ORGANIC LETTERS

2013
Vol. 15, No. 9
2198–2201

Synthesis of the Proposed Structures of Prevezol C

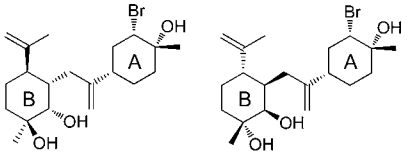
Anna E. Leung, Michael Blair, Craig M. Forsyth, and Kellie L. Tuck*

School of Chemistry, Monash University, Clayton, Vic. 3800, Australia

Kellie.Tuck@monash.edu

Received March 20, 2013

ABSTRACT

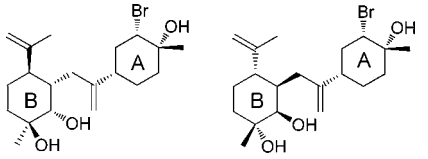


Prevezol C **1** Prevezol C **2**

The first enantioselective synthesis of the proposed relative structures of Prevezol C is reported in 11 linear steps from readily available materials. The unusual *syn* bromohydrin was installed via a multistep sequence culminating in a diastereoselective geminal dibromide reduction. Discrepancies in the spectral data of the synthetic materials and the natural sample have led to the conclusion that the proposed structures are incorrect.

Almost a decade ago, the family of novel diterpenes known as the prevezols was isolated from the organic extracts of the red alga *Laurencia obtusa*, found on the coastal rocks of Preveza in the Ionean Sea, Greece.[1,2] Five prevezols were discovered (Prevezols A−E),[1,2] and their structures were elucidated using spectral data analysis and molecular modeling studies.[1,2] The carbon skeletons of these natural products were unprecedented in the literature. All of the prevezols feature an unusual *syn* bromohydrin motif, which piqued our interest and prompted us to select Prevezol C as a synthetic target. Roussis and coworkers were unable to assign the relative stereochemistry of Prevezol C due to a lack of observed NOE correlations between the two rings (rings A and B);[2] consequently, two diastereomers and their enantiomers were proposed for the natural product (compounds **1** and **2**, Figure 1).[2]

Despite the advances in spectroscopic strategies for the structural elucidation of natural products, total synthesis is often required in order to unambiguously determine the absolute structures. Several excellent reviews of the misassignment of natural products have been published in recent years.[3−5] For several years, our group has been exploring the total synthesis of Prevezol C in the hope of unambiguously determining the absolute structure of the natural product. To the best of our knowledge none of the prevezols have been synthesized.



Prevezol C **1** Prevezol C **2**

Figure 1. Proposed structures of Prevezol C (**1** and **2**).

Herein, we report the first total asymmetric synthesis of both of the proposed diastereomers of Prevezol C (compounds **1** and **2**). This convergent synthesis utilizes a novel strategy for incorporation of the challenging *syn* bromohydrin motif, which may be exploited to facilitate the synthesis of other compounds which possess *syn* orientated bromohydrins.

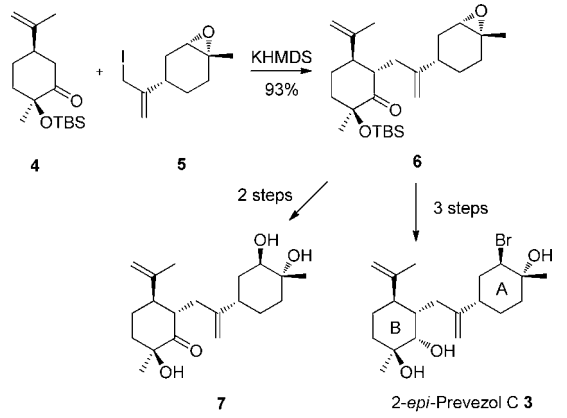
Previous work within our group has culminated in the enantioselective synthesis of 2-*epi*-Prevezol C **3**, an *anti* bromohydrin (Scheme 1).[6] Comparison of the ^{13}C NMR

(1) Mihopoulos, N.; Vagias, C.; Mikros, E.; Scoullos, M.; Roussis, V. *Tetrahedron Lett*. **2001**, *42*, 3749–3752.
(2) Iliopoulou, D.; Mihopoulos, N.; Vagias, C.; Papazafiri, P.; Roussis, V. *J. Org. Chem*. **2003**, *68*, 7667–7674.
(3) Nicolaou, K. C.; Snyder, S. A. *Angew. Chem., Int. Ed*. **2005**, *44*, 1012–1044.
(4) Maier, M. E. *Nat. Prod. Rep*. **2009**, *26*, 1105–1124.
(5) Amagata, T. 2.18 - Misassigned Structures: Case Examples from the Past Decade. In *Comprehensive Natural Products II*; (Eds.-in-Chief) Lew, M., Hung-Wen, L., Eds.; Elsevier: Oxford, 2010; pp 581−621.

