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Biomimetic Syntheses from Squalene-Like Precursors: Synthesis of *ent*-Abudinol B and Reassessment of the Structure of Muzitone

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Abstract: We achieved the stereoselective syntheses of two different structural patterns corresponding to the enantiomers of the marine natural products abudinol B and muzitone, by developing two-directional tandem biomimetic cyclizations of polyepoxides of squalene analogues in which one alkene was functionalized as an enolsilane. In the course of this work, we demonstrated that the structure of muzitone was misassigned.

Introduction

Polycyclic ether terpenoid marine natural products are secondary metabolites from algae and sponges, which present considerable diversity in their structural frameworks with different ring sizes and ring fusion patterns as well as an interesting dependence of biological activities on the ring systems and substituents.[1] A variety of terpenoid compounds have been isolated from a sea sponge (*Ptilocaulis spiculifer* of the Axinellidae family) native to the Red Sea waters of the Dahlak archipelago of Eritrea. Representative compounds arising from this isolation include abudinols A and B (**1** and **2**, Figure 1), the corresponding oxidative degradation products nakorone (**3**) and durgamone (**4**), and a macrocyclic diketone muzitone (**5**).[2] The structural assignment for abudinol A (**1**) was secured by crystallography,[1g] and ozonolysis of abudinol A produced nakorone (**3**) and durgamone (**4**), whereas the structures of abudinol B (**2**) and muzitone (**5**) were assigned solely from spectroscopic analysis.

Abudinols A and B as well as muzitone have been proposed to arise biogenetically from polycyclizations of squalene tetraepoxide (**6**, Figure 2), involving two-stage cascade cyclizations.[3,4] For instance, the all-fused tricyclic sector of abudinol B might

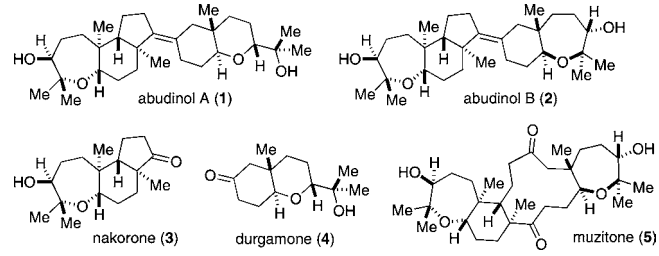

Figure 1. Representative marine terpenoids from *Ptilocaulis spiculifer*.

arise from tandem oxa- and carbacyclizations, by sequential Markovnikov-mode nucleophilic additions terminated by elimination of an allylic hydrogen to provide **7**. A similar mode of cyclization in the opposite direction would provide the pentacyclic structure of abudinol B (**2**) after elimination of the remaining allylic hydrogen (path *a*, Figure 2), possibly with the intermediacy of the tertiary cation **8**. The biosynthesis of muzitone (**5**) has been proposed to involve oxidative cleavage of the tetrasubstituted alkene in the pentacyclic structure "premuzitone" **11** (isomeric to abudinol B). Protonation of abudinol B (**2**) at C14 could form the tertiary cation **8**, which might also arise directly from bicyclization of **6**. Ring expansion of **8** to the spirocyclic **9** with a secondary cation at C14 might be followed by a second ring expansion to structure **10**, with subsequent elimination of the C14-hydrogen to afford "premuzitone" (**11**).

Although neither abudinol B nor muzitone exhibited interesting biological activities, their novel structures made them compelling synthetic target compounds. Given our longstanding interests in exploring higher-order polycyclization cascades in the context of the biomimetic synthesis of oxacyclic compounds,[5,6] we initiated a synthetic program directed toward the enantiomers

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(1) (a) Carmely, S.; Kashman, Y. *J. Org. Chem.* **1983**, *48*, 3517. (b) Carmely, S.; Kashman, Y. *J. Org. Chem.* **1986**, *51*, 784. (c) Rudi, A.; Goldberg, I.; Stein, Z.; Benayahu, Y.; Schleyer, M.; Kashman, Y. *Tetrahedron Lett.* **1993**, *34*, 3943. (d) Rudi, A.; Kashman, Y.; Benayahu, Y.; Schleyer, M. *J. Nat. Prod.* **1994**, *57*, 1416. (e) Rudi, A.; Goldberg, I.; Stein, Z.; Kashman, Y.; Benayahu, Y.; Schleyer, M.; Gravalos, G. *J. Nat. Prod.* **1995**, *58*, 1702. (f) Rudi, A.; Aknin, M.; Gaydou, E. M.; Kashman, Y. *J. Nat. Prod.* **1997**, *60*, 700. (g) Rudi, A.; Stein, Z.; Goldberg, I.; Yosief, T.; Kashman, Y.; Schleyer, M. *Tetrahedron Lett.* **1998**, *39*, 1445.

(2) (a) Rudi, A.; Yosief, T.; Schleyer, M.; Kashman, Y. *Tetrahedron* **1999**, *55*, 5555. (b) The stereochemistry of the C23 alcohol of abudinol B and corresponding C19 alcohol of muzitone is incorrectly shown as the *R* isomer in Figure 2 of ref 2a but correctly depicted with *S* stereochemistry in Scheme 1 (communication with Prof. Yoel Kashman).

(3) Fernández, J.; Souto, M.; Norte, M. *Nat. Prod. Rep.* **2000**, *17*, 215.

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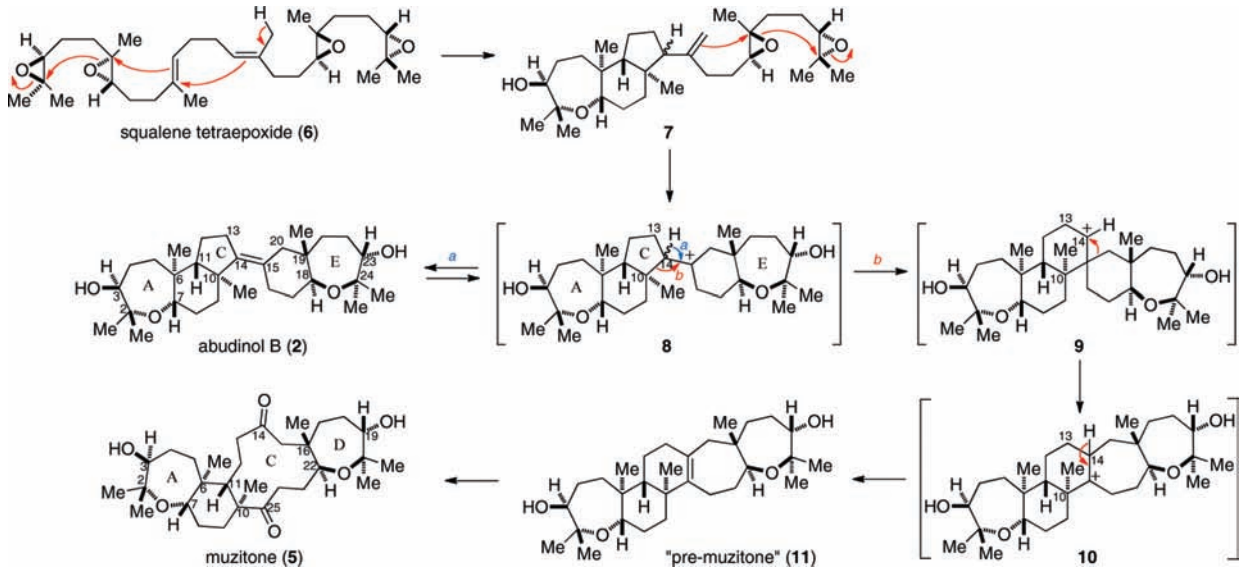

Figure 2. Proposed biosyntheses of abudinol B (**2**) and muzitone (**5**) from squalene tetraepoxide (**3**).

