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

Citation: Tanuwidjaja, Jessica, Sze-Sze Ng, and Timothy F. Jamison. "Total Synthesis of ent-Dioxepandehydrothyrsiferol 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)

Persistent URL: http://hdl.handle.net/1721.1/82115

Version: Author's final manuscript: final author's manuscript post peer review, without publisher's formatting or copy editing

Published in final edited form as:
J Am Chem Soc. 2009 September 2; 131(34): 12084–12085. doi:10.1021/ja9052366.

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

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**.

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] 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 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 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]

tfj@mit.edu.

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 coupling[12] 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 $Pd(Cl_2)$dppf and aqueous Cs_2CO_3 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*-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

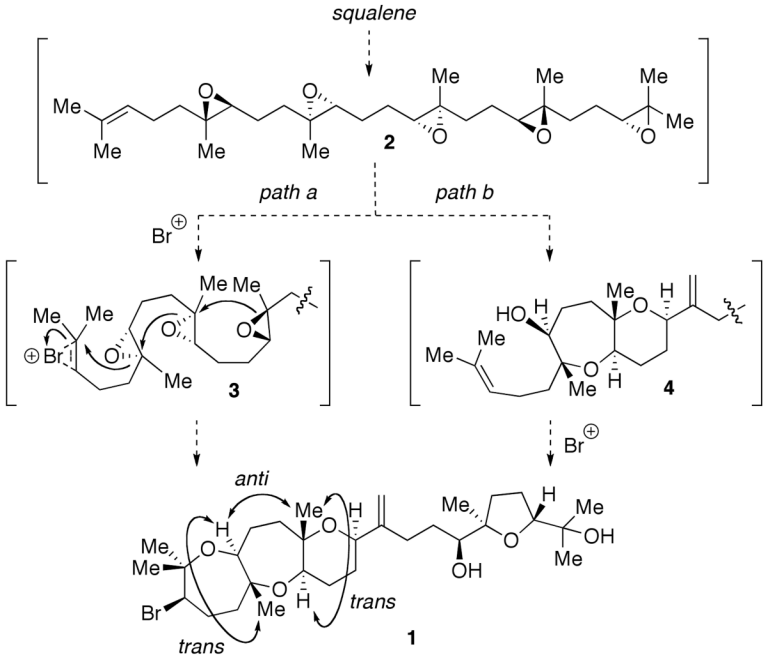
This work was supported by the NIGMS (GM-72566). We thank Dr. Jeffrey H. Simpson for helpful discussions regarding NMR experiments, Li Li for mass spectrometry data, Dr. Peter Müller for the crystal structure of **8**, and Dr. Jose J. Fernández (Universidad de La Laguna) for providing the ^{1}H, ^{13}C,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

References

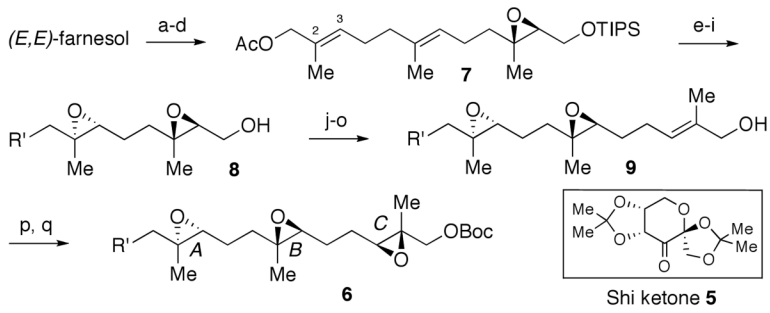
1. Manriquez CP, Souto ML, Gavin JA, Norte M, Fernandez JJ. Tetrahedron 2001;57:3117.
2. (a) Blunt JW, Hartshorn MP, McLennan TJ, Munro MHG, Robinson WT, Yorke SC. Tetrahedron Lett 1978:69. (b) Sakemi S, Higa T. Tetrahedron Lett 1986;27:4287. (c) Matsuo Y, Suzuki M, Masuda M.

