

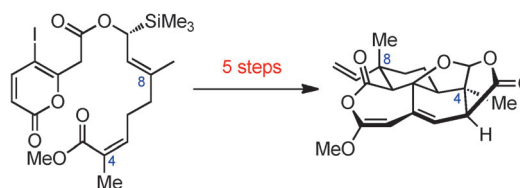
## Communications



### Natural Product Synthesis

H. M. Nelson, J. R. Gordon, S. C. Virgil,  
B. M. Stoltz\* ————— ■■■■—■■■■

Total Syntheses of (–)-Transtaganolide A,  
(+)-Transtaganolide B,  
(+)-Transtaganolide C, and (–)-  
Transtaganolide D and Biosynthetic  
Implications



**‘Dibal’lin’ on a budget:** The enantioselective total syntheses of transtaganolides A–D are rapidly achieved by a highly diastereoselective Ireland–Claisen/Diels–Alder cascade reaction of an enantio-enriched geraniol derivative (see

scheme). Based on X-ray diffraction data, the absolute configuration of these metabolites is established and discussed within the context of existing biosynthetic hypotheses.

Natural Product Synthesis

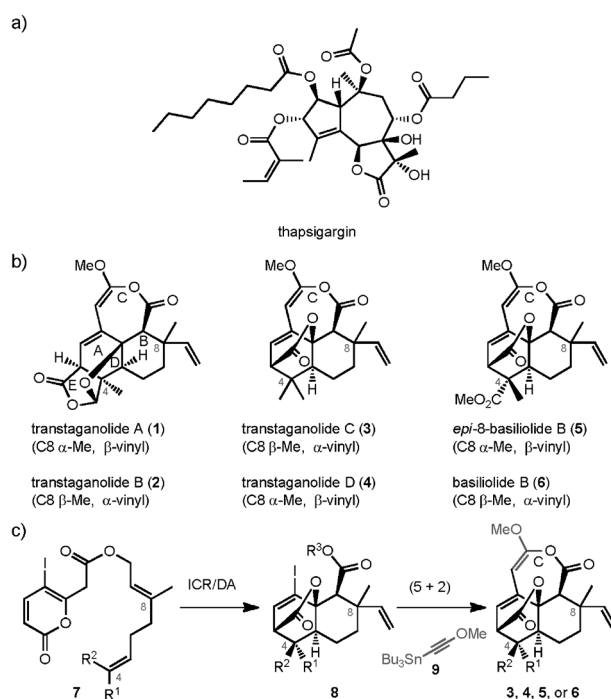
# Total Syntheses of (–)-Transtaganolide A, (+)-Transtaganolide B, (+)-Transtaganolide C, and (–)-Transtaganolide D and Biosynthetic Implications\*\*

Hosea M. Nelson, Jonny R. Gordon, Scott C. Virgil, and Brian M. Stoltz\*

Dedicated to Dr. Victor Prieto and Don Kemp

Plants belonging to the genus *Thapsia* have been acknowledged since antiquity for their remarkable medicinal properties.<sup>[1]</sup> Until very recently, this has been attributed to their primary chemical component thapsigargin (Figure 1a), a widely utilized and structurally complex sesquiterpenoid metabolite known for its potent SERCA inhibition.<sup>[2]</sup> Within the past decade, an additional group of structurally novel natural products, deemed the transtaganolides (**1–4**, Figure 1b) and basililolides (**5–6**, Figure 1b), have been isolated.<sup>[3]</sup> Initial biological evaluation suggests that these natural products also inhibit SERCA, albeit through a mechanistically distinct pathway.<sup>[4]</sup>

Enticed by the opportunity to prepare structurally novel and biologically relevant molecules, our group undertook extensive synthetic efforts which resulted in our disclosure of a general strategy for the total syntheses of several transtaganolide natural products (**3–6**).<sup>[5]</sup> Integral to this approach was an Ireland–Claisen rearrangement/intramolecular pyrone Diels–Alder cyclization (ICR/DA) cascade<sup>[6]</sup> which furnished the stereochemically complex, tricyclic cores (**8**) in a single step from monocyclic, achiral precursors (**7**; Figure 1c). Additionally, a formal (5+2) annulation process forged the formidable C ring.<sup>[5]</sup> While concise and modular, our initial



