

Published in final edited form as:

*Angew Chem Int Ed Engl.* 2013 June 24; 52(26): . doi:10.1002/anie.201301212.

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

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### Keywords

Claisen rearrangement; Diels-Alder react; Biosynthesis; Biomimetic synthesis; Polycyclic compd

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 basiliolides (**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 that 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**). Additionally, a formal (5 + 2) annulation process forged the formidable C ring (Figure 1c).<sup>[5]</sup> 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 due to their lack of an oxabicyclo[2.2.2]octene structural motif (Figure 1b, **1** and **2** vs. **3–6**). In its place is a fused  $\gamma$ -lactone (E ring, **1** and **2**), bridged by an ether linkage (D ring) that contorts the pentacyclic core into a compact, caged structure (Figure 1b and Scheme 1, see boxed insert). 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>

Retrosynthetically, transtaganolides A (**1**) and B (**2**) could derive from 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 aldehyde-hydrate **11**. Tricycle **11** could be derived from an enantiospecific ICR/DA cascade of monocyclic precursor **14** with the requisite aldehyde oxidation state. Notably, enantioenriched transtaganolides C and D (**3** and **4**) could be prepared from 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 transtaganolides C (**3**) and D (**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  $\gamma$ -acyloxy allylsilanes (e.g., **13** and **14** in Scheme 1) as chiral, primary alcohol equivalents in Ireland–Claisen rearrangements. Hoppe's enantioenriched geraniol derivative **16** was prepared by treatment of carbamate **15** with *n*-BuLi, freshly distilled (–)-sparteine, and trimethylsilyl chloride.<sup>[10]</sup> Subsequent reduction of the intermediate carbamate furnished enantioenriched geraniol equivalent **16** in 90% ee and 84% yield over the 2 steps. Coupling of alcohol **16** to pyrone acid **17** provided the desired cascade substrate **13** in 88% yield. Gratifyingly, exposure of pyrone ester **13** to our ICR/DA cascade conditions afforded diastereomeric vinyl silanes **18** and **19** in 77% overall yield and 90% ee and 81% ee, respectively. We were pleased to find that subsequent exposure of the vinyl silanes **18** and **19** to aqueous HBF<sub>4</sub> yielded a mixture of tricycles **12a** and **12b**. Protection of the free acids (**12a** and **12b**) as the silyl esters **12c** and **12d** followed by treatment with stannane **9** and Pd(PPh<sub>3</sub>)<sub>4</sub> yielded (+)-transtaganolide C (**3**) and (–)-transtaganolide D (**4**).

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 enantioenriched transtaganolides A (**1**) and B (**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 aldehydes **21** and **22**, predisposed by proximity to undergo the desired ring-chain tautomerism upon hydration (Scheme 3). However, we found that (*Z*)-enal **14** was challenging to prepare and configurationally unstable under myriad reaction conditions.<sup>[11]</sup>

Prompted by these experimental cues, our efforts were refocused on preparing an aldehyde surrogate. To this end, enantioenriched geraniol derivative **16** was protected as the acetate ester (Scheme 4).<sup>[12]</sup> Selective epoxidation with *m*-CPBA, followed by oxidative cleavage of the intermediate epoxide with aqueous periodic acid provided aldehyde **23**.<sup>[13]</sup> Utilization of the Still–Gennari modification of the Horner–Wadsworth–Emmons reaction followed by cleavage of the acetate group allowed for formation of (*Z*)-methylenoate **25** in good yield and excellent diastereoselectivity.<sup>[14]</sup> Efficient coupling of alcohol **25** to acid **17** yielded the ICR/DA cascade substrate, pyrone ester **26**. Gratifyingly, prolonged heating of ester **26** in toluene with *N,O*-bis(trimethylsilyl)acetamide (BSA) in the presence of a catalytic amount of triethylamine afforded diastereomeric tricycles **27** and **28**.