Chem Lett 1995;24:1043. (d) Ciavatta ML, Wahidulla S, D'Souza L, Scognamiglio G, Cimino G. Tetrahedron 2001;57:617.

3. Syntheses of other *trans-anti-trans* systems: (a)Wan S, Gunaydin H, Houk KN, Floreancig PE. J Am Chem Soc 2007;129:7915. [PubMed: 17547399](b)Nicolaou KC, Cole KP, Frederick MO, Aversa RJ, Denton RM. Angew Chem Int Ed 2007;46:8875.
4. Hashimoto M, Kan T, Nozaki K, Yanagiya M, Shirahama H, Matsumoto T. J Org Chem 1990;55:5088.
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.
6. Selected examples of bromotriterpene syntheses: (a)Morimoto M, Nishikawa Y, Takaishi M. J Am Chem Soc 2005;127:5806. [PubMed: 15839676](b)Morimoto Y, Yata H, Nishikawa Y. Angew Chem Int Ed 2007;46:6481.(c)Corey EJ, Ha DC. Tetrahedron Lett 1988;29:3171.
7. Bravo F, McDonald FE, Neiwert WA, Hardcastle KI. Org Lett 2004;6:4487. [PubMed: 15548057]
8. Zakarian A, Batch A, Holton RA. J Am Chem Soc 2003;125:7822. [PubMed: 12822999]
9. Wang ZX, Shi Y. J Org Chem 1998;63:3099.
10. (a) McDonald FE, Bravo F, Wang X, Wei X, Toganoh M, Rodriguez JR, Do B, Neiwert WA, Hardcastle KI. J Org Chem 2002;67:2515. [PubMed: 11950296] (b) Bravo F, McDonald FE, Neiwert WA, Do B, Hardcastle KI. Org Lett 2003;5:2123. [PubMed: 12790544]
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 $Br(coll)_2ClO_4$.
12. Selected reviews on Suzuki–Miyaura cross coupling reactions: (a)Miyaura N, Suzuki A. Chem Rev 1995;95:2457.(b)Suzuki AJ. Organomet Chem 1999;576:147.
13. (a) Hanson RM. Org React 2002;60:2. (b) Payne GBJ. Org Chem 1962;27:3819.
14. Alcaraz L, Harnett JJ, Mioskowski C, Martel JP, Le Gall T, Shin DS, Falck JR. Tetrahedron Lett 1994;35:5449.
15. Comins DL, Dehghani A. Tetrahedron Lett 1992;33:6299.
16. See Supporting Information for details.



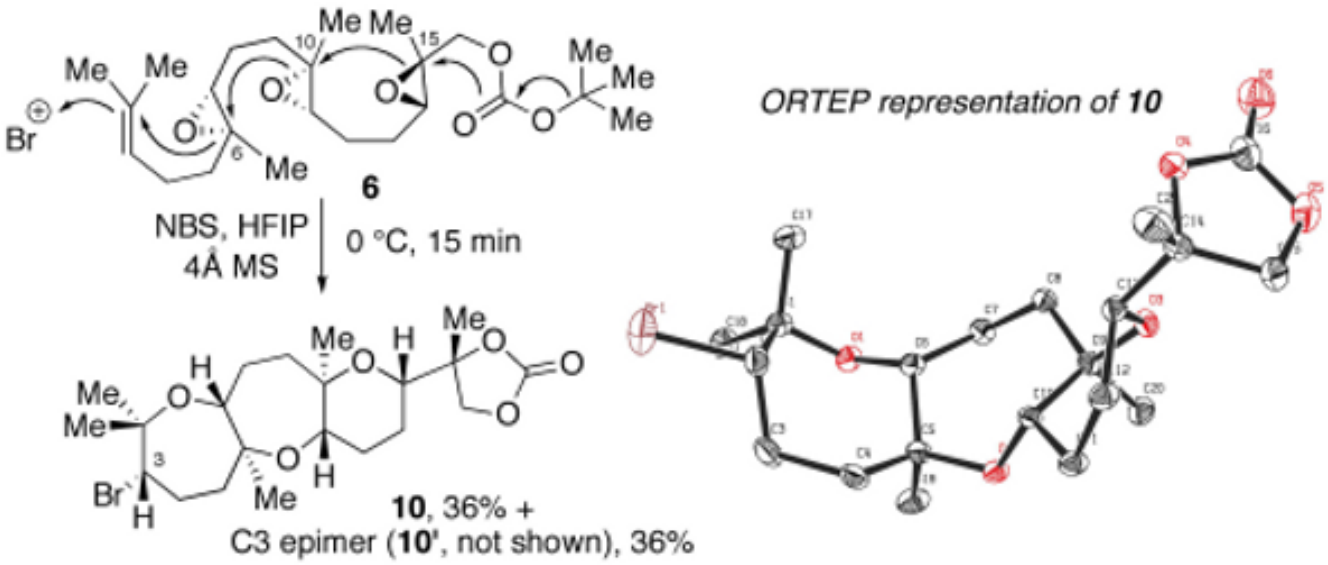
Scheme 1.
Possible Biogenetic Pathways to **1**