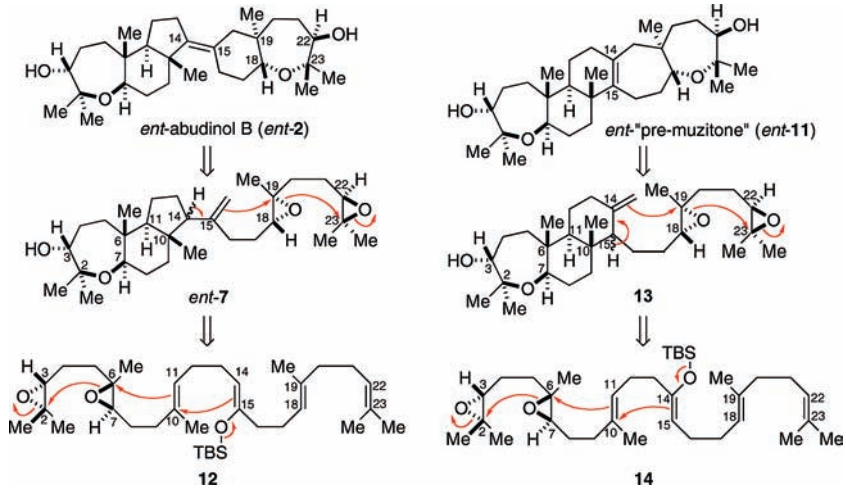

Figure 3. Retrosynthetic analysis for *ent*-abudinol (*ent*-**2**) and *ent*-"pre-muzitone" (*ent*-**11**).

of abudinol B (*ent*-**2**) and "pre-muzitone" (*ent*-**11**).[7,8] Our synthesis of each target structure involved a hybrid of polyene[9] and polyepoxide cyclizations[5,6] as the key steps. Specifically, we envisioned that the enantiomer of abudinol B (*ent*-**2**) would directly form by the bicyclization of the proposed biosynthetic intermediate (*ent*-**7**), which in turn could arise from squalene-like diepoxide **12** bearing an enolsilane as a terminating nucleophile[10] at C15 rather than the methyl group normally present in squalene (Figure 3). For the hypothetical alkene of "pre-muzitone" (*ent*-**11**), our synthesis would not be biomimetic but rather inspired by the mechanistic similarity of forming two fused seven-membered rings of *ent*-**11** by bicyclization of diepoxide (**13**), arising from a C14 enolsilane diepoxide **14**.

Results and Discussion

Initial Methodology Studies for Bicyclizations of Terpene-Derived Diepoxides. In earlier work from our laboratory directed toward the synthesis of a bicyclic substructure of abudinol B, we reported that bicyclization of diepoxide-enolsilane **15** was accomplished with substoichiometric *tert*-butyldimethylsilyl trifluoromethanesulfonate (TBSOTf) in the presence of 2,6-di-

(6) (a) Fujiwara, K.; Hayashi, N.; Tokiwano, T.; Murai, A. *Heterocycles* **1999**, *50*, 561. (b) Tokiwano, T.; Fujiwara, K.; Murai, A. *Synlett* **2000**, 335. (c) Xiong, Z. M.; Corey, E. J. *J. Am. Chem. Soc.* **2000**, *122*, 4831. (d) Xiong, Z. M.; Corey, E. J. *J. Am. Chem. Soc.* **2000**, *122*, 9328. (e) Heffron, T. P.; Jamison, T. F. *Org. Lett.* **2003**, *5*, 2339. (f) Zakarian, A.; Batch, A.; Holton, R. A. *J. Am. Chem. Soc.* **2003**, *125*, 7822. (g) Simpson, G. L.; Heffron, T. P.; Merino, E.; Jamison, T. F. *J. Am. Chem. Soc.* **2006**, *128*, 1056. (h) Vilotijevic, I.; Jamison, T. F. *Science* **2007**, *317*, 1189. (i) Morimoto, Y.; Yata, H.; Nishikawa, Y. *Angew. Chem., Int. Ed.* **2007**, *46*, 6481. (j) Wan, S.; Gunaydin, H.; Houk, K. N.; Floreancig, P. E. *J. Am. Chem. Soc.* **2007**, *129*, 7915. (k) Morten, C. J.; Jamison, T. F. *J. Am. Chem. Soc.* **2009**, *131*, 6678. (l) Tanuwidjaja, J.; Ng, S. S.; Jamison, T. F. *J. Am. Chem. Soc.* **2009**, *131*, 12084. (m) Vilotijevic, I.; Jamison, T. F. *Angew. Chem., Int. Ed.* **2009**, *48*, 5250. (n) Morten, C. J.; Byers, J. A.; van Dyke, A. R.; Vilotijevic, I.; Jamison, T. F. *Chem. Soc. Rev.* **2009**, *38*, 3175.

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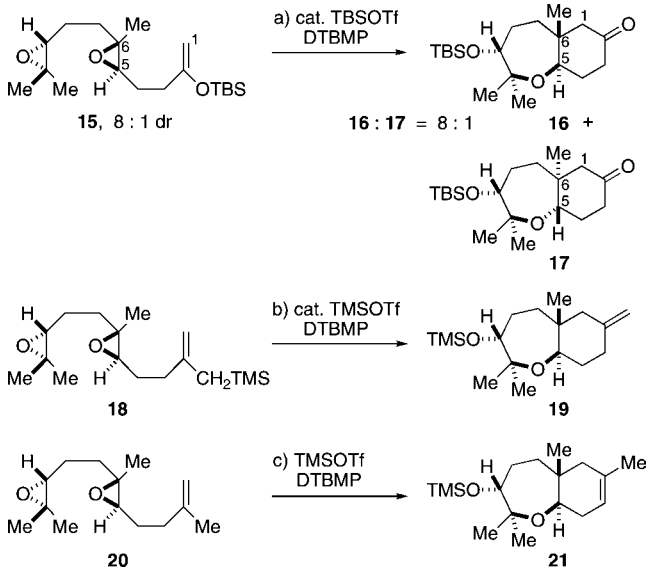
(8) Given that D-epoxone (derived from D-fructose) was more easily prepared than L-epoxone, we intended from the outset to prepare the enantiomers of the natural products **2** and **5**. (a) Zhao, M.-X.; Shi, Y. *J. Org. Chem.* **2006**, *71*, 5377. Review: (b) Wong, O. A.; Shi, Y. *Chem. Rev.* **2008**, *108*, 3958.

