## Synthesis of the DEF-*bis*-spiroacetal of spirastrellolide A exploiting a double asymmetric dihydroxylation/spiroacetalisation strategy<sup>†</sup>

Ian Paterson,\* Edward A. Anderson, Stephen M. Dalby, Jong Ho Lim, Philip Maltas and Christian Moessner

Received (in Cambridge, UK) 4th September 2006, Accepted 6th September 2006 First published as an Advance Article on the web 20th September 2006 DOI: 10.1039/b612697a

An efficient synthesis of the  $C_{26}$ - $C_{40}$  tricyclic [5,6,6]-*bis*spiroacetal segment of the marine macrolide spirastrellolide A has been developed, exploiting a novel double Sharpless asymmetric dihydroxylation/spiroacetalisation sequence.

Spirastrellolide A (1, Fig. 1) is a structurally intriguing antimitotic macrolide isolated by Andersen and co-workers from the Caribbean sponge *Spirastrella coccinea*.<sup>1,2</sup> It induces premature cell mitosis and displays potent ( $IC_{50} = 1 \text{ nM}$ ) and selective inhibition of protein phosphatase 2A, and represents a potential candidate for the development of antitumour therapeutic agents.<sup>3</sup> Despite extensive NMR spectroscopic analysis of its methyl ester derivative **2**,<sup>2</sup> the relationship between four stereoclusters ( $C_3$ – $C_7$ ,  $C_9$ – $C_{24}$ ,  $C_{27}$ – $C_{38}$  and  $C_{46}$ ) and the absolute configuration remain undefined, leading to 16 possible stereoisomers.

We have adopted a flexible, modular synthetic approach towards spirastrellolide based around bond disconnections that isolate regions of known relative configuration. To date, we have described the preparation of two diastereomeric  $C_{1}$ – $C_{25}$  ABC subunits<sup>4</sup> and the tetracyclic  $C_{26}$ – $C_{40}$  DEF subunit 3.<sup>5,6</sup> However, our route to the latter segment was compromised by an inefficient

acetonide deprotection/spirocyclisation step. We now report the development of an improved, second-generation approach to the challenging northern hemisphere of spirastrellolide, leading to a novel double Sharpless asymmetric dihydroxylation/spiroacetalisation sequence to efficiently construct the fully elaborated  $C_{26}$ – $C_{40}$  DEF subunit 4.

As summarised in Scheme 1, we rationalised that a late-stage asymmetric dihydroxylation<sup>7</sup> of the C<sub>26,27</sub> alkene would circumvent the problematic elimination of spirocyclisation substrate 5, leading to competing furan formation in producing DEF subunit 3, by removing the need for diol deprotection. Furthermore, the selectivity of the spirocyclisation process might benefit from reversing the direction of acetalisation from  $F \rightarrow FED$  to  $ED \rightarrow FED$ . Hence, dihydroxylation of olefin 6 and DE ring formation would be followed by silyl ether cleavage, then F ring formation, to give the tetracyclic DEF *bis*-spiroacetal 3. The diketone 6 might arise from a Horner–Wadsworth–Emmons union of aldehyde 7 with phosphonate 8.

The synthetic route adopted for aldehyde 7 (Scheme 2) was improved from our initial studies, in which olefins of type 9 were constructed through olefin cross-metathesis. Instead, deconjugative Knoevenagel condensation of malonic acid with aldehyde 10



Scheme 1 Revised retrosynthesis towards tetracyclic DEF subunit 3.



Fig. 1 Spirastrellolide A and targeted DEF subunits 3 and 4.

University Chemical Laboratory, Lensfield Road, Cambridge, UK CB2 1EW. E-mail: ip100@cam.ac.uk; Fax: +44 1223 336362; Tel: +44 1223 336407

<sup>&</sup>lt;sup>+</sup> Electronic supplementary information (ESI) available: Experimental details; <sup>1</sup>H, <sup>13</sup>C NMR data for 4, 13, 15, 16, 22. See DOI: 10.1039/ b612697a



Scheme 2 Reagents and conditions: (i)  $CH_2(CO_2H)_2$ , piperidine (cat.), xylenes, 136 °C; Me<sub>3</sub>SiCl, MeOH; (ii) K<sub>2</sub>OsO<sub>2</sub>(OH)<sub>4</sub>, (DHQ)<sub>2</sub>PHAL, K<sub>3</sub>Fe(CN)<sub>6</sub>, K<sub>2</sub>CO<sub>3</sub>, *t*-BuOH–H<sub>2</sub>O, 0 °C; (iii) TBSCl, DMF, imid., DCM; (iv) H<sub>2</sub>, Pd/C, EtOH; (v) Dess–Martin periodinane, NaHCO<sub>3</sub>, DCM; (vi) (*E*)-<sup>*d*</sup>Ipc<sub>2</sub>BCH<sub>2</sub>CH=CHCH<sub>3</sub>, -78 °C; (vii) TESOTf, 2,6-lutidine, DCM, -78 °C; (viii) O<sub>3</sub>, DCM, -78 °C; PPh<sub>3</sub>.