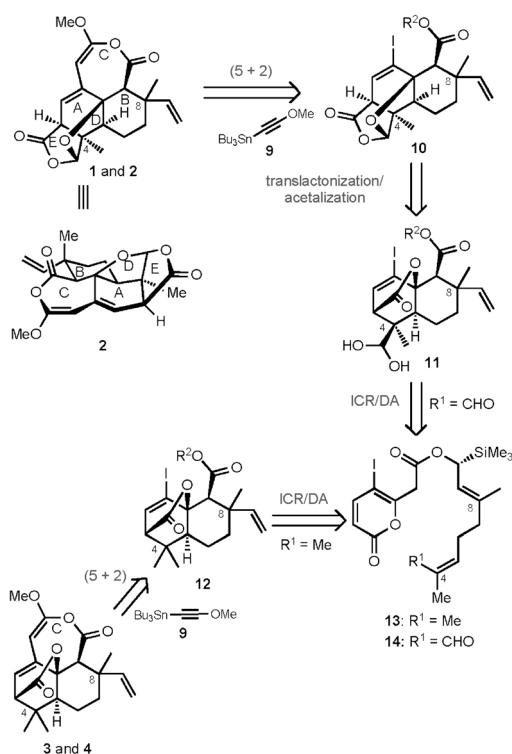
**Figure 1.** a) Thapsigargin. b) Transtaganolides and basililolides. c) General synthetic strategy.

approach fell short of achieving two key goals: 1) the preparation of enantioenriched products and 2) the synthesis of transtaganolides A (**1**) and B (**2**), the most complex members of the natural product family. Transtaganolides A (**1**) and B (**2**) are unique within their class because of their lack of an oxabicyclo[2.2.2]octene structural motif (**1** and **2** versus **3–6**; Figure 1b). In its place is a fused  $\gamma$  lactone (E ring; **1** and **2**), bridged by an ether linkage (D ring) which contorts the pentacyclic core into a compact, caged structure (Figure 1b and Scheme 1). Strategies to overcome these synthetic challenges are presented herein, culminating in the enantioselective total syntheses of (–)-transtaganolide A [(–)-**1**] and (+)-transtaganolide B [(+)-**2**], which to date have eluded total synthesis. Furthermore, (–)-transtaganolide C [(+)-**3**] and (+)-transtaganolide D [(–)-**4**], which were previously prepared as racemates, have now been synthesized enantioselectively. The absolute configurations of these compounds are also disclosed and discussed within the context of existing biosynthetic hypotheses.<sup>[6b, 7]</sup>

[\*] H. M. Nelson, J. R. Gordon, Dr. S. C. Virgil, Prof. Dr. B. M. Stoltz Warren and Katharine Schlinger Laboratory for Chemistry and Chemical Engineering, Division of Chemistry and Chemical Engineering, California Institute of Technology 1200 E. California Boulevard MC 101-20, Pasadena, CA 91125 (USA) E-mail: stoltz@caltech.edu

