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COMMUNICATION

Total synthesis of (+)-bretonin B: access to the (*E*,*Z*,*E*)-triene core by a late-stage Peterson elimination of a convergently assembled silyl ether†

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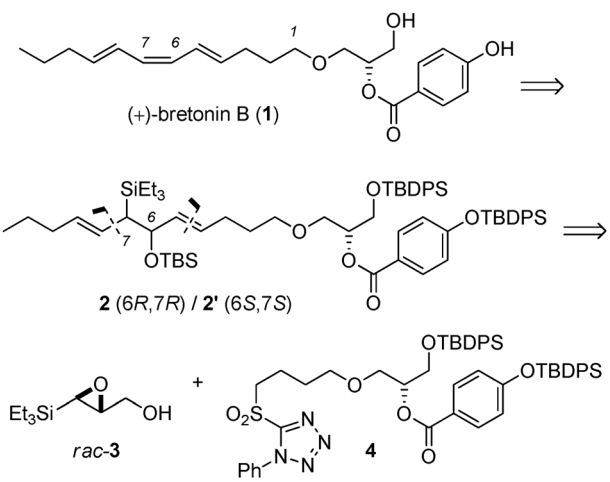
The title compound was synthesised in a concise route (nine linear steps, 31% overall yield) employing an α-silyl epoxide ring opening, a Julia–Kocienski olefination and a late-stage Peterson elimination as key steps.

Bretonin B (**1**) is a minor component in extracts isolated from an unidentified sponge of the *Demospongiae* class, which occurs in North Brittany sea water.[1] Chemically, the compound is a glycerol derivative which is esterified at the secondary alcohol by a *para*-hydroxybenzoyl group and etherified at one primary alcohol position by a (4*E*,6*Z*,8*E*)-trienic C_{12} carbon chain. (+)-Bretonin B has been characterised only by ^{1}H-NMR spectroscopy. However, the diacetate of its enantiomer has been prepared in a non-selective fashion[1] and was compared to the diacetate of the natural product. Furthermore, the structure assignment was based on analogy to its more abundant (*E*,*E*,*E*)-isomer bretonin A.[2]

Our interest in bretonin B was initiated by the presence of the relatively rarely occurring (*E*,*Z*,*E*)-triene moiety. A few natural products of this compound class have been prepared,[3–8] all of which, however, show further conjugation, either to a carbonyl group or to other double bonds. Our preliminary synthetic studies showed the high propensity of the central double bond towards $Z \rightarrow E$ isomerisation and let us consider a synthetic approach, in which this sensitive group would be liberated at the very end of the synthesis. Inspired by work of Nakai *et al.*[9] and by Pohnert and Boland,[10] who had used a Peterson olefination[11,12] for the synthesis of non-functionalised trienes and tetraenes, we envisioned a late-stage elimination from a suitably protected β-silyl-substituted silyl ether **2**/**2′** as an appropriate way to generate the central double bond (Scheme 1). A high convergence in the construction of this key precursor was expected to be possible if epoxide **3** could be ring opened selectively at the silyl-substituted position and if an olefination reaction would subsequently allow for the stereoselective formation of the double bond between C4 and C5. For the latter reaction a Julia–Kocienski olefination[13] was considered to be best suited and an enantioselective approach towards sulfone **4** was therefore required. It was anticipated that the Peterson elimination would be best induced under acidic conditions and the relative configuration at the stereogenic centers had therefore to be (6*R*,7*R*) or (6*S*,7*S*) in order to form a *Z*-double bond *via* a stereospecific *anti*-elimination.[11] Since the absolute configuration at these stereogenic centers is irrelevant, the epoxide precursor had not to be used in enantiomerically pure form but could be used as racemate (*rac*-**3**). In this communication we disclose the successful execution of the delineated strategy, which culminated in the first synthesis of (+)-bretonin B and the proof of its structure.

The synthesis of sulfone **4** commenced with isopropylidene glycerol, which is commercially available in either enantiomeric form and which provides the required stereogenic center. Regioselective functionalisation of this compound is straightforward[14] and it was initially attempted to introduce the *O*-protected *para*-hydroxybenzoyl group by acylation. It turned out, however, that this reaction is more difficult than that expected because the reactivity of the secondary alcohol was low after the two primary positions were appropriately protected or alkylated. Reaction with *O*-protected *para*-hydroxybenzoyl chlorides or with the respective free acids in the presence of a coupling reagent did not produce any of the desired products.



