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

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

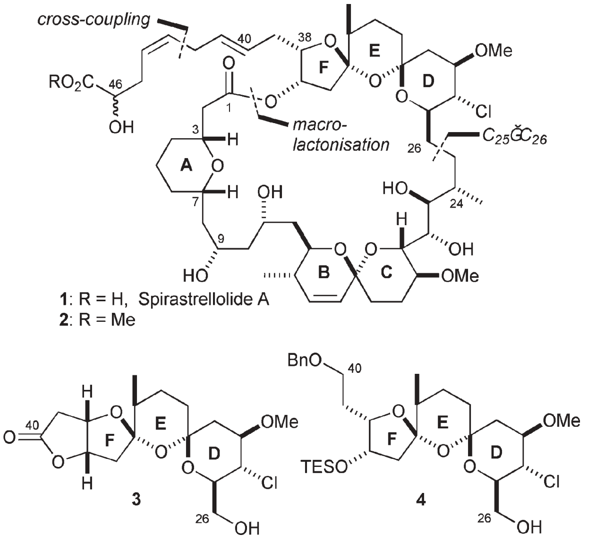
An efficient synthesis of the C_{26}–C_{40} tricyclic [5,6,6]-*bis*-spiroacetal segment of the marine macrolide spirastrellolide A has been developed, exploiting a novel double Sharpless asymmetric dihydroxylation/spiroacetalisation sequence.

Spirastrellolide A (**1**, Fig. 1) is a structurally intriguing antimitotic macrolide isolated by Andersen and co-workers from the Caribbean sponge *Spirastrella coccinea*.[1,2] It induces premature cell mitosis and displays potent (IC_{50} = 1 nM) and selective inhibition of protein phosphatase 2A, and represents a potential candidate for the development of antitumour therapeutic agents.[3] Despite extensive NMR spectroscopic analysis of its methyl ester derivative **2**,[2] 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[4] and the tetracyclic C_{26}–C_{40} DEF subunit **3**.[5,6] 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**.

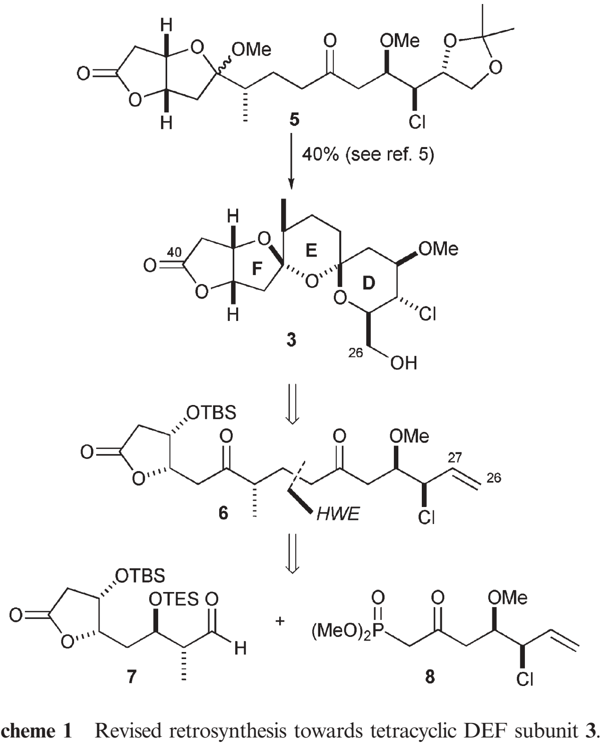
As summarised in Scheme 1, we rationalised that a late-stage asymmetric dihydroxylation[7] of the $C_{26,27}$ alkene would circumvent the problematic elimination of spirocyclisation substrate **5**, leading to competing furan formation in producing DEF subunit **3**, by removing the need for diol deprotection. Furthermore, the selectivity of the spirocyclisation process might benefit from reversing the direction of acetalisation from F → FED to ED → 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**



1: R = H, Spirastrellolide A
2: R = Me
3
4

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

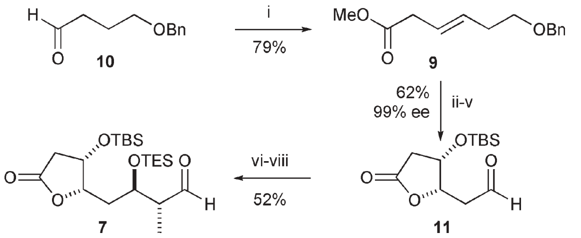


5
3
6
7
8

Scheme 1 Revised retrosynthesis towards tetracyclic DEF subunit **3**.

