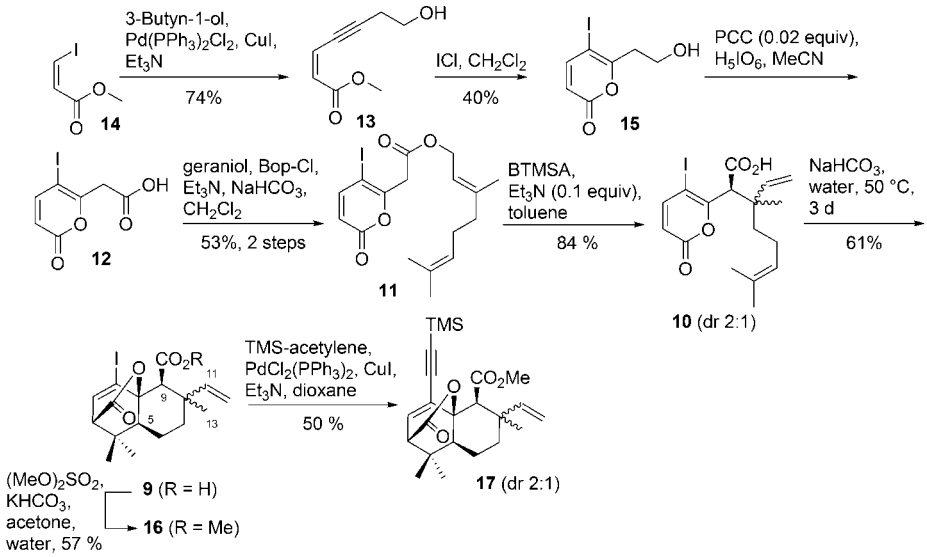
(16) Hunsen, M. *Synthesis* **2005**, *15*, 2487.

(17) Bourgeois, D.; Craig, D.; Grellepois, F.; Mountford, D. M.; Stewart, A. J. W. *Tetrahedron* **2006**, *62*, 483.

Scheme 1. Retrosynthetic Analysis



Scheme 2. Synthesis of Key Intermediate **17**



of 1 equiv of *N*,*O*-bistrimethylsilylacetamide (BTMSA) and 0.1 equiv of TEA.

After 10 min, we could see the formation of a new product which was identified as a 2:1 diastereomeric mixture of **10**. Prolonged heating for 3 h resulted in decomposition of the starting material **10**, but surprisingly, the Diels−Alder product **9** was isolated, albeit in a very low yield (<5%). Encouraged by these findings, we focused on performing the conversion of ester **11** to the tricyclic compound **9** in a stepwise manner, first focusing on the sigmatropic Ireland−Claisen rearrangement. Increasing the amount of BTSMA and heating for 20 min gave an almost complete conversion of **11** to **10** (as a 2:1 diastereomeric mixture). Traces of Diels−Alder product could still be seen. The diastereoselectivity remained unchanged, and the diastereomers were not separated but used as a mixture in the following step.

However, heating **10** in toluene at 120 °C or in benzene at 80 °C did not give the desired product; instead, decarboxylation occurred. Hoping that basic conditions could prevent the decarboxylation and considering the possible biosynthetic relevance of our synthetic strategy, and the numerous reports of successful Diels−Alder reactions in water, we tried to heat acid **10** in water at 50 °C with 1.5 equiv of $NaHCO_3$.[18] After 3 days, **9** could be isolated in 61% yield as an unseparable 2:1 diastereomeric mixture (major: β-methyl, α-vinyl; minor: α-methyl, β-vinyl). The relative configuration of **9** was determined by a NOESY experiment. Strong NOESY correlations were observed between 5-H and 9-H in both isomers, demonstrating that the two protons are on the same side and axial. For the major isomer, a NOESY correlation is observed between 9-H and 11-H, while the corresponding correlation between 9-H and 13-H_3 is observed for the minor isomer. The formation of the observed exo configuration in **9** can be explained by repulsive psuedoaxial 1,3 interactions during the intramolecular Diels−Alder reaction between the iodine and the C-9 carboxylate moiety, thus acting as a directing group, similar to what has been observed in a similar system.[10b]

(18) Li, C.-J. *Chem. Rev.* **2005**, *105*, 3095.

Acid **9** was converted to the corresponding methyl ester **16**, which was coupled with TMS alkyne to give **17** in order to introduce the remaining two carbons and thereby prepare the transtaganolide carbon skeleton.

In conclusion, we have developed a straightforward and robust synthetic strategy toward the transtaganolide class of natural products. The synthetic route devised, in conjunction with the different secondary metabolites isolated from *T. transtagana*, highlights the possibility of the existence of a rare Ireland−Claisen-type rearrangement in a biosynthesis.[19] Also, the very mild conditions that finally brought about the crucial Diels−Alder cyclization gives further creedence and support that this reaction can occur in living tissue.[20] Together this supports the hypothesis that the coumarin derived pyranone **7** is the biosynthetic precursor of the transtaganolides and basiliolides and that the occurrence of an Ireland−Claisen rearrangement in the biosynthesis explains the observed C-8 configurations of the transtaganolides. Further work in completing the synthesis of transtaganolides and studying the biosynthetic importance of the Ireland−Claisen rearrangement/Diels−Alder reaction sequence is now in progress.

(19) A Claisen rearrangement is a key step in the synthesis of chorismate. For the use of a biomimetic Claisen rearrangement, see: Nicolaou, K. C.; Li, J. *Angew. Chem., Int. Ed.* **2001**, *40*, 4264.

(20) Stocking, E. M.; Williams, R. M. *Angew. Chem., Int. Ed.* **2003**, *42*, 3078.

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Note Added after ASAP Publication. There was an error in the structure of compound 11 in Schemes 1 and 2 and the abstract and toc graphic in the version published ASAP January 13, 2009; the corrected version was published on the Web January 29, 2009.

Supporting Information Available: Detailed descriptions of experimental procedures 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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