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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.

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].

Pterosin B displays several interesting pharmacological properties, for example in the treatment of diabetes, obesity [4,7] and osteoarthritis [8]. Unfortunately, typical concentrations of pterosin B in bracken are very low and most chemical syntheses provide only the racemic form [9,10]. A short stereoselective synthesis of pterosin B is therefore highly desirable.

Recently (2*R*)-pterosin B has been prepared in 13 steps from 2-(4-bromo-2,6-dimethylphenyl)ethanol [11]. A key step in this synthesis involves an asymmetric intramolecular aldol reaction of compound **3** to produce **4** (*syn/anti* = 98:2, 85% ee) (Fig. 2). Subsequently, compound **4** was converted into (*2R*)-pterosin B in 3 steps. As 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.

Results and discussion

Our initial attempts towards the synthesis of **5**, involving the Friedel-Crafts acylation of 2-bromo-1,3-xylene using 3-chloropropionyl chloride, produced an inseparable mixture of the regioisomers **6a** and **6b** (Scheme 1). This finding has also been reported by Hsu and co-workers [13] in their synthesis of pterosin A. The ^{1}H NMR spectrum of the mixture revealed a 2.5:1 ratio of products **6a** and **6b**, respectively, based on the signals for the aromatic ring protons.

Heating the mixture of **6a** and **6b** in concentrated sulfuric acid resulted in cyclisation to produce a mixture containing indanones **5** and **7**. The ^{1}H NMR spectrum of the mixture displayed singlets at 7.49 and 7.22 ppm, corresponding to the aromatic protons of the respective indanones **7** and **5**, in agreement with the literature [13]. The relative amounts of the two isomers corresponded to that prior to cyclisation, with **5** being the major product and being produced in a 2.5:1 ratio to **7**. After silica column chromatography and recrystallisation from ethyl acetate, **5** was obtained in 22% yield from bromoxylene. The identity of **5** was further confirmed by both NOESY NMR (NOEs to H-4 and H-2 were observed upon irradiation of H3) (Fig. 3) and X-ray crystallography [14] (ESI Fig. 1).

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

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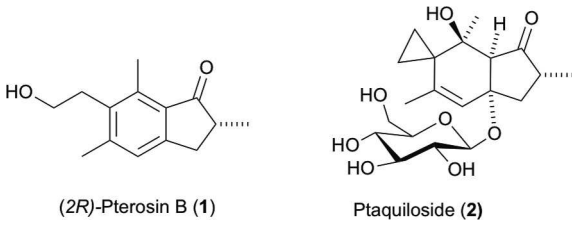


Figure 1. Structures of pterosin B (**1**) and ptaquiloside (**2**).

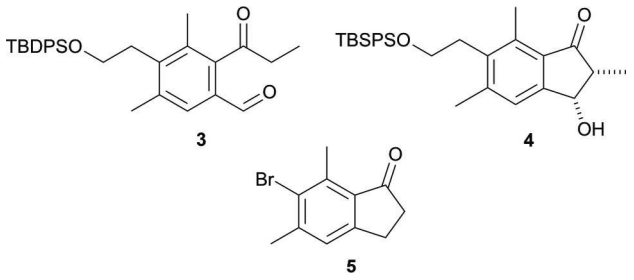
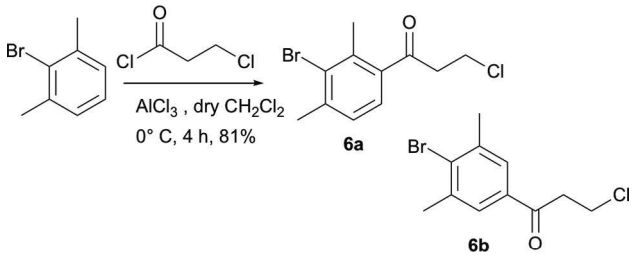


Figure 2. Synthetic precursors to pterosin B.



Scheme 1. Friedel-Crafts acylation of 2-bromo-1,3-xylene to produce an inseparable mixture of isomers **6a** and **6b**.