10.1021/ol400754e
Published on Web 04/22/2013

spectra of 2-*epi*-Prevezol C and the natural product showed excellent correlation between the B rings. Unfortunately all attempts to form the *syn* bromohydrin from the triol **7** were unsuccessful.[6]

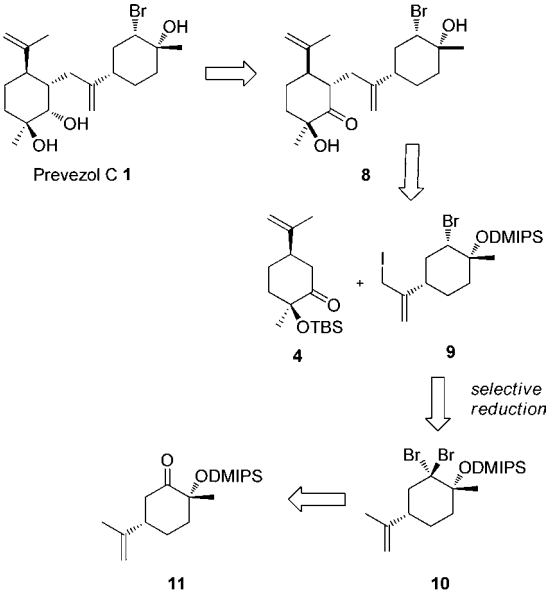
Scheme 1. Diastereoselective Alkyation in the Synthesis of 2-*epi*-Prevezol C **3**, and the Triol **7**[6]



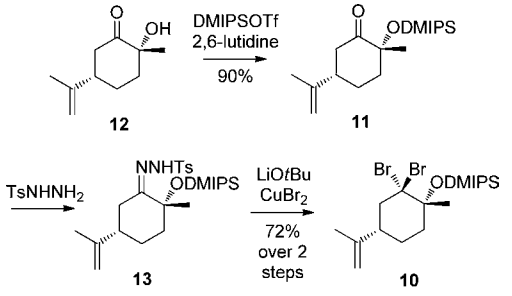
We envisioned that the natural product **1** could be accessed via a stereoselective reduction of the diterpene **8**, which might be obtained via a substrate-controlled, diastereoselective alkylation reaction between ketone **4** and allylic iodide **9** (Scheme 2), using similar conditions to those established for 2-*epi*-Prevezol C **3**.[6] We then turned our attention to establishing methodology for the synthesis of *syn* bromohydrins with quaternary oxygenated centers.[7] It was anticipated that the crucial *syn* bromohydrin motif could be installed prior to the alkylation reaction, via a diastereoselective hydrodebromination of the geminal dibromide **10** which might be accessed from ketone **11** (Scheme 2).

The hydroxyl ketone **12** was synthesized in two steps from (−)-limonene oxide, following published procedures for the corresponding enantiomer.[8] After several protecting groups for the tertiary alcohol were investigated, the dimethylisopropylsilyl ether was selected since it was both tolerant of the reaction sequence and easily removed.[9] Protection of hydroxyl ketone **12** with dimethylisopropylsilyl trifluoromethanesulfonate and 2,6-lutidine in DCM at −78 °C provided the required DMIPS ketone **11** (Scheme 3). Formation of the required *gem*-dibromide was inspired by the work of Takeda and co-workers on the synthesis of *gem*-dihalides from ketones or aldehydes, via the corresponding hydrazones, using LiO*t*Bu/$CuBr_2$.[10] Takeda's two-step procedure was modified to provide the *gem*-dibromide **10**:[10] DMIPS ether **11** was treated with *para*-toluenesulfonylhydrazide in methanol to afford the corresponding tosyl hydrazone **13**, from which *gem*-dibromide **10** was readily accessed (Scheme 3).

Scheme 2. Retrosynthesis of Prevezol C **1**



Scheme 3. Synthesis of *gem*-Dibromide **10**



The dehalogenation of *gem*-dihalocyclopropanes has been well documented in the literature,[11] and various reagents have been reported for this purpose. However,

(6) Blair, M.; Forsyth, C. M.; Tuck, K. L. *Tetrahedron Lett.* **2010**, *51*, 4808–4811.

