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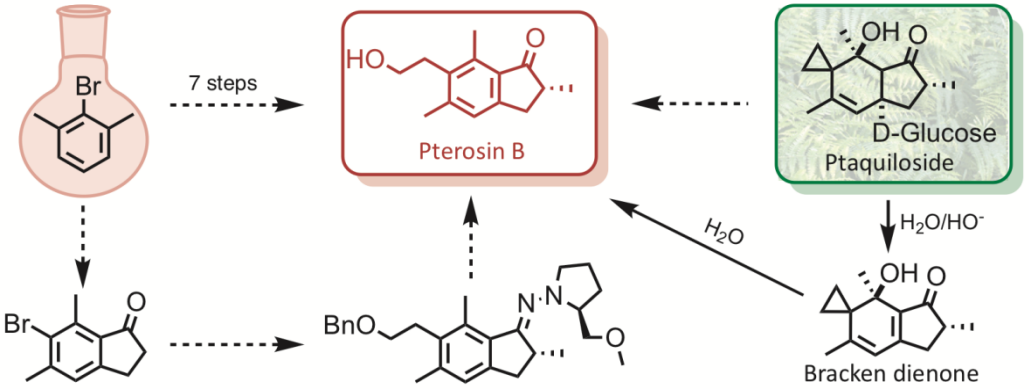


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# A concise stereoselective synthesis of Pterosin B

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ABSTRACT

Pterosin B is a naturally occurring indanone found in bracken fern (Pteridium aquilinum) that displays a variety of interesting pharmacological properties, but for which few stereoselective syntheses exist. Herein we describe a 7-step stereoselective synthesis of (2*R*)-pterosin B *via* 6-bromo-5,7-dimethylindan-1-one whose structure was confirmed by NOE analysis and structure determination by X-ray crystallography. The hydroxyethyl chain was introduced *via* a Suzuki-Miyaura cross-coupling reaction. The 2-methyl group was introduced stereoselectively by methylation of a SAMP [(*S*)-1-amino-2-methoxymethyl)pyrrolidine] hydrazone and the chiral auxiliary was removed to produce (2*R*)-pterosin B. The structure of pterosin B was confirmed by specific rotation and structural determination by X-ray crystallography.



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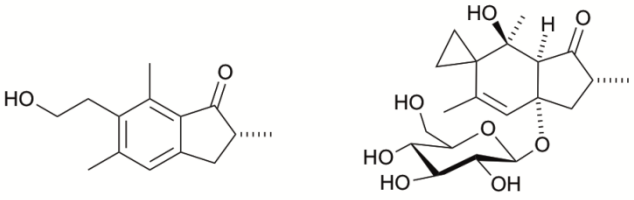
## 1. Introduction

Pterosins are a group of substituted 1-indanones originally characterized following their isolation from the bracken fern *Pteridium aquilinum*.[1–3] Pterosin B (**1**) occurs naturally as its (*2R*) isomer and is a decomposition product of the bracken toxin ptaquiloside (**2**) (Fig. 1). Ptaquiloside is a norsesquiterpene glucoside natural product of the illudane type. Under alkaline conditions, ptaquiloside loses glucose forming an unstable acylfulvene-type compound which subsequently decomposes to form pterosin B.[4-6]

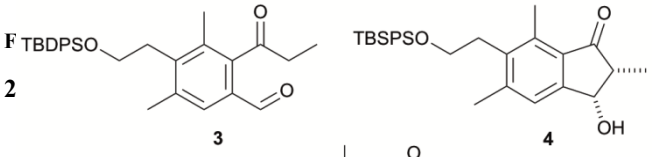
**Fig**




os roperties, for example in the treatment of diabetes, obesity[4,7] and
th B in bracken are very low and most chemical syntheses provide only
B is therefore highly desirable.

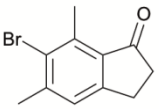
in 2-(4-bromo-2,6-dimethylphenyl)ethanol.[11] A key step in this synthesis
co und **3** to produce **4** (*syn/anti* = 98:2, 85% ee) (Fig. 2). Subsequently,
; an alternative, more concise route to (*2R*)-pterosin B, we envisaged
elaboration of the core indanone structure **5** (Fig. 2), described previously by Sheriden and co-workers[12] and describe herein a stereoselective 7-step synthesis of (*2R*)-pterosin B and its characterisation by X-ray crystallography.