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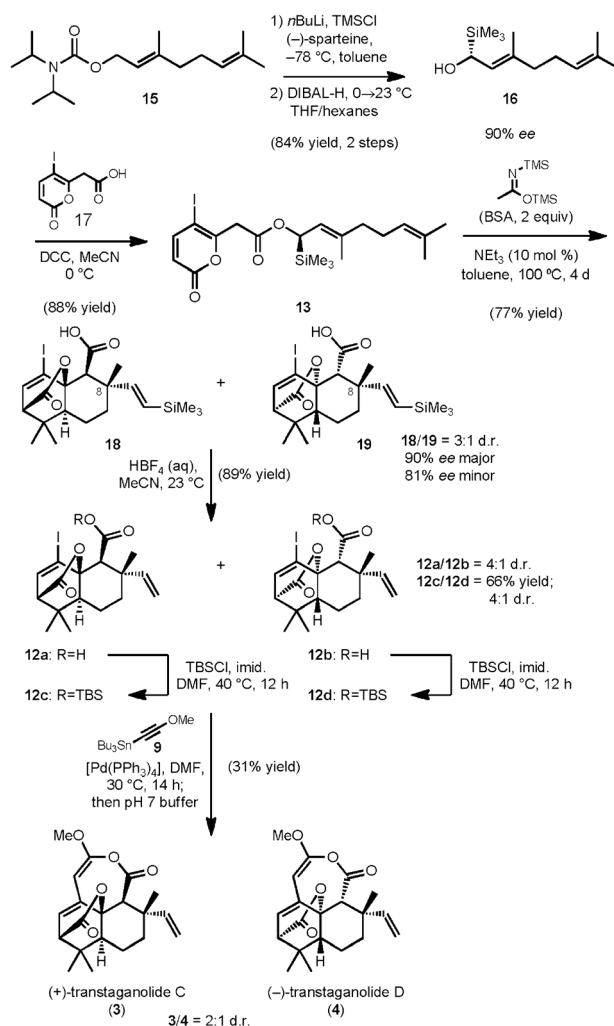
Supporting information for this article is available on the WWW under <http://dx.doi.org/10.1002/anie.201301212>.



**Scheme 1.** Retrosynthetic analysis.

Retrosynthetically, **1** and **2** could derive from the iodotetracycle **10** by application of our (5+2) annulation strategy (Scheme 1).<sup>[5]</sup> We envisioned that the tetracyclic core (**10**) could in turn arise from a translactonization/acetalization reaction of the aldehyde hydrate **11**. The tricycle **11** could be derived from an enantiospecific ICR/DA cascade of the monocyclic precursor **14** with the requisite aldehyde oxidation state. Notably, enantioenriched **3** and **4** could be prepared from the tricycle **12**, which could also derive from a pyrone ester (**13**) by a stereocontrolled ICR/DA cascade reaction.

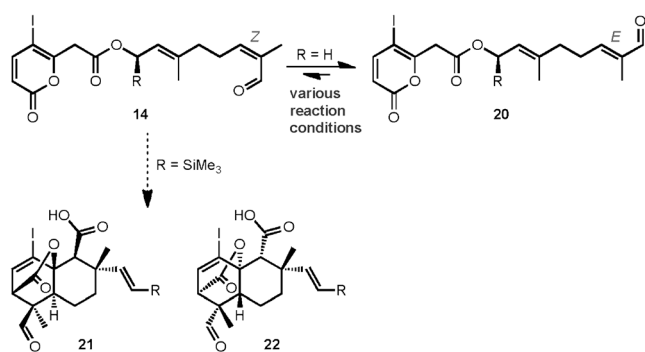
Our studies began with the application of this retrosynthetic hypothesis to (+)-**3** and (–)-**4** (Scheme 2).<sup>[8]</sup> To impart asymmetry we turned to the early work of Ireland and co-workers.<sup>[9]</sup> They demonstrated the efficient employment of  $\alpha$ -acyloxy allylsilanes (e.g., **13** and **14**; Scheme 1) as chiral, primary alcohol equivalents in Ireland–Claisen rearrangements. Hoppe's enantioenriched geraniol derivative **16** was prepared by treatment of the carbamate **15** with *n*BuLi, freshly distilled (–)-sparteine, and trimethylsilyl chloride.<sup>[10]</sup> Subsequent reduction of the intermediate carbamate furnished the enantioenriched geraniol equivalent **16** in 90% *ee* and 84% yield over the two steps. Coupling of **16** to the pyrone acid **17** provided the desired cascade substrate **13** in 88% yield. Gratifyingly, exposure of **13** to our ICR/DA cascade conditions afforded the diastereomeric vinyl silanes **18** and **19** in 77% overall yield and 90 and 81% *ee*, respectively. We were pleased to find that subsequent exposure of **18** and **19** to aqueous HBF<sub>4</sub> yielded a mixture of the tricycles **12a** and **12b**, respectively. Protection of the free acids **12a** and **12b** as the silyl esters **12c** and **12d**, respectively, and subsequent treatment with the stannane **9** and [Pd(PPh<sub>3</sub>)<sub>4</sub>] yielded (+)-**3** and (–)-**4**.



