Natural Products

DOI: 10.1002/anie.200800749

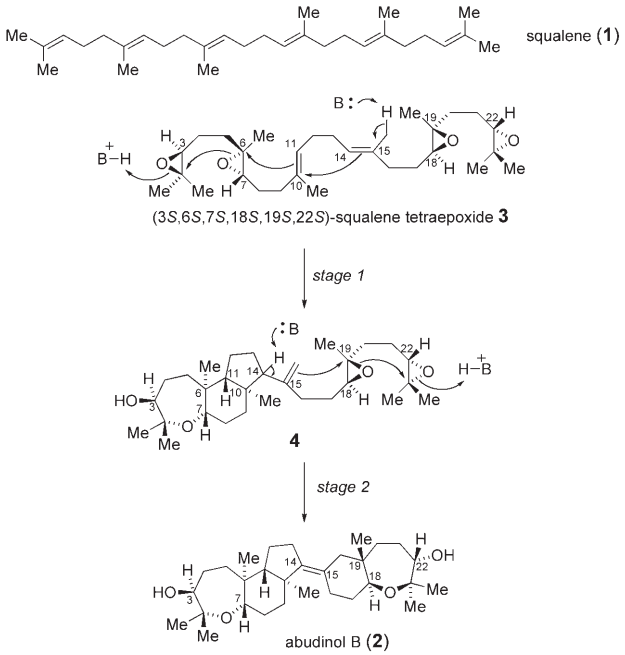
Mimicking Biosynthesis: Total Synthesis of the Triterpene Natural Product Abudinol B from a Squalene-like Precursor**

*Rongbiao Tong and Frank E. McDonald**

In memory of John L. Hogg (1948–2008)

Squalene (**1**) and the (*S*)-2,3-monoepoxide of squalene are precursors for the biogenesis of many 30-carbon terpenoid natural products, including steroids and hopanoids.[1] The demonstrated cascade polycyclization nature of the biosynthetic processes for these important natural products from squalene and squalene epoxide has also revolutionized the development of chemical synthesis strategies that are similar to or inspired by this mode of natural product biosynthesis.[2] More recently, a variety of triterpenoid natural products containing cyclic ethers have been discovered in marine sources including algae and sponges.[3,4] The biosynthetic pathways for these compounds are envisioned to arise from additional oxidations of squalene, accompanied by oxacyclizations to form the cyclic ether structures. Although considerable accomplishments have been recorded in biomimetic or bioinspired cascade cyclizations of polyalkene, polyepoxide, and epoxyalkene cyclizations,[2] the cyclization processes of multiple epoxides with multiple alkenes have not been extensively studied.

Such a hybrid process has been proposed[3] for the biosynthesis of triterpenoids featuring cyclic ethers fused to carbacyclic rings, including the marine triterpenoid natural product abudinol B (**2**, Scheme 1). Abudinol B and several other structurally related triterpenes have been isolated from *Ptilocaulis spiculifer*, a marine sponge of the Axinellidae family indigenous to the Red Sea waters of the Dahlak archipelago of Eritrea.[5] The 30-carbon skeleton of abudinol B as well as the position of methyl substituents is consistent with a triterpene arising from biogenetic oxidative polycyclization of squalene (**1**), and also shares several structural features with other cyclic ether triterpene natural products.[5,6] Although the nature of the biosynthetic polycyclization process has not yet been demonstrated, Fernandez et al. have proposed that tandem oxa- and carbacyclization of two adjacent epoxides and both alkenes of squalene tetraepoxide (**3**) provides the hypothetical intermediate **4** containing the fused tricyclic sector in an initial tricyclization stage,



Scheme 1. Proposed biosynthesis for abudinol B (**2**).