Remarkably, brief exposure of acids **27** and **28** to an excess of DIBAL-H at low temperature, followed by careful quenching with acetic acid resulted in smooth, chemoselective ester reduction to furnish corresponding aldehydes **21** and **22** (Scheme 5). Upon exposure of the crude aldehydes **21** and **22** to aqueous HBF<sub>4</sub>, the desired translactonization/acetalization proceeded and proteodesilylation occurred in one pot to yield caged tetracycles **10a** and **10b**. Transient protection of the free acids (**10a** and **10b**) as the TBS-esters (**10c** and **10d**), followed by application of our (5 + 2) annulation technology allowed for the enantioselective syntheses of (+)-transtaganolide B (**2**) and (–)-transtaganolide A (**1**) 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 due to the withdrawing nature of the pyrone, it could be anticipated that an enzymatic and presumably enantioselective<sup>[15]</sup> rearrangement would produce optically pure C9 diastereomers **30** (with absolute stereocontrol at C8), while 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 pseudo-enantiomeric transtaganolides C (**3**) and D (**4**). Having prepared enantioenriched transtaganolides A–D (**1–4**) via 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 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 esters **13** and **26** could proceed through two ketene-acetal geometry dependent pathways (Scheme 7a, *Z-31* and *E-31*).<sup>[17]</sup> Furthermore, transformations analogous to the ensuing Diels–Alder cyclization are known to proceed through allylic (*A*<sub>1,3</sub>) strain minimized geometries such as *Z-32* and *E-32*.<sup>[16]</sup> These proposed reaction pathways result in the formation of diastereomeric intermediates **18/27** and **19/28**. Acid **18** was converted to 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, we unambiguously assign its absolute structure as **3** (Scheme 2). Furthermore, by analogy we assigned (–) transtaganolide D as **4** (Scheme 2), (–)-transtaganolide A as **1** and (+)-transtaganolide B as **2** (Scheme 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>[20]</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 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 enantiopurity of this series of natural products can be drawn.<sup>[19]</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, pyrone **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.

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 that proceeds with excellent stereofidelity. 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.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

## Acknowledgments

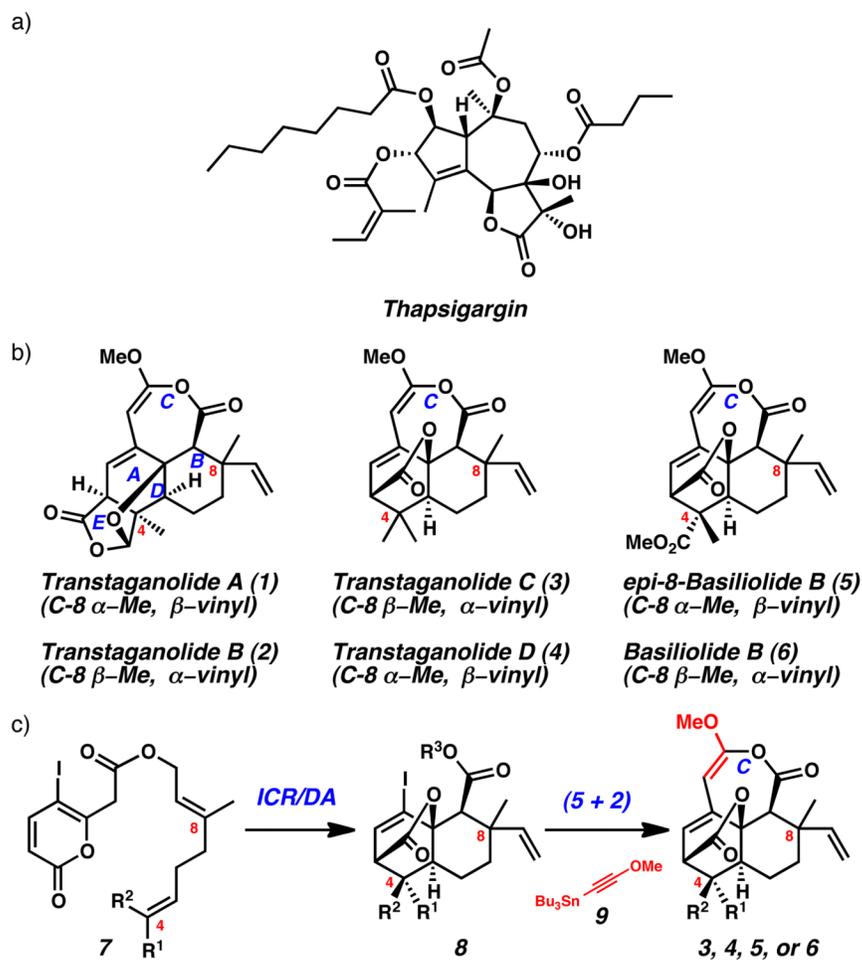
The authors wish to thank the NSF and Ford Foundation (predoctoral fellowships to H.M.N.), Amgen, Abbott, Boehringer Ingelheim, the Gordon and Betty Moore Foundation, and Caltech for financial support. Prof. Giovanni Appendino is acknowledged for providing authentic samples of basililide B. Dr. Kei Murakami is acknowledged for his contribution to the preparation of racemic transtaganolides C and D. Ms. Kelly Kim and Mr. Alexander Goldberg are gratefully acknowledged for assistance in manuscript preparation. Dr. Nolan McDougal is acknowledged for useful discussions regarding biosynthesis. Larry Henling is acknowledged for X-ray analysis of **33**. Dr. David VanderVelde is acknowledged for NMR assistance. The authors wish to thank NIH-NIGMS (R01GM080269) for financial support. The Bruker KAPPA APEXII X-ray diffractometer used in this study was purchased through an NSF CRIF:MU award to Caltech (CHE-0639094).

