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

Jessica Tanuwidjaja, Sze-Sze Ng, and Timothy F. Jamison*

Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139

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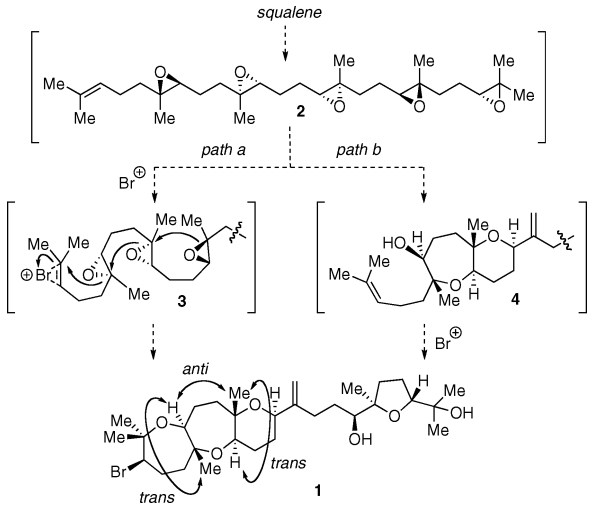
Dioxepandehydrothyrsiferol[1] (**1**, Scheme 1), thyrsiferol, venustatriol, enshuol, and armatols A−F are squalene-derived bromotriterpenes isolated from red algae of the genera *Laurencia* and *Chondria*.[2] Unique among them is the structural motif found in **1**, a *trans-anti-trans* topography, rather 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 thyrsiferol, Higa for venustatriol, and Masuda for enshuol.[2b,c,4] However, isolation from the same natural source of a related metabolite lacking the halogenated ring[1] 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**

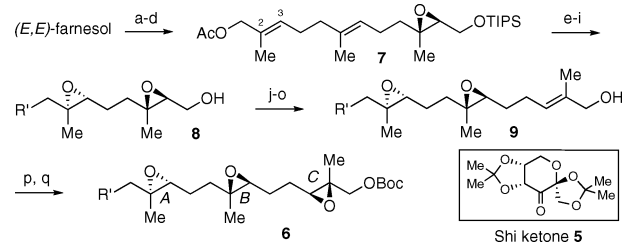


With the aim of investigating the chemical feasibility of the previously unexplored epoxide-opening cascade leading to the tricyclic core (path a), we undertook and now report an enantioselective total synthesis of *ent*-**1**. Notable features of the synthesis include the first example of an halonium-initiated multiepoxide 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] McDonald[7] and Holton[8] 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 multiepoxide-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 epoxidation[9] 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]