(7) Secondary *syn* bromohydrins have been synthesized by Stoltz and co-workers and Dubois and co-workers; see: (a) White, D. E.; Stewart, I. C.; Grubbs, R. H.; Stoltz, B. M. *J. Am. Chem. Soc.* **2007**, *130*, 810–811. (b) Deka, V.; Dubois, J.; Thoret, S.; Guéritte, F.; Guénard, D. *Org. Lett.* **2003**, *5*, 5031–5034. In both cases a mixture of the *syn* and *anti* bromohydrins were obtained by the reduction of a bromoketone precursor. Tertiary bromohydrins have been synthesized by Williams and co-workers in the synthesis of alkaloid intermediates; see: (c) Williams, C. M.; Mander, L. N.; Bernhardt, P. V.; Willis, A. C. *Tetrahedron* **2005**, *61*, 3759–3769. The addition of a deprotonated arylacetylene to a brominated ketone gave the desired *syn* diastereomer as the major product.

(8) (a) Blair, M.; Tuck, K. L. *Tetrahedron: Asymmetry* **2009**, *20*, 2149–2153. (b) Royals, E. E.; Leffingwell, J. C. *J. Org. Chem.* **1966**, *31*, 1937–1944. (c) Blair, M.; Andrews, P. C.; Fraser, B. H.; Forsyth, C. M.; Junk, P. C.; Massi, M.; Tuck, K. L. *Synthesis* **2007**, *10*, 1523–1527.

(9) Attempts to perform the subsequent synthetic steps without first protecting the tertiary alcohol were unsuccessful. Several alternative protecting groups were investigated: they were either too labile under the reaction conditions used or unable to be removed when required.

(10) Takeda, T.; Sasaki, R.; Yamauchi, S.; Fujiwara, T. *Tetrahedron* **1997**, *53*, 557–566.

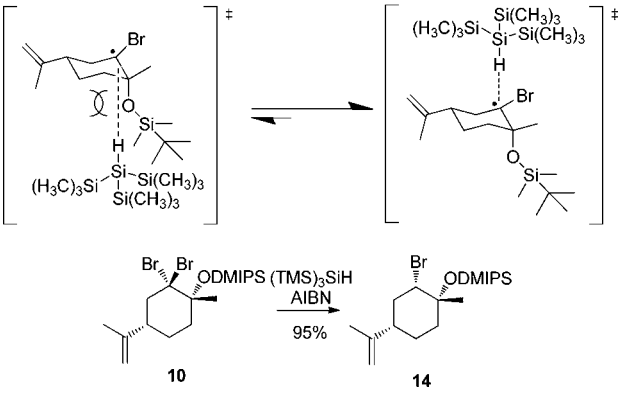
(11) For a general review on the use of *gem*-dihalocyclopropanes in organic synthesis, see: Fedoryński, M. *Chem. Rev.* **2003**, *103*, 1099–1132.

using published procedures, a mixture of stereoisomers is obtained. Furthermore, to the best of our knowledge there are no reports of chemistry of this kind concerning larger cyclic systems. A diethyl phosphite–triethylamine system has been reported by Ohshiro and co-workers to result only in partial dehalogenation of *gem*-dibromocyclopropanes, providing the monobromocyclopropane selectively.[12] We applied these conditions to a TBS protected analogue of the *gem*-dibromide **10**, but no reaction was observed.[9] Oshima and co-workers report the monodehalogenation of *gem*-dibromocyclopropanes with a tributyltin hydride/triethyl borane system,[13] but the toxicity of tributyltin hydride prompted us to investigate the use of tris-(trimethylsilyl)silane, $(TMS)_3SiH$, as an alternative reducing agent. While the reduction of monobromides using $(TMS)_3SiH$ is well documented by Chatgilialoglu and co-workers,[14] use of this reagent for the diastereoselective monoreduction of *gem*-bromides has not been reported.

We rationalized that a system such as this, applied to the monodehalogenation of *gem*-dibromide **10**, might afford the desired diastereoselectivity as follows: the carbon-centered radical formed by abstraction of bromide by the silyl radical equilibrates faster than hydride is delivered, and the less hindered approach of the bulky $(TMS)_3SiH$ is *anti* to the bulky DMIPS ether to provide the *syn* isomer selectively (Scheme 4). Pleasingly, reduction of the *gem*-dibromide **10** with 1.05 equiv of $(TMS)_3SiH$ in refluxing benzene, with AIBN as a radical initiator, afforded a single diastereomer exclusively (Scheme 4).[15] The configuration of the brominated center was assigned via analysis of the bromomethine proton resonance in the ^1H NMR spectrum, which appears as a doublet of doublets with coupling constants of 12.4 and 4.0 Hz, indicative of axial–axial and axial–equatorial coupling (see Supporting Information (SI)). The stereochemistry was later confirmed by X-ray crystallography (Scheme 5).