Scheme 1. Lewis Acid Promoted Bicyclizations of Diepoxide Substrates[a]



[a] Reagents and conditions: (a) TBSOTf (20 mol %), DTBMP (20 mol %), CH_2Cl_2, −78 °C (60% yield of **16**, 7.5% yield of **17**); (b) TMSOTf (20 mol %), DTBMP (1 equiv), CH_2Cl_2, −78 °C (90% yield); (c) TMSOTf (1.2 equiv), DTBMP (2 equiv), CH_2Cl_2, −78 °C; (65% yield).

tert-butyl-4-methylpyridine (DTBMP) to provide the bicyclic ketone **16** (Scheme 1).[7a] The use of DTBMP was necessary to ensure reproducibility by trapping any triflic acid generated from trace amounts of adventitious water. Although the diepoxide **15** was a mixture of diastereomers due to lower stereoselectivity in the epoxidation of the internal C5−C6 alkene precursor to **15**, the ratio of diastereomeric products **16**:**17** matched the diastereomer ratio of diepoxide **15**. However, the minor product **17** was formed at a much slower rate than **16**, which was observed by carefully monitoring the reaction by TLC. Subsequently, we observed that the allylic silane of **18** was a superior terminating group for bicyclizations,[11] which upon reaction with substoichiometric trimethylsilyl triflate (TMSOTf) and DTBMP afforded an excellent yield of the bicyclic structure **19** bearing an exocyclic methylene. Of greater relevance to the biosynthetic pathway for the formation of abudinol B (**2**) from alkenyldiepoxide **7**, the disubstituted alkene of diepoxide **20** also participated in the tandem oxacyclization transformation with stoichiometric TMSOTf/DTBMP to provide trisubstituted alkene **21** as the major product. Notably, the isomeric product **19** was not observed as a byproduct in the bicyclization of **20**.

Our working hypothesis for these results is that initial activation of the terminal epoxide results in the generation of a bicyclo[4.1.0]epoxonium ion **23** (Figure 4),[5] which then undergoes addition of nucleophilic C1 with inversion of configuration at C6 in the formation of cation **24**. The catalytic cycle is then propagated by transfer of trialkylsilicon from **24** to the terminal epoxide oxygen in substrates **15**/**18**, regenerating activated epoxide **22** along with the stable products **16**/**19**. For the bicyclization of disubstituted alkene substrate **20** with stoichiometric TMSOTf, product **21** arises through the intermediacy of a nonclassical carbenium ion **25** or tertiary carbocation **26**, followed by elimination of a C3 hydrogen to provide the thermodynamically stable trisubstituted alkene. These preliminary experiments have demonstrated that (1) tandem bicyclizations proceed with *endo*-selectivity in *anti*-parallel addition with a variety of nucleophilic alkenes, (2) trialkylsilyl Lewis acids (TMSOTf or TBSOTf) in the presence of a bulky nonnucleophilic base (DTBMP) are optimal reagents for these transformations, and (3) the stereochemistry of the epoxides affects the cyclization rate, but not the course, so that the rate of cyclization is faster with epoxides of the same configuration, i.e. all-*R*,*R*-diepoxides rather than mixed *R*,*R* and *S*,*S*-diepoxides.

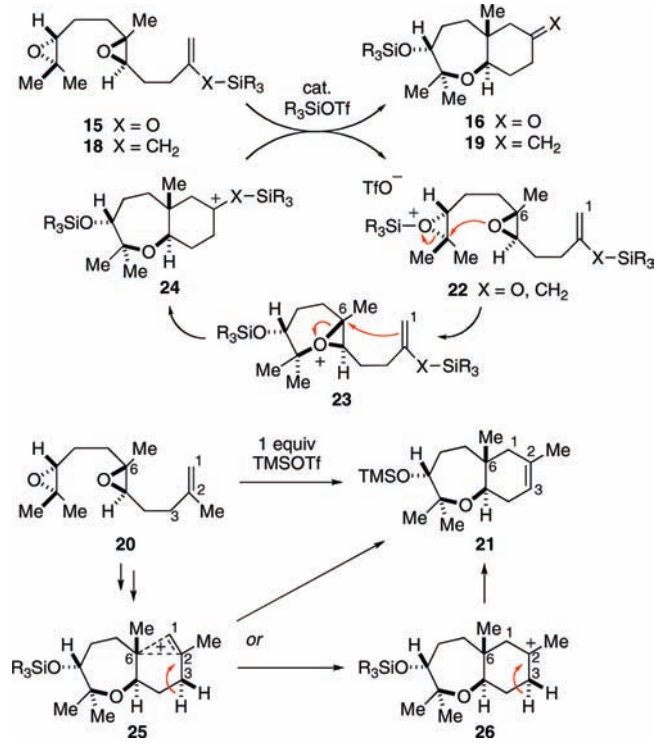


Figure 4. Mechanisms for bicyclizations of diepoxide substrates.

Preparation of Squalene Diepoxide Analogues Bearing Enolsilanes. The squalene-like substrates for the syntheses of *ent*-abudinol B and *ent*-muzitone were each prepared by a common strategy, involving alkylation of the anion generated from 1,2-Brook rearrangement,[12] either with the diepoxy-allylic bromide **29** or with geranyl bromide. The diepoxy-allylic bromide **29** was prepared beginning with regio- and enantioselective epoxidation[8] of farnesyl *p*-nitrobenzoate (**27**),[13] with the

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(10) (a) Corey, E. J.; Sodeoka, M. *Tetrahedron Lett.* **1991**, *32*, 7005. (b) Corey, E. J.; Roberts, B. E. *Tetrahedron Lett.* **1997**, *38*, 8921. (c) Corey, E. J.; Luo, G.; Lin, L. S. *J. Am. Chem. Soc.* **1997**, *119*, 9927.

(11) (a) Fish, P. V.; Johnson, W. S. *J. Org. Chem.* **1994**, *59*, 2324. (b) Fish, P. V. *Tetrahedron Lett.* **1994**, *35*, 7181.

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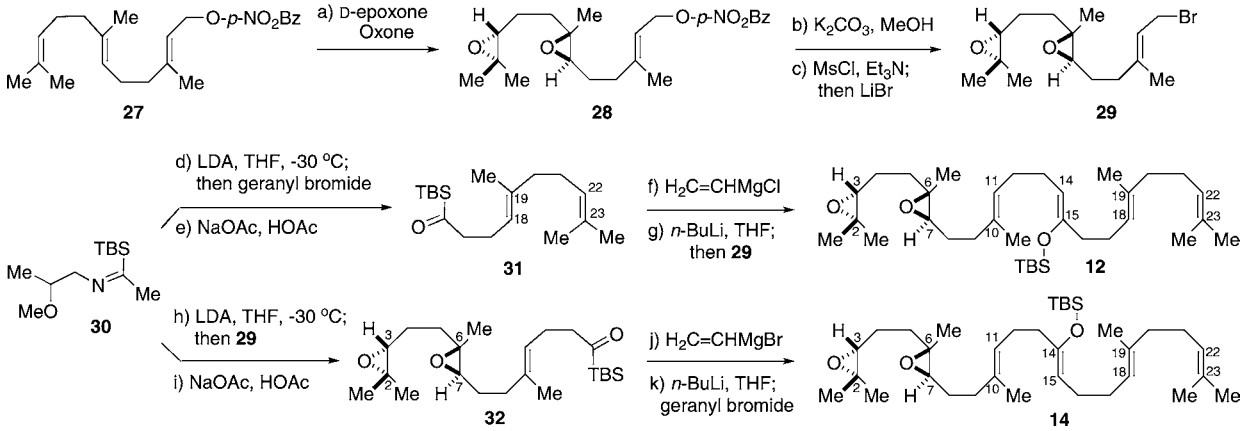
(13) Tong, R.; Boone, M. A.; McDonald, F. E. *J. Org. Chem.* **2009**, *74*, 8407.