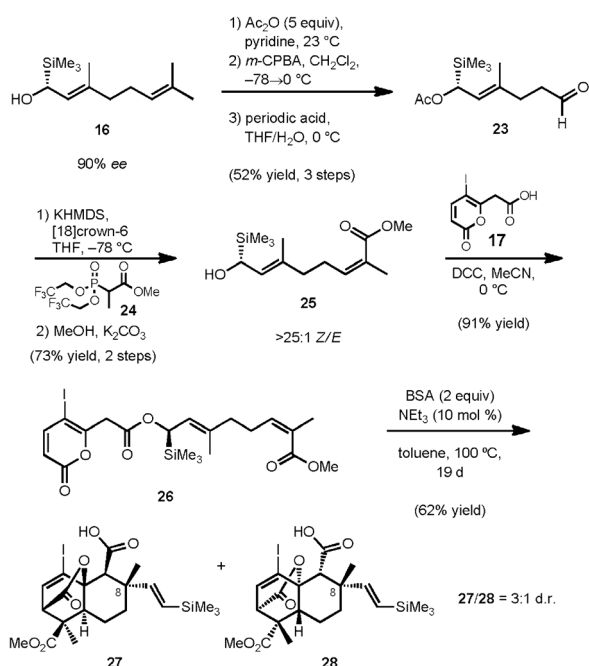
**Scheme 2.** Enantioselective total syntheses of transtaganolides C and D (**3** and **4**). DCC = 1,3-dicyclohexylcarbodiimide, DIBAL-H = diisobutylaluminum hydride, DMF = *N,N*-dimethylformamide, imid. = imidazole, TBS = *tert*-butyldimethylsilyl, TMS = trimethylsilyl.

Having established the feasibility of the chiral geraniol derivative approach to setting the critical absolute stereochemistry in this series of natural products, we sought to prepare the enantioenriched (–)-**1** and (+)-**2**. The most apparent path to this goal relies on the utilization of a chiral Z enal such as **14** in our ICR/DA cyclization cascade to produce the aldehydes **21** and **22**, predisposed by proximity to undergo the desired ring-chain tautomerism upon hydration (Scheme 3). However, we found that **14** was challenging to prepare and configurationally unstable under a myriad of reaction conditions.<sup>[11]</sup>

Prompted by these experimental cues, our efforts were refocused on preparing an aldehyde surrogate. To this end, the enantioenriched geraniol derivative **16** was protected as the acetate ester (Scheme 4).<sup>[12]</sup> Selective epoxidation with *m*-CPBA and subsequent oxidative cleavage of the intermediate epoxide with aqueous periodic acid provided the aldehyde **23**.<sup>[13]</sup> Utilization of the Still–Gennari modification of the Horner–Wadsworth–Emmons reaction and subsequent cleavage of the acetate group allowed formation of the *Z* methyl-