Scheme 1 Retrosynthetic disconnection of (+)-bretonin B (**1**) leading to epoxide *rac*-**3** and olefination reagent **4** as key building blocks.

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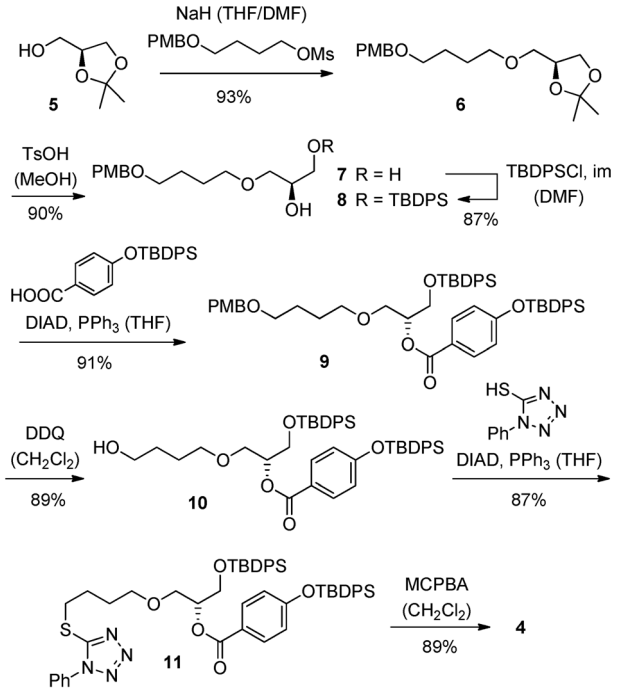
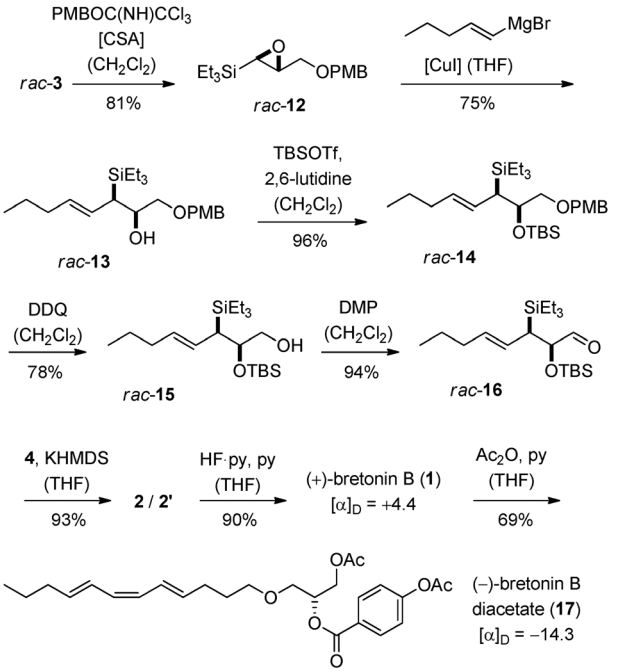


Scheme 2 Preparation of 1-phenyl-1*H*-tetrazol-5-yl-sulfone **4** from glycerol derivative **5**.



Scheme 3 Synthetic sequence of (+)-bretonin B (**1**) and its diacetate (**17**) from epoxide *rac*-**3** including a regioselective epoxide ring opening and a Julia–Kocienski olefination.

Under more forceful conditions, protecting group migration from the primary to the secondary alcohol was observed in some instances with the acylation occurring at the primary alcohol site. In order to circumvent this issue we resorted to the Mitsunobu reaction[15] for the introduction of the benzoate. Consequently, the (*S*)-configured isopropylidene glycerol **5** was alkylated with the *para*-methoxybenzyl (PMB) protected mesylate derived from 1,4-butanediol[16] (Scheme 2). Removal of the diol protecting group from the resulting product **6** was achieved under acidic conditions delivering diol **7**. After monosilyl protection with *tert*-butyldiphenylsilyl chloride (TBDPSCl), benzoate **9** could be smoothly formed from alcohol **8** using TBDPS-protected *para*-hydroxybenzoic acid as a nucleophile in the Mitsunobu reaction. The PMB group at the distal alcohol group was removed under oxidative conditions with 2,3-dichloro-5,6-dicyanoquinone (DDQ).[17] The 1-phenyl-1*H*-tetrazol-5-yl-sulfone was introduced *via* the respective sulfide in a Mitsunobu reaction[18] of alcohol **10**. Oxidation of sulfide **11** to the olefinating reagent **4** was achieved using *meta*-chloroperbenzoic acid (MCPBA).[19] The enantiomeric purity (>95% ee) of this compound was proven after TBDPS removal by chiral HPLC (see ESI† for further information).

