Synthesis of the C_1–C_{21} Southern Hemisphere of the Originally Proposed Structure of Spirastrellolide A

Ian Paterson,* Edward A. Anderson, Stephen M. Dalby

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

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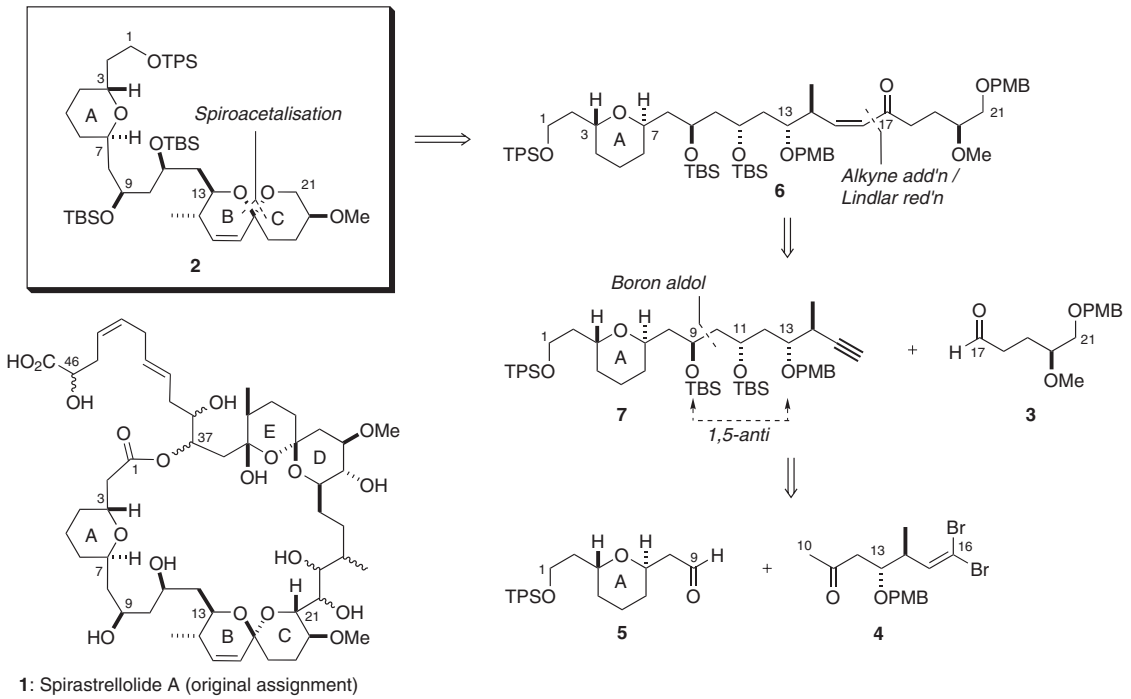
Dedicated to Professor Steven Ley on the occasion of his 60th birthday

Abstract: A stereocontrolled synthesis of the C_1–C_{21} [6,6]-spiroacetal-containing domain of the originally assigned structure of spirastrellolide A is reported, exploiting asymmetric boron aldol methodology and an alkyne addition to a C_{17} aldehyde. Comparison of the ^{1}H NMR data obtained for this synthetic fragment with that for the corresponding region of spirastrellolide suggested some stereochemical reassignment was required.

Key words: total synthesis, spiro compounds, macrolides, aldol reactions, asymmetric synthesis

Spirastrellolide A, a novel antimitotic macrolide isolated by Andersen and co-workers from the Caribbean sponge *Spirastrella coccinea* in 2003,[1] is a potent (IC_{50} = 1 nM) and selective inhibitor of protein phosphatase 2A (PP2A).[2] As such, it appears to exhibit a similar mode of action to other Ser/Thr phosphatase inhibitors, including fostriecin, okadaic acid and the calyculins, which induce premature cell mitosis.[3] Synthetic interest in spirastrellolide A derives not only from its unique molecular architecture,[4] but also from its potential development as an antitumour therapeutic agent. Given the central regulatory role of PP2A in the cell, it may also have some value as a lead in the treatment of neurological and metabolic disorders.

At the outset of our synthetic studies, extensive NMR spectroscopic analysis performed by the Andersen group[1] had led to a partial structural assignment of spirastrellolide as a 38-membered macrolide, as indicated in **1** but without assigning any stereochemistry in the C_1–C_{11} region[5] (Scheme 1). The spirastrellolide macrolactone itself was characterized as containing a 2,6-disubstituted tetrahydropyran (A ring) and two [6,6]-spiroacetals (BC and DE rings). Significantly, both spiroacetal motifs appear to benefit from stabilisation by a double anomeric ef-



Scheme 1 Retrosynthetic analysis of the C_1–C_{21} southern hemisphere of the originally proposed structure **1** for spirastrellolide A.[1,5]