afforded the *E*-( $\beta$ , $\gamma$ )-unsaturated ester **9** (79%,  $\beta$ , $\gamma$  :  $\alpha$ , $\beta$  10 : 1).<sup>8</sup> Sharpless asymmetric dihydroxylation<sup>7</sup> of **9**, followed by hydroxyldifferentiating lactonisation and functional group manipulation, then gave aldehyde **11** (62%, 99% ee). This aldehyde was subjected to a Brown crotylation,<sup>9</sup> TES ether formation, and ozonolysis to afford aldehyde **7** (52%), the substrate for HWE olefination.

Coupling partner **8** was prepared from allylic chloride  $12^5$  (Scheme 3) by cleavage of the silyl ether and subsequent oxidation/ phosphonate introduction (53%). HWE coupling of phosphonate **8** with aldehyde **7** using Ba(OH)<sub>2</sub> as base<sup>10</sup> provided the corresponding enone (70%), which was subjected to a 1,4reduction using Stryker's reagent (96%).<sup>11</sup> Following TES ether deprotection, Dess–Martin oxidation of the resulting crude hydroxy ketone (presumably in equilibrium with the hemiacetal) provided 1,5-diketone **6** (68%).<sup>12</sup> This diketone was subjected to Sharpless asymmetric dihydroxylation using our optimised conditions with the (DHQ)<sub>2</sub>PYR ligand.<sup>5</sup> Hemiacetal **13** incorporating



Scheme 3 Reagents and conditions: (i) CSA (cat.), MeOH; (ii) Dess-Martin periodinane, NaHCO<sub>3</sub>, DCM; (iii) (MeO)<sub>2</sub>POCH<sub>2</sub>Li, THF, -78 °C; Dess-Martin periodinane, DCM; (iv) Ba(OH)<sub>2</sub>, THF-H<sub>2</sub>O (40 : 1); (v) [(PPh<sub>3</sub>)CuH]<sub>6</sub>, PhMe-H<sub>2</sub>O (200 : 1); (vi) PPTS, DCM-MeOH (3 : 1); (vii) Dess-Martin periodinane, DCM; (viii) K<sub>2</sub>OsO<sub>2</sub>(OH)<sub>4</sub>, (DHQ)<sub>2</sub>PYR, K<sub>3</sub>Fe(CN)<sub>6</sub>, K<sub>2</sub>CO<sub>3</sub>, *t*-BuOH-H<sub>2</sub>O, 0 °C; (ix) HF·py, THF.

the D ring could be isolated from this reaction in moderate yield, attributed to its lability during chromatographic purification. Treatment of **13** with HF·py led to silyl ether cleavage and cyclisation to a mixture of the desired DEF spiroacetal  $3^5$  and its isomer **14**, epimeric at the C<sub>35</sub> acetal carbon, in a 3:1 ratio (67%). This spirocyclisation process is believed to proceed under kinetic control, while attempts to isomerise **14** to generate further **3** were plagued by competing elimination reactions.

Recognising that the sense of asymmetric induction in the two separate dihydroxylation steps was the same for both olefins, we decided to remove the need for protecting groups on both diols. By exploiting a late-stage double asymmetric dihydroxylation to install the required oxygenation at  $C_{26}$ ,  $C_{27}$ ,  $C_{37}$  and  $C_{38}$  directly (Scheme 4), we speculated that the pivotal *bis*-spirocyclisation to generate the modified DEF segment **15** from diene **16** might be accomplished under especially mild conditions. This approach again utilises a HWE reaction with phosphonate **8** to assemble the key dihydroxylation substrate **16**.

The aldehyde **17** required for HWE union was assembled from the previously prepared methyl ester **9** (Scheme 5) using our lactate aldol chemistry.<sup>13–15</sup> Oxidation state adjustment of **9** delivered aldehyde **18** (93%), which underwent a highly selective (> 20 : 1 dr) boron aldol reaction with ethyl ketone **19** to provide the *anti* adduct **20** (86%).<sup>14</sup> TBS etherification of **20** and cleavage of the lactate auxiliary then gave aldehyde **17** (86%). Once again, the Ba(OH)<sub>2</sub> protocol<sup>10</sup> proved the method of choice for the HWE olefination with phosphonate **8**, and following a similar sequence



Scheme 4 The double AD strategy for tricyclic DEF subunit 15.



