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Toward the Synthesis of Spirastrellolide A: Construction of a Tetracyclic C_{26}–C_{40} Subunit Containing the DEF-Bis-Spiroacetal

Ian Paterson,* Edward A. Anderson, Stephen M. Dalby, and Olivier Loiseleur

University Chemical Laboratory, University of Cambridge, Lensfield Road, Cambridge CB2 1EW, UK

ip100@cam.ac.uk

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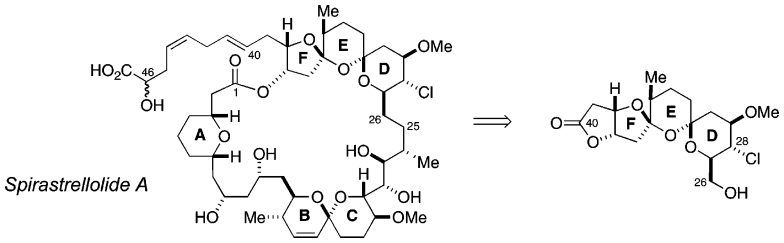
ABSTRACT



A stereocontrolled synthesis of the fully elaborated C_{26}–C_{40} tricyclic [5,6,6]-bis-spiroacetal of spirastrellolide A containing the C_{28} chlorine substituent is reported, exploiting asymmetric Sharpless dihydroxylation and boron-mediated allylation methodology.

Spirastrellolide A is a novel cytotoxic polyketide isolated by Andersen and co-workers from the Caribbean sponge *Spirastrella* coccinea in 2003.[1] Biological testing has shown spirastrellolide A to be a potent (IC_{50} = 1 nM) and selective inhibitor of protein phosphatase 2A (PP2A).[1b] As such, it may exhibit a similar mode of action to other Ser/Thr phosphatase inhibitors, including fostriecin, okadaic acid, and the calyculins, which induce premature cell mitosis.[2] Spirastrellolide A represents a potential candidate for the development of antitumor therapeutic agents and, given the central regulatory role of PP2A in the cell, may find further applications as a lead in the treatment of neurological and metabolic disorders.

Extensive NMR spectroscopic analysis of the methyl ester derivative of spirastrellolide led to a partial structural assignment and characterization of a 38-membered macrolactone core.[1a] Further structural analysis and derivatization revealed several inconsistencies in this original assignment and resulted in a second report from the Andersen group containing a revision of the structure of spirastrellolide A as **1** (Figure 1).[1b]

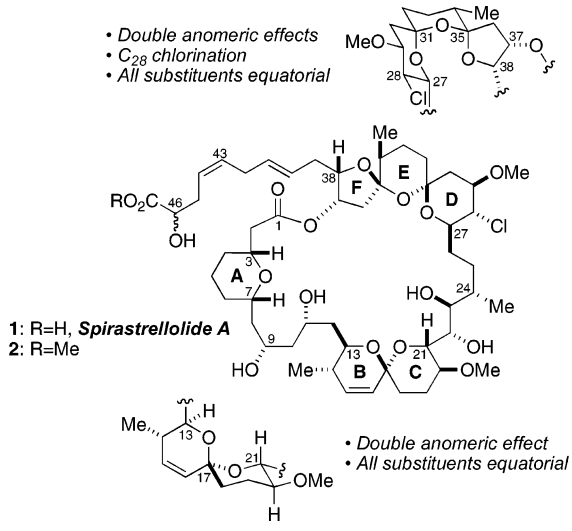


Figure 1.

Spirastrellolide contains 21 stereocenters, of which 20 are embedded within the 38-membered macrolactone. This ring

(1) (a) Williams, D. E.; Roberge, M.; Van Soest, R.; Andersen, R. J. *J. Am Chem. Soc.* **2003**, *125*, 5296. (b) Williams, D. E.; Lapawa, M.; Feng, X.; Tarling, T.; Roberge, M.; Andersen, R. *J. Org. Lett.* **2004**, *6*, 2607.

