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Citation: Tanuwidjaja, Jessica, Sze-Sze Ng, and Timothy F. Jamison. “Total Synthesis of ent-Dioxepanhydrothysiferol via a Bromonium-Initiated Epoxide-Opening Cascade.” Journal of the American Chemical Society 131, no. 34 (September 2, 2009): 12084-12085.

As Published: http://dx.doi.org/10.1021/ja9052366

Publisher: American Chemical Society (ACS)

Version: Author's final manuscript

Accessed: Fri Jun 23 21:02:34 EDT 2017

Citable Link: http://hdl.handle.net/1721.1/82115

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Total Synthesis of \textit{ent}-Dioxepandehydrothyrsiferol via a Bromonium-Initiated Epoxide-Opening Cascade

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Dioxepandehydrothyrsiferol\textsuperscript{1} (1, Scheme 1), thyrsiferol, venustatriol, enshuol, and armatols A-F are squalene-derived bromotriterpenes isolated from red algae of the genera \textit{Laurencia} and \textit{Chondria}.\textsuperscript{2} Unique among them is the structural motif found in 1, a \textit{trans-anti-trans} topography, rather than the more commonly observed \textit{trans-syn-trans} at junctions between fused oxygen heterocycles.\textsuperscript{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.\textsuperscript{2b-c,4} However, isolation from the same natural source of a related metabolite lacking the halogenated ring\textsuperscript{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.

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 \textit{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 \textit{trans-anti-trans} fused tricyclic subunit.\textsuperscript{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.\textsuperscript{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.\textsuperscript{4,6} McDonald\textsuperscript{7} and Holton\textsuperscript{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 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 (\textit{E,E})-farnesol (Scheme 2). Site-selective installation of epoxide A using a Shi epoxidation\textsuperscript{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 \textalpha,\beta-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 \textit{tert}-butyl carbonate) was attached, giving 6.\textsuperscript{10}
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. 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). The yield of this four-ring-forming process is in fact similar to bromoetherification reactions in which a single ring is formed. 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 coupling commenced with hydrolysis of cyclic carbonate 10 and oxidative cleavage of the diol to form ketone 11 (Scheme 4). Epoxy furan 12, prepared by way of a Payne rearrangement of a known diepoxide, was treated with an ylide derived from trimethylsulfonium iodide à la Falck. Hydroboration of the resulting terminal alkene in 13 (9-BBN dimer) and in situ treatment of the alkylborane with a triflate derived from 11 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 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). 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).

**Supplementary Material**

Refer to Web version on PubMed Central for supplementary material.

**Acknowledgments**

This work was supported by the NIGMS (GM-72566). We thank Dr. Jeffrey H. Simpson for helpful discussions regarding NMR experiments, Li Li for mass spectrometry data, Dr. Peter Müller for the crystal structure of 8, and Dr. Jose J. Fernández (Universidad de La Laguna) for providing the 1H, 13C, and 2D NMR spectra of natural 1.

**References**

5. We selected ent-1 in order to use the more readily available enantiomer of fructose-derived ketone 5 to establish the configuration of the central, isolated epoxide (B, Scheme 2). Wang ZX, Tu Y, Frohn M, Zhang JR, Shi Y. J Am Chem Soc 1997;119:11224.  
11. Absence of stereoselectivity has been observed in related cases (ref. 4, 6) and was not surprising in this case, given the distance between the alkene in 6 and the nearest stereogenic center (epoxide A). A combined isolated yield of 67% was obtained using Br(coll)2ClO4.  
16. See Supporting Information for details.
Scheme 1.
Possible Biogenetic Pathways to 1
Scheme 2.
Synthesis of the Left-Hand Triepoxide Fragment 6a

R' = (CH₃)₂C=C(H)CH₂. Reagents and conditions: (a) L-(+)-DIPT, Ti(Oi-Pr)₄, t-BuOOH, 4Å MS, CH₂Cl₂, −48 °C, 88%, 82% ee; (b) TIPSCI, imid, CH₂Cl₂, rt, 90%; (c) SeO₂, salicylic acid, t-BuOOH, CH₂Cl₂, rt, 73% (2 resubjectives); (d) Ac₂O, Et₃N, DMAP, CH₂Cl₂, rt, 89%; (e) Shi ketone (5). Oxone, Bu₄NHSO₄, K₂CO₃, Na₂B₄O₇, 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=CH₂CHO, C₆H₆, reflux, 64%, >95:5 E/Z; (o) NaBH₄, MeOH, 0 °C, 81%; (p) L-(+)-DET, Ti(Oi-Pr)₄, t-BuOOH, 4Å 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$^a$

$^a$Reagents and conditions: (a) NaOH, MeOH, rt, 83%; (b) NaIO$_4$, THF/H$_2$O, rt, 30 min, 96%; (c) (CH$_3$)$_3$Si, $n$-BuLi, THF, −13 to 5 °C, 73%; (d) TESCl, imidazole, DMF, rt, 95%; (e) (SO$_2$CF$_3$)$_2$NC$_5$H$_3$NCl, LHMDS, THF, −78 °C, quant.; (f) 9-BBN dimer, THF, 60 °C, 20 h; (g) PdCl$_2$(dpdf), aq. Cs$_2$CO$_3$, THF/DMF/H$_2$O, 40 °C, 36 h, 78% (h) TBAF, THF, rt, 83%.
### Table 1

Studies of Diepoxide Model Systems

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\(^a\) 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)\(_2\)ClO\(_4\) used.