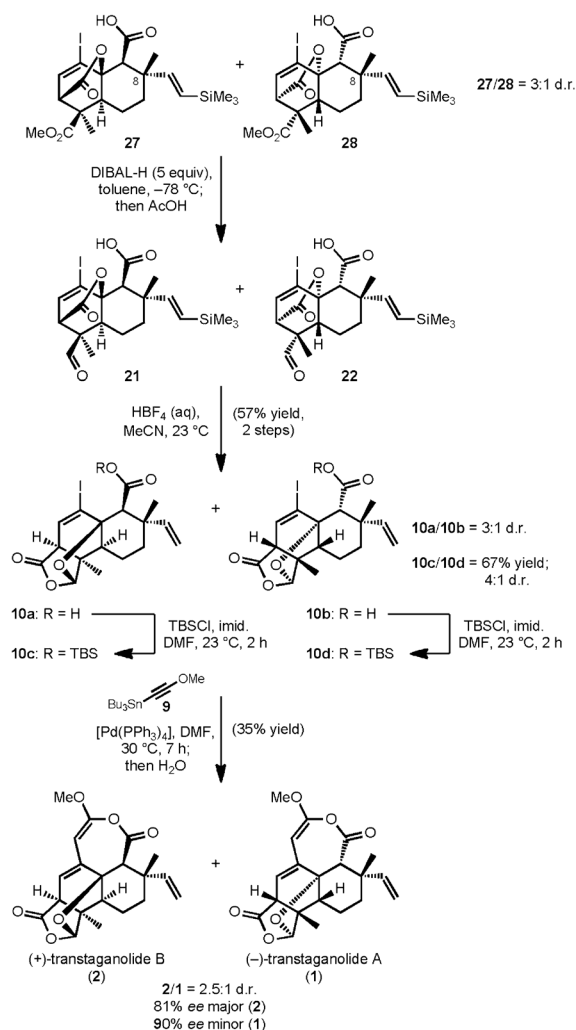
**Scheme 3.** Initial attempts at preparing the tricyclic cores of transtaganolides A and B (**21** and **22**).



**Scheme 4.** Syntheses of enantioenriched tricyclic cores of transtaganolides A and B (**27** and **28**). *m*-CPBA = *meta*-chloroperbenzoic acid, THF = tetrahydrofuran.

enoate **25** in good yield and excellent diastereoselectivity.<sup>[14]</sup> Efficient coupling of **25** to **17** yielded the ICR/DA cascade substrate, the pyrone ester **26**. Gratifyingly, prolonged heating of **26** in toluene with *N,O*-bis(trimethylsilyl)acetamide (BSA) in the presence of a catalytic amount of triethylamine afforded the diastereomeric tricycles **27** and **28**.

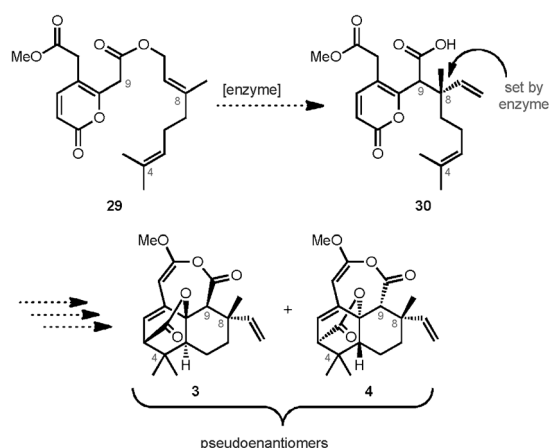
Remarkably, brief exposure of **27** and **28** to an excess of DIBAL-H at low temperature, followed by careful quenching with acetic acid resulted in chemoselective ester reduction to furnish the corresponding aldehydes **21** and **22** (Scheme 5). Upon exposure of the crude mixture of the aldehydes **21** and **22** to aqueous HBF<sub>4</sub>, the desired transactonization/acetalization proceeded and proteodesilylation occurred in one pot to yield caged the tetracycles **10a** and **10b**, respectively. Transient protection of the free acids (**10a** and **10b**) as the TBS esters (**10c** and **10d**, respectively), and subsequent application of our (5+2) annulation technology allowed the



**Scheme 5.** Enantioselective total syntheses of transtaganolides A and B (**1** and **2**).

enantioselective syntheses of (+)-**2** and (–)-**1**, respectively, in 35% yield and good optical purity.