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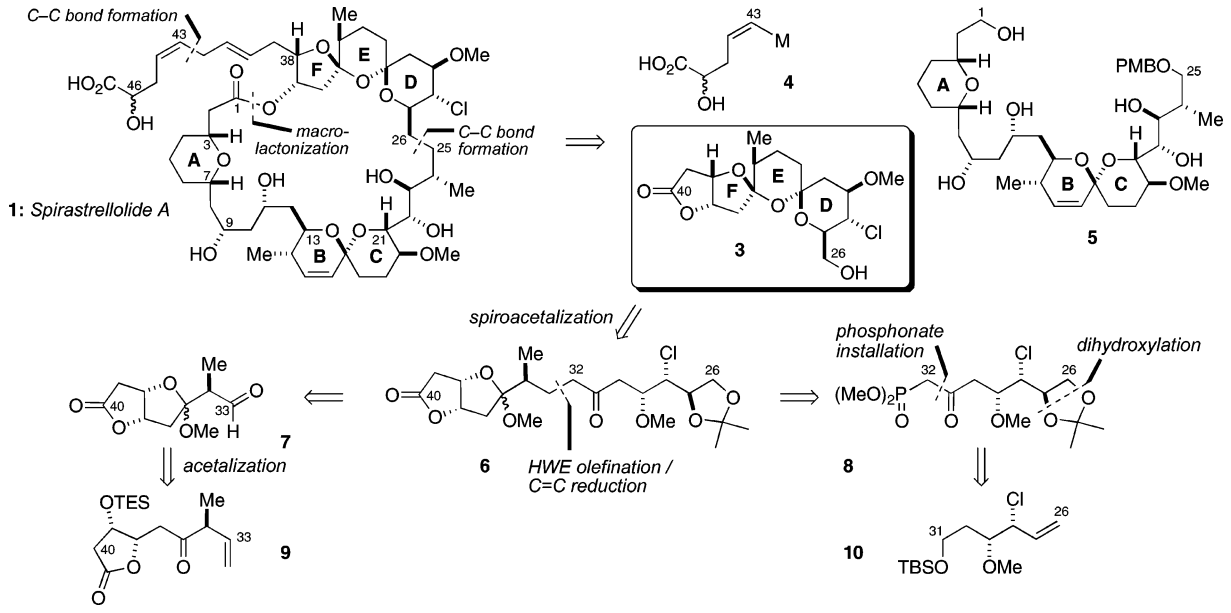
Scheme 1. Retrosynthetic Analysis of Spirastrellolide A



itself contains a *cis*-fused tetrahydropyran (A ring), a [6,6]-spiroacetal (BC rings), and an intriguing chlorinated [5,6,6]-bis-spiroacetal (DEF rings). Significantly, both spiroacetal motifs appear to benefit from stabilization by a double anomeric effect, with all substituents equatorially disposed. The remaining C_{46} stereocenter appears as part of a nine-carbon side chain, also featuring a (*Z*,*E*)-1,4-diene, appended to C_{38}.

While the atomic connectivity of spirastrellolide and its methyl ester derivative **2** has been determined, several stereochemical uncertainties remain. In addition to the remote, unassigned C_{46} stereocenter, the absolute configuration of the natural product remains undetermined. More significantly from a synthetic viewpoint,[3] the *relative* stereochemistry between the three stereoclusters (C_3-C_7, C_9-C_{24}, and $C_{27}-C_{38}$) within the macrolide core is also unknown.

The initial aim of any synthetic effort directed toward spirastrellolide must be the elucidation of the stereochemical relationship between these subunits. A flexible, modular strategy was envisaged in which each region of known relative stereochemistry could be independently constructed. Subsequent union of these subunits, followed by detailed NMR comparisons with spirastrellolide, may then enable the determination of the stereochemical interconnection between these regions. Toward this end, we report herein an asymmetric synthesis of the $C_{26}-C_{40}$ segment **3** (Scheme 1), containing the complete [5,6,6]-bis-spiroacetal DEF-ring system of the northern hemisphere.

Our proposed retrosynthesis of spirastrellolide is outlined in Scheme 1. Simplification of the diastereomer problem might be achieved through a late-stage attachment of the C_{46} hydroxyl-containing side chain, as in **4**, after macrolactonization of an appropriate *seco*-acid precursor. The DEF-bis-spiroacetal subunit may then be isolated as a single region of known relative stereochemistry through disconnection across the $C_{25}-C_{26}$ bond. This bis-spiroacetal **3** was envisaged to arise from a thermodynamically controlled spiroacetalization of the open-chain precursor **6**, following acetonide deprotection. This ketone **6** could itself be derived from the Horner−Wadsworth−Emmons olefination of the aldehyde **7** with phosphonate **8**, followed by olefin reduction. Aldehyde **7** may, in turn, be constructed by acetalization of the ketone **9**, while phosphonate **8** could arise from a dihydroxylation of the allylic chloride **10**, followed by the installation of the dimethyl phosphonate moiety.