Scheme 2. Synthesis of Diepoxy-Enolsilane Substrates for *ent*-Abudinol B and *ent*-Muzitone Syntheses[a]



[a] Reagents and conditions: (a) D-epoxone (0.5 equiv), Oxone (2.8 equiv), K_2CO_3 (8.0 equiv), Bu_4NHSO_4 (0.1 equiv), Na_2EDTA, $Na_2B_4O_7$, DMM/MeCN (2:1), H_2O, 0 °C (49−61% yield); (b) K_2CO_3, MeOH (88% yield); (c) MsCl, Et_3N, THF, −40 °C, then LiBr, THF, 0 °C (96% yield); (d) LDA, THF, −30 to −10 °C, then geranyl bromide, −30 to −10 °C; (e) NaOAc, HOAc, H_2O/pentane (84% yield, 2 steps); (f) vinylmagnesium chloride, Et_2O/THF, 0 °C (88% yield); (g) *n*-BuLi, hexane/THF, −78 °C, then **29**, −40 to −20 °C (50% yield); (h) LDA, THF, −30 to −10 °C, then **29**, −30 to −10 °C; (i) NaOAc, HOAc, H_2O/pentane (74% yield, 2 steps); (j) vinylmagnesium bromide, Et_2O/THF, −40 °C (99% yield); (k) *n*-BuLi, Et_2O/THF, −78 °C, then geranyl bromide, −20 °C (39% yield).

electron-withdrawing nature of the *p*-nitrobenzoate ester suppressing epoxidation of the alkene bearing the allylic ester. The diepoxide product **28** was then converted into the highly reactive diepoxy-allylic bromide **29** by a standard sequence of ester saponification, mesylation, and substitution with bromide.[13] Acylsilane **31** was prepared by alkylation of geranyl bromide with the metalloenamine derived from **30**,[14] followed by imine hydrolysis to reveal the *alpha*-silyl ketone in **31**. Addition of vinylmagnesium chloride to the acylsilane **31** was followed by the Brook rearrangement−*in situ* alkylation sequence pioneered by Reich and Kuwajima,[15] for incorporation of the diepoxy-allylic bromide **29** to provide **12** bearing the silyloxy substituent at C15 and 29 of the 30 carbons required for the synthesis of abudinol B. The isomeric substrate **14** with a silyloxy substituent at C14 was prepared by reordering the steps in this protocol, so that initial alkylation of the metalloenamine derived from **30** with diepoxy-allylic bromide **29** afforded the acylsilane **32**, which was similarly subjected to vinylmagnesium bromide addition and Brook rearrangement−*in situ* alkylation with geranyl bromide to provide isomeric substrate **14**.

Synthesis of *ent*-Abudinol B from Diepoxy-enolsilane 12. For the first stage of biomimetic tricyclization (Scheme 3), we observed that 1.1 equiv of TMSOTf selectively activated the terminal epoxide of **12** and effectively promoted regio- and stereoselective tandem tricyclization to provide the *trans-anti-trans*-fused tricyclic ketone **33** as the major product, consistent with *anti*-parallel addition and an expected chairlike conformation **34**.[7b] To our surprise, substrate **12** was unreactive with TBSOTf, in contrast to previous observations with compound **15** (Scheme 1).[16] The best yield of **33** (50%, single diastereomer) was achieved when the reaction was quenched with 1.1 equiv of tetrabutylammonium fluoride at −78 °C within 10 min of TMSOTf addition, whereas longer reaction times or aqueous quench resulted in the generation of the C14-epimeric byproduct **37**, perhaps through silyloxonium ion intermediates **35** and **36**. Bicyclic ether **38** and monocyclic ether **39** were also isolated as minor products resulting from truncated cyclization and *beta*-hydrogen elimination, processes that have been well documented in polyene carbacyclizations.[17]

To explore the ultimate bicyclization of the hypothetical biogenesis of *ent*-abudinol B from the enantiomer of compound **7** (Figure 2), our synthetic compound **33** underwent methylenation of the C15-ketone to introduce the 30th carbon of the triterpenoid structure (Scheme 4). After evaluating a variety of reagents for this transformation,[18] we found that the classical Wittig reagent prepared *in situ* from a refluxing benzene solution of methyltriphenylphosphonium bromide (Ph_3PCH_3Br) and potassium *tert*-butoxide (KO-*t*-Bu)[9c] gave good yields of the disubstituted alkene product, albeit with some epimerization at C14 under the basic reaction conditions of the Wittig methylenation. Due to the steric hindrance of the C10-methyl substituent, olefination of **33** proceeded more slowly than with epimer **37**, so that a mixture of C14-epimers **40** and **41** was consistently produced, even when isomerically pure samples of ketone **33** were used. However, diastereomers **40** and **41** were separable by careful silica gel chromatography. Regio- and stereoselective double epoxidations of each triene **40** and **41** provided the corresponding diepoxides *ent*-**7α** and *ent*-**7*β***, by careful control of the reaction temperature, concentration, amount of D-epoxone, and reaction time. To the best of our knowledge, this was the first example of epoxone-catalyzed regioselective epoxidation of trisubstituted alkenes in the presence of a *gem*-disubstituted alkene.

At the outset of this study, we were concerned that only one of the diastereomers of *ent*-**7α/*β*** would have the proper

(14) (a) Nowick, J. S.; Danheiser, R. L. *Tetrahedron* **1988**, *44*, 4113. (b) Corey, E. J.; Lin, S. *J. Am. Chem. Soc.* **1996**, *118*, 8765.

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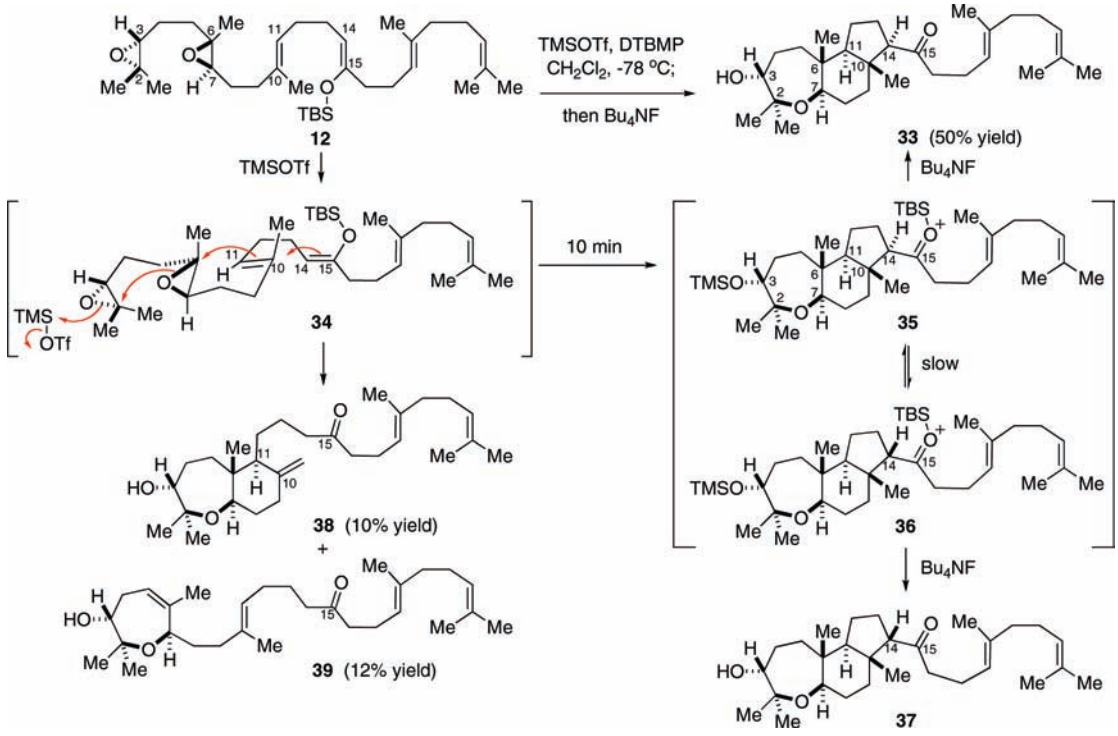
(16) Other Lewis acids, including BF_3-OEt_2, $MeAlCl_2$, and TBSCl/$AgClO_4$, resulted in lower yields of products or no reaction.