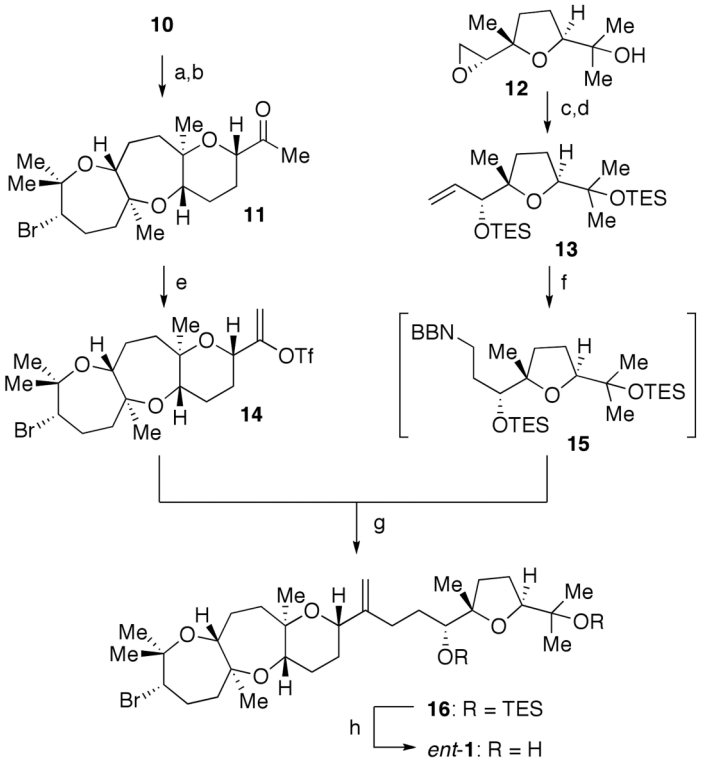
Scheme 2.

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, 4Å 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, 4Å MS, CH_2Cl_2, −48 °C, 80%, 95:5 dr; (q) Boc_2O, NMI, PhMe, 0 °C to rt, 68%.



Scheme 3.
Bromonium-Initiated Epoxide-Opening Cascade



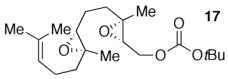
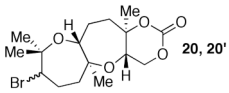
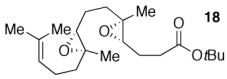
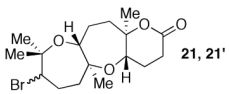
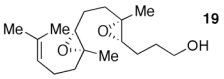
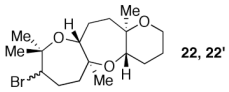
Scheme 4.

Fragment Coupling and Completion of the Synthesis[a]

[a]Reagents and conditions: (a) NaOH, MeOH, rt, 83%; (b) $NaIO_4$, THF/H_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%.

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] $Br(coll)_2ClO_4$ used.