## References

1. Accounts of *T. garganica* L.'s medicinal qualities were first reported by Hippocrates in 400 B.C.; see: Christensen SB, Ramussen U. *Tetrahedron Lett.* 1980; 21:3829–3830. Christensen SB, Andersen A, Smitt UW. *Prog Chem Org Nat Prod.* 1997; 71:130–167.
2. Lytton J, Westlin M, Hanley MR. *J Biol Chem.* 1991; 266:17067–17071. [PubMed: 1832668]
3. a) Saouf A, Guerra FM, Rubal JJ, Moreno-Dorado FJ, Akssira M, Mellouki F, Lopez M, Pujadas AJ, Jorge ZD, Massanet GM. *Org Lett.* 2005; 7:881–884. [PubMed: 15727465] b) Appendino G, Prosperini S, Valdivia C, Ballero M, Colombano G, Billington RA, Genazzani AA, Sterner O. *J Nat Prod.* 2005; 68:1213–1217. [PubMed: 16124763]
4. Navarrete C, Sancho R, Caballero FJ, Pollastro F, Fiebich BL, Sterner O, Appendino G, Munoz E. *J Pharmacol Exp Ther.* 2006; 319:422–430. [PubMed: 16840645]
5. Nelson HM, Murakami K, Virgil SC, Stoltz BM. *Angew Chem Int Ed.* 2011; 50:3688–3691.
6. a) Nelson HM, Stoltz BM. *Tetrahedron Lett.* 2009; 50:1699–1701. b) Larsson R, Sterner O, Johansson M. *Org Lett.* 2009; 11:657–660. [PubMed: 19140719]
7. Rubal JJ, Moreno-Dorado FJ, Guerra FM, Zacarias DJ, Abderrahmane S, Mohamed A, Fouad M, Raul RG, Massanet GM. *Phytochemistry.* 2007; 68:2480–2486. [PubMed: 17669447]
8. All attempts to utilize reported methods for asymmetric ester-enolate–Claisen rearrangements were unsuccessful: Corey EJ, Lee DH. *J Am Chem Soc.* 1991; 113:4026–4028. Kazmaier U, Krebs A. *Angew Chem Int Ed.* 1995; 34:2012–2014. Kazmaier U, Krebs A. *Angew Chem.* 1995; 107:2213–2214.
9. Ireland RE, Varney MD. *J Am Chem Soc.* 1984; 106:3668–3670.
10. Zeng W, Fröhlich R, Hoppe D. *Tetrahedron.* 2005; 61:3281–3287. b) Hoppe has reported that longer reaction times result in higher yields but lower ee's: i.e. 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 coworkers, we

observed consistently higher ee's for this extended reaction time, which is necessary to drive the reaction to completion. Reproducibility was somewhat of a challenge as ee's varied from values 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 CaH<sub>2</sub> by kugelrohr distillation. We believe the variability in ee results directly from the quality of the distilled (–)-sparteine used in the reaction