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

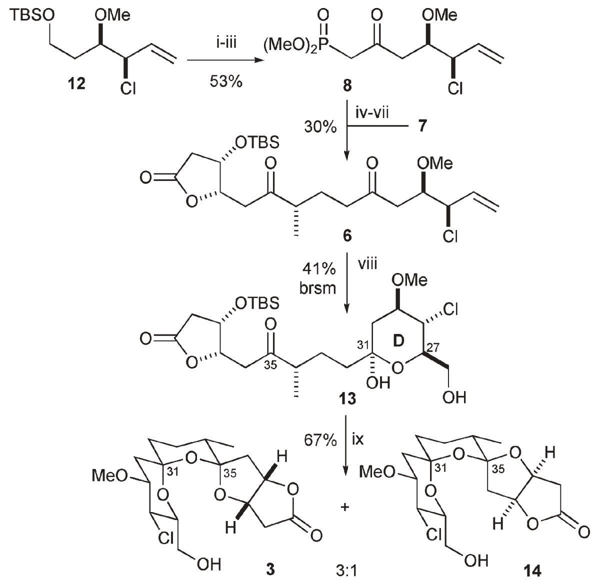
† Electronic supplementary information (ESI) available: Experimental details; ^1H, ^{13}C NMR data for **4**, **13**, **15**, **16**, **22**. See DOI: 10.1039/b612697a



Scheme 2 *Reagents and conditions*: (i) $CH_2(CO_2H)_2$, piperidine (cat.), xylenes, 136 °C; Me_3SiCl, MeOH; (ii) $K_2OsO_2(OH)_4$, $(DHQ)_2PHAL$, $K_3Fe(CN)_6$, K_2CO_3, t-BuOH–H_2O, 0 °C; (iii) TBSCl, DMF, imid., DCM; (iv) H_2, Pd/C, EtOH; (v) Dess–Martin periodinane, $NaHCO_3$, DCM; (vi) (E)-^{d}Ipc$_2$BCH$_2$CH=CHCH$_3$, −78 °C; (vii) TESOTf, 2,6-lutidine, DCM, −78 °C; (viii) O_3, DCM, −78 °C; PPh_3.

afforded the E-(β,γ)-unsaturated ester **9** (79%, β,γ : α,β 10 : 1).[8] Sharpless asymmetric dihydroxylation[7] of **9**, followed by hydroxyl-differentiating lactonisation and functional group manipulation, then gave aldehyde **11** (62%, 99% ee). This aldehyde was subjected to a Brown crotylation,[9] TES ether formation, and ozonolysis to afford aldehyde **7** (52%), the substrate for HWE olefination.

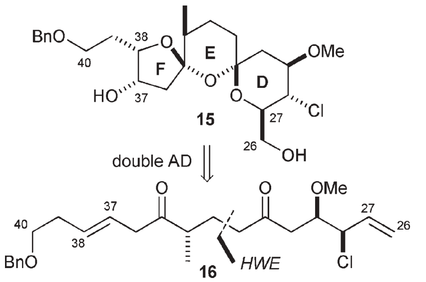
Coupling partner **8** was prepared from allylic chloride **12**[5] (Scheme 3) by cleavage of the silyl ether and subsequent oxidation/phosphonate introduction (53%). HWE coupling of phosphonate **8** with aldehyde **7** using $Ba(OH)_2$ as base[10] provided the corresponding enone (70%), which was subjected to a 1,4-reduction using Stryker's reagent (96%).[11] 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%).[12] This diketone was subjected to Sharpless asymmetric dihydroxylation using our optimised conditions with the $(DHQ)_2PYR$ ligand.[5] Hemiacetal **13** incorporating 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_{35} 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.