Recently, Larsson and co-workers have proposed that the co-isolated prenylated pyrone **29** is the direct biosynthetic precursor of transtaganolides C (**3**) and D (**4**; Scheme 6).<sup>[6]</sup> They suggest that a rare naturally occurring ester-enolate Claisen rearrangement is responsible for the production of optically pure transtaganolides. Enzymatically controlled Claisen processes are particularly uncommon, but are known, as in Chorismate mutase. Under this scenario, and assuming that the C9 proton is relatively acidic as a result of the withdrawing nature of the pyrone, it could be anticipated that an enzymatic and presumably enantioselective<sup>[15]</sup> rearrangement would produce the optically pure C9 diastereomers **30** (with absolute stereocontrol at C8), whereas a non-enzymatically governed process would likely result in a racemic mixture of C9 diastereomers. The demonstrated propensity of these systems to undergo diastereoselective Diels–Alder rearrangements under allylic strain control,<sup>[16]</sup> would lead to pseudoenantiomeric transtaganolides C (**3**) and D (**4**). Having prepared the enantioenriched transtaganolides A–D



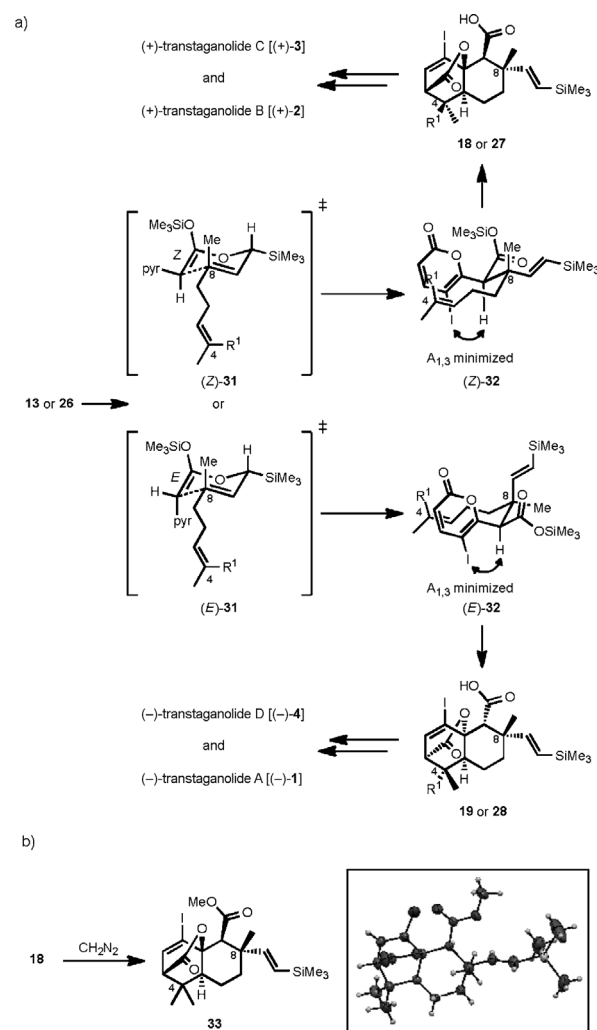
**Scheme 6.** Hypothetical enzymatically controlled biosynthetic proposal.

[(-)-1, (+)-2, (+)-3, and (-)-4] by an analogous, synthetic enantioselective Ireland–Claisen rearrangement, we believed that determination of the absolute stereochemistries of the synthetic transtaganolides could provide insight into this biosynthetic hypothesis.

Hoppe and co-workers has previously established the absolute stereochemistry of geraniol derivatives such as **16** prepared by (-)-sparteine-mediated deprotonation as the *R* enantiomer (Scheme 7a).<sup>[10]</sup> As acyclic Ireland–Claisen rearrangements prefer chair transition states, we postulated that the Ireland–Claisen rearrangement of the esters **13** and **26** could proceed through two ketene acetal geometry dependent pathways [(*Z*)-**31** and (*E*)-**31**].<sup>[17]</sup> Furthermore, transformations analogous to the ensuing Diels–Alder cyclization are known to proceed through allylic-strain-minimized (*A*<sub>1,3</sub>) geometries such as shown for (*Z*)-**32** and (*E*)-**32**.<sup>[16]</sup> These proposed reaction pathways result in the formation of the diastereomeric intermediates **18** and **27** and **19** and **28**. The acid **18** was converted into the corresponding methyl ester **33** by treatment with diazomethane, and anomalous dispersion analysis of a single crystal confirmed the hypothesized stereochemistry of **33** (Scheme 7b).<sup>[18]</sup> As **18** was advanced to (+)-transtaganolide C [(+)-**3**], we unambiguously assign its absolute structure as shown in Scheme 2. Furthermore, by analogy we assigned (-)-transtaganolide D [(-)-**4**], (-)-transtaganolide A [(-)-**1**], and (+)-transtaganolide B [(+)-**2**] as depicted (Schemes 2 and 5).

