Total Synthesis

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A Biomimetic Synthesis of (±)-Basiliolide B**

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Abstract: *A highly diastereoselective and practical biomimetic total synthesis of (±)-basiliolide B has been achieved through the study of the two proposed biosynthetic pathways (O-methylation and O-acylation) for the unprecedented 7-methoxy-4,5-dihydro-3H-oxepin-2-one (C ring). The synthesis featured a cyclopropanation/ring opening strategy for establishing the stereogenic centers at C8 and C9, a biomimetic 2-pyrone Diels–Alder cycloaddition for the synthesis of the ABD ring system, and finally a highly efficient biomimetic intramolecular O-acylation for the C ring formation. This result provides an important perspective on the biosynthetic origin of the unprecedented 7-membered acyl ketene acetal moiety of the C ring.*

Basiliolides and transtaganolides are structurally related natural products isolated independently by two different groups from plants of *Thapsia* genus in 2005,[1,2] and have been shown to be potent inhibitors against sacroendoplasmic reticulum Ca^{2+}-ATPases.[3] This class of natural products contains a remarkable array of structural features including a *trans*-decalin framework with either a bridging lactone constituting the ABD ring system of the basiliolide skeleton, or a fused γ-lactone bridged by an ether linkage forming the ABDE ring system of transtaganolides A and B (Figure 1). More interestingly, the basiliolides and transtaganolides contain an unprecedented 7-methoxy-4,5-dihydro-3*H*-oxepin-2-one (C ring). Due to the unique structural features and the interesting biological activities, a considerable amount of efforts toward the biosynthesis and biomimetic synthesis of the basiliolide/transtaganolide family have been reported.[4–8] As shown in Figure 1, an Ireland–Claisen rearrangement of prenyl 2-pyrone **2** (isolated along with the transtaganolides by Massanet's group) followed by an intramolecular 2-pyrone Diels–Alder (DA) cycloaddition sequence has been proposed for the biosynthesis of the tricyclic core structure of transtaganolide E and F, which are the seco acid derivatives of transtaganolide D and C (basiliolide A1 and A2).[4] Later on, the groups of Johansson/Sterner[6] and Stoltz[7] have independently demonstrated the construction of the ABD ring system through the proposed biosynthetic sequence either in a sequential or cascade manner.

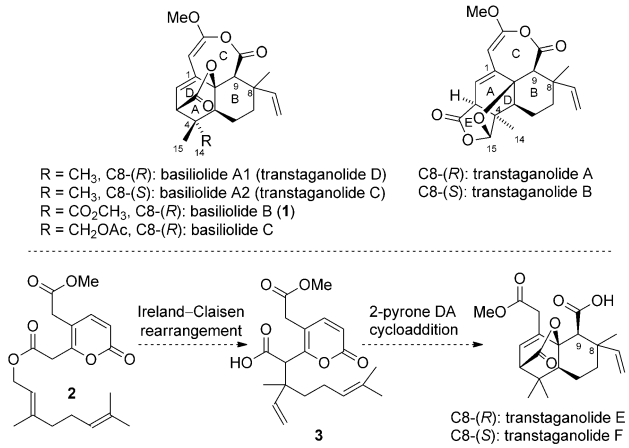

Figure 1. The structures of the basiliolide/transtaganolide family and the proposed biosynthesis of transtaganolide E and F.

On the other hand, there are only a handful of reports on the C ring formation. The C ring is a seven-membered acyl ketene acetal, which could be easily hydrolyzed and gave the seco acid derivatives.[4] Moreover, methods for construction of cyclic acyl ketene acetals are highly limited, which made the synthesis of the C ring a very challenging task. Until now, only Stoltz's group has successfully established the C ring through a formal [5+2] annulation process,[7c,d] which assembled the seven-membered acyl ketene acetal in one-pot with reasonable yields (Figure 2). Based on this strategy, they