The left-hand fragment of bretonin B was assembled starting from propargyl alcohol, which was converted in two steps into the known epoxy-alcohol *rac*-**3**.[20] The respective PMB ether *rac*-**12** was best prepared by alkylation with PMB trichloroacetimidate (Scheme 3). A regioselective ring opening of epoxide *rac*-**12** was achieved by treatment with (*E*)-configured 1-pentenyl-1-magnesium bromide and copper(I) iodide (10 mol%).[21,22] The magnesium reagent was prepared by halogen–lithium exchange from the respective bromide and subsequent transmetalation. Product *rac*-**13** was obtained as a single regio- and diastereoisomer.

Attempts to open epoxide *rac*-**12** with alkenylstannanes[23] or alkenyllithium compounds[24] were not successful. Only tetravinylstannane delivered stereospecifically the parent product after transmetalation with $Bu_2CuCNLi_2$ in the presence of $BF_3{\cdot}OEt_2$. Further experiments to convert this terminal alkene into a 1,2-disubstituted alkene by cross metathesis were not undertaken, however. Silylation with *tert*-butyldimethylsilyl triflate (TBSOTf) at the secondary alcohol position of *rac*-**13** delivered protected diol *rac*-**14**, which was chemoselectively converted into aldehyde *rac*-**16**[25] *via* the deprotected primary alcohol *rac*-**15**. Aldehyde *rac*-**16** was stable to chromatographic purification and was taken as the limiting reagent in the Julia–Kocienski olefination. Optimised reaction conditions include the preformation of the deprotonated sulfone at −78 °C and the subsequent addition of an aldehyde solution in THF to an excess (2 equiv.) of the olefination reagent. Under these conditions clean (4*E*)-configured products **2** and **2′** were obtained. Although ^{1}H- and ^{13}C-NMR spectra did not allow a distinction between **2** and **2′**, it is clear that the products must be a *ca.* 1/1-mixture of diastereoisomers because aldehyde *rac*-**16** was used in racemic form.

The final elimination reaction was initially performed with an excess of $ZnBr_2$ (5 equiv.) in CH_2Cl_2 generating the doubly TBDPS-protected product in 89% yield (three steps from *rac*-**15**). However, after complete deprotection to **1**, minor impurities (<10%) of the (*E*,*E*,*E*)-product, bretonin A, were detectable by ^{1}H-NMR. It was subsequently found that the elimination–deprotection can be performed more cleanly with HF–pyridine (HF·py) and pyridine in THF. Under these conditions, no other isomer was observed and (+)-bretonin B (**1**) was the only product. ^{1}H-NMR-spectral data were identical to the natural product with the coupling constant between protons H6 and H7 (^3J = 10.9 Hz) supporting the

(*Z*)-configuration at the central double bond. The compound was dextrorotatory but the specific rotation was relatively small. The compound was therefore converted into the diacetate, which was – if derived from the natural product – levorotatory.[1] Acetylation was facile and delivered bretonin B diacetate (**17**) in 69% yield. Indeed, this compound turned out to show a significant levorotatory specific rotation and matched the reported spectral data of the diacetate.[1] The conversion of aldehyde *rac*-**16** to (+)-bretonin B was also feasible without isolation of the intermediary products by immediate treatment of the crude product mixture of the olefination reaction with HF·py and py in THF. Although the $Z \rightarrow E$ isomerisation of bretonin B to bretonin A was observed upon standing at room temperature, a quantitative double bond isomerisation was possible neither under photochemical conditions nor under thermal conditions.

In summary, the first total synthesis[26] of (+)-bretonin B has been achieved starting from propargyl alcohol (commercially available precursor to epoxide *rac*-**3**) in a longest linear sequence of nine steps and a total yield of 31%. The synthesis demonstrates that the late-stage Peterson elimination is a useful tool for the stereoselective generation of (*Z*)-configured double bonds in conjugated oligo- and polyenes.

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