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An expedient stereoselective route to the ACE tricyclic core of manzamine A via a palladium-catalysed arylative allene spirocyclisation cascade

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ABSTRACT

Application of a novel palladium-catalysed stereoselective arylative allene spirocyclisation cascade as the key step for the construction of the ACE tricyclic core of manzamine A is described.

Complexity building cascade reactions are attractive for synthetic chemists particularly when the cascade products are themselves desired or, are useful intermediates in complex (natural product) target synthesis. Such processes allow the formation of new carbon–carbon or carbon–heteroatom bonds, the generation of new, often contiguous stereocentres and the introduction of desirable functionality in one pot, in an atom-economic and efficient manner.[1]

We recently reported a novel palladium-catalysed stereoselective allene spirocyclisation cascade reaction[2] to form densely functionalised spirocyclic structures that are common motifs in many natural products. As part of our ongoing programme in the development and application of cascade reactions[3] in total synthesis, we wished to employ this reaction cascade as a key step in the synthesis of an architecturally complex natural product. Herein, we present our findings leading to an efficient synthesis of the ACE tricyclic core of the marine alkaloid, manzamine A (**1**).

Manzamine A (**1**), first isolated in 1986 by Higa and co-workers[4] from a marine sponge in the Okinawa Sea has been reported to show a number of significant biological properties, including insecticidal, antibacterial, anti-inflammatory, but perhaps most notably, antimalarial activity.[5] Over 90% of activity in *Plasmodium berghei* was inhibited after a single injection of manzamine A in infected mice.

It also exhibits high in vitro activity against P388 mouse cells (IC_{50} 0.07 μg/mL). Manzamine A (**1**) contains eight rings in total; five aliphatic (ABCDE) including one 13-membered and one 8-membered ring, a β-carboline system, two *Z*-olefins and five stereocentres including four contiguous and two quaternary centres.

The antitumor and antimalarial properties of manzamine A, as well as its complex structure makes it a desirable target for synthesis. To date, there have been many publications[6] describing synthetic efforts towards the core and four total syntheses by Winkler,[7] Martin,[8] Fukuyama[9a] and most recently, by our group.[9b]

Our retrosynthetic analysis identified the tricyclic structure **4a** as a key late stage intermediate possessing three of the five stereogenic centres, the 6,5-spirocyclic core and the β-carboline moiety (Scheme 1). A chemoselective reduction of the piperidinone ring[10] followed by a precedented one-carbon homologation of the pyrrolidinone carbonyl would give **3**. A carbocyclisation from the conjugated double bond onto the nitrile carbon atom followed by hydrolysis of the resulting imine would give **2**. Only two steps remain; a stereoselective organometallic addition followed by a ring-closing metathesis would furnish manzamine A (**1**).

We envisaged that **4a** could be accessed directly from amide bicycle **5** and iodide **6** via our stereoselective arylative allene spirocyclisation reaction cascade.[2a] However, this would be non-trivial as the relative stereochemistry of the major cascade product (dr range 3:1–47:1) in the original methodology was not matched to that needed for the core of manzamine A (**1**). Therefore our task was to maintain reactivity in the cascade, whilst inverting the stereocontrol. Unlike any previous syntheses, this approach would install the β-carboline, key for biological activity, relatively early in the synthesis allowing access to potentially biologically interesting manzamine A precursors.