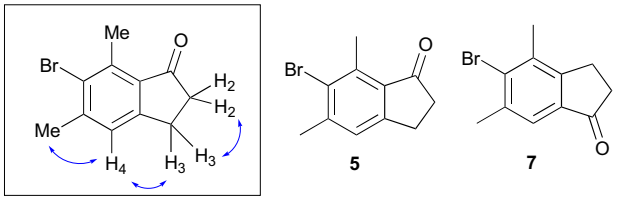
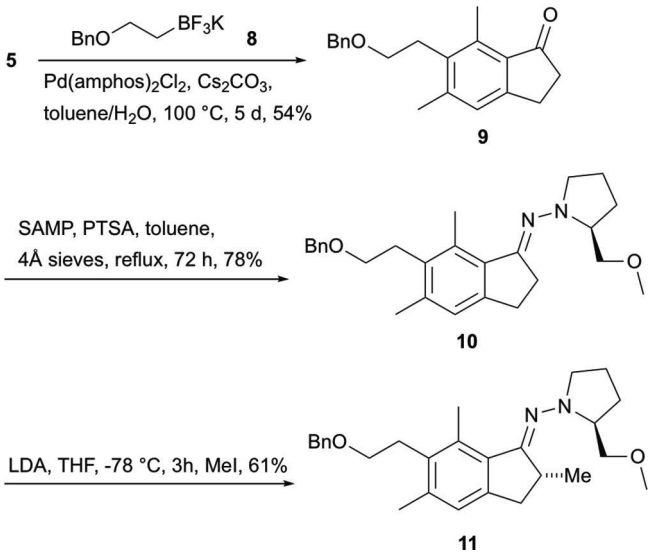


Figure 3. Structures of indanones **5** and **7** and observed NOE interactions in the ^{1}H NMR of **5**.

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).

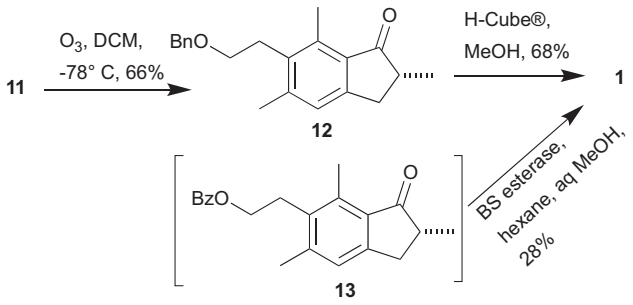
A variety of methods for asymmetric enolate alkylation are available [18,19] for achieving selective methylation of **9**. These include well-established procedures using Enders' chiral hydrazone (SAMP/



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

RAMP) methodology [20–22] or *via* chiral *N*-amino cyclic carbamate (AAC) hydrazones [23]. We elected to use Enders' methodology due to the ready availability of the chiral auxiliary and the expectation that the methylated diastereomeric hydrazones would be resolvable. To introduce the methyl group with the correct *R*-configuration, delivery to the bottom face of the aza-enolate requires the use of SAMP. Thus compound **9** was converted to its corresponding SAMP hydrazone **10** by heating at reflux with SAMP and PTSA in toluene in the presence of molecular sieves. Methylation of **10** was achieved by treatment with LDA in THF at −78 °C followed by the addition of iodomethane. This provided **11** as a mixture of diastereoisomers following silica column chromatography. Although we were unable to separate these two diastereoisomers using silica chromatography, they could be fully resolved by reversed-phase HPLC (RP-HPLC) using an isocratic elution of water/acetonitrile (15/85) (ESI Fig. 2)). Based on HPLC analysis a d. r. of 85:15 in favour of the *2R* diastereoisomer (**11**) was obtained. Following purification by RP-HPLC, **11** was obtained in 61% yield.

To remove the chiral auxiliary from **11** we investigated using O_3 in CH_2Cl_2 as described previously [24,25]. During our initial attempts to obtain the benzylated indanone **12** (Scheme 3) by ozonolysis, we found that the desired product contained small amounts of 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 ozone, 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 68% yield following final purification by RP-HPLC.



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

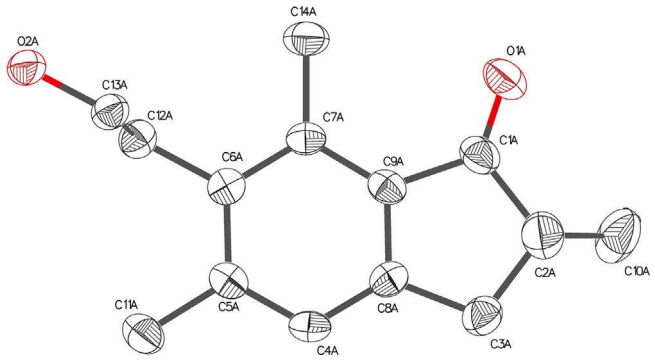


Figure 4. ORTEP structure of (*2R*)-pterosin B obtained by X-ray crystallography.[19.]