In preparation for the key alkylation reaction, the *syn* bromohydrin **14** was subjected to an allylic chlorination reaction employing modified Massanet conditions;[16] a subsequent Finkelstein reaction using sodium iodide in dry acetone provided the required allylic iodide **9**, which was typically used directly in the subsequent alkylation reaction due to its instability (Scheme 5). TBS ketone **4** (see SI) was treated with freshly prepared KHMDS and then allylic iodide **9** to afford the requisite diterpene core **16** (which was inseparable from any unreacted ketone **4**) in modest yields, but as a single diastereomer. The newly formed asymmetric center was assigned via analysis of the α-methine resonance in the ^1H NMR spectrum, the coupling constants of which were consistent with an axially positioned proton. The observed diastereoselectivity was justified by proposed 1,3-diaxial interactions between the sterically demanding TBS ether and the incoming electrophile. Attempts to promote the complete consumption of the TBS ketone **4**, using an excess of allylic iodide **9** and/or KHMDS, gave rise to complicated mixtures of products, and so the diterpene **16** was typically isolated with the ketone **4** impurity. Fortunately, after global deprotection of the silyl ethers with an excess of TBAF, the diterpene diol **8** was easily separated from any impurities (Scheme 5). The diterpene diol **8** was then treated with sodium borohydride in a THF/methanol mixture to provide the 2*S*,3*R*,6*S*,9*S*,10*R*,13*S*,14*S* diastereomer[17] **1** of the proposed structure of Prevezol C exclusively. The stereochemistry of the newly formed asymmetric center was assigned as *S*, based on analysis of the coupling constants of the hydroxymethine resonance, and was later confirmed by X-ray crystallography (Scheme 5). The observed diastereoselectivity was postulated to arise from coordination of sodium borohydride to the α-hydroxyl group, encouraging hydride delivery *syn* to this moiety.

Scheme 4. Diastereoselective Monodehalogenation of *gem*-Dibromide **10** to *syn* Bromohydrin **14**



The ^1H and ^{13}C NMR spectra of diterpene **1** were markedly different from the data for the natural product (see SI). We thus concluded that the natural product must have an alternative structure and turned our attention to the synthesis of the other proposed diastereomer, Prevezol C **2**. Employing the previously established alkylation conditions, and the enantiomer of ketone **4**, ketone **17** (see SI), the requisite diterpene core **18** was prepared diastereoselectively, though this material was inseparable from any unreacted ketone **17** (Scheme 6). Global deprotection of the silyl ethers using TBAF, followed by diastereoselective

(12) Hirao, T.; Masunaga, T.; Ohshiro, Y.; Agawa, T. *J. Org. Chem.* **1981**, *46*, 3745–3747.

(13) Miura, K.; Ichinose, Y.; Nozaki, K.; Fugami, K.; Oshima, K.; Utimoto, K. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 143–147.

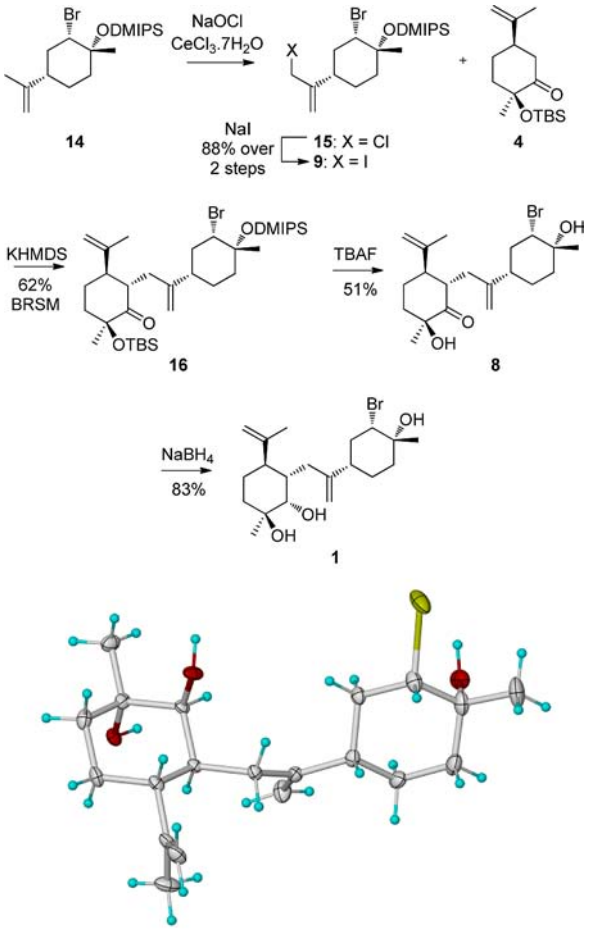
(14) (a) Ballestri, M.; Chatgilialoglu, C.; Clark, K. B.; Griller, D.; Giese, B.; Kopping, B. *J. Org. Chem.* **1991**, *56*, 678–683. (b) Chatgilialoglu, C. *Chem.—Eur. J.* **2008**, *14*, 2310–2320. (c) Chatgilialoglu, C.; Lalevée, J. *Molecules* **2012**, *17*, 527–555. (d) Chatgilialoglu, C.; Ferreri, C.; Gimisis, T. Tris(trimethylsilyl)silane in Organic Synthesis. In *The Chemistry of Organic Silicon Compounds*; John Wiley & Sons, Ltd: 2003; pp 1539–1579.