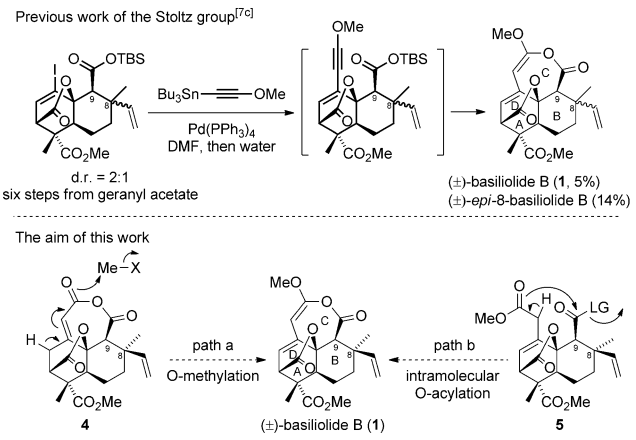

Figure 2. Previous work of the Stoltz's group and the aim of this work toward the C ring formation.

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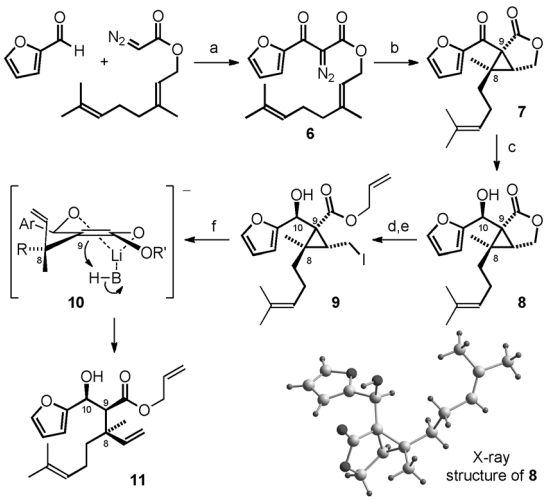
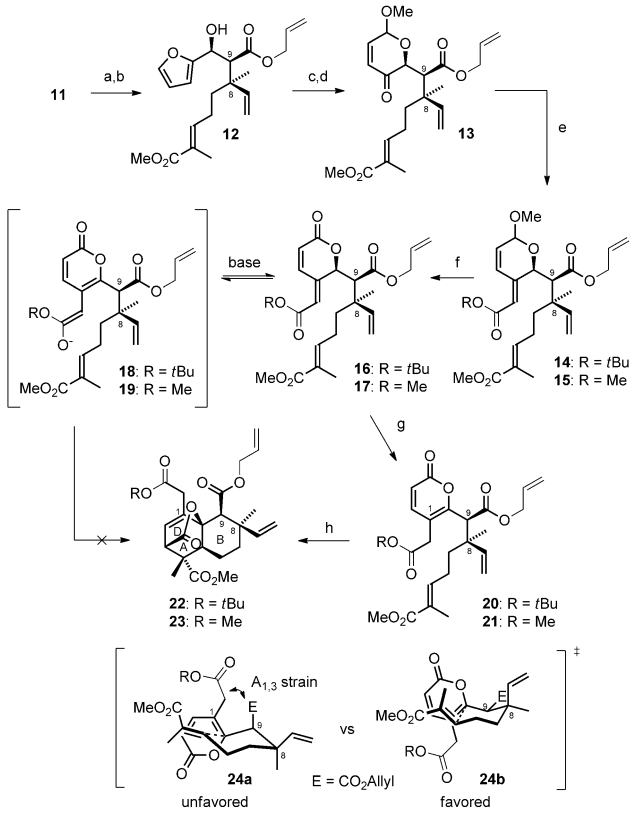
reported the first total synthesis of (±)-basiliolide B in seven steps from geranyl acetate with 1.1% overall yield.[7c] We are particularly interested in developing new methods for the construction of the intriguing C ring based on the proposed biosynthesis including the O-methylation[2] of acid anhydride **4** (path a, Figure 2) and the intramolecular O-acylation[4,6] of seco acid derivative **5** (path b, Figure 2). Up to now there is only one unsuccessful attempt on the biosynthesis of the C ring through an intramolecular O-acylation of transtaganolide E and F has been reported.[6b] In the course of a biomimetic study of the basiliolide/transtaganolide family, our group has previously reported a new type of base-catalyzed 2-pyrone DA cycloaddition for the construction of the ABD ring system of basiliolide B.[8] We herein report a study on the C ring formation based on the proposed biosynthetic strategies as well as a highly diastereoselective total synthesis of (±)-basiliolide B.