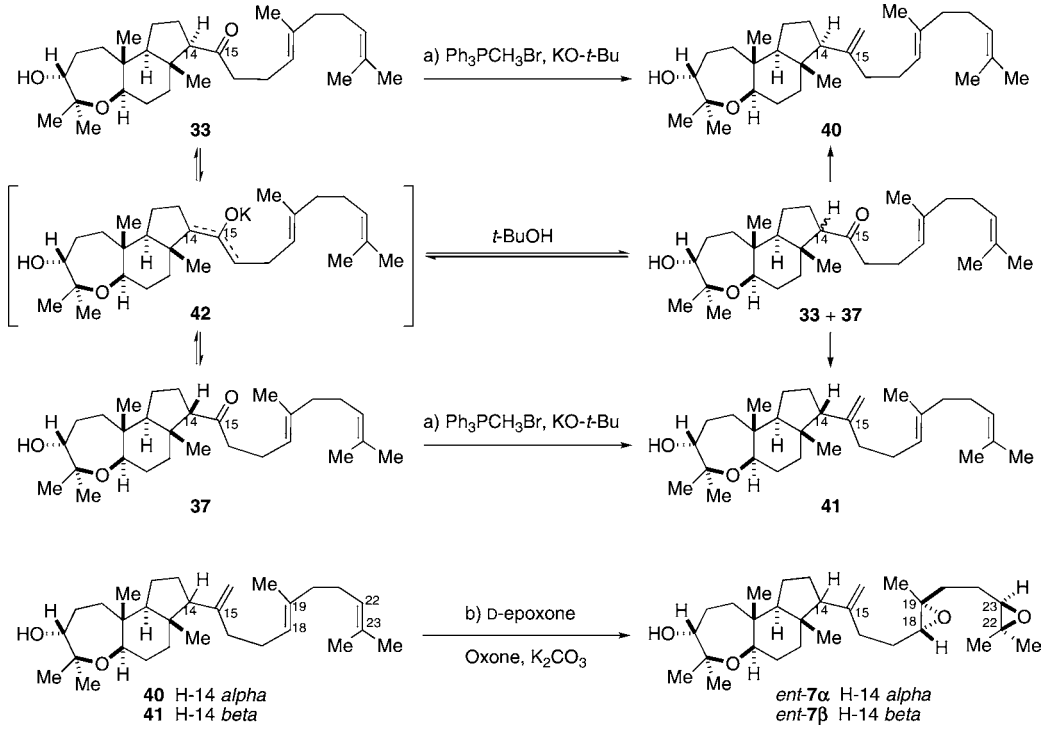
(17) For selected papers, see: (a) Stork, G.; Burgstahler, A. W. *J. Am. Chem. Soc.* **1955**, *77*, 5068. (b) Eschenmoser, A.; Ruzicka, L.; Jeger, O.; Arigoni, D. *Helv. Chim. Acta* **1955**, *38*, 1890. (c) Gamboni, G.; Schinz, H.; Eschenmoser, A. *Helv. Chim. Acta* **1954**, *37*, 964. (d) van Tamelen, E. E.; Leiden, T. M. *J. Am. Chem. Soc.* **1982**, *104*, 2061. (e) Ishihara, K.; Ishibashi, H.; Yamamoto, H. *J. Am. Chem. Soc.* **2001**, *123*, 1505. (f) Ishihara, K.; Ishibashi, H.; Yamamoto, H. *J. Am. Chem. Soc.* **2002**, *124*, 3647.

(18) Other methylenation reagents attempted included the Tebbe reagent, Petasis reagent, and Julia tetrazole sulfone under various conditions.

Scheme 3. First-Stage Tricyclization of Diepoxy-enolsilane **12**



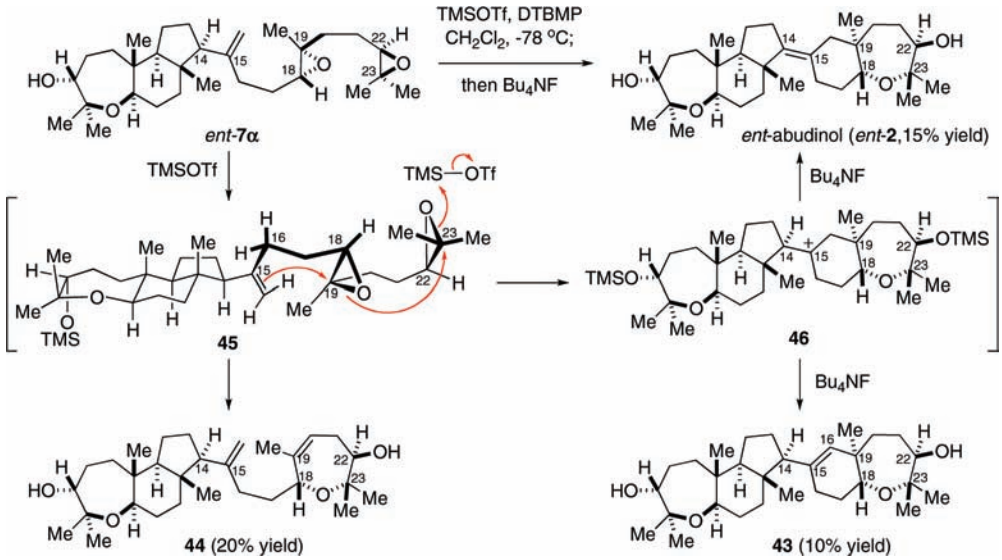
Scheme 4. Preparation of Diepoxyalkene Substrates *ent*-**7α** and *ent*-**7β**[a]



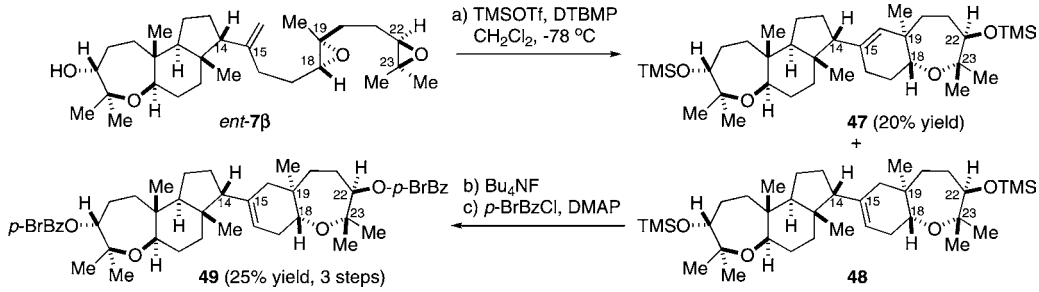
[a] Reagents and conditions: (a) Ph_3PCH_3Br, KO-*t*-Bu, benzene, 80 °C (82% yield; from **33**, ratio **40**/**41** = 1:1.8; from **37**, ratio **40**/**41** = 1:2.5); (b) D-epoxone (0.5 equiv), Oxone (2.9 equiv), K_2CO_3 (11 equiv), Bu_4NHSO_4 (0.1 equiv), Na_2EDTA, $Na_2B_4O_7$, DMM/MeCN (2:1), H_2O, 0 °C (37% yield; 50% combined yield after a second cycle with 0.5 equiv of reagents).