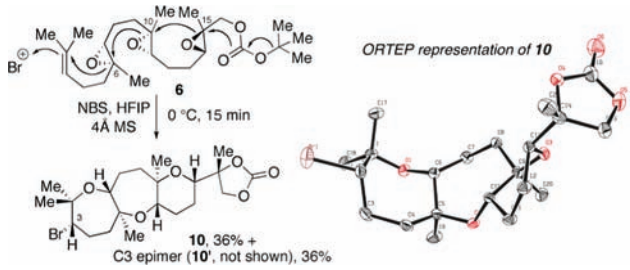
[a] R′ = $(CH_3)_2C{=}C(H)CH_2$. Reagents and conditions: (a) L-(+)-DIPT, Ti(O*i*-Pr)$_4$, *t*-BuOOH, 4 Å MS, CH_2Cl_2, −48 °C, 88%, 82% *ee*; (b) TIPSCl, imid, CH_2Cl_2, rt, 90%; (c) SeO_2, salicylic acid, *t*-BuOOH, CH_2Cl_2, rt, 73% (2 resubjections); (d) Ac_2O, Et_3N, DMAP, CH_2Cl_2, rt, 89%; (e) Shi ketone (**5**), Oxone, Bu_4NHSO_4, K_2CO_3, $Na_2B_4O_7$, pH 10.5, DMM/CH_3CN/H_2O, 0 °C, 30 min, 75%, 3:1 dr; (f) LiOH, THF/MeOH/H_2O, rt, 84%; (g) (i) MsCl, Et_3N, CH_2Cl_2, −78 to −10 °C; (ii) LiBr, THF, 0 to 8 °C, 1 h; (h) $LiBEt_3H$, THF, −78 °C, 69% (3 steps); (i) TBAF, THF, rt, 85%; (j) SO_3·pyr, Et_3N, DMSO, CH_2Cl_2, 0 °C to rt, 81%; (k) $Ph_3P{=}CHCO_2Et$, CH_2Cl_2, rt, 99%; (l) $[(Ph_3P)CuH]_6$, $PhSiH_3$, THF, 0 °C to rt, 95%; (m) DIBAL-H, PhMe, −78 °C, 45 min, 73%; (n) $Ph_3P{=}C(CH_3)CHO$, C_6H_6, reflux, 64%, >95:5 *E*/*Z*; (o) $NaBH_4$, MeOH, 0 °C, 81%; (p) L-(+)-DET, Ti(O*i*-Pr)$_4$, *t*-BuOOH, 4 Å MS, CH_2Cl_2, −48 °C, 80%, 95:5 dr; (q) Boc_2O, 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 coupling[12] commenced with hydrolysis of cyclic carbonate **10** and oxidative cleavage

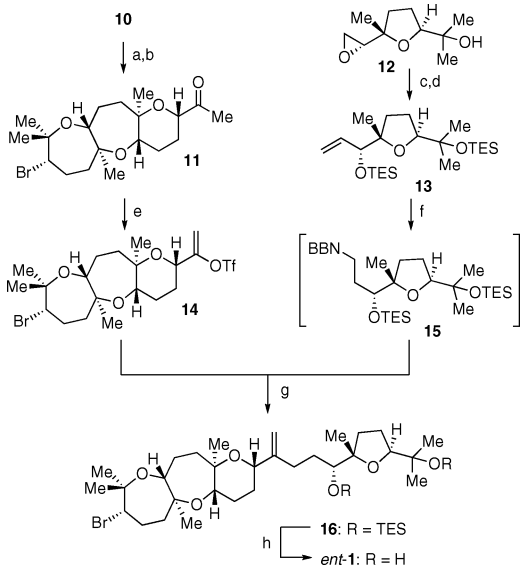
10.1021/ja9052366 CCC: $40.75

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 $Pd(Cl_2)$dppf and aqueous Cs_2CO_3 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]



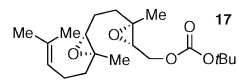
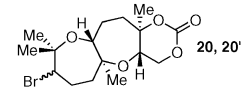
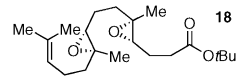
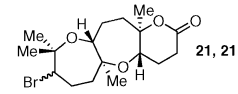
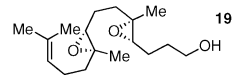
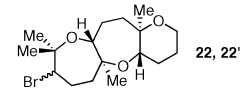
[a] Reagents and conditions: (a) NaOH, MeOH, rt, 83%; (b) $NaIO_4$, THF/H_2O, rt, 30 min, 96%; (c) $(CH_3)_3SI$, *n*-BuLi, THF, −13 to 5 °C, 73%; (d) TESCl, imidazole, DMF, rt, 95%; (e) $(SO_2CF_3)_2NC_5H_3NCl$, LHMDS, THF, −78 °C, quant.; (f) 9-BBN dimer, THF, 60 °C, 20 h; (g) $PdCl_2$(dppf), aq. Cs_2CO_3, THF/DMF/H_2O, 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*-dioxepandehydrothyrsiferol (*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]
 **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 (approximately 4:1 in all cases). See Supporting Information. [b] NBS used. [c] $Br(coll)_2ClO_4$ 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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