Total synthesis of (±)-aspercyclide A and its C19 methyl ether†

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The total syntheses of (±)-aspercyclide A (1) and its C19 methyl ether (15a) featuring Heck–Mizoroki macrocyclisation to form the 11-membered (*E*)-styrenyl biaryl ether lactone core are described.

Allergic disorders such as asthma are caused by inflammatory mediators (*e.g.* leukotrienes) released by mast cells and basophils.[1] Binding of allergen specific soluble immunoglobin E (IgE) to its membrane bound high affinity receptor (FcεRI) on these cells, and then cross-linking of these complexes by multivalent allergens, is the trigger for the inflammatory mediator release.[2] Blocking of the IgE–FcεRI protein–protein interaction (PPI) therefore constitutes a strategy for therapeutic intervention.[3] In 2005 the European Commission approved the humanised monoclonal anti-IgE antibody omalizumab (Xolair®, Novartis/Genentech), which has this mode of action, for the treatment of severe asthma in all member states.[4] However, the antibody is expensive to manufacture and requires subcutaneous injection every 2–4 weeks; a comparably efficacious small molecule antagonist could have tremendous potential for the treatment of asthma and other allergic disorders.[5]

Several peptides,[6a] oligonucleotides[6b] and fluorescein dyes[6c] have been reported to block the IgE–FcεRI PPI, but arguably the most promising small molecule antagonist for drug development reported to date is the fungal metabolite aspercyclide A (**1**).[7] This natural product is the most active member (IC_{50} = 200 μM) of three closely related 11-membered biaryl ether lactones (aspercyclides A–C, **1–3**) that were isolated and characterised by Singh *et al.* following enzyme-linked immunosorbent assay (ELISA)-guided fractionation of *Aspergillus* sp. found in soil extracts collected in Tanzania and published in 2004 (Fig. 1).[7]

The synthesis of (+)-aspercyclide C was reported by Fürstner and Müller in 2005 and featured Duthaler–Hafner asymmetric oxy-allylation of hexanal to prepare an *anti*-1,2-diol-PMP ether derivative (>90% de, 92% ee) then ring-closing metathesis

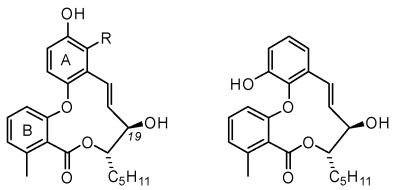

Fig. 1 Structures of aspercyclides A–C.

(RCM) to effect macrocyclisation (→ 5 : 1, *E* : *Z*).[8a] In 2007, Ramana *et al.* reported a similar approach to this natural product *via* the corresponding *anti*-1,2-diol-PMB ether (prepared from D-ribose) then RCM using the Fürstner conditions.[8b] They obtained the *E*-isomer exclusively and oxidative deprotection of the PMB ether proved higher yielding than for the PMP congener but they were unable to isolate clean aspercyclide C following the final C11 aryl methyl ether deprotection using BBr_3. Very recently, Fürstner *et al.* disclosed the first syntheses of (+)-aspercyclides A and B from (*S*)-glycidol employing an intramolecular Nozaki–Hiyama–Kishi (NHK) reaction to effect macrocyclisation and form the *anti*-1,2-diol motif (>90% de). (+)-Aspercyclide B was fully characterised but (+)-aspercyclide A proved labile to chromatography and no spectral data were reported.[8c]

We report here our synthesis and full characterisation of (±)-aspercyclide A and ELISA studies that demonstrate that synthetic aspercyclide A (**1**) and its C19 methyl ether (**15a**) display comparable antagonist activity against the IgE–FcεRI PPI. A single crystal X-ray structure determination on methyl ether **15a** has also been obtained.

Our synthesis of (±)-aspercyclide A differs significantly from Fürstner's in that we employ a Heck–Mizoroki reaction to effect macrocyclisation. We have explored routes that deploy both methyl and PMB ether protection of the eventual C19 hydroxy group. The synthetic sequences are similar and both start with a Boeckman modified Takai–Utimoto acrolein acetal–hexanal condensation,[9] that is catalytic in Cr(II) and stoichiometric in Mn(0), to access mono-protected *anti*-diols **5a** (56% yield)‡ and **5b** (64% yield).§ Esterification in the case of alcohol **5a** was accomplished by deprotonation with *n*-BuLi followed by addition of benzoyl chloride **6**¶ at −78 °C and warming to RT (→ **7a** in 66% yield). For the PMB congener, NaH was employed in place of *n*-BuLi as this gave superior yields (→ **7b** in 85% yield). We, like Fürstner, then selected to use acetonide protected bromobenzoquinol **8**‖ as our ring A precursor. We were unable to identify useful Pd-mediated conditions for biaryl ether formation and Cu-mediated

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Ullmann coupling protocols resulted in dehalogenation except when pyridine was employed as the solvent as described by Kulkarni *et al.*[10] Using their protocol, biaryl ethers **9a** and **9b** could be isolated in 70% and 54% yields, respectively (Scheme 1).