(15) This reaction must be carefully followed by ^1H NMR spectroscopy: if excess $(TMS)_3SiH$ is used, the over-reduced species is obtained. The *anti* bromohydrin was not observed in the ^1H NMR spectra of the crude or purified product.

(16) Moreno-Dorado, F. J.; Guerra, F. M.; Manzano, F. L.; Aladro, F. J.; Jorge, Z. D.; Massanet, G. M. *Tetrahedron Lett.* **2003**, *44*, 6691–6693.

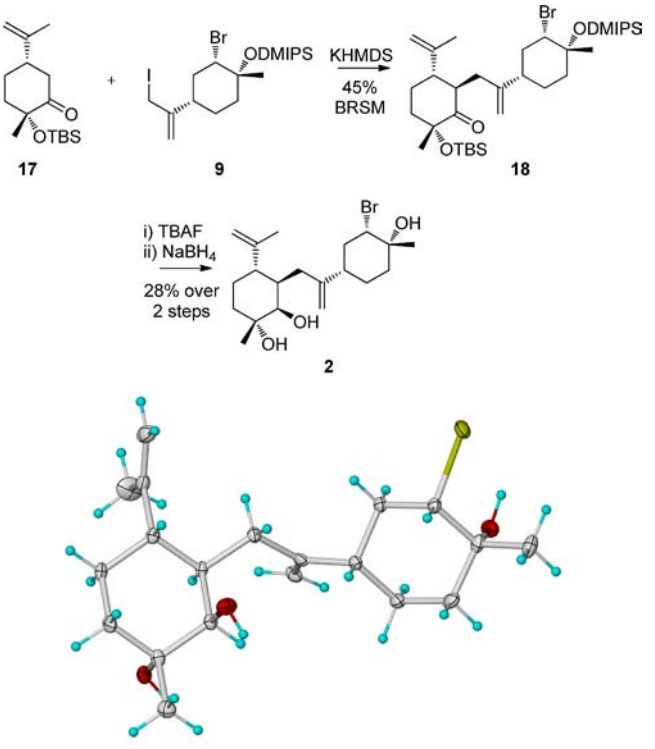
(17) Numbered in accordance with Roussis and co-workers; see: Iliopoulou, D.; Mihopoulos, N.; Vagias, C.; Papazafiri, P.; Roussis, V. *J. Org. Chem.* **2003**, *68*, 7667–7674.

Scheme 5. Diastereoselective Alkylation and Subsequent Transformations To Form Prevezol C **1**



X-ray structure of Prevezol C **1**

Scheme 6. Diastereoselective Alkylation and Subsequent Transformations To Form Prevezol C **2**



X-ray structure of Prevezol C **2**

reduction of the ketone using sodium borohydride, provided the 2*S*,3*R*,6*S*,9*R*,10*S*,13*R*,14*R* diastereomer[17] **2** of the proposed structure of Prevezol C (Scheme 6). The absolute structure of **2** was confirmed by X-ray crystallography (Scheme 6). The ^{1}H and ^{13}C NMR spectra of diterpene **2** were also markedly different from the data for the natural product (see SI). Having confirmed the absolute structures of **1** and **2** via X-ray crystallography, these NMR deviations call into question the validity of the structural assignment of Prevezol C.

In conclusion, we have accomplished the first total synthesis of the proposed structures of Prevezol C, in a stereoselective manner. A novel synthetic strategy was employed to install the challenging *syn* bromohydrin functionality. Continuous efforts toward structural determination of Prevezol C are underway and will be reported in due course.

Acknowledgment. The authors acknowledge the support of the School of Chemistry, Monash University and Monash University. A.E.L. gratefully acknowledges receipt of a Faculty of Science Dean's Postgraduate Research Scholarship.

Supporting Information Available. Experimental procedures and NMR and X-ray crystallography data. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.