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Enantioselective synthesis of (+)-aspercyclide A

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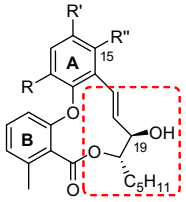
ABSTRACT

An efficient synthesis of the natural IgE-FcεRI PPI inhibitor (+)-aspercyclide A (**1**) was achieved through the use of a Krische iridium-catalyzed diastereo- and enantioselective alkoxyallylation to form the key mono-protected *anti*-diol intermediate **4**, in high optical purity. A derivative of the natural product (**15**), containing an oxathiazine dioxide ring in place of the ring-A hydroxyaldehyde unit has also been prepared and found to display comparable ELISA activity to the parent compound, indicating that the aldehyde group is not the key determinant of activity.

In 2004, Singh et al. isolated (+)-aspercyclide A (**1**) and congeners B and C, through activity-guided fractionation of an *Aspergillus* sp. soil bacterium sourced from Tanzania (Fig. 1).[1] Aspercyclide A was shown, via an enzyme-linked immunosorbent assay (ELISA), to inhibit the binding of human IgE to its high affinity receptor FcεRI with an IC_{50} of ~200 μM. Therefore, aspercyclide A and its analogues constitute interesting leads for the development of anti-asthma and anti-allergic therapeutics.[2]

In 2005, Fürstner and co-workers reported the first synthesis of (+)-aspercyclide C in which the chirality was introduced via a Duthaler–Hafner alkoxyallylation reaction employing stoichiometric (*S*,*S*)-taddol and macrocyclization was via ring-closing metathesis (RCM).[3a] Similar syntheses of (+)-aspercyclide C and its C12 methyl ether, also deploying RCM macrocyclization but using D-ribose and L-tartaric acid as the sources of chirality, were subsequently reported by the Ramana[3b] and Prasad[3c] groups, respectively. In 2009, Fürstner and co-workers reported an approach to (+)-aspercyclide A employing (*S*)-glycidol to establish the C20 stereocentre and an intramolecular Nozaki–Hiyama–Kishi (NHK) reaction to effect macrocyclization with concomitant diastereoselective *anti*-1,2-diol formation.[4] Subsequently, we reported a synthesis of (±)-aspercyclide A and its C19 methyl ether employing a diastereoselective Takai–Utimoto alkoxyallylation to establish the *anti*-1,2-diol function followed by either a Heck–Mizoroki[5] or a germyl-Stille macrocyclization reaction.[6] Most recently, Sato and co-workers reported the first asymmetric synthesis of (+)-aspercyclide A (14 steps from salicylic acid, 20% overall yield).[7]



1, R = H, R' = OH, R'' = CH=O, (+)-aspercyclide A
R = H, R' = OH, R'' = CH_2OH, aspercyclide B
R = OH, R' = H, R'' = H, (+)-aspercyclide C

Figure 1. Structures of the aspercyclides, with numbering system and *anti*-diol unit highlighted.

Their route featured a Sharpless asymmetric epoxidative desymmetrization catalyzed by sub-stoichiometric (−)-DIPT to establish the *anti*-1,2-diol motif, and using an elegant and potentially biomimetic intramolecular oxidative diaryl etherification to close the macrocycle.

Herein, we describe an enantioselective synthesis of (+)-aspercyclide A and also a ring-A derivative in which the intramolecularly hydrogen-bonded C14 phenol and C15 aldehyde have been replaced by an oxathiazine dioxide ring moiety. Our synthesis employs an iridium-catalyzed diastereo- and enantioselective *anti*-alkoxyallylation developed by Krische and co-workers to establish the two stereocentres.[8] This group have developed protocols for diastereo- and enantioselective carbonyl allylation/crotylation and related reactions[9] via the iridium-catalyzed transfer hydrogenation.[10] We envisaged using their *anti*-alkoxyallylation

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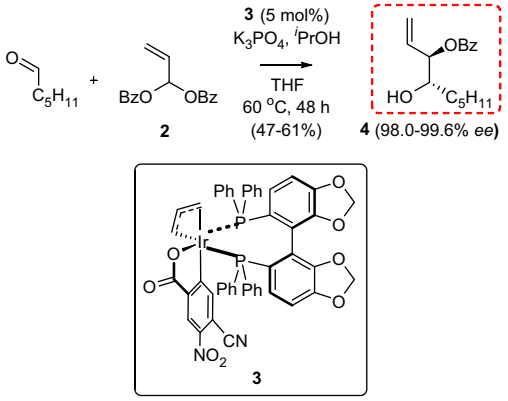
method, wherein an allyl *gem*-dicarboxylate acts as the allyl donor,[8] to obtain optically pure mono-protected *anti*-diol **4**, which could then be taken through to (+)-aspercyclide A by a route analogous to that which we developed in our racemic synthesis.[5] Due to problems with migration of an acetyl protecting group during the initial optimization of the reaction, the method described by Krische and co-workers involves acylative capping of the crude mono-protected diol to give diester products.[8] However, we suspected that the migration would not occur with the mono-benzoate. Gratifyingly, this was indeed the case, eliminating the need for a potentially difficult selective deprotection of the homoallylic alcohol over the allylic alcohol. Thus, in our hands, treatment of *n*-hexanal with *gem*-dibenzoate **2** and iridium catalyst **3** furnished mono-protected *anti*-diol **4** in moderate to good yields (47–61%) and high optical purity (98.0–99.6% ee) on both small and medium scale (i.e., 20–400 mg of hexanal) (Scheme 1).