The synthesis of the $C_{33}-C_{40}$ aldehyde **7** commenced with the cross-metathesis of buten-3-ol benzyl ether **11** with methyl vinyl acetate **12**, using the Grubbs second-generation catalyst (Scheme 2).[4] The β,γ-unsaturated ester **13** was obtained in 82% yield as a 4:1 mixture of (*E*)- and (*Z*)-isomers, which were further submitted to a Sharpless asymmetric dihydroxylation,[5a] with concurrent hydroxyl-differentiating lactonization.[5b] A subsequent recrystallization efficiently removed the minor dihydroxylation byproduct, originating from the (*Z*)-isomer of **13**, while increasing the enantiomeric purity of the desired lactone **14**[5b] from 91 to >99% ee. TES protection of alcohol **14**, followed by debenzylation and Dess−Martin oxidation, delivered the

(2) (a) Le, L. H.; Erlichman, C.; Pillon, L.; Thiessen, J. J.; Day, A.; Wainman, N.; Eisenhauer, E. A.; Moore, M. J. *Invest. New Drugs* **2004**, *22*, 159. (b) Honkanen, R. E.; Golden, T. *Curr. Med. Chem.* **2002**, *9*, 2055.

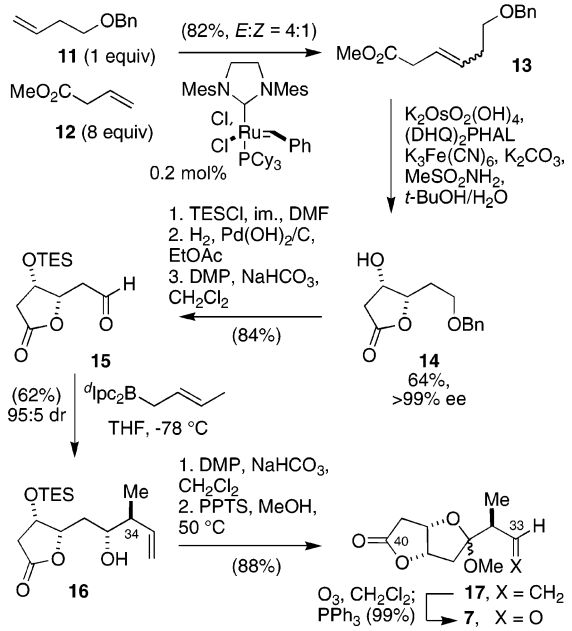
(3) For other synthetic studies, see: (a) Liu, J.; Hsung, R. P. *Org. Lett.* **2005**, *7*, 2273. (b) Paterson, I.; Anderson, E. A.; Dalby, S. M.; Loiseleur, O.; *Abstracts of Papers*, 229th National Meeting of the American Chemical Society, San Diego, Mar 13−17, 2005; American Chemical Society: Washington, DC, 2005; ORGN-331. (c) Wang, C.; Forsyth, C. J. *Abstracts of Papers*, 229th National Meeting of the American Chemical Society, San Diego, Mar 13−17, 2005; American Chemical Society: Washington, DC, 2005; ORGN-414.

(4) Chatterjee, A. K.; Choi, T.-L.; Sanders, D. P.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 11360. For an example of cross-metathesis using ester **28**, see: Vasbinder, M. M.; Miller, S. J. *J. Org. Chem.* **2002**, *67*, 6240.

(5) (a) Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483. (b) The enantiomer of **14** has previously been reported; see: Garcia, C.; Martin, T.; Martin, V. S. *J. Org. Chem.* **2001**, *66*, 1420.

aldehyde **15** in 84% yield (three steps), in readiness for a Brown asymmetric crotylation.[6]

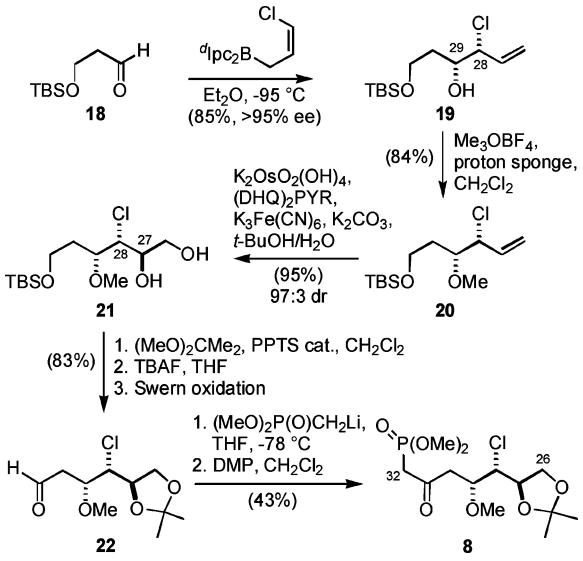
Scheme 2



In the event, treatment of **15** with (−)-*B*-(*E*)-crotyldiisopinocampheylborane provided alcohol **16** in 62% yield, installing the C_{34} methyl-bearing stereocenter (dr = 95:5). Oxidation of the alcohol **16** with Dess−Martin periodinane set the stage for the first acetalization, which was performed with a catalytic amount of PPTS in MeOH at 50 °C, providing the methyl acetals **17**. Finally, the aldehyde **7** was revealed by ozonolysis of the terminal olefin in **17** (88%, three steps).[7]