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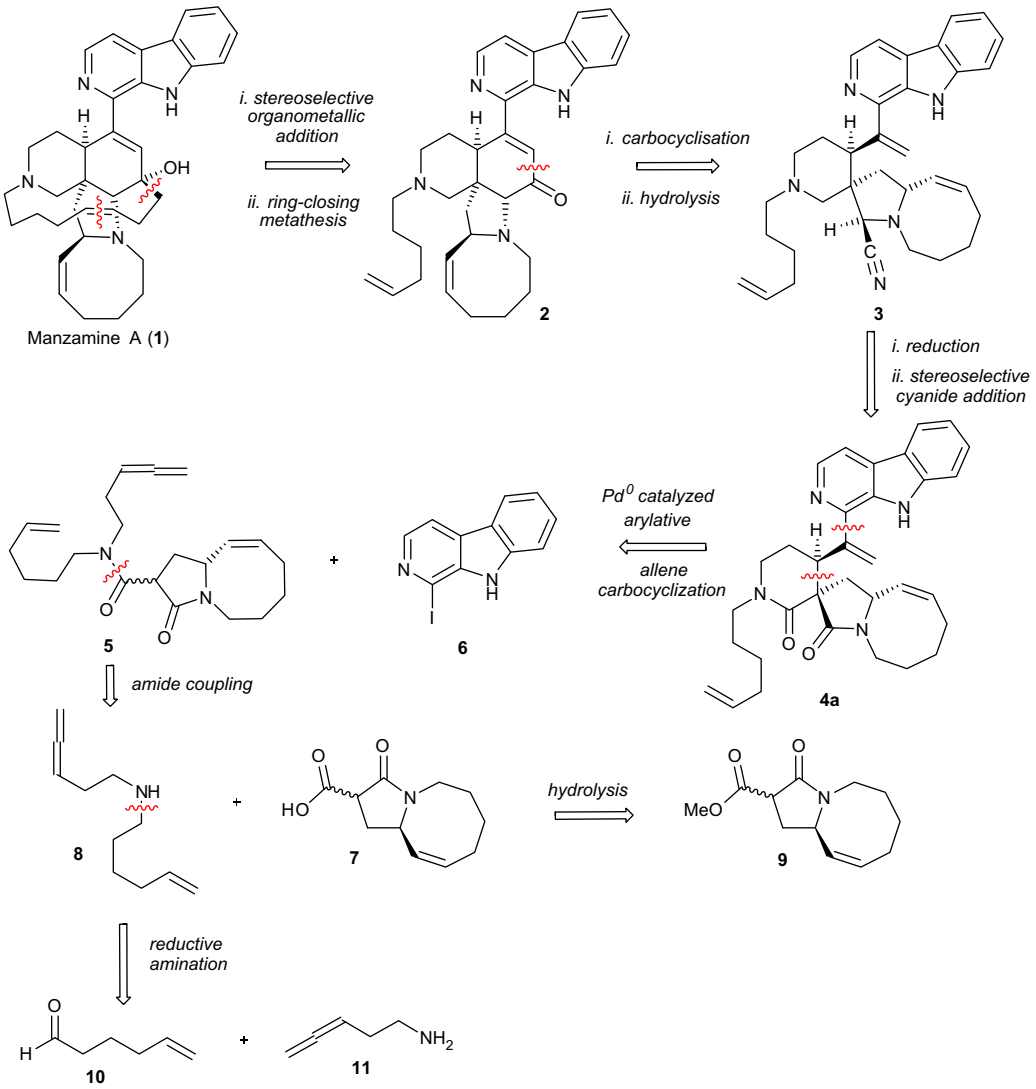


Scheme 1. Retrosynthetic analysis of manzamine A.

Spirocyclisation precursor **5** would be accessible from amine **8** and acid **7** through amide coupling. Acid **7** would come from known methyl ester **9**.[10,12] Amine **8** would be synthesised from a reductive amination of hex-5-enal (**10**) and penta-3,4-diene-1-amine (**11**). Overall, four simple fragments **6**, **9**, **10** and **11** would be required to access rapidly complex intermediates in our synthesis towards manzamine A.

Penta-3,4-dien-1-amine (**11**) was prepared in three steps from commercial 3-butyn-1-ol (**12**) (Scheme 2). Crabbé homologation of **12** followed by standard mesylation gave mesylate **13** in 27% yield over two steps. Nucleophilic substitution with sodium azide in warm DMSO (50 °C) followed by Staudinger work-up efficiently gave the desired amine **11** which was used crude in the next step.