geometry for the formation of abudinol B, and thus the epimerization of the C14 chiral center in the Wittig reaction of ketone **33** was not entirely unwelcome. TMSOTf-promoted reaction of *ent*-**7α** did provide *ent*-abudinol B (*ent*-**2**, Scheme 5), albeit in modest yield, and was accompanied by several byproducts including the trisubstituted alkene isomer **43** as well as the truncated monocyclization structure **44**. The spectroscopic properties of our synthetic product *ent*-**2** matched the reported literature data as well as direct comparison with another sample of *ent*-abudinol B generated in our first generation synthesis, which was confirmed by X-ray crystallography of the bis-silyl ether of *ent*-abudinol B.[7a] The byproduct **44** presumably resulted

Scheme 5. Bicyclization of *ent*-**7α** to *ent*-Abudinol B (*ent*-**2**)



Scheme 6. Bicyclization of *ent*-**7β**[a]



[a] Reagents and conditions: (a) TMSOTf (1.5 equiv), DTBMP (1.5 equiv), CH_2Cl_2, −78 °C; (b) Bu_4NF, THF; (c) *p*-BrBzCl, DMAP, CH_2Cl_2.

from *beta*-hydrogen elimination from the C15-methyl substituent after diepoxide cyclization. The mechanism for the tandem bicyclization process to *ent*-**1** and the trisubstituted alkene isomer **43** is consistent with the intermediacy of a C15 carbenium ion **46** or ion pair, perhaps due to the relatively poor nucleophilicity of the *gem*-disubstituted C15-alkene of *ent*-**7α**.

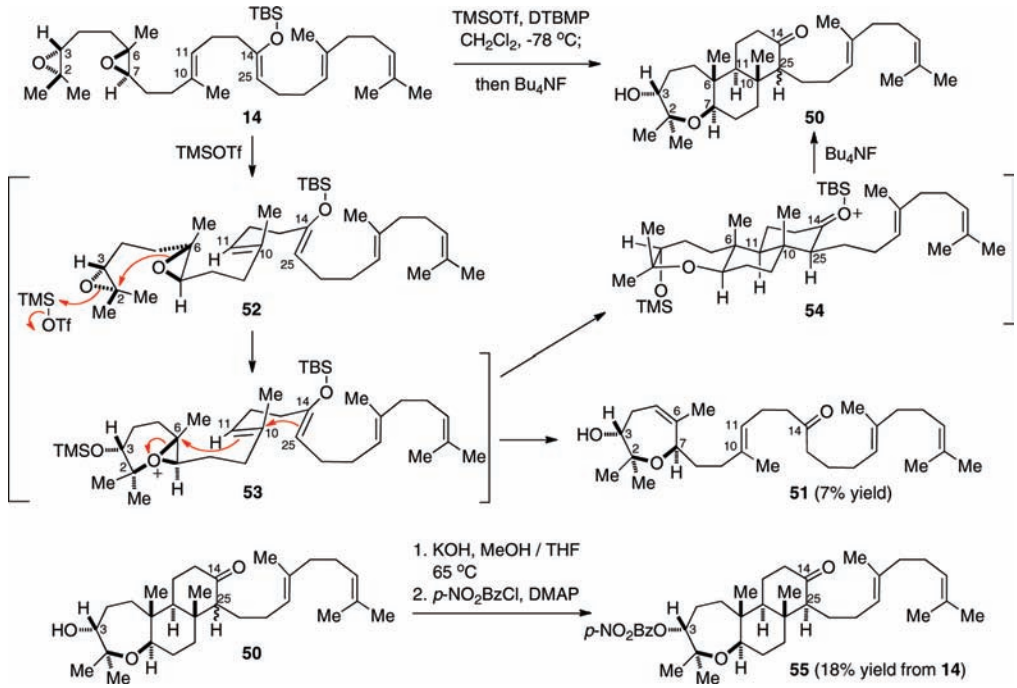
Interestingly, TMSOTf-promoted bicyclization of the C14-diastereomer *ent*-**7*β*** provided a mixture of trisubstituted alkenes **47** and **48** (Scheme 6), but no trace of *ent*-abudinol B or the corresponding *Z*-tetrasubstituted alkene isomer of abudinol B was found in the crude reaction mixture or in any of the isolated byproducts. The structure of **48** was unambiguously confirmed by X-ray crystallography of the bis-*p*-bromobenzoate derivative **49**, which also clarified the structural assignments for the key precursor compounds **40**, **41**, and *ent*-**7α/*β*** and provided a lead structure for confidently assigning the structures of analogous compounds such as **43** and **47**.

The dependence of the regioselectivity of alkene formation on C14 stereochemistry was unexpected, especially since examination of models had suggested that the C14−H14 bond was better aligned with the C18−O bond of epoxide *ent*-**7*β*** vs the diastereomer *ent*-**7α**. Moreover, if a C15-tertiary carbenium ion **49** was indeed an advanced mechanistic intermediate, one would have expected that some of the product distribution would have included the tetrasubstituted alkene of abudinol B arising from both substrate diastereomers *ent*-**7α/*β***. Nonetheless, the successful bicyclization of *ent*-**7α** to *ent*-abudinol B has provided the first chemical evidence for the viability of the biosynthetic pathway proposed for abudinol B (**2**) from precursor compound **7**.

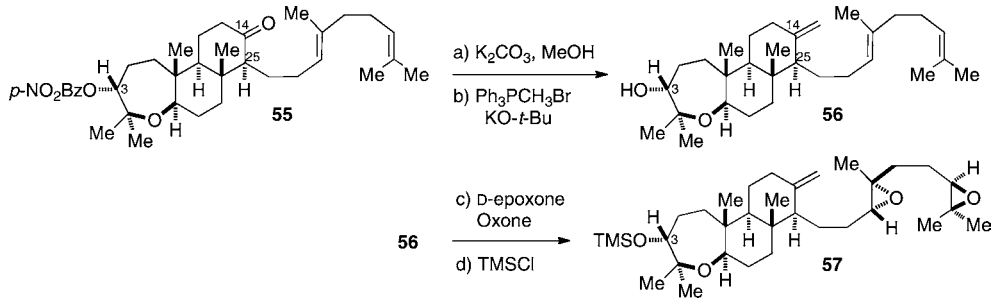
Synthesis of the Structure Proposed for *ent*-Muzitone from Diepoxy-enolsilane 14. We subsequently explored the analogous tandem cyclizations beginning with the regioisomeric substrate **14** bearing the silyloxy substituent on C14, thus making C25 (muzitone numbering) the more nucleophilic terminus of the diepoxide substrate. We perceived that this all-*endo*-regioselective cyclization would be more challenging, due to formation of a six-membered ring by closure of the C10−C25 bond, but would be a critical component of a synthesis of the tetrasubstituted alkene precursor to muzitone. The first-stage tricyclization of **14** was initiated with TMSOTf in the presence of DTBMP at −78 °C (Scheme 7). This transformation was somewhat slower than the corresponding transformation of **12**, as expected for six-membered ring formation, but the desired product **50** was formed as an inseparable 1:1 mixture of C25 diastereomers, along with the monocyclization byproduct **51**.[19] Although it was not certain if this diastereomeric mixture resulted from nonstereoselective formation of intermediate **54** or occurred in the course of the slow conversion of possible bicyclic epoxonium ion **53** to tricyclic **54**, we could convert the mixture of C25 diastereomers by reaction with KOH in refluxing methanol[20] to provide a single C25 stereoisomer of

(19) A bicyclic compound bearing *exo*-methylene at C10 was also observed as a minor byproduct. However, this byproduct could not be purified and thus was not unambiguously characterized.