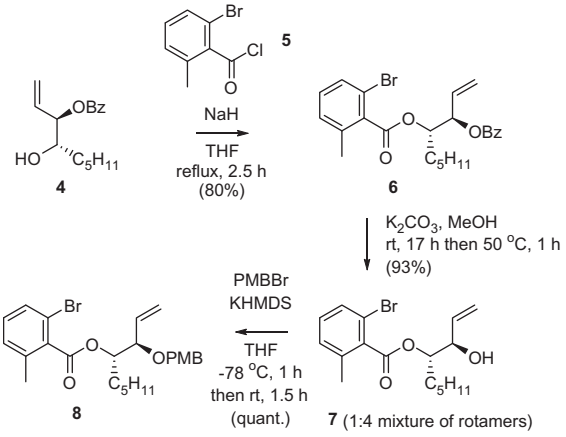
Initially, we carried this Bz-protected *anti*-diol forward in the synthesis, but we were unable to achieve Heck–Mizoroki macrocyclization, possibly due to π-allyl palladium formation. We therefore decided to switch protecting groups early on in the synthesis. Thus, treatment of *anti*-diol **4** with sodium hydride and 2-bromo-6-methylbenzoyl chloride (**5**) furnished benzoic ester **6** in good yield. Removal of the benzoate protecting group was achieved by treatment with K_2CO_3 in methanol[11] giving alcohol **7** as what we believe to be a mixture of rotamers (1:4) in excellent yield (Scheme 2).[12]

The presence of these rotamers is likely due to hindered rotation about the aryl–carbonyl carbon bond, the magnitude of the barrier for which is presumably amplified by internal hydrogen bonding between the OH and the carbonyl group (cf. compounds **6** and **8**). Re-protection of the alcohol as the PMB ether by treatment with KHMDS in the presence of PMBBr[13] furnished Ullmann coupling precursor **8** in quantitative yield (Scheme 2). Cu-mediated Ullmann coupling with functionalized phenol **9**[5] proceeded in moderate yield using 30 mol % of either a Cu(I) or Cu(II) catalyst in pyridine.[14] However, employing a mixed Cu(I)/Cu(II) catalyst system (1:1, 30 mol % copper in total) resulted in an improved yield of 72% of biaryl ether **10** (Scheme 3).

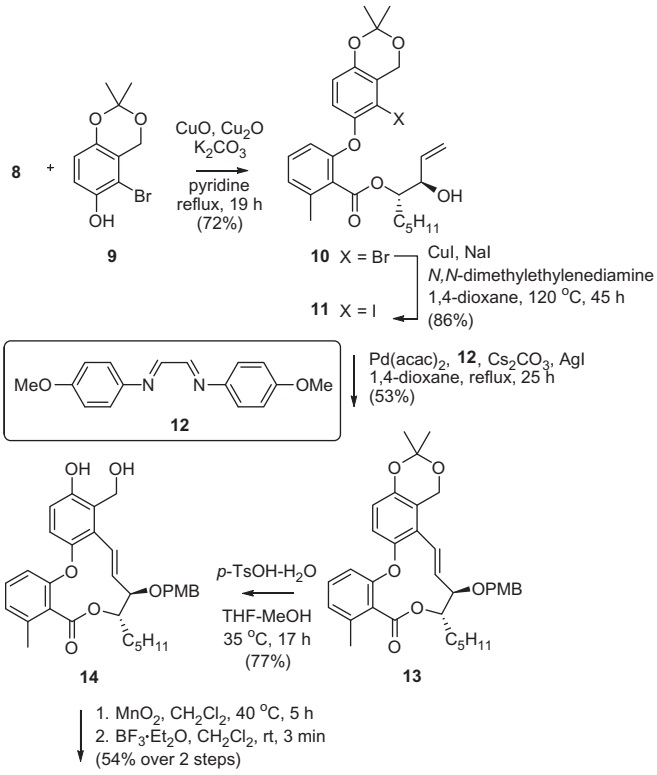
Copper-mediated aromatic Finkelstein halogen exchange[15] then gave the corresponding aryl iodide **11**, which underwent the Heck–Mizoroki[16] macrocyclization in the presence of AgI (to suppress dibenzofuran formation through direct arylation via C–H activation[17]) to afford macrocycle **13** in 53% isolated yield. *p*-TsOH-catalyzed acetonide removal proceeded smoothly to afford diol **14** in good yield. Oxidation of the benzyl alcohol with MnO_2 followed by removal of the PMB ether with $BF_3{\cdot}Et_2O$ gave (+)-aspercyclide A (**1**) in 54% yield from **14** (Scheme 3). The optical rotation measured for our material (+278) is higher than that reported by Singh et al. (+191)[1] and Sato and co-workers (+196)[7],