Installation of the challenging C_{28} chlorine substituent of spirastrellolide employed the asymmetric chloroallylation reaction developed by Oehlschlager (Scheme 3).[8] Thus, treatment of the aldehyde **18** with (−)-*B*-(*Z*)-chloroallyldiisopinocampheylborane in Et_2O at −95 °C provided the allylic chloride **19** in 85% yield with excellent C_{28}/C_{29} syn stereocontrol (dr > 95:5) and enantiomeric excess (ee > 95%). The C_{29} hydroxyl was subsequently methylated with Meerwein's salt, in the presence of proton sponge, to give **20** in 84% yield. With the methyl ether **20** in hand, dihydroxylation of the terminal double bond was investigated. Interestingly, the C_{28} stereocenter bearing the electronegative chlorine substituent was found to direct dihydroxylation onto the *Re*-face of the double bond.[9] Thus, exposure of **20** to standard Upjohn conditions (OsO_4, NMO)[10] provided a 6:1 mixture of diols, with the major diastereomer **21** possessing the desired 27,28-anti relationship. Surprisingly, this selectivity was reduced to 2:1 when a Sharpless asymmetric dihydroxylation was applied using the standard DHQ_2PHAL ligand.[5a] However, by switching the ligand to DHQ_2PYR,[5a] a matched situation occurred and a high selectivity of 97:3 dr was achieved, providing diol **21** in 95% yield.

Scheme 3



Following successful dihydroxylation, the diol **21** was protected as the corresponding acetonide. Desilylation with TBAF, followed by Swern oxidation, delivered aldehyde **22** in 83% yield. Treatment of **22** with $(MeO)_2P(O)CH_2Li$ and subsequent oxidation with Dess−Martin periodinane gave the required β-ketophosphonate **8** (43%).

Treatment of aldehyde **7** and phosphonate **8** with $Ba(OH)_2$ in wet THF realized an efficient Horner−Wadsworth−Emmons fragment coupling to provide the corresponding enone in good yield (85%, Scheme 4).[11] The reduction of the C=C bond of this enone was then attempted; however, Pd-catalyzed hydrogenation under a variety of conditions led to decomposition. In contrast, conjugate reduction with Stryker's reagent[12] delivered the ketone **6** smoothly (66%, two steps). The use of wet toluene as a solvent accelerated the reaction and reduced the quantity of reagent required to effect reduction.

The stage was now set for investigation of the crucial spiroacetalization reaction. In the event, treatment of ketone **6** with the acidic Dowex 50Wx8 resin, in a mixture of MeOH/water at 70 °C, led to acetonide removal and

(6) Brown, H. C.; Bhat, K. S. *J. Am. Chem. Soc.* **1986**, *108*, 293.

(7) Some limited epimerization at the sensitive C34 methyl-bearing center took place during acetalization (dr = 92:8) and ozonolysis (dr = 88:12).

(8) Hu, S.; Jayaraman, S.; Oehlschlager, A. C. *J. Org. Chem.* **1996**, *61*, 7513.