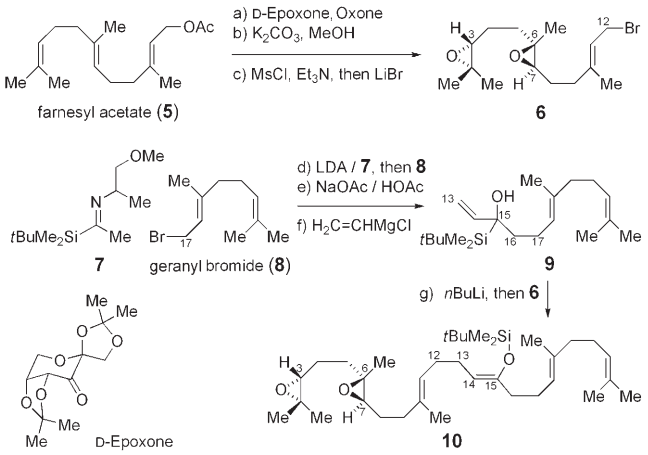
followed by a subsequent stage featuring bicyclization of the remaining two epoxides to afford the structure of abudinol B.[3,6] In 2007 we reported the synthesis of *ent*-abudinol B (*ent*-**2**),[7] via separate syntheses of the tricyclic and bicyclic sectors from related but different bisepoxide cyclizations, concluding with joining the two sectors by constructing the tetrasubstituted alkene. Our synthesis clarified an ambiguous stereochemical assignment for abudinol B and provided valuable insights into the synthesis of the condensed oxepane-cycloalkane sectors of **2**.

Herein we describe a novel enantioselective chemical synthesis of *ent*-abudinol B (*ent*-**2**) arising from a squalene-like 29-carbon substrate (**10**, Scheme 2), which closely mimics the proposed biosynthetic pathway for abudinol B.[3] Compound **10** and the synthetic route utilized for this compound were designed so that two epoxides could be regioselectively introduced by farnesol-derived bromide **6**. To more effectively promote the initial tricyclization cascade to the fused tricyclic network of abudinol B as observed in the proposed biogenetic intermediate **4**, the enolsilane at C14–C15 of **10** was introduced for efficient nucleophilic termination of the cascade cyclization. Diepoxybromide **6** was coupled with the Brook rearrangement product of the lithium alkoxide of **9**,[8,9] providing the enolsilane **10** exclusively as the *Z* isomer. The

[*] Dr. R. Tong, Prof. Dr. F. E. McDonald
Department of Chemistry, Emory University
1515 Dickey Drive NE, Atlanta, GA 30322 (USA)
Fax: (+1) 404-727-6586
E-mail: fmcdona@emory.edu

[**] Financial support was provided by the National Science Foundation (CHE-0516793). We also acknowledge the use of shared instrumentation provided by grants from NSF and NIH.

Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.



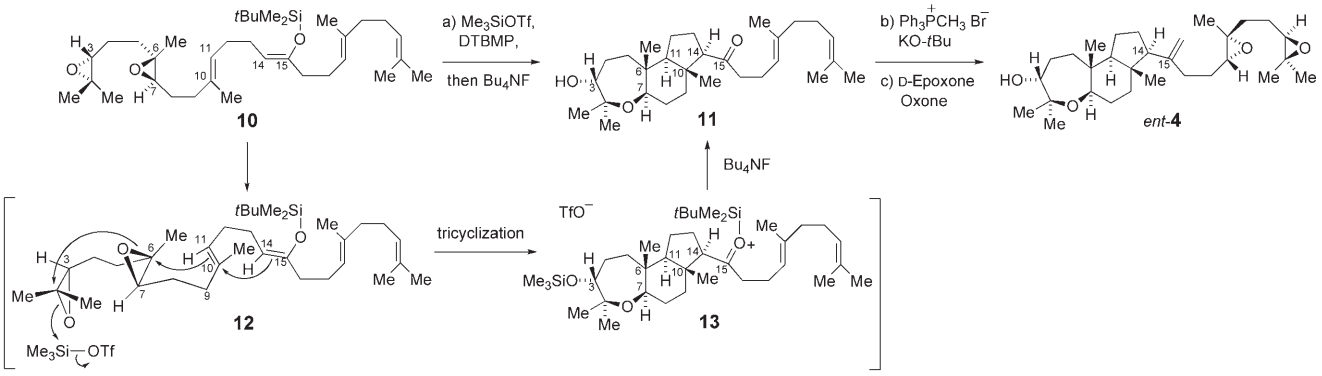
Scheme 2. Synthesis of squalene-like substrate **10** for biomimetic cyclizations. Reagents and conditions: a) D-Epoxone (0.5 equiv), Oxone, pH 10.5 buffer, DMM/MeCN/H_2O. −5 °C, 54%; b) K_2CO_3, MeOH, 99%; c) MsCl, Et_3N, −40 °C, then LiBr, THF, 0 °C, 60%; d) LDA, THF, −30 °C, then **8**; e) NaOAc, HOAc, 84% (2 steps); f) H_2C=CHMgCl, Et_2O, 0 °C, then HCl, 88%; g) *n*BuLi, hexane/THF, −78 °C, then **6**, 50%. DMM = dimethoxymethane.