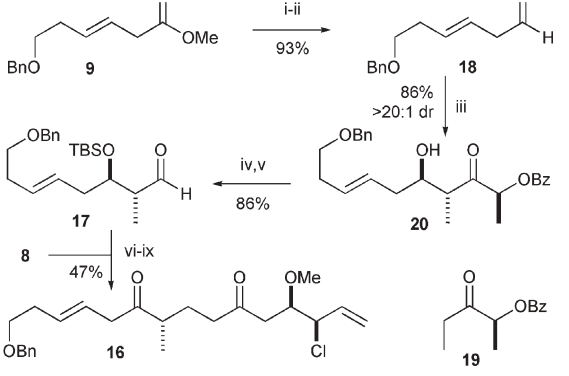
Scheme 3 *Reagents and conditions*: (i) CSA (cat.), MeOH; (ii) Dess–Martin periodinane, $NaHCO_3$, DCM; (iii) $(MeO)_2POCH_2Li$, THF, −78 °C; Dess–Martin periodinane, DCM; (iv) $Ba(OH)_2$, THF–H_2O (40 : 1); (v) $[(PPh_3)CuH]_6$, PhMe–H_2O (200 : 1); (vi) PPTS, DCM–MeOH (3 : 1); (vii) Dess–Martin periodinane, DCM; (viii) $K_2OsO_2(OH)_4$, $(DHQ)_2PYR$, $K_3Fe(CN)_6$, K_2CO_3, t-BuOH–H_2O, 0 °C; (ix) HF·py, THF.

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**.

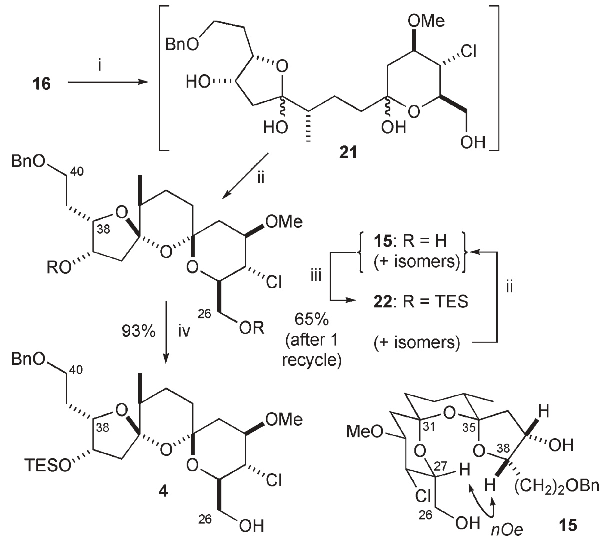
The aldehyde **17** required for HWE union was assembled from the previously prepared methyl ester **9** (Scheme 5) using our lactate aldol chemistry.[13–15] Oxidation state adjustment of **9** delivered aldehyde **18** (93%), which underwent a highly selective (> 20 : 1 dr) boron aldol reaction with ethyl ketone **19** to provide the *anti* adduct **20** (86%).[14] TBS etherification of **20** and cleavage of the lactate auxiliary then gave aldehyde **17** (86%). Once again, the $Ba(OH)_2$ protocol[10] 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) $LiAlH_4$, THF; (ii) Dess–Martin periodinane, DCM; (iii) **19**, c-Hex$_2$BCl, Et_3N, Et_2O, 0 °C, then **18**, −78 °C; (iv) TBSOTf, 2,6-lutidine, DCM; (v) $NaBH_4$, MeOH then K_2CO_3; $NaIO_4$, THF–pH 7 buffer; (vi) $Ba(OH)_2$, THF–H_2O (40 : 1); (vii) $[(PPh_3)CuH]_6$, PhMe–H_2O (200 : 1); (viii) MeCN–HCl; (ix) Dess–Martin periodinane, DCM.



