

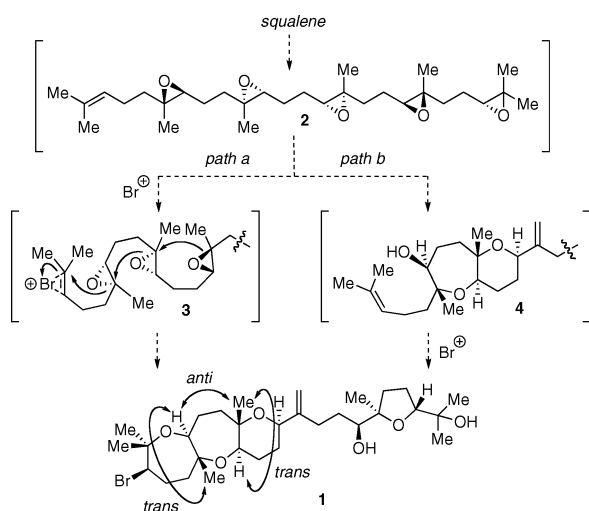
Total Synthesis of *ent*-Dioxepandehydrothysiferol via a Bromonium-Initiated Epoxide-Opening Cascade

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Dioxepandehydrothysiferol¹ (**1**, Scheme 1), thysiferol, venustatriol, enshuol, and armatols A–F are squalene-derived bromotriterpenes isolated from red algae of the genera *Laurencia* and *Chondria*.² Unique among them is the structural motif found in **1**, a *trans-anti-trans* topography, rather than the more commonly observed *trans-syn-trans* at junctions between fused oxygen heterocycles.³ One conceivable biogenesis of **1** involves an epoxide-opening cascade initiated by formation of a bromonium species (Scheme 1, path a) and would be analogous to that proposed by Matsumoto for thysiferol, Higa for venustatriol, and Masuda for enshuol.^{2b,c,4} However, isolation from the same natural source of a related metabolite lacking the halogenated ring¹ has added another possibility to such discussions (path b); initial construction of **4**, followed by a discrete haloetherification step (ring closure via bromonium formation), would also lead to **1**.

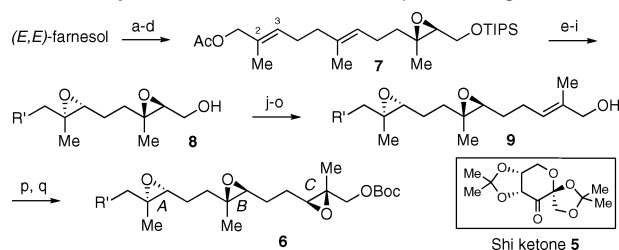
Scheme 1. Possible Biogenetic Pathways to **1**

With the aim of investigating the chemical feasibility of the previously unexplored epoxide-opening cascade leading to the tricyclic core (path a), we undertook and now report an enantioselective total synthesis of *ent*-**1**. Notable features of the synthesis include the first example of an halonium-initiated multipoxide cascade and the first total synthesis of any natural product with the *trans-anti-trans* fused tricyclic subunit.³ The cascade is high yielding, averaging 90% yield per epoxide. Representing the first synthesis of either enantiomer of **1**, the absolute configuration of the natural product is confirmed.⁵

Bromoetherifications to form a single bromo-oxepane or bromo-oxane ring (analogous to path b in Scheme 1) is a well-documented late-stage operation in the total syntheses of various bromotriterpenes.^{4,6} McDonald⁷ and Holton⁸ have demonstrated that an epoxide-opening event can be initiated by electrophilic activation of an alkene (using a bromonium or phenylselenium ion,

respectively) to afford two rings simultaneously. Yet to be described, however, are analogous cascades involving a multipoxide-opening transformation (analogous to path a, Scheme 1).

