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Total Synthesis of (–)-Angiopterlactone B

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Supporting Information Placeholder

ABSTRACT: An enantioselective total synthesis of (–)-angiopterlactone B has been accomplished in four steps. The synthesis features a proposed biomimetic domino ring-contraction/oxa-Michael/Michael dimerization sequence, forming three new bonds, two new rings and three new contiguous stereogenic centres in a single step. It has been determined that the originally proposed absolute configuration of natural (+)-angiopterlactone B needs revision. This reveals that angiopteriside, a known glycoside natural product, is the likely biosynthetic precursor to (+)-angiopterlactone B.

(+)-Angiopterlactone B (**1**) is a structurally complex bis-lactone metabolite isolated from the rhizome of *Angiopteris caudatiformis* by Zou and co-workers in 2009 (Scheme 1).¹ The connectivity and relative stereochemistry of (+)-angiopterlactone B (**1**) was determined by extensive NMR and MS studies and secured by X-ray crystallography. The CD excitation chirality method and modified Mosher ester analysis were used to propose the absolute configuration shown in Scheme 1.¹

Zou and co-workers noted that (+)-angiopterlactone B (**1**) may be derived from the co-isolated (–)-angiopterlactone A (**2**) by an intramolecular Michael reaction (Scheme 1).¹ With no further biosynthetic speculation provided, we ventured that (–)-angiopterlactone A (**2**) might be formed by an intermolecular oxa-Michael reaction between γ -lactone **3** and δ -lactone **4**.² This proposal was driven by the recognition that lactones **3** and **4** are isomers of one another. The chemical feasibility of a δ - to γ -lactone isomerization (*i.e.*, **4** to **3**) is well precedented; osmundalactone **5** (the aglycone of osmundalin **6**) is reported to undergo ring contraction to give the γ -lactone **7** under acidic or basic conditions (Scheme 1).^{3a} Furthermore, the known natural products osmundalin (**6**)³ and angiopteriside (**8**)⁴ prompted us to consider that a diastereomer of these structures, glycoside **9**, might represent a plausible biosynthetic precursor to (+)-angiopterlactone B (**1**). This biosynthetic proposal raises many questions concerning reactivity and selectivity. Are enzymes required for the domino ring-contraction/oxa-Michael/Michael reaction sequence,⁵ or is it the result of predisposed reactivity? Are angiopterlactones A (**2**) and B (**1**) the only natural dimers formed, through a highly selective process, or do they hint at the potential for an entire family of related dimers? In an attempt to answer these questions, we decided to embark upon efforts towards achieving a biomimetic total synthesis.

Scheme 1. Proposed biosynthesis of angiopterlactones A (**2**) and B (**1**).^{1,3,4}

The required δ -lactone **4** was prepared following an approach recently reported by Tang, Guo and co-workers.⁶ The synthesis began with an enantioselective multi-gram scale Noyori transfer hydrogenation of commercially available 2-acetylfuran **10**,⁷ which gave highly enantioenriched (*S*)-alcohol **11** in near quantitative yield (Scheme 2). Achmatowicz rearrangement of alcohol **11** using *N*-bromosuccinimide (NBS) gave pyranone **12** as an inconsequential mixture of diastereomers.⁸ Dynamic kinetic isomerization of pyranone **12** using tandem Brønsted-acid and iridium catalysis gave δ -lactone **4** in 62–71% yield on a multi-gram scale.⁶ Following extensive screening of various reaction conditions, three and a

half grams of δ -lactone **4** were dissolved in 1,2-dichloroethane and a sub-stoichiometric quantity of potassium carbonate was added.^{2c} This mixture was heated at 70 °C overnight to give (–)-angiopterlactone B (**1**) in 25% isolated yield (>0.85 g), thus completing a four step enantioselective total synthesis (Scheme 2).⁹ Attempts to improve the yield for this final dimerization, by extending the reaction time, varying the concentration and adding more base, were ineffective (see the Supporting Information for full details). Nevertheless, analysis of the ¹H NMR spectrum of the crude dimerization product (see Scheme 2) revealed a remarkably selective reaction, with δ -lactone **4**, γ -lactone **3** and γ -lactone **7** (presumably formed through base-mediated epimerization of γ -lactone **3**) accounting for the majority of the remaining material. When the three monomeric lactones (**4**, **3** and **7**) are present, there are a total of 72 dimeric structures that could conceivably form through a domino oxa-Michael/Michael reaction sequence.¹⁰ It is, therefore, fascinating that we observe the highly selective formation of just one, (–)-angiopterlactone B (**1**).

Scheme 2. Total synthesis of (–)-angiopterlactone B (1**),^a its X-ray crystal structure,⁹ and diagnostic upfield-region of the crude ¹H NMR spectrum for the dimerization reaction.**

^aYields are reported as a range, representing the isolated yields obtained from several reactions. The reaction scale corresponds to the approximate quantity of product isolated from a single reaction.

An $[\alpha]_D^{20}$ of +22 (*c* 0.04, EtOAc)¹ is reported for natural angiopterlactone B (**1**), whereas an $[\alpha]_D^{20}$ of –25 (*c* 0.04, EtOAc) was obtained for our synthetic material. Therefore, it must be concluded that the absolute configuration of natural (+)-angiopterlactone B (**1**) needs revision.¹¹ Importantly, this reveals that angiopteriside **8** (see Scheme 1), a glycoside natural product previously isolated from various *Angiopteris* plants,⁴ is a likely biosynthetic precursor to natural (+)-angiopterlactone B (**1**).

In summary, a scalable, protecting-group-free, enantioselective total synthesis of (–)-angiopterlactone B (**1**) has been achieved in four steps. Our experimental results indicate that (+)-angiopterlactone B (**1**) is likely the result of an inherently selective dimerization of the aglycone of angiopteriside (**8**).¹² Detailed mechanistic studies, both experimental and computational, are currently underway in our laboratory to investigate the reactivity and selectivity of this dimerization process and will be reported in due course.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Experimental procedures and analytical data for all compounds (PDF)

X-ray crystallographic analysis for **1** (CIF)

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Notes

The authors declare no competing financial interest.

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- (9) CCDC 1540485 (**1**) contains the supplementary crystallographic data for this paper. This is provided free of charge by The Cambridge Crystallographic Data Centre.
- (10) There are nine possible permutations for combining two of the three lactones (**4**, **3** and **7**) and eight diastereomeric products could result from each pairing ($9 \times 8 = 72$).
- (11) The absolute configuration of synthetic (–)-angiopterlactone B (**1**) can be inferred from the known absolute configuration of the preceding intermediates (**11** and **4**). Furthermore, this was confirmed from the Flack parameter, 0.02(3), obtained during our X-ray crystallographic studies.⁹ For information on using the Flack parameter to evaluate absolute configuration, see; Flack, H. D.; Bernardinelli, G. *J. Appl. Crystallogr.* **2000**, *33*, 1143–1148.
- (12) It remains unclear whether this remarkably selective reaction is being harnessed in nature constructively, or is generating products that are artefacts of the extraction/isolation/purification process.
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