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An enantioselective synthesis of the bicyclic core of the marine natural product awajanomycin

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ABSTRACT

A concise stereoselective synthesis of the N-benzylated bicyclic core of the marine natural product awajanomycin is described starting with naturally occurring L-alanine. Key steps in the synthesis include a ring-closing metathesis to establish a δ-lactam ring followed by a stereoselective hydroxylation to instal the quaternary centre.

Awajanomycin (**1**) is a highly functionalised secondary metabolite from the marine-derived fungus *Acremonium* sp.[1] It was isolated and characterised in 2006 during a programme designed to isolate new structures with novel biological activity. It has attracted interest due to its cytotoxic activity, inhibiting the growth of human lung adenocarcinoma cells (A549 cells) with an IC_{50} value of 27.5 μg mL^{-1}.[1] At present, only one full total synthesis of the enantiomer of this molecule is present in the literature, which has helped to establish the complete stereochemical profile of the molecule as 3*R*,5*R*,6*S*,8*S*,11*S*.[2] Additionally, one racemic approach to the core skeleton has been reported.[3] In addition to awajanomycin, the ring-opened product **2** has also been isolated (Fig. 1).[1]

A number of structural features of these molecules make them worthy of further investigation. Firstly, the bicyclic γ-lactone-δ-lactam core of **1** is rare in natural products and few reports are given in the literature for the synthesis of this type of structure. It has been noted that **2** is rather less active than **1** and this suggests that the rigid core of the molecule is responsible, at least in part, for its biological activity.[1]

At the outset of our programme, only the relative stereochemistry of the awajanomycin core had been elucidated and the stereochemistry of the C11 hydroxy group was unknown. Our first thoughts directed towards an enantioselective total synthesis of awajanomycin involved the disconnection outlined in Scheme 1 which would employ the union of aldehyde **4** derived from commercially available D- or L-alanine with diethyl malonate (**3**). In this way we believed that we would be able to control the absolute ste-

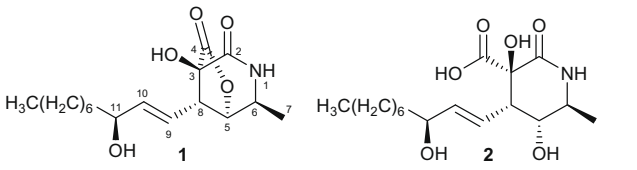
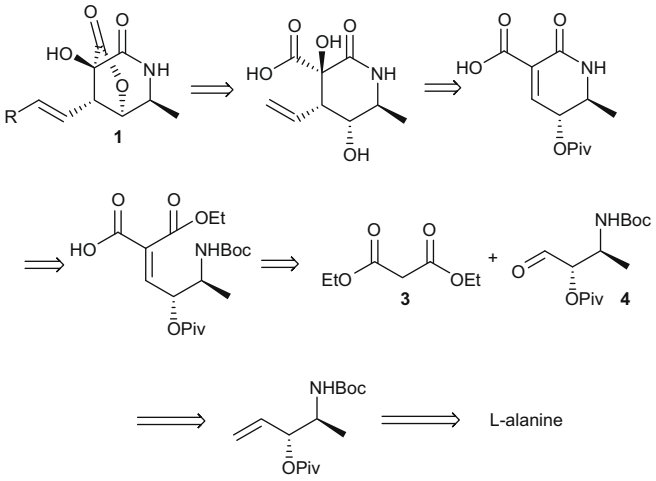


Figure 1.



Scheme 1.

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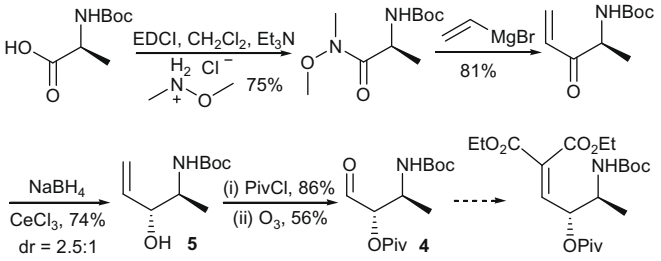


Scheme 2.

reochemistry of each newly created centre via stereorelay from the C6 centre derived from the amino acid. In this way both enantiomers of the natural product core would be available to us to compare the analytical data to ascertain the absolute stereochemistry of the naturally occurring material.

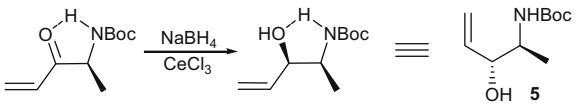
Preparation of the chiral aldehyde **4** was achieved without incident by the method outlined in Scheme 2 to yield an inseparable 2.5:1 mixture of diastereoisomers in favour of the alkene **5**. The yields and diastereoselectivity of this sequence are comparable to those of similar reactions found in the literature.[4]

The diastereoselectivity of the reduction can be explained by an internal hydrogen bond that restricts the rotation of the C5–C6 σ-bond resulting in hydride delivery from the opposite face to the methyl substituent (Scheme 3).