**F**



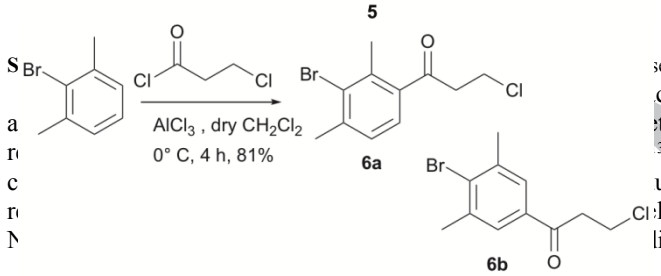

**2**

c Friedel-Crafts acylation of 2-bromo-1,3-xylene using 3-chloropropionyl
c **6a** and **6b** (Scheme 1). This finding has also been reported by Hsu and
r spectrum of the mixture revealed a 2.5:1 ratio of products **6a** and **6b**,




**S** separable mixture of isomers **6a** and **6b**.

a cid resulted in cyclisation to produce a mixture containing indanones **5**
r ts at 7.49 and 7.22 ppm, corresponding to the aromatic protons of the
c [3] The relative amounts of the two isomers corresponded to that prior to
r uced in a 2.5:1 ratio to **7**. After silica column chromatography and
N ld from bromoxylene. The identity of **5** was further confirmed by both
liation of H3) (Fig. 3) and X-ray crystallography[14] (ESI Fig. 1).



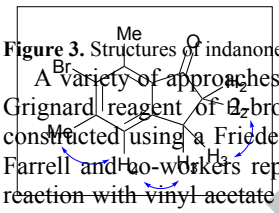
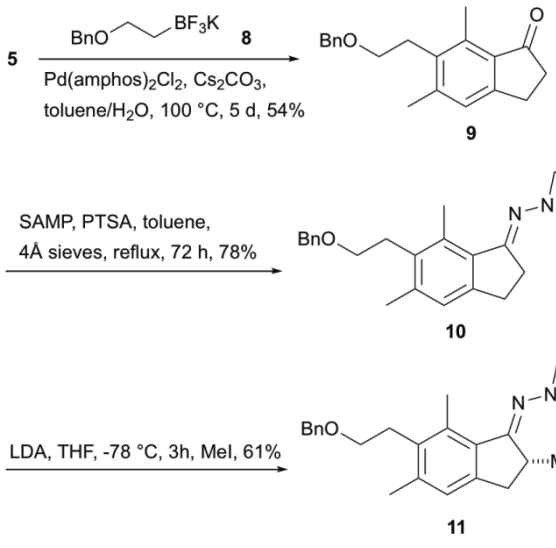




**Figure 3.** Structures of indanones **5** and **7** and observed NOE interactions in the $^1$H NMR of **5**.

A variety of approaches have been used previously for introducing the hydroxyethyl group. McMorris and co-workers[15] reacted the Grignard reagent of 2-bromo-1,3-xylene with oxirane. Following acetylation of the hydroxyethyl group, the indanone ring was constructed using a Friedel Crafts acylation with chloropropionyl chloride followed by an acid-catalysed cyclisation.[12,15] In contrast, Farrell and co-workers reported the first example of a Pd-catalysed method in which a 6-bromoindanone was employed in a Heck reaction with vinyl acetate in the synthesis of pterosin Z.[16] This cross-coupling reaction gave a 1:1 mixture of *E* and *Z* isomers in 29% yield together with a 6-vinyl indanone by-product. Reduction and de-acetylation afforded the hydroxyethyl side chain. More recently a Suzuki-Miyaura reaction was used to produce a 6-vinylated indanone precursor of pterosin A. Unfortunately this could not be resolved from the reduced (6H) by-product. The hydroxyethyl group was obtained following subsequent hydroboration.[13]

In the synthesis of pterosin B we sought to introduce the hydroxyethyl group directly onto indanone **5** using a Suzuki-Miyaura cross-coupling with the benzyl-protected trifluoroborate salt **8**.[17] Thus, cross-coupling of **8** with compound **5** afforded indanone **9** in 54% yield (Scheme 2).