Scheme 6 *Reagents and conditions*: (i) $K_2OsO_2(OH)_4$, $(DHQ)_2PYR$, $MeSO_2NH_2$, $K_3Fe(CN)_6$, K_2CO_3, *t*-BuOH–H_2O, 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[5] 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,[7] 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 silylated products now proved more stable to purification and the desired DEF *bis*-spiroacetal **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 ^1H 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**),[2] 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** → **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.

Notes and references

1 K.-S. Yeung and I. Paterson, *Chem. Rev.*, 2005, **105**, 4237; R. D. Norcross and I. Paterson, *Chem. Rev.*, 1995, **95**, 2041; I. Paterson and E. A. Anderson, *Science*, 2005, **310**, 451.
2 D. E. Williams, M. Roberge, R. Van Soest and R. J. Andersen, *J. Am. Chem. Soc.*, 2003, **125**, 5296; D. E. Williams, M. Lapawa, X. Feng, T. Tarling, M. Roberge and R. J. Andersen, *Org. Lett.*, 2004, **6**, 2607.
3 L. H. Le, C. Erlichman, L. Pillon, J. J. Thiessen, A. Day, N. Wainman, E. A. Eisenhauer and M. J. Moore, *Invest. New Drugs*, 2004, **22**, 159; R. E. Honkanen and T. Golden, *Curr. Med. Chem.*, 2002, **9**, 2055.
4 I. Paterson, E. A. Anderson, S. M. Dalby and O. Loiseleur, *Org. Lett.*, 2005, **7**, 4125.
5 I. Paterson, E. A. Anderson, S. M. Dalby and O. Loiseleur, *Org. Lett.*, 2005, **7**, 4121.
6 For other synthetic studies, see: J. Liu and R. P. Hsung, *Org. Lett.*, 2005, **7**, 2273; I. Paterson, E. A. Anderson and S. M. Dalby, *Synthesis*, 2006, 3225; Y. Pan and J. K. De Brabander, *Synlett*, 2006, 853; C. Wang and C. J. Forsyth, *Org. Lett.*, 2006, **8**, 2997; A. Fürstner, M. D. B. Fenster, B. Fasching, C. Godbout and K. Radkowski, *Angew. Chem., Int. Ed.*, 2006, **45**, 5506; A. Fürstner, M. D. B. Fenster, B. Fasching, C. Godbout and K. Radkowski, *Angew. Chem., Int. Ed.*, 2006, **45**, 5510; J. Liu, J. H. Yang, C. Ko and R. P. Hsung, *Tetrahedron Lett.*, 2006, **47**, 6121.
7 H. C. Kolb, M. S. VanNieuwenhze and K. B. Sharpless, *Chem. Rev.*, 1994, **94**, 2483.
8 C. García, T. Martín and V. S. Martín, *J. Org. Chem.*, 2001, **66**, 1420; N. Ragoussis, *Tetrahedron Lett.*, 1987, **28**, 93.
9 H. C. Brown and K. S. Bhat, *J. Am. Chem. Soc.*, 1986, **108**, 293.
10 I. Paterson, K.-S. Yeung and J. B. Smaill, *Synlett*, 1993, 774.
11 W. S. Mahoney, D. M. Brestensky and J. M. Stryker, *J. Am. Chem. Soc.*, 1988, **110**, 291.
12 Varying amounts of a dihydropyran side-product **i** were isolated from this oxidation; this could be readily recycled to the oxidation substrate upon exposure to PPTS in THF–water.

i

13 I. Paterson, D. J. Wallace and C. J. Cowden, *Synthesis*, 1998, 689.
14 I. Paterson, D. J. Wallace and S. M. Velázquez, *Tetrahedron Lett.*, 1994, **35**, 9083.
15 I. Paterson and D. J. Wallace, *Tetrahedron Lett.*, 1994, **35**, 9087.