11. Even under mild esterification conditions, i.e. low-temperature DCC coupling, olefin isomerization would occur. Compounding the issue was a difficult separation of the *E* and *Z* isomers via chromatography. Ultimately, the isomers were separated by HPLC, however, any attempts to induce the Ireland–Claisen rearrangement resulted in isomerization as well
12. Snyder SA, Treitler DS. *Angew Chem Int Ed*. 2009; 48:7899–7903.
13. Fillion E, Beingssner RL. *J Org Chem*. 2003; 68:9485–9488. [PubMed: 14629177]
14. Still WC, Gennari C. *Tetrahedron Lett*. 1983; 24:4405–4408.
15. Batista JM, López SN, Da Silva Mota J, Vanzolini KL, Cass QB, Rinaldo D, Vilegas W, Da Silva Bolzani V, Kato MJ, Furlan M. *Chirality*. 2009; 21:799–801. [PubMed: 19023875]
16. Kozytska MV, Dudley GB. *Tetrahedron Lett*. 2008; 49:2899–2901.
17. a) Ireland RE, Wipf P, Xiang JN. *J Org Chem*. 1991; 56:3572–3582. b) Gul S, Schoenebeck F, Aviyente V, Houk KN. *J Org Chem*. 2010; 75:2115–2118. [PubMed: 20166688]
18. Comparison of CD spectra to the bulk material confirmed that the mounted crystal represented the major enantiomer in the 89.5% ee bulk
19. Extensive efforts were made to obtain authentic samples of 1-4 from the isolation chemists to no avail
20. 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)



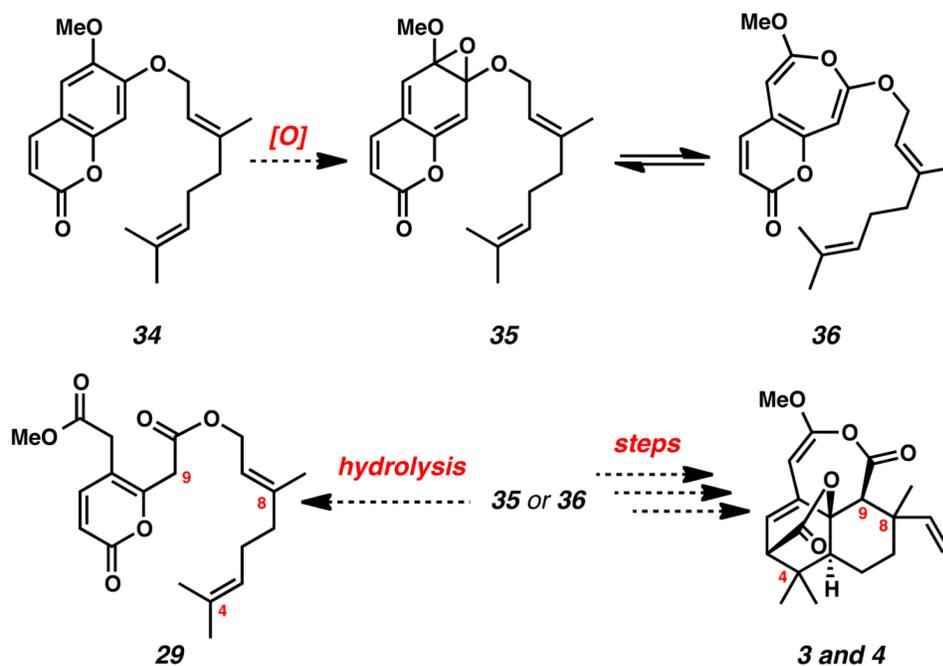
**Figure 1.**  
a) Thapsigargin. b) Transtaganolides and basiliolides. c) General synthetic strategy.