Scheme 5 *Reagents and conditions:* (i) LiAlH<sub>4</sub>, THF; (ii) Dess–Martin periodinane, DCM; (iii) **19**, *c*-Hex<sub>2</sub>BCl, Et<sub>3</sub>N, Et<sub>2</sub>O, 0 °C, then **18**, -78 °C; (iv) TBSOTf, 2,6-lutidine, DCM; (v) NaBH<sub>4</sub>, MeOH then K<sub>2</sub>CO<sub>3</sub>; NaIO<sub>4</sub>, THF–pH 7 buffer; (vi) Ba(OH)<sub>2</sub>, THF–H<sub>2</sub>O (40 : 1); (vii) [(PPh<sub>3</sub>)CuH]<sub>6</sub>, PhMe–H<sub>2</sub>O (200 : 1); (viii) MeCN–HCl; (ix) Dess–Martin periodinane, DCM.



Scheme 6 Reagents and conditions: (i)  $K_2OsO_2(OH)_4$ , (DHQ)<sub>2</sub>PYR, MeSO<sub>2</sub>NH<sub>2</sub>,  $K_3Fe(CN)_6$ ,  $K_2CO_3$ , *t*-BuOH–H<sub>2</sub>O, 0 °C; (ii) PPTS (cat.), DCM–MeOH (1 : 1); (iii) TESOTf, 2,6-lutidine, DCM, -78 °C; (iv) PPTS (cat.), DCM–MeOH (6 : 1), 0 °C.

of reactions to those already described, 1,5-diketone **16** was obtained on a gram scale in 47% yield.

We were now ready to perform the crucial double asymmetric dihydroxylation reaction. Our original route<sup>5</sup> utilised the  $(DHQ)_2PHAL$  ligand for the internal olefin, whilst the  $(DHQ)_2PYR$  ligand was optimal for the terminal olefin. Guided by this and other precedents,<sup>7</sup> we opted for the latter conditions (Scheme 6). In the event, exposure of diene **16** to Sharpless conditions led to rapid (1 h) dihydroxylation of the internal olefin, followed by reaction at the terminal double bond (3 h), where NMR analysis indicated the formation of a complex mixture of isomeric products **21**. As purification did not prove fruitful, the crude reaction mixture was exposed to PPTS in DCM–MeOH (1 : 1), leading to cyclisation to give the targeted DEF subunit **15**, together with other isomers.

The use of PPTS for this equilibration/cyclisation process was found to be essential, as stronger acids (CSA, HCl) led to competitive formation of furan-containing by-products. To overcome material losses in the chromatographic isolation of 15, protection of the crude mixture of isomeric DEF diols was carried out (TESOTf, 2,6-lutidine). The resulting silvlated products now proved more stable to purification and the desired DEF bisspiroacetal 22 was readily separated from other isomers. Pleasingly, these other isomers could be recycled via re-exposure to PPTS in DCM-MeOH (1 : 1), which cleaved both TES ethers and effected spiroacetal equilibration without competing elimination side-reactions. Subsequent reprotection afforded more of the targeted DEF tricycle 22, giving a 65% yield overall from 16 after one recycle. Finally, to enable investigation of fragment union with the southern hemisphere,4 the primary TES ether was selectively cleaved using PPTS (DCM-MeOH, 6:1,0 °C) leading to the fully functionalised DEF subunit 4 (93%).

The stereochemistry of the newly formed *bis*-spiroacetals was confirmed using <sup>1</sup>H NMR spectroscopy. As with our previous

DEF fragment **3**, a close match of chemical shift data was found between **4** and **15** and the spirastrellolide methyl ester (**2**),<sup>2</sup> with all substituents on the DE-ring spiroacetal equatorial. Additionally, a diagnostic NOE enhancement was observed between  $H_{27}$  and  $H_{38}$ , consistent with the *bis*-spiroacetal possessing the doubly anomeric effect-stabilised configuration at  $C_{31}$  and  $C_{35}$ .

In conclusion, we have developed an improved approach to the construction of the challenging  $C_{26}-C_{40}$  DEF region of the marine macrolide spirastrellolide, employing a novel double Sharpless dihydroxylation/spiroacetalisation sequence, as in  $16 \rightarrow 15$ . This eliminates the need for protecting groups and enhances the supply of the northern hemisphere, enabling the initiation of fragment coupling studies to unravel the remaining stereochemical ambiguities and further advance the total synthesis of this potent bioactive polyketide.

We thank the EPSRC (EP/C541677/1), Merck Research Laboratories, Homerton College, Cambridge (Research Fellowship to E.A.A.), SK Corporation (J.H.L.) and the German Academic Exchange Service (DAAD, Postdoctoral Fellowship to C.M.) for support and Professor Raymond Andersen (University of British Columbia) for helpful discussions.

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