Scheme 1. Synthesis of optically pure *anti*-diol **4**.



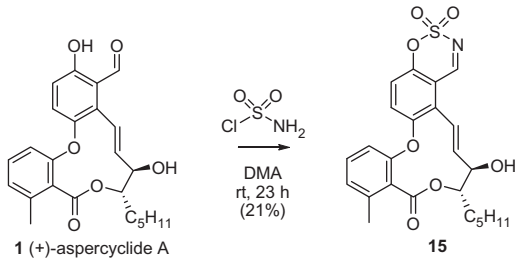
Scheme 2. Synthesis of Ullmann coupling precursor **8**.



Scheme 3. Completion of the synthesis of (+)-aspercyclide A (**1**).

however the circular dichroism (CD) spectra recorded for our material match that recorded for an original sample of (+)-aspercyclide A (kindly provided by Merck). The overall yield from hexanal was 4.8–6.2% over the 10 steps.

A significant concern about the utility of (+)-aspercyclide A as a lead for further development towards a therapeutic agent for asthma and allergy is the presence of the ring-A aldehyde moiety. Aldehydes can potentially react with protein lysine side chains to form Schiff bases leading to unselective irreversible toxicity.[18] To discount this mode of reactivity as being responsible for the bioactivity of (+)-aspercyclide A we decided also to prepare a derivative of aspercyclide A which did not contain an aldehyde group—compound **15**. We targeted a cyclic structure designed to loosely mimic ring-A plus the six-membered ring formed by the intramolecularly H-bonded hydroxyaldehyde motif. We envisaged



Scheme 4. Synthesis of non-aldehydic derivative **15** of (+)-aspercyclide A.

benzoxathiazine-2,2-dioxide analogue **15** to be accessible through treatment of (+)-aspercyclide A with sulfamoyl chloride,[19] as described by Du Bois and co-workers.[20]

Thus, benzoxathiazine analogue (+)-**15** was obtained in 21% yield by treatment of (+)-aspercyclide A (**1**) with sulfamoyl chloride in dry dimethylacetamide (DMA) at room temperature (Scheme 4).[20]

The ability of compound (+)-**15** to inhibit the human IgE-FcεRIα protein–protein interaction (PPI) was assessed using an ELISA (see Supplementary data) which revealed that it displayed only marginally reduced potency as compared to the parent natural product: (+)-**15**, IC_{50} = 160–460 μM, cf. (+)-**1**, IC_{50} = 50–200 μM.[1,6]

In conclusion, an efficient route to (+)-aspercyclide A of high optical purity has been developed. The route features a Krische iridium-catalyzed diastereo- and enantioselective *anti*-alkoxyallylation to establish the two stereocentres (C19 and C20) and a Heck macrocyclization. A derivative of the natural product (**15**), lacking the benzaldehyde ring-A moiety has been found to exhibit comparable inhibition of the human IgE-FcεRI PPI to that of the parent natural product in an ELISA, which indicates that the activity of (+)-aspercyclide A cannot be attributed to non-specific irreversible Schiff base formation with protein lysine residues.

We are currently in the process of preparing a number of additional aspercyclide A analogues to enable further studies into the structure activity relationship (SAR) of aspercyclide A. The results of these studies will be reported in due course.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.07.038.

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12. The rotamers of alcohol **7** can be separated by silica gel chromatography. Each rotamer was taken through the synthesis to (+)-aspercyclide A. After PMB-protection (→ 8), all ^1H and ^{13}C NMR data and optical rotations of intermediates were identical irrespective of the starting rotamer. Furthermore, CD spectra of the material obtained from both rotamers were identical and matched that 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. Resubjection of a pure sample of the *minor* rotamer from the Bz-deprotection step, to the deprotection conditions (K_2CO_3 in MeOH, 50 °C, 1 h), resulted in the isolation of a 4:10 mixture favoring the *major* isomer from the Bz-deprotection step. This supports the notion that the two isomers are rotamers.
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