epoxides of compounds **6** and **10** were antipodal to those required for abudinol B, due to the ready availability of the D-fructose-derived chiral ketone (D-Epoxone) for enantioselective epoxidation.[10]

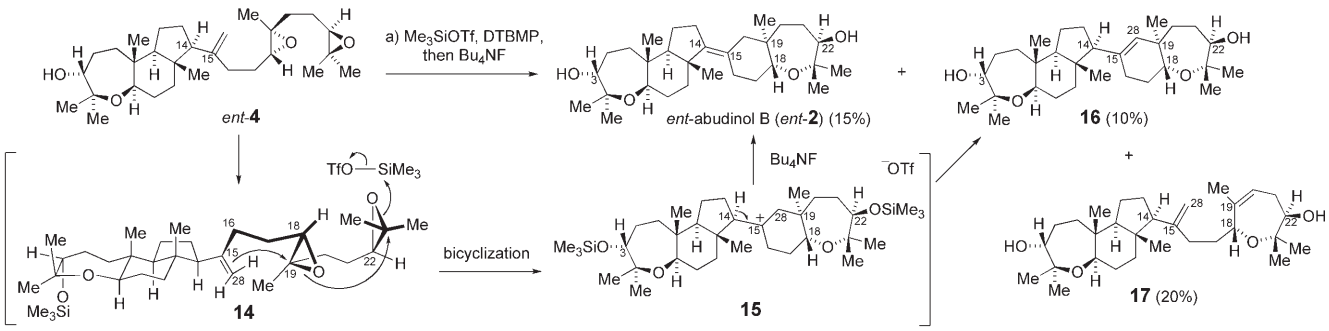
For the first stage of biomimetic tricyclization, we found that 1.1 equivalents of trimethylsilyl triflate,[11] in the presence of the bulky base 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP), selectively activated the terminal epoxide of **10** and effectively promoted regio- and stereoselective tandem cyclization to provide *trans,anti,trans*-fused tricyclic ketone **11** as the major product (Scheme 3), consistent with concerted antiparallel addition and an expected chairlike conformation **12**.[12–17] The best yield of **11** (50%, single diastereomer) was achieved when the reaction was quenched with 1.1 equivalents of tetrabutylammonium fluoride at −78 °C within ten minutes of trimethylsilyl triflate addition, whereas longer reaction times or aqueous quench resulted in the generation of the epimeric product at C14 (see the Supporting Information for details), perhaps through silyloxonium ion intermediate **13**. No significant by-products arising from side reactions of the remaining diene of **10** or **11** were observed. Compound **11** and its C14 epimer (not shown) were thoroughly characterized by ^{1}H NMR, ^{13}C NMR, ^{1}H-^{1}H-COSY, and NOESY spectroscopy, as well as high-resolution mass spectrometry.

In order to explore the ultimate bicyclization of the hypothetical biogenesis of *ent*-abudinol B (**2**) from the enantiomer of substrate **4** under abiological conditions, the conversion of **11** into *ent*-**4** required methylenation of the C15 ketone and double epoxidation of the trisubstituted alkenes of a triene intermediate. After evaluating a variety of reagents for this olefination, we found that the classical Wittig reagent prepared in situ from a refluxing benzene solution of Ph_3PCH_3Br and KO*t*Bu[18] gave good yields of the disubstituted alkene product, albeit with some epimerization at C14 prior to methylenation. Regio- and enantioselective epoxidations[10] of the two trisubstituted alkenes was then achieved in the presence of the disubstituted alkene by careful control of the reaction temperature, concentration, amount of D-Epoxone and reaction time, to provide *ent*-**4**. To the best of our knowledge, this is the first example of Epoxone-catalyzed regioselective epoxidation of trisubstituted alkenes in the presence of a disubstituted alkene.