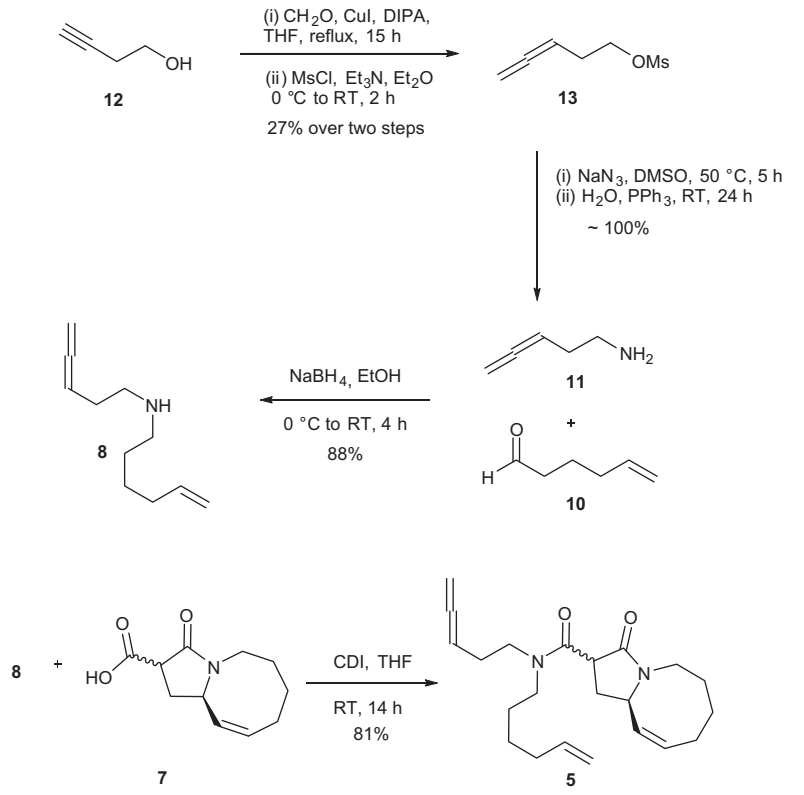
Reductive amination with aldehyde **10** (made in 82% yield via a Swern oxidation of 5-hexen-1-ol[11]) with sodium borohydride in ethanol gave the desired secondary amine **8** in 88% yield. Standard CDI coupling of amine **8** with acid **7** (made via lithium hydroxide hydrolysis of known methyl ester **9**[10,12]) afforded **5** in 81% yield. The robustness and scalability of the chemistry allowed for multi-gram quantities of **5** to be synthesised.

The last remaining fragment, iodide **6**, was prepared directly from bromide **14**[13,14] via formation of the dianion[13] followed by an iodine quench (Scheme 3). With **6** in hand the key palladium-catalysed arylative allene spirocyclisation cascade was investigated.

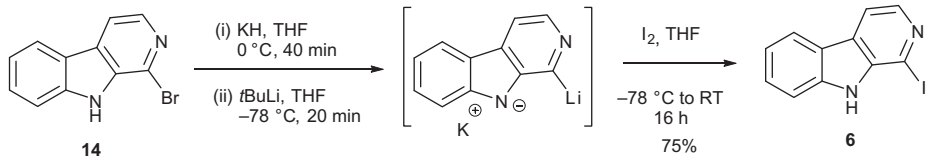
To validate that pro-nucleophile **5** and iodide **6** were reactive coupling partners for the spirocyclisation cascade, control experiments with each substrate were carried out with a coupling partner from our published study[2a] under optimised conditions (Scheme 4).

Accordingly, the cyclisation of iodide **6** with known allene lactam **15**[2a] under standard conditions was performed. Pleasingly, heteroarylated spirocyclic lactam **16** was obtained as a single diastereomer in an unoptimised 18% yield. However, when allene **5** was reacted with known iodide **17**, no product was obtained under standard conditions,[2a] even after prolonged heating (Scheme 4). This model reaction highlighted the inherent lack of reactivity of **5** (presumably due to the low acidity of the methine proton combined with the sterically demanding bicyclic pro-nucleophile **5**), but provided the ideal test system to alter conditions to regain reactivity. Pleasingly, application of the Burton conditions[15] which employed LHMDS as base and $Pd(dppf)Cl_2$ with copper iodide at reflux in THF gave the desired spirocycle **18** as a mixture of two major diastereomers (**18a,18b**) in 45% yield.