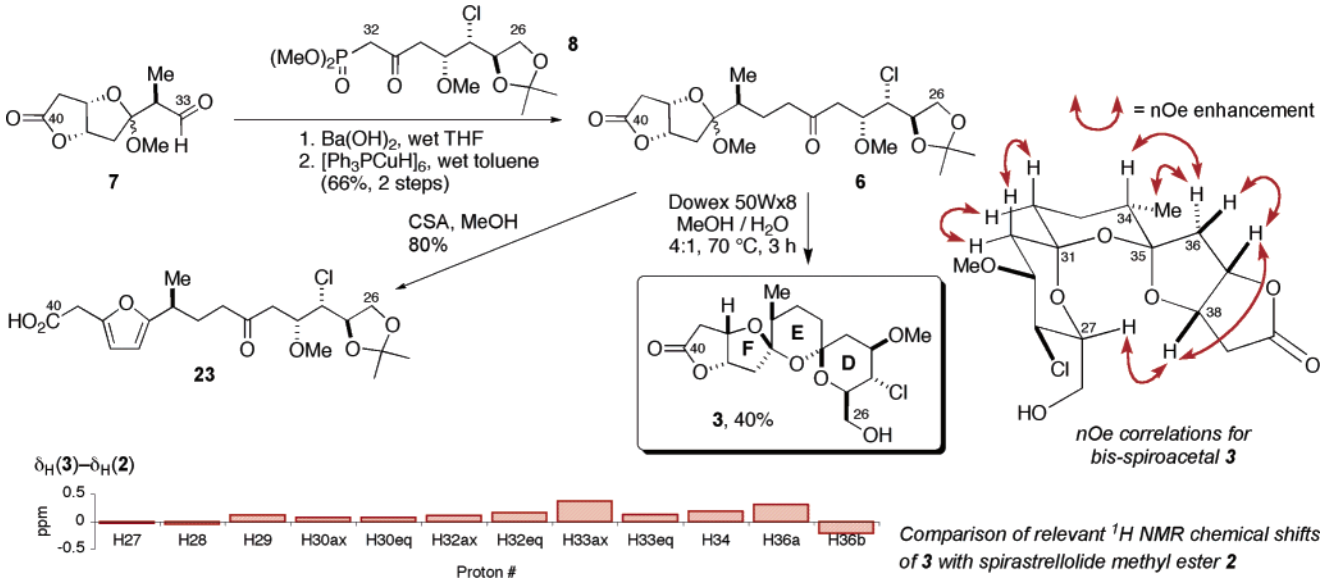
(9) The same sense of π-facial selectivity is induced by a hydroxyl group in the dihydroxylation of allylic alcohols. See: Cha, J. K.; Christ, W. J.; Kishi, Y. *Tetrahedron* **1984**, *40*, 2247. For a discussion of the stereoelectronic effect underlying this selectivity, see: Houk, K. N.; Moses, S. R.; Wu, Y.-D.; Rondan, N. G.; Jäger, V.; Schohe, R.; Fronczek, F. R. *J. Am. Chem. Soc.* **1984**, *106*, 3880.

(10) VanRheenen, V.; Kelly, R. C.; Cha, D. Y. *Tetrahedron Lett.* **1976**, *14*, 1973.

(11) Paterson, I.; Yeung, K.-S.; Smaill, J. B. *Synlett* **1993**, 774.

(12) Mahoney, W. S.; Brestensky, D. M.; Stryker, J. M. *J. Am. Chem. Soc.* **1988**, *110*, 291.

Scheme 4



formation of the tetracyclic bis-spiroacetal product **3** in 40% yield. Under these equilibrating conditions, **3** was obtained as a single diastereomer. The choice of the Dowex resin to mediate this reaction was crucial to the success of the cyclization. Indeed, use of CSA/MeOH led to rapid elimination to form the furan **23**, with the acetonide remaining intact.

That spiroacetal formation had indeed occurred could be readily confirmed by comparison of the ^{1}H and ^{13}C NMR data of **3** with that of the methyl ester derivative **2** of spirastrellolide.[1b] As shown by the chart of ^{1}H NMR chemical shift differences between **3** and the same region of spirastrellolide (Scheme 4), there was an excellent match, while the coupling constants were also in good agreement.[13] The ^{13}C NMR spectrum exhibited diagnostic acetal resonances at 98.2 (C_{31}) and 111.6 ppm (C_{35}), also in close agreement with those of the natural product (C_{31} 97.6 ppm, C_{35} 108.7 ppm). In addition, the establishment of the desired spiroacetal configurations at C_{31} and C_{35} was reinforced by the observation of strong NOE enhancements between H_{38} and H_{27}, H_{38} and H_{36a}, and H_{36b} and both H_{34} and the C_{34} methyl substituent.

In summary, we have completed a highly convergent synthesis of the fully elaborated chlorinated [5,6,6]-bis-spiroacetal **3**, exploiting asymmetric Sharpless dihydroxylation and allylation methodology. Notably, the advanced intermediate **3** provides additional support for the stereochemical assignment of the DEF region of spirastrellolide[1b] and bears functionality at C_{26} and C_{40} that should allow connection with the remaining C_1−C_{25} and C_{41}−C_{47} subunits. The following paper[14] describes a synthesis of the C_1−C_{25} subunit **5** (see Scheme 1), corresponding to the southern hemisphere of spirastrellolide A.

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Supporting Information Available: Spectroscopic data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL051403C

(13) See Supporting Information for full NMR comparisons.

(14) Paterson, I.; Anderson, E. A.; Dalby, S. M.; Loiseleur, O. *Org. Lett.* **2005**, *7*, 4125.