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

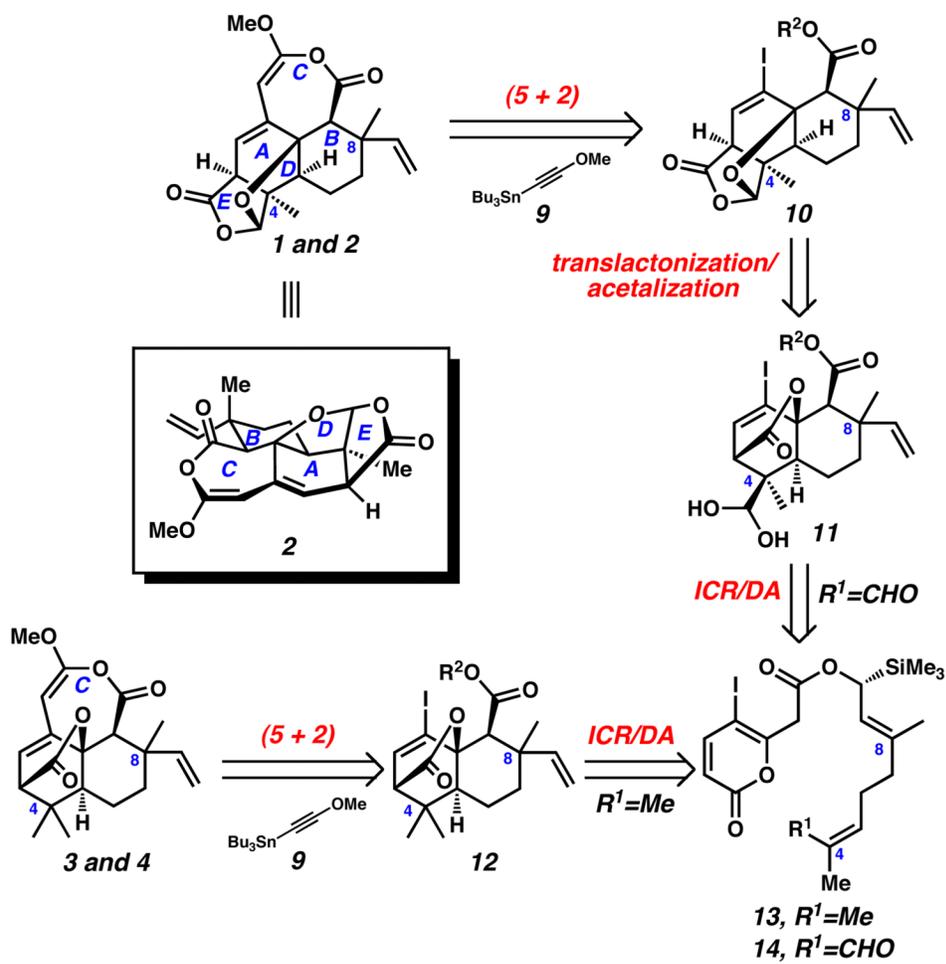
[a] For the purposes polarametric analysis intermediate **13** was enriched to enantiopurity by chiral phase chromatography.

b)

