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

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Dioxepandehydrothysiferol¹ (**1**; Scheme 1), thysiferol, venustatriol, ensuol, 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 ensuol.^{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**.

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 multi-epoxide 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 multi-epoxide-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

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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>.

The highly polar non-nucleophilic solvent 1,1,1,3,3,3-hexafluoro-*iso*-propanol (HFIP) was chosen in order 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 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 towards the Suzuki–Miyaura fragment coupling¹² commenced with hydrolysis of cyclic carbonate **10** and oxidative cleavage 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 in order 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.

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).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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

Scheme 2.

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

^aR' = (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%.

Scheme 3.
Bromonium-Initiated Epoxide-Opening Cascade

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

^aReagents 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)₂NC₅H₃NCl, 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%.

Table 1

Studies of Diepoxide Model Systems

diepoxide	product	yield (%) ^a
17	20, 20'	66 ^b , 65 ^c
18	21, 21'	73 ^b , 61 ^c
19	22, 22'	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 (approx. 4:1 in all cases). See Supporting Information

^b NBS used.

^c Br(coll)₂ClO₄ used.