A comment on the stereochemistry of *ent*-**4** is warranted before describing our results on the ultimate bicyclization to abudinol B: although the relative configuration at C14 is consistent with the lower energy conformation for the tandem cyclization process from **10** to **11** (Scheme 4), we were concerned that the C14 configuration might not be consistent with a concerted cyclization mechanism terminating with cleavage of the C–H sigma bond at C14 resulting from orbital alignment with the C15 alkene, when in a favorable conformation for cyclization onto the two epoxides. Thus we were pleased to observe that trimethylsilyl triflate-promoted reaction of *ent*-**4** did provide *ent*-abudinol B (*ent*-**2**), albeit in modest yield accompanied by several by-products including the trisubstituted alkene isomer **16** and the partial cyclization structure **17**.[19] The spectroscopic properties of our synthetic product *ent*-**2** matched the reported literature data[5] as well as direct comparison with another sample of *ent*-**2** generated in our first-generation synthesis of *ent*-abudinol B, which in turn



Scheme 3. Biomimetic tricyclization of **10** to **11**, and conversion into *ent*-**4**. Reagents and conditions: a) Me_3SiOTf, DTBMP, CH_2Cl_2, −78 °C, then Bu_4NF, 50%; b) Ph_3PMeBr, KO-*t*Bu, benzene, 80 °C, 30% (+ 55% C14 epimer); c) D-Epoxone (0.5 equiv), Oxone, pH 10.5 buffer, DMM/MeCN/H_2O, −5 °C, 50%.



Scheme 4. Biomimetic bicyclization of *ent*-**4** to *ent*-abudinol (*ent*-**2**) and isomeric by-products. Reagents and conditions: a) Me_3SiOTf, DTBMP, CH_2Cl_2, −78 °C, then Bu_4NF.

had been previously confirmed by X-ray diffractometry of the bis-silyl ether of *ent*-abudinol B.[7] The partial cyclization product **17**, resulting from proton-elimination from C20 after diepoxide cyclization, may arise due to the relatively low nucleophilicity expected for the C15–C28 disubstituted alkene. The mechanism for the tandem bicyclization process to *ent*-**2** and trisubstituted alkene isomer **16** is consistent with the intermediacy of a C15 carbenium ion or ion pair, perhaps due to the relatively poor nucleophilicity of the 1,1-disubstituted alkene of *ent*-**4**, which is also consistent with the generation of partial cyclization product **17** as a significant by-product.

In conclusion, a short total synthesis of *ent*-abudinol B (*ent*-**2**) has been accomplished from a squalene-like substrate **10**, following a synthetic strategy inspired by and closely mimicking the proposed biosynthetic pathway. This synthesis demonstrates the viability of tandem oxa- and carbacyclizations of structurally complex polyepoxide–alkene substrates. More significantly, the cyclization behavior of *ent*-**4**, which is the enantiomer of a possible advanced biosynthetic precursor to abudinol B, provides the first chemical evidence for the biosynthesis pathway proposed for abudinol B and other oxepane-containing triterpenoid marine natural products. We speculate that isomeric compounds **16** and/or **17** may also be present in the mixture of natural products arising from *Ptilocaulis spiculifer*, which if true would provide another point of connection between the synthetic work described herein and natural products biosynthesis.