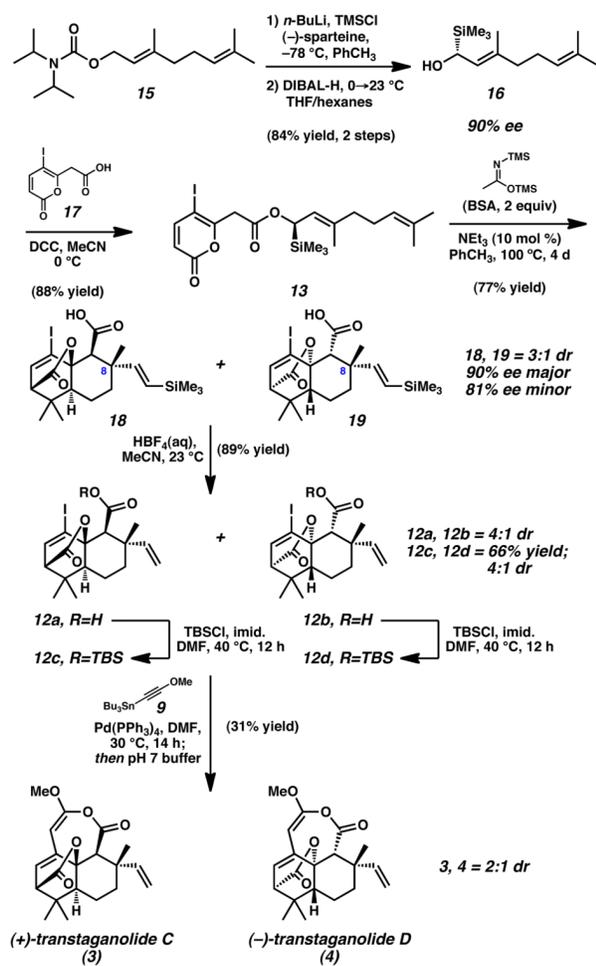


**Figure 2.**

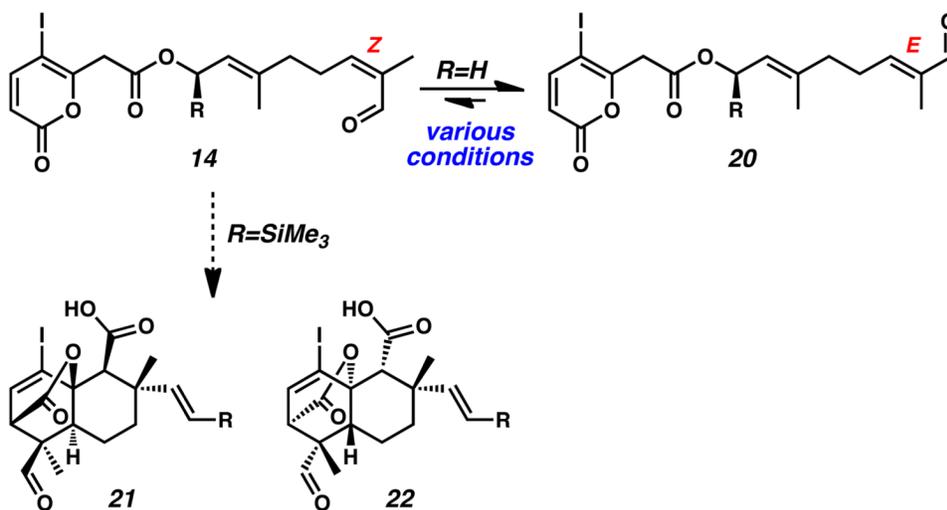
a) Comparison of the optical rotations of synthetic and natural transtaganolides A–D (1–4).  
 b) Proposed biosynthesis of **29**.



