Plants belonging to the genus *Thapsia* have been acknowledged since antiquity for their remarkable medicinal properties. 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. Within the past decade, an additional group of structurally novel natural products, deemed the transtaganolides (1–4, Figure 1b) and basiliolides (5–6, Figure 1b), have been isolated. Initial biological evaluation suggests that these natural products also inhibit SERCA, albeit through a mechanistically distinct pathway. 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). Integral to this approach was an Ireland–Claisen rearrangement/intramolecular pyrone Diels–Alder cyclization (ICR/DA) cascade 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. While concise and modular, our initial 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 γ 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.
Retrosynthetically, 1 and 2 could derive from the iodotetra
cycle 10 by application of our (5+2) annulation strategy
(Scheme 1). We envisioned that the tetracyclic core (10) could in turn arise from a trans lactonization/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 oxida-
tion state. Notably, enantioenriched 3 and 4 could be prepared
from the tricycle 12, which could also derive from a pyrone
ester (13) by a stereoregulated ICR/DA cascade reaction.

Our studies began with the application of this retrosyn-
thetic hypothesis to (+)-3 and (–)-4 (Scheme 2). To impart
asymmetry we turned to the early work of Ireland and co-
workers. They demonstrated the efficient employment of
acyloxy allylsilanes (e.g., 13 and 14; Scheme 1) as chiral,
primary alcohol equivalents in Ireland–Claisen rearrange-
ments. Hoppe’s enantioenriched geraniol derivative 16 was
prepared by treatment of the carbamate 15 with nBuLi,
freshly distilled (–)-sparteine, and trimethylsilyl chloride. Subsequent reduction of the intermediate carbamate fur-
nished the enantioenriched geraniol equivalent 16 in 90 % ee
and 84 % yield over the two steps. Coupling of 16 to the
pyrrole 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, respec-
tively. We were pleased to find that subsequent exposure of 18 and 19 to aqueous HBF4 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(PPh3)4]2 yielded (+)-3 and (–)-4.

Having established the feasibility of the chiral geraniol
derivative approach to setting the critical absolute stereo-
chemistry 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.

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). Selective epoxidation with m-
CPBA and subsequent oxidative cleavage of the intermediate
epoxide with aqueous periodic acid provided the aldehyde
23. Utilization of the Still–Gennari modification of the
Horner–Wadsworth–Emmons reaction and subsequent cleav-
age of the acetate group allowed formation of the Z methyl-

Scheme 1. Retrosynthetic analysis.

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

Scheme 3.
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 HBF₄, the desired trans lactonization/acetalization proceeded and proteodesilylation occurred in one pot to yield 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 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). 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 rear-
rangement would produce the optically pure C9 diastereo-
mers 30 (with absolute stereocontrol at C8), whereas a non-
enzymatically governed process would likely result in a rac-
emic mixture of C9 diastereomers. The demonstrated pro-
pensity of these systems to undergo diastereoselective Diels–
Alder rearrangements under allylic strain control would lead to pseudoenantiomeric transtaganolides C (3) and D (4). Having prepared the enantioenriched transtaganolides A–D.
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). 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 [Scheme 7a; (Z)-31 and (E)-31]. Furthermore, transformations analogous to the ensuing Diels–Alder cyclization are known to proceed through allylic-strain-minimized (A1,3) geometries such as shown for (Z)-32 and (E)-32. 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 diazo-methane, and anomalous dispersion analysis of a single crystal confirmed the hypothesized stereochemistry of 33 (Scheme 7b). 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.[3] Interestingly, the synthetic transtaganolides uniformly rotate plane polarized light to a much greater extent than their naturally occurring counterparts.[19] 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...
from a synthetic, enantioselective Ireland–Claisen rearrangement rotate light with opposite sign (Figure 2a). This data does not support the action of an enzymatic enolate Claisen rearrangement, as metabolites resulting from this pathway would likely have analogous rotations to the synthetic transtaganolides (Scheme 6).

Comparison of the natural compounds to the synthetic counterparts by chiral phase chromatography is needed before conclusions about the stereochemistry and enantio-purity of this series of natural products can be drawn.[20] 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 oxepline 36, which can be derived from co-isolated coumarin 34 by oxidation (Figure 2b).[37] Furthermore, these high-energy intermediates (35 and 36) could undergo a series of non-enzymatic, pericyclic transformations to produce the natural products.

In conclusion, enantioenriched transtaganolides A–D (1–4) have been prepared by the use of a chiral geraniol equivalent (16) in an Ireland–Claisen/Diels–Alder cascade which proceeds with excellent stereospecificity. Remarkably, all of the titled natural products were prepared in 10 steps or less from this simple chiral geraniol derivative. Single-crystal X-ray diffraction studies of a synthetic intermediate have unambiguously determined the absolute stereochemistry of (+)-transtaganolide C [(+)-3]. By inference, the absolute stereochemistries of (–)-transtaganolide D [[(–)-4], (–)-transtaganolide A [[(–)-1], and (+)-transtaganolide B [(+)-2] have been proposed. Finally, analysis of optical rotation data does not support the role of a putative Claisenase in the biosynthesis of the transtaganolides.

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[10] a) W. Zeng, R. Frohlich, D. Hoppe, Tetrahedron 2005, 61, 3281–3287; b) Hoppe has reported that longer reaction times result in higher yields but lower ee values: that is, 1.5 h = 37% yield, 87% ee; and 3 h = 76% yield, 77% ee. In our hands, using the 3 h procedure outlined by Hoppe and co-workers, we observed consistently higher ee values for this extended reaction time, which is necessary to drive the reaction to completion. Reproducibility was somewhat of a challenge as ee values varied from as high as 90% ee and as low as 82% ee for the 3 hour reaction time. In all reactions the (–)-sparteine was dried and distilled from CaH₂ by kugelrohr distillation. We believe the variability in ee value results directly from the quality of the distilled (–)-sparteine used in the reaction.
[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.
[18] Comparison of CD spectra to the bulk material confirmed that the mounted crystal represented the major enantiomer in the 89.5% ee bulk. CCDC 937177 contains 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.
[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 enantioreniched synthetic transtaganolides, the specific rotation of natural basiliolide B was measured as –173° (c 2, 1.24 c).
[20] Extensive efforts were made to obtain authentic samples of 1–4 from the isolation chemists to no avail.