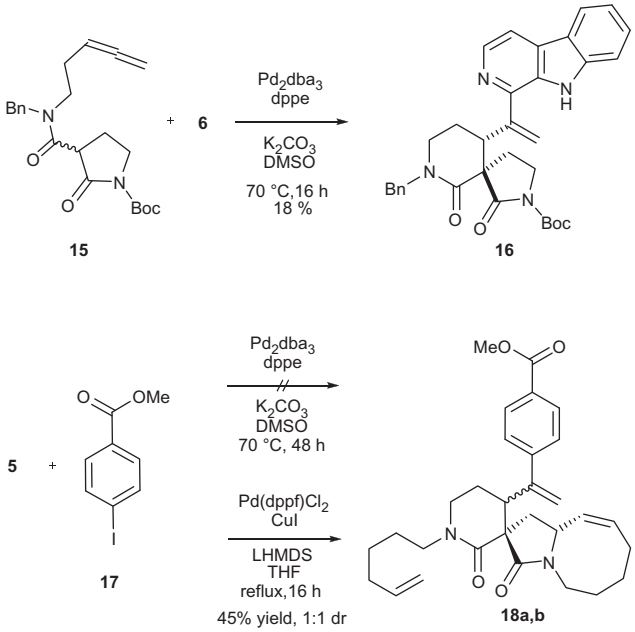
Importantly, when these conditions were applied to the real system (**5** + **6**) the desired product **4**, as a 1:1 mixture of two of



Scheme 2. Synthesis of key building blocks **5** and **8**.



Scheme 3. Synthesis of β-carboline **6**.



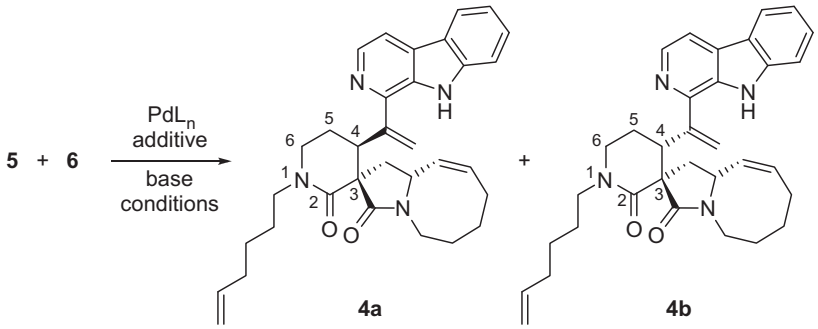
Scheme 4. Validation of key building blocks **5** and **6**.

the possible four diastereomers, **4a** and **4b**, albeit in 6% yield (Table 1, entry 1) was formed. A subsequent optimisation study via screening of solvent, base and source of palladium was carried out and selected notable examples are presented in Table 1.

The use of dimethyl sulfoxide gave, as expected based on the original methodology, the undesired diastereomer (Table 1, entry 2). Use of less polar, higher boiling solvents, such as toluene and 1,4-dioxane, biased the diastereoselectivity towards the desired diastereomer (**4a**:**4b** = 3:2) for manzamine A (**1**) and increased the yield (Table 1, entries 3 and 4). Lower temperatures led to a decrease in yield (Table 1, entry 5) while changing the base to KHMDS or NHMDS inhibited reactivity (Table 1, entries 6 and 7). It was found that CuI was not required and omitting it slightly increased the reaction yield (Table 1, entry 8). Attempts to improve the diastereoselectivity via screening a range of chiral ligands, different palladium sources and counter ions (Table 1, entries 9–11), unfortunately led to no significant improvement in diastereoselectivity at C-4. However, increasing the amount of allene **5** to 1.5 equiv relative to the β-carboline **6** furnished the desired product in a good 62% yield and acceptable 3:2 diastereomeric ratio (Table 1, entry 12).

The observation of only one epimer at C-3 led us to believe that the stereochemistry at the newly formed quaternary stereogenic centre[16] (C-3) was fully controlled by the 8,5-bicycle (rings CE),

Table 1
Optimisation of Pd^0-catalysed arylative allene spirocyclisation[a]



Entry	Solvent	Base	Temp (°C)	PdL_n	Additive	Yield (%) (dr **4a**:**4b**)	
1	THF	LHMDS	66	$Pd(dppf)Cl_2$	CuI	6	1:1
2	DMSO	Cs_2CO_3	70	$Pd(dppf)Cl_2$	—	21	1:3
3	Toluene	LHMDS	95	$Pd(dppf)Cl_2$	CuI	39	3:2
4	1,4-dioxane	LHMDS	95	$Pd(dppf)Cl_2$	CuI	40	3:2
5	toluene	LHMDS	60	$Pd(dppf)Cl_2$	CuI	16	1:1
6	1,4-dioxane	KHMDS	95	$Pd(dppf)Cl_2$	CuI	nr	—
7	1,4-dioxane	NHMDS	95	$Pd(dppf)Cl_2$	CuI	nr	—
8	1,4-dioxane	LHMDS	95	$Pd(dppf)Cl_2$	—	45	3:2
9	1,4-dioxane	LHMDS	95	$Pd(dppf)Cl_2$	$AgSbF_6$	21	3:2
10	1,4-dioxane	LHMDS	95	$Pd(PPh_3)_4$	JOSIPHOS	29	3:2
11	1,4-dioxane	LHMDS	95	$Pd(OAc)_2$	(*R*)-BINAP	21	2:1
12[b]	1,4-dioxane	LHMDS	95	$Pd(dppf)Cl_2$	—	62	3:2