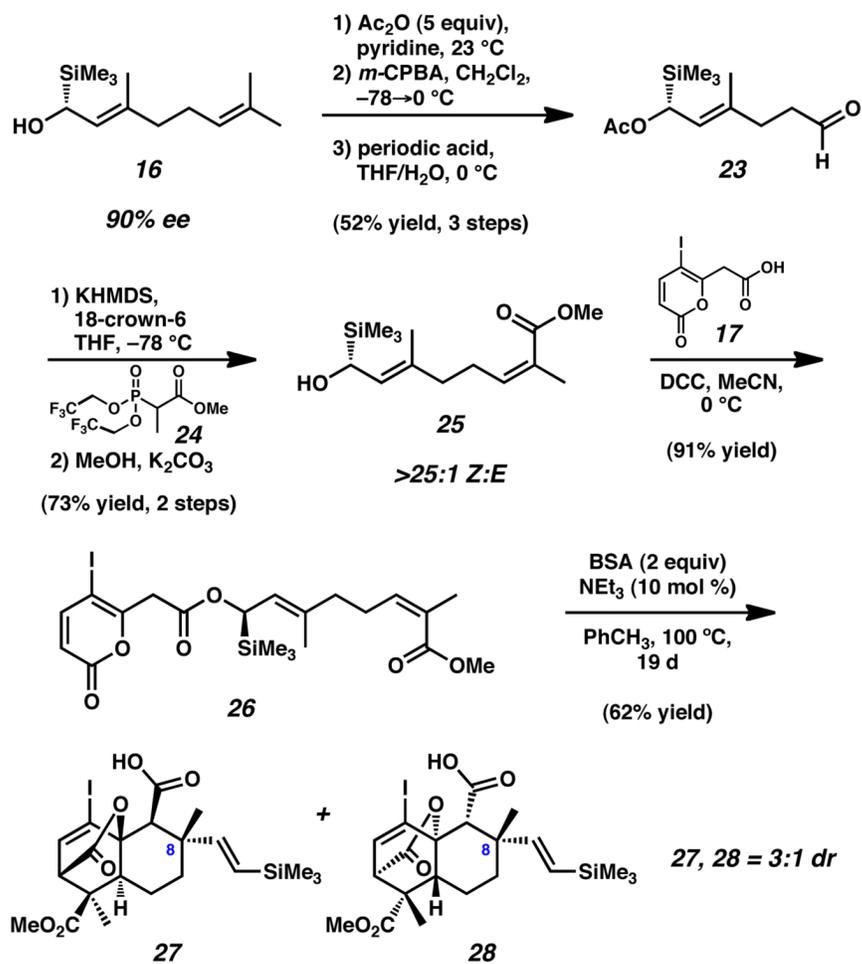
**Scheme 1.**  
Retrosynthetic analysis.



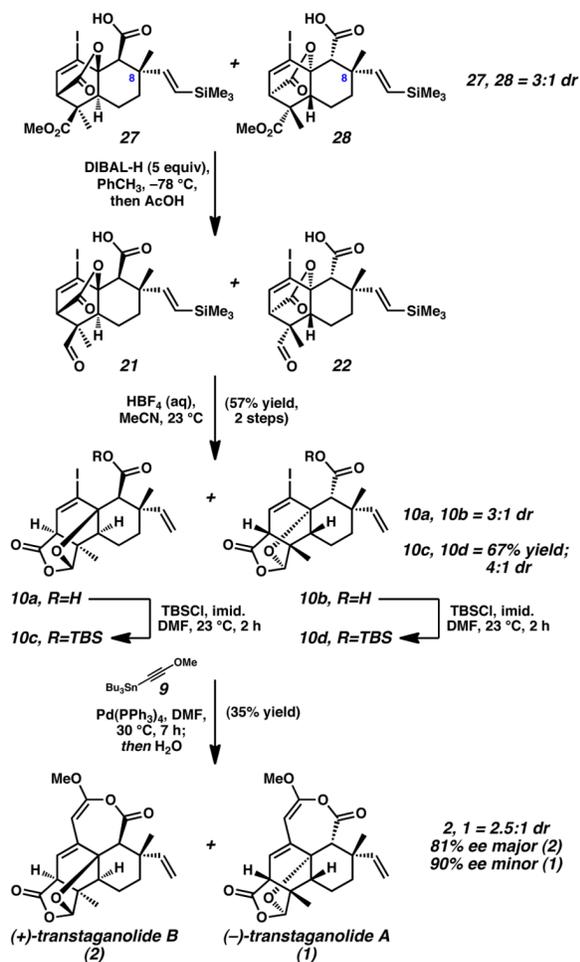
**Scheme 2.**  
Enantioselective total syntheses of transtaganolides C and D (**3** and **4**).