Among the reported synthetic studies, the Ireland–Claisen rearrangement is the only method that has been employed for establishing the stereogenic centers at C8 (an all-carbon quaternary carbon) and C9.[5–7] However, this type of reaction generally requires high reaction temperatures and provides only poor to modest diastereoselectivity. Moreover, the isolation of the diastereomers is reported to be troublesome. Because of this, we have decided to develop a cyclopropanation/ring opening strategy for establishing the stereogenic centers at C8 and C9. As shown in Scheme 1, the cyclopropanation precursor **6** was prepared by oxidative coupling of 2-furaldehyde and geranyl diazoacetate.[9] After a survey of a variety of Rh and Cu catalysts,[10] $Cu(TBS)_2$[11] was found to be an efficient catalyst for the cyclopropanation reaction and provided 74% of the expected product **7** as a single diastereomer in 80 °C toluene. The reduction of the ketone moiety of **7** with $NaBH_4$ at low temperature provided alcohol **8** with good diastereoselectivity (d.r. = 10:1). The structure of the major diastereomer was characterized unambiguously by X-ray crystallography.[12] The lactone ring of **8** was then hydrolyzed under basic conditions. Subsequent esterification followed by iodination gave compound **9**. After an extensive study on a variety of cyclopropane ring-opening and diastereoselective protonation conditions,[13] we found that compound **9** underwent lithium–halogen exchange followed by cyclopropane ring opening upon treatment with *n*BuLi at −80 °C and afforded compound **11** as a single diastereomer in an excellent yield. The high diastereoselectivity of the protonation of enolate **10** could be rationalized by Mohrig's model,[14] in which protonation should preferentially occur at the α-face of the half-chair transition state due to the chelation of the proton source (BH) toward the lithium ion, and lead to compound **11** with the desired stereochemistry at C9. This cyclopropanation/ring opening strategy established all the stereogenic centers at C8–C10 of compound **11** from furan-2-carbaldehyde and geranyl diazoacetate in six steps with good overall yields in decagram-scale reactions.

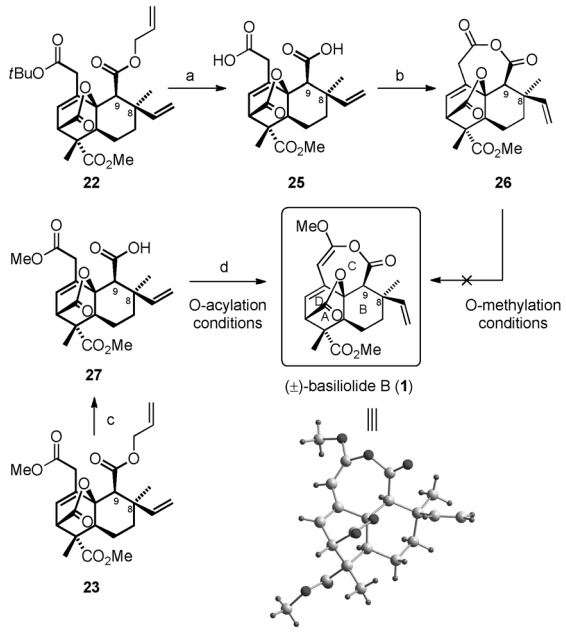


Scheme 1. Establishment of the stereogenic centers at C8 and C9 through the cyclopropanation/ring opening strategy. a) DBU (10 mol%), IBX, DMSO, RT, 5 h (65%); b) $Cu(TBS)_2$ (10 mol%), toluene, 80 °C, 20 h (74%, single diastereomer); c) $NaBH_4$, MeOH, −78–−20 °C, 4 h (77%, d.r. = 10:1, 70% for major diastereomer); d) 4 N $KOH_{(aq)}$, EtOH, 90 °C, 2 h; then allyl bromide, DMF, RT, 2 h (98%); e) PPh_3, I_2, imidazole, THF, 0 °C, 15 min (85%); f) *n*BuLi, THF, < −80 °C, 15 min (97%, single diastereomer). DBU = 1,8-diazabicyclo-[5.4.0]undec-7-ene, IBX = *o*-iodoxybenzoic acid, $Cu(TBS)_2$ = bis(*N*-*t*butylsalicylamidinato)copper(II).