Received: February 14, 2008
Published online: May 5, 2008

Keywords: biomimetic synthesis · epoxides · ring closure · terpenes · total synthesis

[1] I. Abe, M. Rohmer, G. D. Prestwich, *Chem. Rev.* **1993**, *93*, 2189.
[2] a) R. A. Yoder, J. N. Johnston, *Chem. Rev.* **2005**, *105*, 4730. See also: b) A. Zakarian, A. Batch, R. A. Holton, *J. Am. Chem. Soc.* **2003**, *125*, 7822; c) I. Vilotijevic, T. F. Jamison, *Science* **2007**, *317*, 1189.
[3] J. Fernández, M. Souto, M. Norte, *Nat. Prod. Rep.* **2000**, *17*, 235.
[4] Y. Kashman, A. Rudi, *Phytochem. Rev.* **2004**, *3*, 309.
[5] A. Rudi, T. Yosief, M. Schleyer, Y. Kashman, *Tetrahedron* **1999**, *55*, 5555.
[6] Several other natural products have also been proposed to arise from squalene tetraepoxide (**3**), including raspacionins and sodwanones (refs. [3–5]).
[7] R. Tong, J. C. Valentine, F. E. McDonald, R. Cao, X. Fang, K. I. Hardcastle, *J. Am. Chem. Soc.* **2007**, *129*, 1050.
[8] Preparation and alkylation of imine **7**: a) J. S. Nowick, R. L. Danheiser, *Tetrahedron* **1988**, *44*, 4113; b) E. J. Corey, S. Lin, *J. Am. Chem. Soc.* **1996**, *118*, 8765.
[9] a) H. J. Reich, R. E. Olson, M. C. Clark, *J. Am. Chem. Soc.* **1980**, *102*, 1423; b) M. Kato, A. Mori, H. Oshino, J. Enda, K. Kobayashi, I. Kuwajima, *J. Am. Chem. Soc.* **1984**, *106*, 1773; c) J. Enda, I. Kuwajima, *J. Am. Chem. Soc.* **1985**, *107*, 5495.
[10] a) Y. Shi, *Acc. Chem. Res.* **2004**, *37*, 488; b) For L-Epoxone, see: M.-X. Zhao, Y. Shi, *J. Org. Chem.* **2006**, *71*, 5377.
[11] Substrate **10** was unreactive with *tert*-butyldimethylsilyl triflate (TBSOTf) under a variety of conditions, in contrast with our previous observations with a simpler enolsilane–diepoxide substrate (ref. [7]).
[12] R. B. Woodward, K. Bloch, *J. Am. Chem. Soc.* **1953**, *75*, 2023.
[13] G. Stork, A. W. Burgstahler, *J. Am. Chem. Soc.* **1955**, *77*, 5068.
[14] A. Eschenmoser, L. Ruzicka, O. Jeger, D. Arigoni, *Helv. Chim. Acta* **1955**, *38*, 1890.
[15] E. E. van Tamelen, J. D. Willett, R. B. Clayton, K. E. Lord, *J. Am. Chem. Soc.* **1982**, *104*, 648.
[16] A. Eschenmoser, D. Arigoni, *Helv. Chim. Acta* **2005**, *88*, 3011.
[17] For representative examples of other transformations in which the epoxide oxygen acts as a nucleophile, see: a) F. David, *J. Org. Chem.* **1981**, *46*, 3512; b) E. Alvarez, M. T. Díaz, R. Pérez, J. L. Ravelo, A. Regueiro, J. A. Vera, D. Zurita, J. D. Martín, *J. Org. Chem.* **1994**, *59*, 2848; c) N. Hayashi, K. Fujiwara, A. Murai, *Chem. Lett.* **1996**, 341; d) M. Tokumasu, A. Sasaoka, R. Takagi, Y. Hiraga, K. Ohkata, *Chem. Commun.* **1997**, 875; e) J. C. Valentine, F. E. McDonald, *Synlett* **2006**, 1816.
[18] J. Zhang, E. J. Corey, *Org. Lett.* **2001**, *3*, 3215.
[19] Preliminary cyclization experiments with the C-14 diastereomer of *ent*-**4** have not resulted in the production of *ent*-abudinol B or a possible *Z* isomer of the central tetrasubstituted alkene. Reactions of *ent*-**4** with other Lewis acids such as BF_3-OEt_2 gave a complicated mixture of products containing neither *ent*-abudinol (*ent*-**2**) nor the by-products **16** or **17**.