The optical rotations obtained from synthetic and natural transtaganolides A–D (**1–4**) are depicted in Figure 2a.<sup>[3]</sup> Interestingly, the synthetic transtaganolides uniformly rotate plane polarized light to a much greater extent than their naturally occurring counterparts.<sup>[19]</sup> As demonstrated by our synthetic efforts, the Ireland–Claisen/Diels–Alder cascade of prenylated pyrones similar to **29** is a facile process: the metabolites may be biosynthetically derived from **29**, but without action of an enzymatic Claisen rearrangement.

Furthermore, while the naturally occurring C8 diastereomeric pairs [e.g. transtaganolides C (**3**) and D (**4**)] rotate plane-polarized light with the same sign, the samples derived



**Scheme 7.** a) Analysis of chiral silane directed ICR/DA cascade (where pyr = iodopyrone). b) Determination of the absolute stereochemistry of the intermediate **18**. Thermal ellipsoids shown at 50% probability.

a)

|           | transtaganolide A | transtaganolide B | transtaganolide C              | transtaganolide D             |
|-----------|-------------------|-------------------|--------------------------------|-------------------------------|
| synthetic | -98.8 (90% ee)    | +207.9 (81% ee)   | +120.7 (96% ee) <sup>[a]</sup> | -51.6 (92% ee) <sup>[a]</sup> |
| natural   | -44.8             | -25.8             | -10.0                          | -14.2                         |

[a] For the purposes polarimetric analysis intermediate **13** was enriched to enantiopurity by chiral phase chromatography.

b)

**Figure 2.** a) Comparison of the optical rotations of synthetic and natural transtaganolides A–D (**1–4**). b) Proposed biosynthesis of **29**.

Comparison of the natural compounds to the synthetic counterparts by chiral phase chromatography is needed before conclusions about the stereochemistry and enantiopurity of this series of natural products can be drawn.<sup>[20]</sup> Unfortunately, it appears that there are no available samples of natural **1–4** for thorough comparison. At this juncture, however, our optical data strongly suggest that prenylated pyrone **29** is not a Claisenase substrate in the biosynthesis of transtaganolides C and D (**3** and **4**). As previously proposed by Massanet and co-workers, **29** can instead be viewed as a decomposition product of epoxide **35** or oxepine **36**, which can be derived from co-isolated coumarin **34** by oxidation (Figure 2b).<sup>[7]</sup> Furthermore, these high-energy intermediates (**35** and **36**) could undergo a series of non-enzymatic, pericyclic transformations to produce the natural products.

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**Keywords:** biomimetic synthesis · biosynthesis · cycloaddition · rearrangement · total synthesis

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- [11] Even under mild esterification conditions, that is, low-temperature DCC coupling, olefin isomerization would occur. Compounding the issue was a difficult separation of the *E* and *Z* isomers by chromatography. Ultimately, the isomers were separated by HPLC, however, any attempts to induce the Ireland–Claisen rearrangement resulted in isomerization as well.
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- [19] Subsequent to submission of this manuscript Prof. Giovanni Appendino generously provided our group with an authentic sample of the structurally, and presumably biosynthetically, related basiliolide B (**6**). Comparison to racemic synthetic basiliolide B (see Ref. [5]) by chiral phase chromatography clearly demonstrated that naturally occurring basiliolide B is enantiopure upon isolation. Furthermore, consistent in magnitude with the enantioenriched synthetic transtaganolides, the specific rotation of natural basiliolide B was measured as –173° (0.24 c).
- [20] Extensive efforts were made to obtain authentic samples of **1–4** from the isolation chemists to no avail.