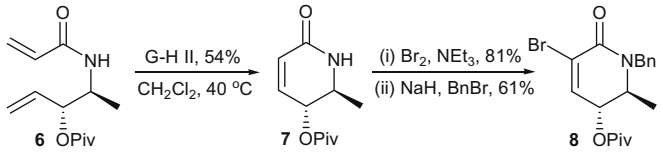
Treatment of **5** with ozone gave the aldehyde **4** in good yield. Disappointingly, however, exposure of this aldehyde to diethyl malonate under classic Knoevenagel conditions yielded none of the desired unsaturated diester and only the starting materials were isolated. It seems that the aldehyde is unstable to the reaction conditions, and consequently only polymeric material was obtained from the reaction.

Despite this setback, we were keen to use the intermediate **5** since two of the stereogenic centres are correctly installed. We therefore decided to modify our strategy to include a ring-closing metathesis step which would allow us to construct the six-membered ring of awajanomycin while still utilising the intermediate **5**.[5] The modified disconnection is shown in Scheme 4.

Pivaloyl protection of **5** followed by TFA-mediated Boc deprotection and then treatment with acryloyl chloride yielded the unsaturated amide **6** in good yield. Dropwise addition of the Grubbs–Hoveyda 2nd generation catalyst (G–H II) to a dichloromethane solution of **6** at reflux then yielded the cyclised product **7** in 54% yield. We were pleased to observe however that the 2.5:1 diastereoisomeric mixture was easily separable by column chromatography, and as such, the major (*S*,*R*) diastereoisomer was readily isolated in pure form (Scheme 5).



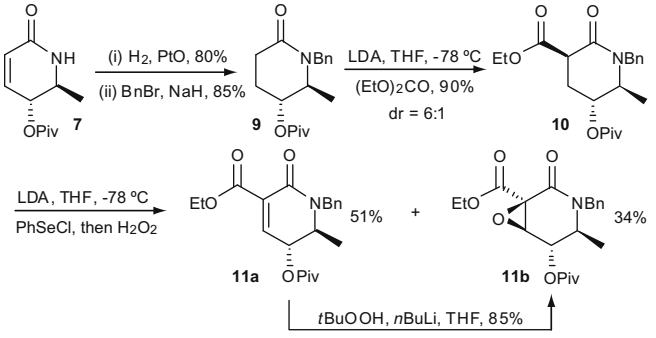
Scheme 3.



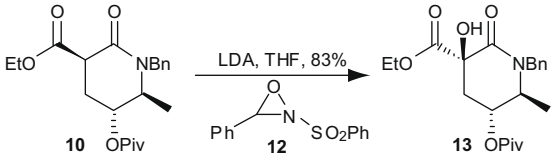
Scheme 5.

At this stage our intention was to introduce a halogen atom alpha to the amide carbonyl group in order that we could introduce the ester functionality at this position. Disappointingly however, despite the initial bromination proceeding smoothly, all our attempts to convert compound **8** into the ester failed. Attempts to form reactive organometallic species (lithium, zinc and magnesium)[6] at low temperatures by metal–halogen exchange followed by quenching with methyl chloroformate generally resulted in only the reduced non-halogenated compounds on work up. Similarly, attempts at introducing the ester via palladium-catalysed carbonylation protocols also met with failure.[7] Various other methods from the literature for introducing this group were also attempted, however, none were successful in our hands.

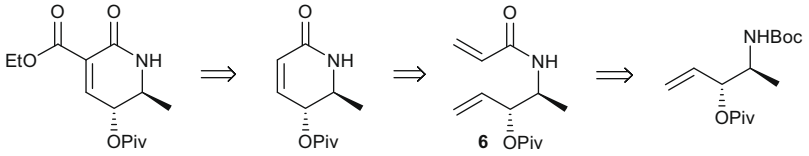
Given the difficulties with utilising the bromine functional group we decided to seek an alternative route. Removal of the alkene of **7** by hydrogenation followed by benzyl protection of the nitrogen atom was effected in order that we might be able to functionalise the 3-position via standard enolate chemistry.[8] Indeed, we were pleased to observe that deprotonation of the saturated species with LDA followed by treatment with diethyl carbonate yielded the ester **10** in good yield as a 6:1 mixture of diastereoiso-



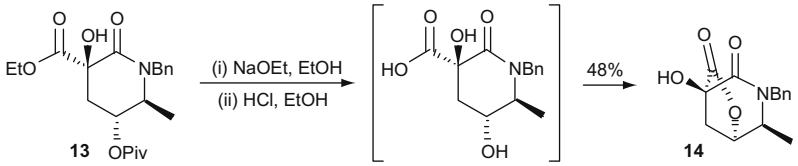
Scheme 6.



Scheme 7.



Scheme 4.



Scheme 8.