Scheme 7. Tricyclization of Diepoxy-enolsilane **14**



Scheme 8. Preparation of Diepoxyalkene **57**[a]



[a] Reagents and conditions: (a) K_2CO_3, MeOH/THF (4:1), (89% yield); (b) Ph_3PCH_3Br, KO-*t*-Bu, THF, benzene, 70 °C (81% yield); (c) D-Epoxone (0.5 equiv), Oxone (2.6 equiv), K_2CO_3 (8 equiv), Bu_4NHSO_4 (0.1 equiv), $Na_2B_4O_7$, DMM/MeCN (2:1), H_2O, −5 °C (four cycles total); (d) TMSCl (2 equiv), imidazole (4 equiv), CH_2Cl_2 (39% yield from **56**).

50, which was fully purified and characterized as the *p*-nitrobenzoate ester **55**.

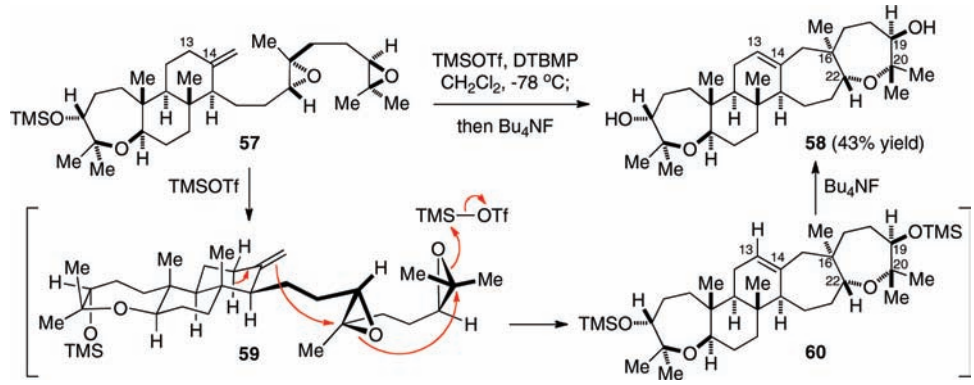
After saponification of the ester from compound **55**, installation of the 30th carbon was accomplished by Wittig reaction as described in our abudinol B synthesis, to provide triene **56** in good yield (Scheme 8). However, the regio- and enantioselective epoxidation of triene **56** was a considerable challenge and required careful monitoring by TLC to minimize overoxidation of the *gem*-disubstituted alkene at C14. The epoxidation reaction was stopped upon evidence of significant triepoxide formation, and after isolation of the triene, monoepoxide, and desired diepoxide via silica gel chromatography, the recovered monoepoxide was resubjected to the Shi epoxidation conditions following the same procedure, but modifying the stoichiometry of K_2CO_3 and Oxone. Ultimately, this required four cycles of the Shi epoxidation. Although this process was cumbersome, the desired diepoxide **57** was cleanly obtained upon protection of the alcohol as the trimethylsilyl ether derivative.

The second-stage bicyclization was conducted on diepoxyalkene **57**, to provide pentacyclic structure **58** (Scheme 9). Even though the placement of the alkene relative to the proximal epoxide required the formation of two seven-membered rings, this transformation proceeded in relatively high yield, especially when compared to our results in the abudinol synthesis. Surprisingly, we found no trace of products corresponding to the desired C14−C15 tetrasubstituted alkene ("*ent*-pre-muzitone", *ent*-**11**, Figures 2, 3), nor could we modify the reaction conditions to provide this regioisomer, such as changes of temperature (i.e., −40 °C) or reactant stoichiometry (i.e., equivalents of DTBMP). As we anticipated that a C14 carbocationic intermediate would have given at worst a mixture of alkene products including the desired tetrasubstituted isomer, we suspected that the formation of trisubstituted alkene **58** was the result of a concerted cyclization process, at least with regard to formation of the C14−C19 bond and the C13−C14 alkene.

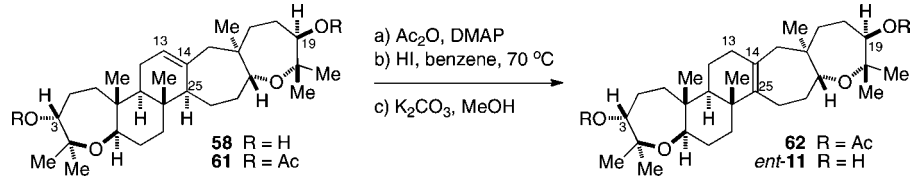
Thus, we focused on the isomerization of the trisubstituted alkene of **58** to generate the desired alkene regioisomer. As we anticipated that the alcohol and tertiary-substituted oxepane functional groups would be sensitive to the strongly acidic conditions for alkene migration, we protected the alcohols as the diacetate **61** (Scheme 10), with the expectation that the electron-withdrawing esters would inductively deactivate the

(20) Zhang, J.; Corey, E. J. *Org. Lett.* **2001**, *3*, 3215.

Scheme 9. Bicyclization of Diepoxyalkene **57**



Scheme 10. Isomerization of Trisubstituted Alkene **61** to Tetrasubstituted Alkene **62**[a]



[a] Reagents and conditions: (a) Ac_2O, DMAP, CH_2Cl_2 (91% yield); (b) HI, benzene, 70 °C, 1 h (95% yield); (c) K_2CO_3, MeOH, rt to reflux (100% yield).

nearby oxepanes from protonation. Compound **61** was also crystalline, which allowed for crystallographic confirmation of the bond connectivity and stereochemistry achieved in the previous cyclization steps. Reaction of diacetate **61** with catalytic HI in hot benzene[21] resulted in the predominant formation of the tetrasubstituted alkene isomer **62** (**62**:**61** = 20:1), and basic methanolysis of the acetate esters afforded the enantiomer of "pre-muzitone" (*ent*-**11**). With the spectra of *ent*-**11** in hand, we firmly demonstrated that this isomer was *not* produced in detectable quantities in the course of the bicyclization of diepoxyalkene **57**. The structure of *ent*-**11** was also confirmed by crystallography.