**Scheme 2.** Suzuki-Miyaura cross-coupling, and methylation of SAMP hydrazone.

A variety of methods for asymmetric enolate alkylation are availal le well-established procedures using Enders' chiral hydrazone (SAMP/R te (AAC) hydrazones.[23] We elected to use Enders' methodology due to the at the methylated diastereomeric hydrazones would be resolvable. To n, delivery to the bottom face of the aza-enolate requires the use of SAM P hydrazone **10** by heating at reflux with SAMP and PTSA in toluene as achieved by treatment with LDA in THF at -78 °C followed by the of diastereoisomers following silica column chromatography. Although we a chromatography, they could be fully resolved by reversed-phase HPL le (15/85) (ESI, Fig. 2)). Based on HPLC analysis a d.r. of 85:15 in fa g purification by RP-HPLC, **11** was obtained in 61% yield.

To remove the chiral auxiliary from **11** we investigated using $O_3$ in C to obtain the benzylated indanone **12** (Scheme 3) by ozonolysis, we f a

contaminant that was isolated by RP-HPLC. This was subsequently identified by $^1$H NMR and mass spectrometry as the benzoylated compound **13**. However, by using a low flow of ~0.2 mL/min, short reaction times and low temperature, oxidation of the benzyl group could be minimized. Removal of the benzyl group from **12**, by catalytic hydrogenation using an H-Cube® afforded (*2R*)-pterosin B as a single enantiomer in 66% yield following final purification by RP-HPLC.

We also investigated whether the benzoylated indanone **13** could be successfully converted into pterosin B. Although removal of the benzoyl group using aqueous ammonia resulted in the expected racemization (as evidenced by chiral phase HPLC, ESI Fig. 3), de-acylation could be achieved without loss of stereochemistry using an esterase from *Bacillus subtilis* (ESI Fig. 3).

**Scheme 3.** Completion of the synthesis of (*2R*)-pterosin B (**1**).

Crystallisation of (*R*)-pterosin B (**1**) from a mixture of chloroform and hexane provided a sample with an ee of 100%, identical specific rotation to that described in the literature[11] and permitted confirmation of its structure by X-ray crystallography (Fig. 4).[26]

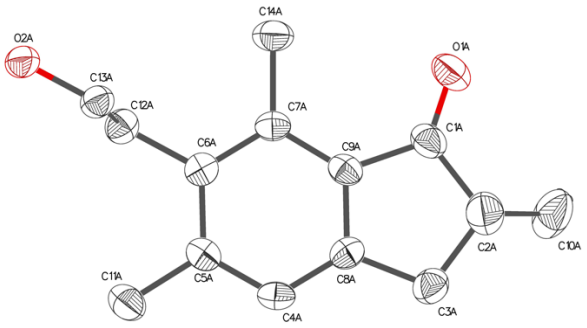



**Figure 4.** ORTEP structure of (*2R*)-pterosin B obtained by X-ray crystallography.[19]

## 3. Conclusion

In conclusion we have developed a concise stereoselective synthesis of the naturally occurring (*R*)-enantiomer of pterosin B in 7-steps from commercially available 2-bromo-1,3-xylene. The ready availability of (*R*)-pterosin will enable further evaluation of its biological properties.

## 4. Acknowledgements

We are very grateful to the Engineering and Physical Sciences Research Council (EPSRC) UK EP/P010075/1 (DMW, EA) and to QuantuMDx Ltd. (HRD) for financial support.

## 5. Supplementary data

Electronic supplementary information (ESI) related to this article containing $^1$H NMR and $^{13}$C NMR spectra for all new compounds, HPLC data (PDF) and X-ray structures for compounds **1** and **5** (CIF) can be found at xxx

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- Stereoselective synthesis of natural 2R isomer of pterosin B
- Concise 7-step synthesis of natural pterosin B
- X-ray structure of pterosin B