Our synthesis of the left-hand triepoxide fragment (**6**) commenced with installation of epoxide B with a Sharpless asymmetric epoxidation of (*E,E*)-farnesol (Scheme 2). Site-selective installation of epoxide A using a Shi epoxidation⁹ was achieved by first converting the C2–C3 alkene to an allylic acetate (**7**). A two-carbon Wittig homologation, 1,4-reduction of the resulting α,β -unsaturated ester, and reduction of the ester to the aldehyde opened the way for a second Wittig homologation. Following 1,2-reduction to afford allylic alcohol **9**, epoxide C was installed by another Sharpless epoxidation, and a well-documented terminating nucleophile in acid-promoted cascades (a *tert*-butyl carbonate) was attached, giving **6**.¹⁰

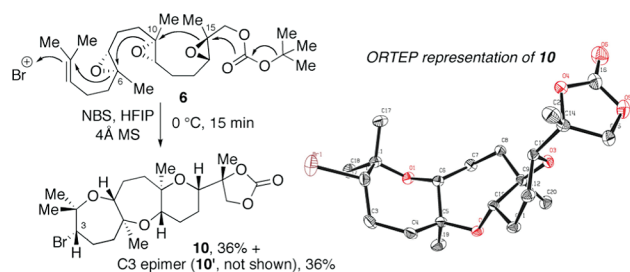
Scheme 2. Synthesis of the Left-Hand Triepoxide Fragment **6**^a

^a R' = (CH₃)₂C=C(H)CH₂. Reagents and conditions: (a) L-(+)-DIPT, Ti(Oi-Pr)₄, *t*-BuOOH, 4 Å MS, CH₂Cl₂, –48 °C, 88%, 82% *ee*; (b) TIPSCl, imid, CH₂Cl₂, rt, 90%; (c) SeO₂, salicylic acid, *t*-BuOOH, CH₂Cl₂, rt, 73% (2 resubjections); (d) Ac₂O, Et₃N, DMAP, CH₂Cl₂, rt, 89%; (e) Shi ketone (**5**), Oxone, Bu₄NHSO₄, K₂CO₃, Na₂B₄O₇, pH 10.5, DMM/CH₃CN/H₂O, 0 °C, 30 min, 75%, 3:1 dr; (f) LiOH, THF/MeOH/H₂O, rt, 84%; (g) (i) MsCl, Et₃N, CH₂Cl₂, –78 to –10 °C; (ii) LiBr, THF, 0 to 8 °C, 1 h; (h) LiBEt₃H, THF, –78 °C, 69% (3 steps); (i) TBAF, THF, rt, 85%; (j) SO₃·pyr, Et₃N, DMSO, CH₂Cl₂, 0 °C to rt, 81%; (k) Ph₃P=CHCO₂Et, CH₂Cl₂, rt, 99%; (l) [(Ph₃P)CuH]₆, PhSiH₃, THF, 0 °C to rt, 95%; (m) DIBAL-H, PhMe, –78 °C, 45 min, 73%; (n) Ph₃P=C(CH₃)CHO, C₆H₆, reflux, 64%, >95:5 *E/Z*; (o) NaBH₄, MeOH, 0 °C, 81%; (p) L-(+)-DET, Ti(Oi-Pr)₄, *t*-BuOOH, 4 Å MS, CH₂Cl₂, –48 °C, 80%, 95:5 dr; (q) Boc₂O, NMI, PhMe, 0 °C to rt, 68%.

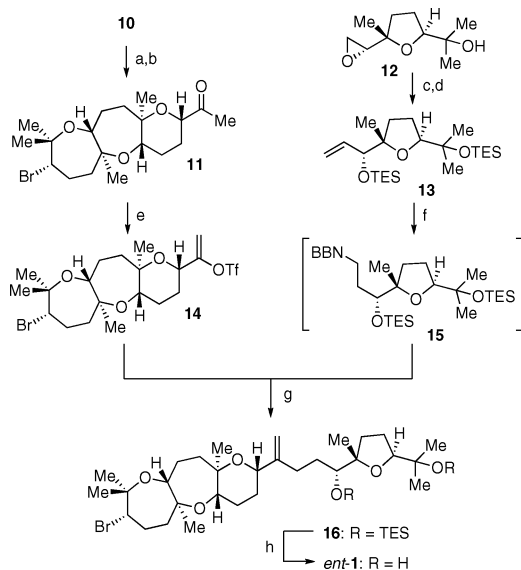
The highly polar non-nucleophilic solvent 1,1,1,3,3,3-hexafluoro-*iso*-propanol (HFIP) was chosen to facilitate the presumably cationic cascade and thus maximize the directing influence of the methyl groups.⁸ Upon treatment of **3** with NBS in HFIP, the cascade proceeded with the predicted regioselectivity in the bromonium-opening and all epoxide-opening events, furnishing a 72% combined yield (90% per epoxide) of a 1:1 mixture of the desired product (**10**) and a diastereomer (**10'**) resulting from unselective bromonium formation (Scheme 3).¹¹ The yield of this four-ring-forming process is in fact similar to those of bromoetherification reactions in which a *single* ring is formed.^{4,6} All the quaternary stereocenters in **6** (C6, C10, and C15) underwent clean inversion during the cascade to afford the desired *trans-anti-trans* geometry of ring junctions in **10**.