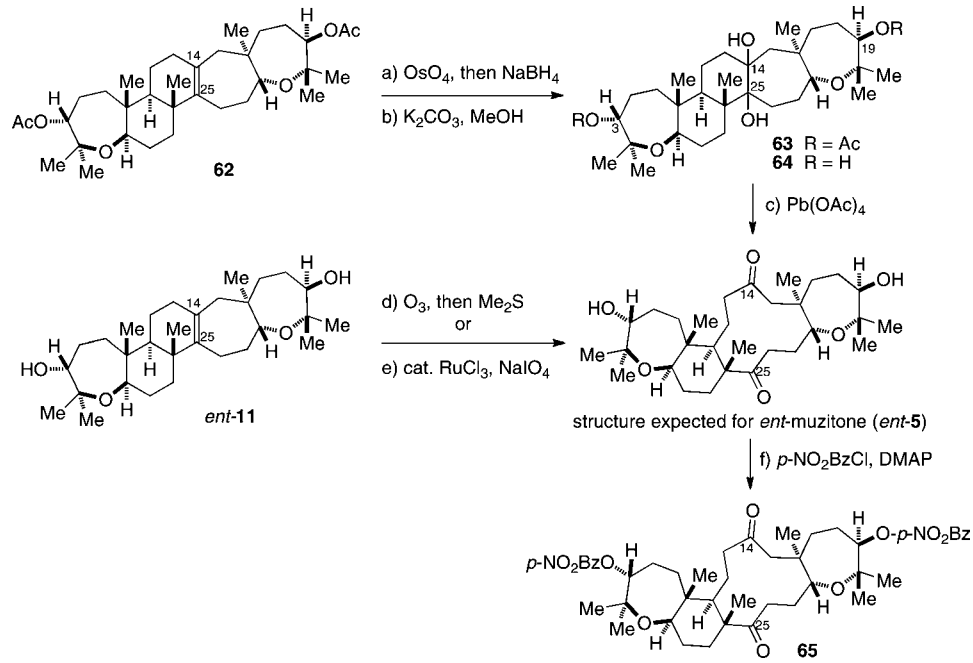
The synthesis then concluded with oxidative cleavage of the tetrasubstituted alkene of *ent*-**11**. Preliminary experiments indicated that the diketone arising from oxidative cleavage of diacetate ester **62** was susceptible to transannular aldol reaction[22] under the basic conditions required for acetate removal, and thus we recognized that C14−C25 bond cleavage to the diketone would be the final step of our synthesis. Several different approaches from diol **63** afforded the desired diketone *ent*-**5**, albeit in low yields, including ozonolysis with reductive workup, as well as the Johnson−Lemieux method for ruthenium-catalyzed oxidative cleavage (Scheme 11).[23] Ultimately, the best yields were obtained by conducting the oxidative cleavage process stepwise, beginning with initial osmylation of the tetrasubstituted alkene of diacetate **62**. This alkene reacted sluggishly with osmium tetraoxide, and regardless of the additives used (*N*-methylmorpholine-*N*-oxide or methanesulfonamide), this transformation required an excess of osmium tetraoxide. Furthermore, the cyclic osmate ester was stable to typical reduction reagents such as sodium bisulfite or sodium thiosulfate and was subjected to silica gel chromatography without degradation. However, the crude osmate ester from **62** was rapidly reduced with sodium borohydride in methanol,[24] thus liberating the diacetate diol **63**, which was deacetylated to the corresponding tetraol **64** by basic methanolysis. Although the oxidative cleavage of tetraol **64** with sodium periodate was extremely sluggish (only a trace of *ent*-**5** was produced after 48 h), lead tetraacetate promoted the rapid and clean oxidative cleavage of **64** to afford diketone *ent*-**5**, which matched the material obtained by ozone-promoted or ruthenium-catalyzed oxidative cleavages of *ent*-**11**.

Unfortunately, we observed some discrepancies in our characterization data for *ent*-**5** when compared to those reported for muzitone by the Kashman laboratory. Most obvious among these differences was the report that the natural product was an oil, whereas our synthetic material was a white crystalline solid with a melting point of 210−213 °C. There were also differences in the chemical shifts and coupling constants for some of the ^{1}H NMR resonances. After some effort, we were able to solve the crystal structure for the derived bis-*p*-nitrobenzoate derivative **65**, confirming that we had indeed prepared the intended structure *ent*-**5**, corresponding to the enantiomer of the structure proposed for muzitone. Thus the Kashman laboratory's assignment for muzitone was incorrect.

Upon further consideration of key characterization details, we focused on the discrepancies in the ^{1}H NMR data. Specifically, the four most deshielded hydrogens were the obvious choice for comparisons. In particular, we were intrigued by the coupling constant values of the hydrogen assigned at C19 for the synthetic and natural materials. Our synthetic material showed a chemical shift for the C19 hydrogen at 4.24 ppm (600 MHz, C_6D_6) and was a doublet of doublets with coupling constants of 2.4 and 6.0 Hz; for instructive comparison, the shift of this hydrogen in the pentacyclic precursor alkene *ent*-**11** was 3.49 ppm (400 MHz, $CDCl_3$) with coupling constants of 5.2 and 11.6 Hz. In contrast, the Kashman laboratory reported a chemical shift of 3.88 ppm (500 MHz, C_6D_6) and coupling

(21) Marcos, I. S.; Pedrero, A. B.; Sexmero, M. J.; Diez, D.; García, N.; Escola, M. A.; Basabe, P.; Conde, A.; Moro, R. F.; Urones, J. G. *Synthesis* **2005**, 3301.
(22) Herr, M. E.; Fonken, G. S. *J. Org. Chem.* **1967**, *32*, 4065.
(23) Pappo, R.; Allen, D. S.; Lemieux, R. U.; Johnson, W. S. *J. Org. Chem.* **1956**, *21*, 478.
(24) Herranz, E.; Sharpless, K. B. *Org. Synth., Coll. Vol. VII* **1990**, 375.

Scheme 11. Completion of the Synthesis of the Structure *ent*-**5** Assigned to *ent*-Muzitone[a]



[a] Reagents and conditions: (a) OsO_4 (2 equiv), THF/H_2O (3:1), then $NaBH_4$, MeOH (64% yield of **63** + 15% recovered **62**); (b) K_2CO_3, MeOH/THF (2.5:1), reflux (100% yield); (c) $Pb(OAc)_4$, benzene (71% yield); (d) O_3, CH_2Cl_2, −78 °C; then Me_2S (21% yield); (e) $RuCl_3$ (2 mol %), $NaIO_4$, CCl_4/MeCN/H_2O (2:2:3), 15 min (24% yield); (f) *p*-NO_2BzCl, DMAP, CH_2Cl_2 (83% yield).

constants of 5.3 and 11.3 Hz. Considering the conformational freedom achieved upon oxidative cleavage of the tetrasubstituted alkene, our data were more consistent with the expected conformational change, whereas Kashman's coupling constant data were more consistent with a rigid system, such as *ent*-**11**. Nonetheless, the Kashman laboratory clearly isolated a diketone, as they reported δ 218.0, 207.0 in C_6D_6 (we observed δ 216.3, 211.6 in C_6D_6 for compound *ent*-**5**). As an authentic sample of muzitone is no longer available, it is not possible to determine the correct structure at this time.

Conclusion

In the course of achieving the total synthesis of the enantiomer of the natural product abudinol B, we have demonstrated the chemical viability of a proposed biogenetic pathway for this structurally complex triterpenoid natural product, particularly the final bicyclization stage which exactly matches the structural elements that would be present in a natural product intermediate. Unfortunately, our efforts to extend this concept to prepare a hypothetical biosynthetic intermediate to muzitone have revealed that the structure of muzitone has been misassigned, and thus it is pointless to comment further on the biogenesis of muzitone until its structure has been correctly determined. Nonetheless, the synthetic approach has demonstrated that six- and even seven-membered carbocyclic rings can be generated by tandem bicyclizations of the appropriate substrates, thus providing an important expansion of the types of structures that can be prepared.

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Supporting Information Available: Experimental details and characterization of new compounds, including ^1H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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