[a] Unless otherwise stated reactions were carried out on a 50 mg scale for 16 h with **5** (1 equiv), **6** (1.5 equiv), base (1.2 equiv), 2.5% Pd-complex, 5% ligand, 5% CuI, 0.16 M.
[b] Compound **5** (1.5 equiv), **6** (1.0 equiv) and LHMDS (1.7 equiv).

and therefore control at the newly formed C-4 stereocentre was a result of other factors (Fig. 1).

The use of non-polar solvents indeed furnished the major diastereomer with the desired C-4 stereochemistry (**4a**) which we postulate is due to the favourable Pd^{II} chelation to the enolate system as well as the π-allyl cation (Fig. 1). However, the minor and undesired epimer at C-4, **4b**, is possibly formed in a transition state where the chelation is disrupted.[17,18]

The diastereomers were separated by preparative HPLC and nOe experiments confirmed their relative stereochemical configurations (Fig. 2).

In summary we have successfully applied the palladium-catalysed arylative allene spirocyclisation cascade as a key step in a novel and expedient route to the ACE tricyclic core of manzamine A, where two new carbon–carbon bonds and two new stereocentres, and the majority of the carbon skeleton of manzamine A were installed in one step. Systematic modification of the reaction conditions allowed tuning of the diastereoselectivity in favour of the desired diastereomer for manzamine A synthesis. Importantly, our route allows the relatively early incorporation of

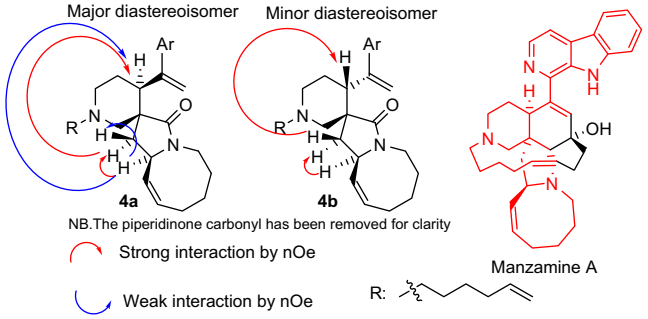


Figure 2. NOE data.

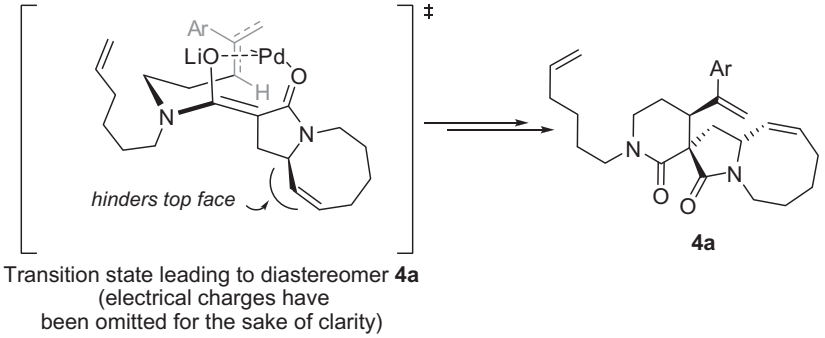


Figure 1. Postulated model to rationalise the origin of the diastereoselectivity.

the β-carboline moiety, critical for biological activity, and therefore could lend itself readily to analogue preparation of manzamine A precursors through modification of the (hetero)aryl group. This suitably functionalised advanced key intermediate could lead to manzamine A in only a handful of steps and studies are ongoing in our laboratories to realise this.

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Supplementary data

Supplementary (characterisation data for all novel compounds) data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.10.111.

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