Progress toward the Suzuki–Miyaura fragment coupling¹² commenced with hydrolysis of cyclic carbonate **10** and oxidative cleavage

Scheme 3. Bromonium-Initiated Epoxide-Opening Cascade



of the diol to form ketone **11** (Scheme 4). Epoxy furan **12**,^{10a,13} prepared by way of a Payne rearrangement of a known diepoxide, was treated with an ylide derived from trimethylsulfonium iodide à la Falck.¹⁴ Hydroboration of the resulting terminal alkene in **13** (9-BBN dimer) and *in situ* treatment of the alkylborane with a triflate derived from **11**¹⁵ in the presence of Pd(Cl₂)dppf and aqueous Cs₂CO₃ at 40 °C effected the fragment coupling in 78% yield. Temperature control was critical to prevent side reactions involving the Br atom. Deprotection with TBAF provided *ent*-**1**, displaying the opposite specific rotation to that of **1**,¹ hence confirming the relative and absolute configuration of the natural product.

Scheme 4. Fragment Coupling and Completion of the Synthesis^a

^a Reagents and conditions: (a) NaOH, MeOH, rt, 83%; (b) NaIO₄, THF/H₂O, rt, 30 min, 96%; (c) (CH₃)₃Si, *n*-BuLi, THF, −13 to 5 °C, 73%; (d) TESCl, imidazole, DMF, rt, 95%; (e) (SO₂CF₃)₂NC₃H₃NCl, LHMDs, THF, −78 °C, quant.; (f) 9-BBN dimer, THF, 60 °C, 20 h; (g) PdCl₂(dppf), aq. Cs₂CO₃, THF/DMF/H₂O, 40 °C, 36 h, 78% (h) TBAF, THF, rt, 83%.

We explored the generality of this strategy with a series of related model systems (Table 1).¹⁶ In most cases the yield did not depend significantly upon the reagent used for bromonium formation, yet a *tert*-butyl carbonate or a *tert*-butyl ester trapping nucleophile generally gave a higher yield than did a primary alcohol. This brief survey suggests that further applications of bromonium-initiated epoxide-opening cascades would be merited.

In summary, we have achieved the first total synthesis of *ent*-dioxepandehydrothysiferol (*ent*-**1**). The signature *trans-anti-trans* 7,7,6-fused tricyclic polyether framework was constructed in a single bromonium-initiated epoxide-opening cascade that incorporates both *endo*- and *exo*-selective epoxide openings, each directed by the substitution pattern of the epoxide (Me groups).

While the studies reported herein do not establish the natural biogenesis of **1**, they certainly demonstrate the feasibility of an alternative sequence that constructs the *trans-anti-trans* tricycle in a single operation (Figure 1, path a), in contrast to the iterative ring assembly that has been proposed (path b).

Table 1. Studies of Diepoxide Model Systems

diepoxide	product	yield (%) ^a
		66 ^b , 65 ^c
		73 ^b , 61 ^c
		58 ^b , 52 ^c

^a Isolated as a 1:1 mixture of diastereomers in all cases. Yields are not corrected for the dr of the diepoxide starting materials (approximately 4:1 in all cases). See Supporting Information. ^b NBS used. ^c Br(coll)₂ClO₄ used.

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Supporting Information Available: Experimental procedures and spectroscopic data for all new intermediates. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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