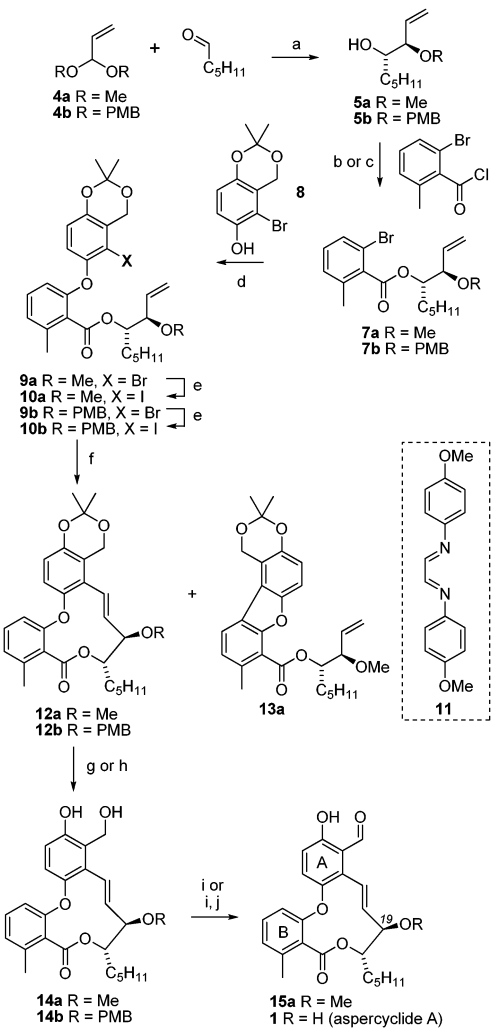
Our initial investigation of the Heck–Mizoroki[11] macrocyclisation reaction focussed on the Me ether containing arylbromide **9a**. This substrate was found to form dibenzofuran **13a** (*via* direct arylation),[12] more readily than the desired macrocycle **12a** under many conditions assayed, typically giving a ~4 : 1 ratio of these two products. The best conversions (>90%) were obtained using conditions modified from those reported by Nolan *et al.*[13] but using the novel diazabutadiene (DAB) ligand **11**. Cognisant, that the rate of direct arylation might be suppressed by the addition of stoichiometric iodide,[12] AgI was explored as an additive. Use of 100 mol% indeed reversed the product ratio but we could not find conditions that also allowed acceptable conversion (*e.g.* → **13a** : **12a**, ~1 : 5; 31% conv. at 72 h). A copper-mediated aromatic Finkelstein halogen exchange process[14] was therefore applied to arylbromide **9a** to give the corresponding aryliodide **10a** (94% yield). Pleasingly, this substrate underwent Heck–Mizoroki macrocyclisation under identical conditions with improved selectivity and conversion (*i.e.* → **13a** : **12a**, ~1 : 10; 74% conv. at 48 h) to afford macrocycle **12a** in 52% isolated yield (Scheme 1).

Interestingly, the PMB protected substrates **9b** and **10b** (**10b** obtained from **9b** in 88% yield by an aromatic Finkelstein halogen exchange process) were not prone to dibenzofuran formation. This allowed reduced amounts of $Pd(acac)_2$ to be deployed and for the AgI to be omitted from the Heck–Mizoroki macrocyclisation but the isolated yields from both these PMB ether arylbromide and iodide substrates were comparable with those from the corresponding Me ethers (**9b** → **12b**, 34%; **10b** → **12b**, 47%).

Acid catalysed acetal deprotection of both macrocycles **12a** and **12b** proceeded smoothly affording diols **14a** and **14b** in 94% yield and 82% yield respectively. Oxidation of benzyl alcohol **14a** with MnO_2 afforded (±)-aspercyclide A methyl ether **15a** in 42% yield. Conversion of methyl ether **15a** to (±)-aspercyclide A itself did not prove possible in our hands. However, oxidation of benzyl alcohol **14b** with MnO_2 then immediate C19 PMB ether removal using $BF_3{\cdot}Et_2O$ gave (±)-aspercyclide A (**1**)** in 72% yield (from **14b**). We did not observe this compound to be unstable or sensitive to flash chromatography.[8c]

Methyl ether **15a** was subject to a single crystal X-ray structure determination which confirmed the styrene stereochemistry as being *E* as required and the presence of an intramolecular H-bond between the ring A aldehyde oxygen and the phenol OH as expected (Fig. 2).