With compound **11** in hand, the trisubstituted alkene was converted to the α,β-unsaturated methyl ester through the standard oxidative cleavage/olefination protocol (Scheme 2). Ring expansion of the furan ring through the Achmatowicz reaction[15] followed by methylation of the resultant lactol afforded compound **13**, which is intended to be converted to **14** and **15** by olefination. Surprisingly, the ketone moiety of compound **13** was found to be unreactive under a variety of conventional olefination conditions probably due to its steric hindrance. To our delight, we finally found that *t*butyl and methyl 2-(tri-*n*butylphosphoranylidene)acetate[16] in toluene at 100 °C afforded the expected (*E*)-olefins **14** and **15**, respectively, in good yields. To the best of our knowledge, this is the first example of an olefination of sterically hindered ketones using alkyl 2-(tri-*n*butylphosphoranylidene)acetates. After the optimization of the olefination conditions, the methyl lactol moieties of **14** and **15** were directly oxidized to lactones **16** and **17** using Jones reagent.[17] According to our previous model study,[18] compounds **16** and **17** are expected to equilibrate to 2-pyrones **18** and **19** upon treatment with a base, and undergo 2-pyrone DA cycloaddition in one-pot (Scheme 3). However, the expected DA product was not observed and 2-pyrones **20** and **21** with epimerization at C9 were isolated as the major side products under various basic conditions. After a survey of different bases, we found that DABCO[19] can cleanly equilibrate **16** and **17** to 2-pyrones **20** and **21**, respectively, without epimerization at C9. The optimal condition for the 2-pyrone DA cycloaddition of **20** and **21** were found to be 120 °C with toluene as the solvent in a sealed tube; this completely suppressed the formation of the decarboxylation side product[20] and afforded the DA products (**22** and **23**) in 85–89% yield as single diastereomers. The high diastereoselectivity of the 2-pyrone DA reactions could be rationalized by the more favorable chair-like transition state **24b**, which can avoid the unfavorable $A_{1,3}$ interactions between the ester moieties at C1 and C9. The stereochemistry



Scheme 2. Biomimetic 2-pyrone DA cycloaddition. a) *m*CPBA, CH_2Cl_2, 0 °C, 15 min (86 %); b) $NaIO_4$, 1 N $HCl_{(aq)}$, THF/H_2O = 2:1, 0 °C, 4 h; then methyl 2-(triphenylphosphoranylidene)propanoate, CH_2Cl_2, RT, 20 h (81 %); c) $VO(acac)_2$, TBHP, CH_2Cl_2, RT, 3 h (95 %); d) Ag_2O, CH_3I, acetone, 50 °C, 10 h (92 %); e) *t*butyl or methyl 2-(*n*butylphosphoranylidene)acetate, toluene, 100 °C, 1.5 h (60–65 %); f) $Na_2Cr_2O_7$, H_2SO_4, acetone, 0 °C, 2.5 h (75 %); g) DABCO, toluene, 70 °C, 17 h (80–90 %, single diastereomers); h) toluene, 120 °C (sealed tube), 3–5 d (76–85 %, single diastereomers). *m*CPBA = *m*-chloroperbenzoic acid, TBHP = *t*butyl hydroperoxide, DABCO = 1,4-diazabicyclo-[2.2.2]octane.