**Scheme 3.**

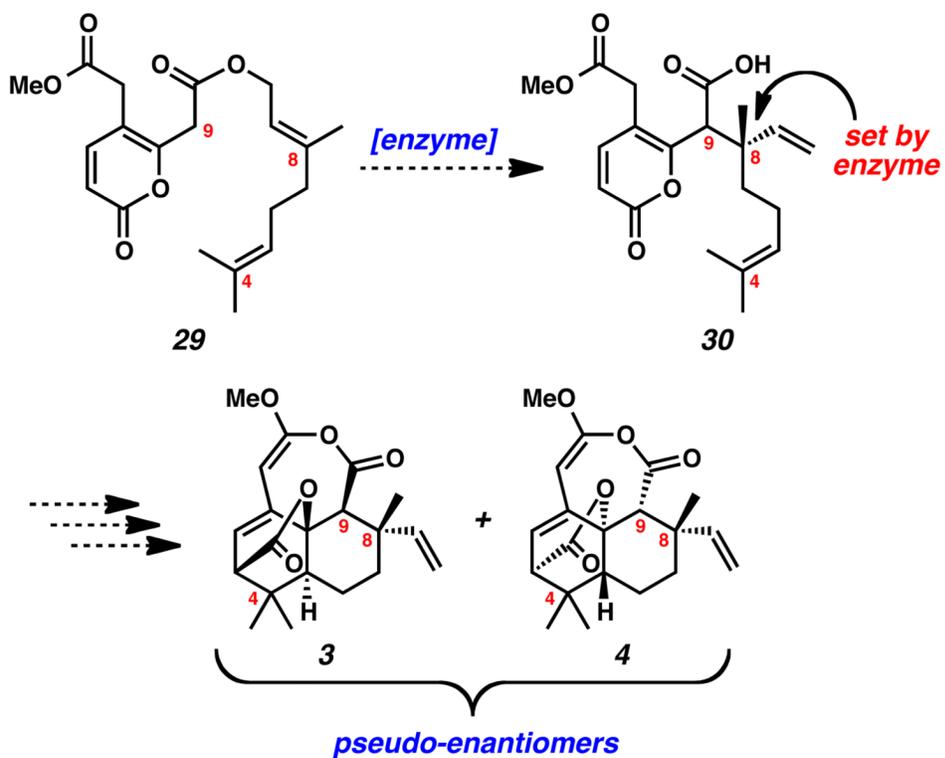
Initial attempts at preparing the tricyclic cores of transtaganolides A and B (**21** and **22**).



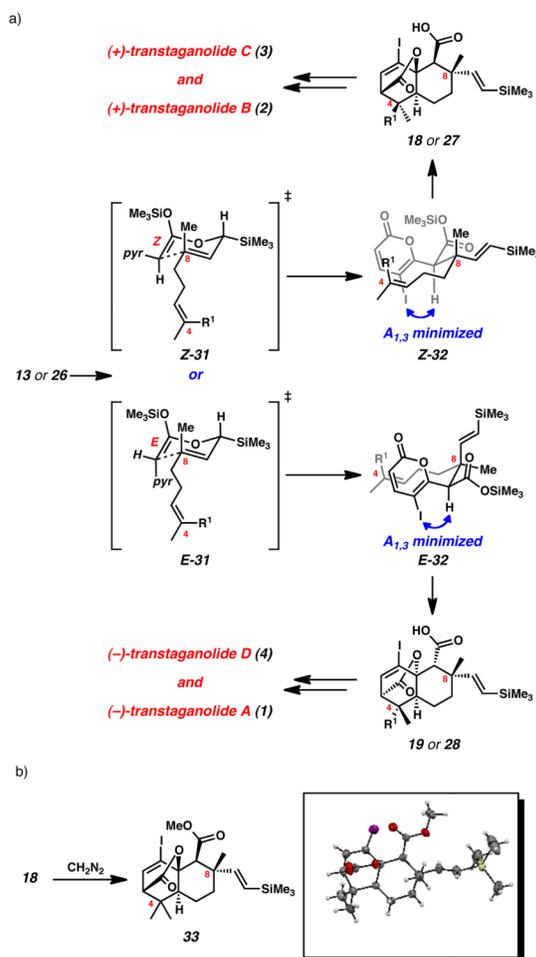
**Scheme 4.**  
Syntheses of enantioenriched tricyclic cores of transtaganolides A and B (**27** and **28**).



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



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

**Scheme 7.**

a) Analysis of chiral silane directed ICR/DA cascade (where pyr = iodopyrone). b) Determination of the absolute stereochemistry of intermediate **18**.