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).

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].

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.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2018.10.056.

References

[1] M. Fukuoka, M. Kuroyanagi, K. Yoshihira, S. Natori, Chem. Pharm. Bull. 26 (1978) 2365–2385.
[2] K. Yoshihira, M. Fukuoka, M. Kuroyanagi, S. Natori, M. Umeda, T. Morohoshi, M. Enomoto, M. Saito, Chem. Pharm. Bull. 26 (1978) 2346–2364.
[3] K. Yoshihira, M. Fukuoka, M. Kuroyanagi, S. Natori, Chem. Pharm. Bull. 19 (1971) 1491–1495.
[4] K. Yamada, H. Ojika, H. Kigoshi, Nat. Prod. Rep. 24 (2007) 798–813.
[5] M. Tanasova, S.J. Sturla, Chem. Rev. 112 (2012) 3578–3610.
[6] M.E. Alonso-Amelot, Nat. Prod. Rep. 26 (2002) 685–739.
[7] H. Feng-Lin, Use of pterosin compounds for treating diabetes and obesity, WO 2010085811 A2, 2010.
[8] Y. Yahara, H. Takemori, M. Okada, A. Kosai, A. Yamashita, T. Kobayashi, K. Fujita, Y. Itoh, M. Nakamura, H. Fuchino, N. Kawahara, N. Fukui, A. Watanabe, T. Kimura, N. Tsumaki, Nat. Commun. 7 (2016) 10959.
[9] P. Wessig, J. Teubner, Synlett. 2006 (2006) 1543–1546.
[10] M. Attya, M. Nardi, A. Tagarelli, G. Sindona, Molecules 17 (2012) 5795–5802.
[11] Y. Ueda, T. Furuta, T. Kawabata, Angew. Chemie Int. Ed. 54 (2015) 11966–11970.
[12] H. Sheridan, S. Lemon, N. Frankish, P. McArdle, T. Higgins, J.P. James, P. Bhandari, Eur. J. Med. Chem. 25 (1990) 603–608.
[13] S.-C. Hsu, M. Narsingam, Y.-F. Lin, F.-L. Hsu, B.-J. Uang, Tetrahedron 69 (2013) 2572–2576.
[14] Structure for compound 5 deposited at CCDC. Accession number 1851094.
[15] K.M.E. Ng, T.C. McMorris, Can. J. Chem. 62 (1984) 1945–1953.
[16] R. Farrell, F. Kelleher, H. Sheridan, J. Nat. Prod. 59 (1996) 446–447.
[17] N. Fleury-Brégeot, M. Presset, F. Beaumard, V. Colombel, D. Oehlrich, F. Rombouts, G.A. Molander, J. Org. Chem. 77 (2012) 10399–10408.
[18] R. Lazny, A. Nodzewska, Chem. Rev. 110 (2010) 1386–1434.
[19] R. Cano, A. Zakarian, G.P. McGlacken, Angew. Chemie Int. Ed. 56 (2017) 9278–9290.
[20] E.J. Corey, D. Enders, Tetrahedron Lett. 1 (1976) 3–6.
[21] L. Kurti, B. Czako, Strategic Applications of Named Reactions in Organic Synthesis, Elsevier Academic Press: Burlington, MA 1 (2005) 150–151.
[22] M. Heravi, V. Zadsirjan, D. Mansoureh, In *Current Organic Synthesis*, Bentham Science Publishers 14 (2017) 61–111.
[23] S.E. Wengryniuk, D. Lim, D.M. Coltart, J. Am. Chem. Soc. 113 (2011) 8714–8720.
[24] D. Enders, H. Eichenauer, Chem. Ber. 112 (1979) 2933–2960.
[25] P. Angibeaud, J. Defaye, A. Gadelle, J.-P. Utille, Synthesis 1985 (1985) 1123–1125.
[26] Structure for compound 1 deposited at CCDC. Accession number CCDC 1851093.