Scheme 3. Biomimetic approaches toward the C ring formation and total synthesis of (±)-basiliolide B. a) $Pd(PPh_3)_4$, PPh_3, pyrrolidine, CH_2Cl_2, 0 °C, 2.5 h; then HCO_2H, RT, 10 h (90 %); b) EDCI, DMAP, CH_2Cl_2, RT, 4 h (70 %); c) $Pd(PPh_3)_4$, PPh_3, pyrrolidine, CH_2Cl_2, 0 °C, 30 min (96 %); d) Tf_2O, Et_3N, toluene, −78 for 10 min and 0 °C for 5 min (92 %). EDCI = 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride, DMAP = *N*,*N*-4-dimethylaminopyridine.

of the DA products (**22** and **23**) was characterized unambiguously by NOESY experiments (see the Supporting Information for details).

To study the biomimetic synthesis of the C ring, acid anhydride **26** and seco acid derivative **27** were prepared from DA products **22** and **23**, respectively. As shown in Scheme 3, acid anhydride **26** was obtained by using EDCI/DMAP[21] in 70 % yield after deprotection of the allyl and *t*butyl esters. Acid anhydride **26** can be purified by silica gel column chromatography and characterized by NMR experiments. With **26** in hand, a variety of O-methylation conditions[22] for the C ring formation was studied extensively. Unfortunately, acid anhydride **26** was found to be highly unstable and rapidly decomposed under basic conditions. We then turned our attention to the intramolecular O-acylation strategy. Seco acid derivative **27** was readily prepared by deprotection of the allyl ester of **23** (Scheme 3). The acid moiety of **27** was converted to a variety of leaving groups using trifluoroacetic anhydride, $(COCl)_2$, $SOCl_2$, EDCI, or *t*BuCOCl. The intermediates generated in situ are anticipated to undergo intramolecular O-acylation to form the C ring. However, this reaction is found to be very difficult and always resulted in a mixture of unidentifiable side products. These observations are also consistent with those reported by Sterner and Johanson.[6b] After an extensive effort on surveying the appropriate conditions, we finally found that the C ring can be established efficiently using Tf_2O/Et_3N in toluene at −78 to 0 °C, which afforded (±)-basiliolide B (**1**) in 92 % yield. The structure of the synthetic natural product was characterized unambiguously by X-ray crystallography.[12] Although the cyclic acyl ketene acetal moiety of the C ring has been reported to be labile and transtaganolide E and F have been referred to as biosynthetic dead-ends,[6b] our results strongly suggest that the seco acid derivative **27** is a potential biosynthetic precursor of basiliolide B.

In summary, the highly diastereoselective and practical biomimetic total synthesis of (±)-basiliolide B has been achieved in 17 steps from geranyl diazoacetate by studying the two proposed biosynthetic pathways (O-methylation and O-acylation) for the unprecedented 7-methoxy-4,5-dihydro-3*H*-oxepin-2-one (C ring). Although the synthetic route is longer than that reported by the Stoltz team, our biomimetic synthesis can be done in gram to decagram scales (hundreds of milligram scale for the biomimetic intramolecular O-acylation that lead to the natural product) in 5.3 % overall yield with precise control of stereochemistry. The synthesis featured a cyclopropanation/ring opening strategy for the diastereoselective construction of the stereogenic centers at C8 and C9, the preparation of the DA precursor **17** by olefination of hindered ketone **13** using an uncommon Wittig

reagent (methyl 2-(tri*n*butylphosphoranylidene)acetate), a biomimetic 2-pyrone DA cycloaddition for the synthesis of the ABD ring system, and finally a highly efficient biomimetic intramolecular O-acylation for the C ring formation. This result strongly supports the hypothesis of the seco acid derivatives being the potential biosynthetic precursors of basiliolides and transtaganolides. Moreover, the biomimetic intramolecular O-acylation reaction would provide a new access to the cyclic acyl ketene acetal ring systems. This synthesis would be readily extended to an asymmetric synthesis by employing an asymmetric cyclopropanation reaction of compound **6**. We currently prepare other members of the basiliolide/transtaganolide family and their structural analogues based on our synthetic strategy to probe their biological mode of action.

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[12] CCDC 984549 (**8**) and 984576 (**1**) contain 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.

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