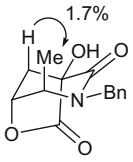


Figure 2.

mers. Interestingly, further enolate formation followed by treatment with phenyl selenyl chloride and aqueous hydrogen peroxide work-up led not only to the expected alkene **11a**, but also to the epoxide **11b** directly. Presumably selenide elimination is followed by rapid nucleophilic oxidation of the extremely electron-deficient alkene. The product was also obtained as a single diastereoisomer, presumably due to the steric bulk of the pivaloyl group shielding the lower face of the alkene. The remainder of the material was easily converted into the epoxide, again as a single diastereoisomer, by treatment with the lithium salt of *tert*-butyl hydroperoxide generated in situ from *n*-butyllithium and the peroxide. This result was particularly welcome as all but one of the stereogenic centres were now installed with the appropriate stereochemistry for the awajanomycin core. The centres at C4, C5 and C6 have the correct relative stereochemistry and the centre at C8 has the appropriate inverted stereochemistry which will allow us to instal the side chain via S_N2 inversion with an organocopper reagent (Scheme 6). Unfortunately, as yet, our attempts to achieve the epoxide ring opening with a variety of organometallic reagents have resulted in only trace amounts of products being obtained.

At this stage we decided to modify our procedure and focus on the synthesis of the bicyclic core of the molecule in order to validate our strategy and include the side chain (C9–18) at a later stage. Starting with compound **10**, sequential enolate formation followed by treatment with the oxaziridine reagent[9] **12** gave the alcohol **13** as a single diastereoisomer with the desired stereochemistry for the awajanomycin core (Scheme 7).

With the compound **13** in hand all that was required to complete the synthesis of the core of the natural product was the removal of the ethyl ester and pivaloyl groups. We reasoned that these would be simultaneously removed under basic conditions and that under these conditions the molecule would spontaneously form the second five-membered ring of the awajanomycin core. We were pleased to observe that this occurred smoothly, albeit in moderate yield at this stage, to yield the bicyclic molecule **14** in good yield (Scheme 8).

Stereochemical confirmations have been made on the basis of NOE experiments which revealed that in the bicyclic structure, irradiation of the methyl group at C7 resulted in a 1.7% enhancement of the axial proton resonance at C8 (Fig. 2) confirming the (3*R*,5*R*,6*S*) stereochemistry of the core. A number of attempts have been made to remove the benzyl-protecting group (H_2/Pd/C, NH_4HCO_2/Pd/C, Pearlman's Catalyst, H_2/PtO),[10,11] however, these have so far been proved unsuccessful.

In conclusion, we have described a concise enantioselective synthesis of the N-benzylated core of the marine natural product awajanomycin starting with L-alanine. One of the key features of the synthesis is the capacity to prepare either enantiomer of the final product simply by starting with either D- or L-alanine since stereocontrol is achieved by stereorelay in the order C6→C5→C3. We have also demonstrated a potential strategy for the inclusion of the side chain at C8 with stereochemical control. Work is underway in our laboratory to refine the synthesis in order to complete the full total synthesis of awajanomycin.

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Supplementary data

Supplementary data (spectroscopic assignments and experimental procedures) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.01.123.

References and notes

1. Jang, J.-H.; Kanoh, K.; Adachi, Y. S. *J. Nat. Prod.* **2006**, *69*, 1358.
2. Fu, R.; Chen, J.; Guo, L.-C.; Ye, J. L.; Ruan, Y. P.; Huang, P.-Q. *Org. Lett.* **2009**, *11*, 5242.
3. Hiroya, K.; Kawamoto, K.; Inamoto, K.; Sakamoto, T.; Doi, T. *Tetrahedron Lett.* **2009**, *50*, 2115.
4. Kano, S.; Yokomatsu, T.; Iwasawa, H.; Shibuya, S. *Tetrahedron Lett.* **1987**, *28*, 6331.
5. For a similar approach to unsaturated lactones, see: (a) Bassetti, M.; Pasquini, C. *J. Org. Chem.* **2007**, *72*, 6067; For reviews on ring-closing metathesis, see: (b) Grubbs, R. H. *Tetrahedron* **2004**, *60*, 7117; (c) Schrock, R. R.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2003**, *115*, 4740; For a RCM approach to lactams, see: (d) Sośnicki, J. G. *Tetrahedron Lett.* **2009**, *50*, 178.
6. Thibonnet, J.; Vu, V. A.; Bérillon, L.; Knochel, P. *Tetrahedron* **2002**, *58*, 4787.
7. (a) Martin, L. D.; Stille, J. K. *J. Org. Chem.* **1982**, *47*, 3630; (b) Brennfuhrer, A.; Neumann, H.; Klaus, S.; Riermeier, T.; Almena, J.; Beller, M. *Tetrahedron* **2007**, *63*, 6252.
8. For an enantioselective synthesis of a lactam with the same stereochemical profile as 9, see: Andrés, J. M.; Pedrosa, R.; Pérez-Encabo, A. *Tetrahedron Lett.* **2006**, *47*, 5317.
9. For a review of oxaziridine oxidation of enolates, see: Davis, F. A.; Chen, B.-C. *Chem. Rev.* **1992**, *92*, 919.
10. Chen, C.-Y.; Huang, Y.-P.; Kan, W. M. *Tetrahedron Lett.* **2003**, *44*, 1039.
11. Ram, S.; Spicer, L. D. *Tetrahedron Lett.* **1987**, *28*, 515.