The overall conformation of the macrocycle in the crystal lattice is similar to that predicted by Singh *et al.*[7] for (+)-aspercyclide A by computation based on NMR nOe data. It is also similar to that of (+)-aspercyclide C C11 methyl ether[8b] and its C19 PMP ether,[8c] suggesting that the ring A substitution pattern has little influence on the macrocycle



Scheme 1 Synthetic route to aspercyclide A (**1**) and derivatives. *Reagents and conditions*: [a] $CrCl_2$, TMS–Cl, NaI, Mn(0), THF, −30 °C, 56% (**5a**), 64% (**5b**); [b] **5a**, *n*-BuLi, THF, −78 °C *then* acid chloride **6**, −78 °C → rt, 66% (**7a**); [c] **5b**, NaH, acid chloride **6**, THF reflux, 85% (**7b**); [d] Phenol **9**, CuO, K_2CO_3, pyridine, 120 °C, 70% (**9a**), 54% (**9b**); [e] CuI, NaI, *N*,*N*-dimethylethylenediamine, 1,4-dioxane, 110 °C, 94% (**10a**), 88% (**10b**); [f] $Pd(acac)_2$, **11**, Cs_2CO_3, AgI, 1,4-dioxane, 120 °C, 52% (**12a**), 47% (**10b** → **12b**), 34% (**9b** → **12b**); [g] 2 M HCl–THF (1 : 1), 60 °C, 94% (**14a**); [h] *p*-TSA·H_2O, THF–MeOH (1 : 3), 40 °C, 82% (**14b**); [i] MnO_2, CH_2Cl_2, 40 °C, 42% (**15a**); [j] $BF_3{\cdot}Et_2O$, CH_2Cl_2, rt, 72% (**14b** → **1**).

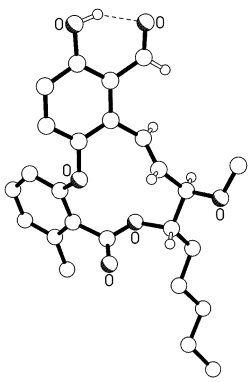


Fig. 2 Single crystal X-ray structure of (±)-aspercyclide A C19 methyl ether (**15a**).

conformation and that this is largely dictated by the out-of-plane sterically hindered ring B benzoate, the *anti*-diol and the *E*-alkene moieties.

The ability of compounds (±)-**1** and (±)-**15a** to block the IgE–FcεRI PPI was investigated using an ELISA binding assay (see ESI†). Interestingly, aspercyclide A (**1**) and its methyl ether **15a** were found to be comparably potent antagonists of the IgE–FcεRI PPI [(±)-**15a** IC_{50} = 95 ± 10 μM; (±)-**1** IC_{50} = 110 ± 10 μM].†† Since the synthesis of methyl ether **15a** benefits from having commercially available acetal **4a** as starting material, analogues of this compound may prove useful for future structure–activity relationship (SAR) studies.

In summary, we have developed a short synthesis of (±)-aspercyclide A (7 steps, 6% yield overall) that employs a Boeckman modified Takai–Utimoto acrolein acetal–hexanal condensation to establish the *anti*-diol motif and a Heck–Mizoroki reaction to close the 11-membered ring. We plan to use this route to prepare more analogues and build up SAR data. We also plan to employ surface plasmon resonance (SPR) direct binding studies with both protein partners to establish the binding site of these derivatives as a prelude to trying to obtain co-crystals with the appropriate protein partner.

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Notes and references

‡ The *anti* stereochemistry of the major diastereomer was confirmed by obtaining a single crystal structure determination on its ester derivative **7a**. See ESI.†

§ PMB-acetal **4b** was prepared from acrolein and the TMS-ether of 4-methoxybenzyl alcohol. See ESI.†

¶ The benzoic acid precursor to acid chloride **6** is commercially available. We employed $(COCl)_2$ and DMF (cat.) in CH_2Cl_2 for its conversion to acid chloride **6**. See ESI.†

‖ Synthesis of bromoquinol **8** was *via* bromination of gentisaldehyde (Br_2, $CHCl_3$), reduction ($NaBH_4$, $NaOH_{aq}$) and protection (DMP, CSA). The regioselectivity of the bromination was verified by a single crystal structure determination on the benzoate of bromoquinol **8**. See ESI.†

** The ^1H and ^{13}C NMR spectra of synthetic (±)-**1** matched those of the natural (+)-aspercyclide A, a sample of which was kindly supplied by Sheo B. Singh, Merck Research Laboratories, Rahway Basic Chemistry NMR, NJ, USA.

†† These IC_{50} values are for racemic samples for which the unnatural (−)-enantiomer is expected to be inactive. They are lower than that reported for the natural (+)-aspercyclide (IC_{50} 200 μM, ref. 7) but our ELISA protocol does differ from that reported, see ESI.†

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