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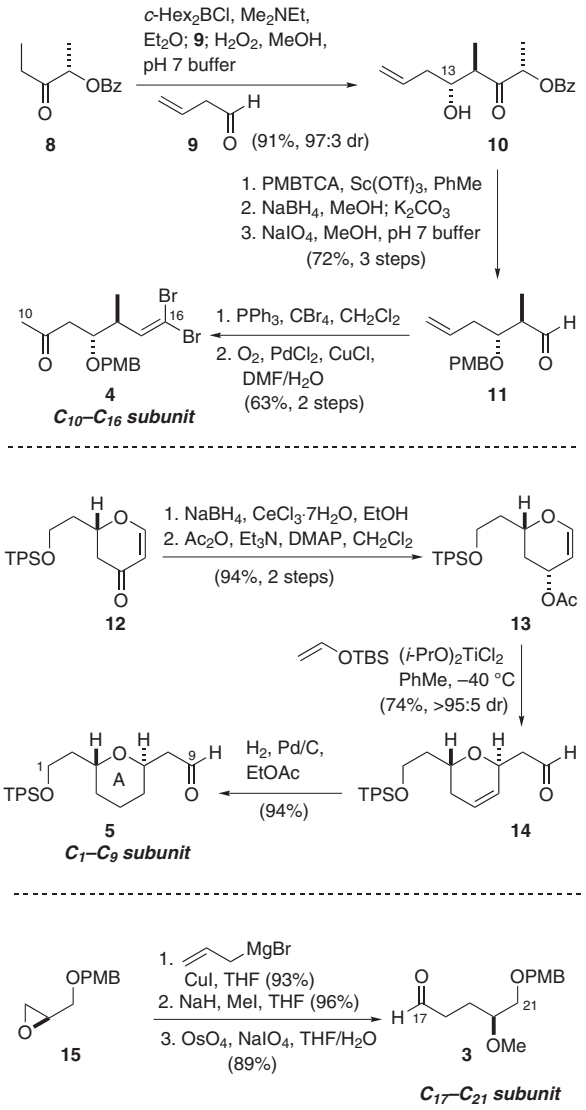
fect, with all substituents equatorially disposed. Altogether, there are some 19 stereocentres embedded within this elaborate macrolactone core, along with two hydroxyl-bearing stereocentres in the (*Z*,*E*)-1,4-diene side chain appended to C_{37}.

At this early stage in the structural elucidation of spirastrellolide, only a partial stereochemical assignment was available,[5] where the relationship between three stereoclusters (C_1–C_7, C_9–C_{24} and C_{27}–C_{38}) was unknown. In view of this ambiguity, our initial synthetic efforts towards spirastrellolide focussed on constructing the C_1–C_{21} southern hemisphere segment **2**, containing both the [6,6]-spiroacetal and a candidate *trans*-disubstituted tetrahydropyran, as reported herein.

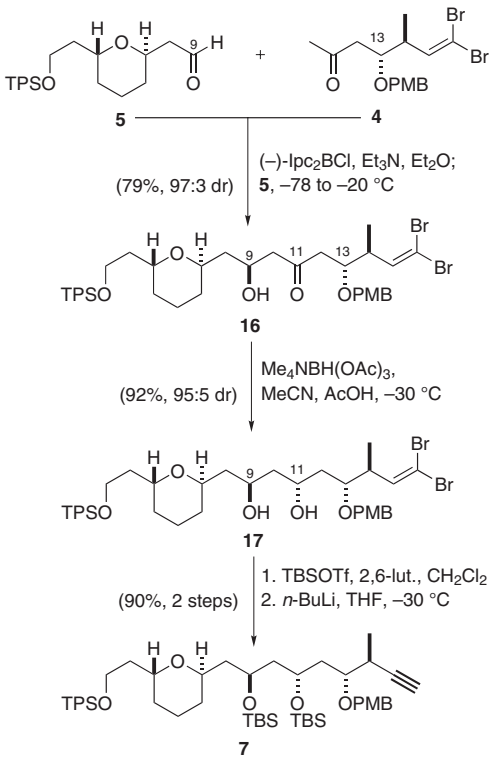
Our retrosynthesis of the C_1–C_{21} segment **2** of spirastrellolide, as outlined in Scheme 1, is based on the planned coupling of three key subunits **3**, **4** and **5**. We envisaged that a suitable open-chain precursor **6** to the required [6,6]-spiroacetal **2** might be derived from the coupling of alkyne **7** with aldehyde **3**. Recognition of a 1,5-*anti* relationship between C_9 and C_{13} guided our choice of a strategic C_9–C_{10} bond disconnection to reveal the methyl ketone **4**, containing a masked alkyne functionality, and the A-ring aldehyde **5**. Following precedent set by ourselves[6] and the Evans group,[7] a boron-mediated aldol coupling[8] between **4** and **5** was anticipated to install the desired C_9 configuration relative to the inducing C_{13} stereocentre. A subsequent hydroxyl-directed 1,3-*anti* reduction should then generate the required C_{11} stereocentre.

As shown in Scheme 2, the synthesis of the C_{10}–C_{16} subunit **4** commenced from our lactate-derived ketone **8**[9] and the aldehyde **9** (prepared from glyoxal[10]). An *anti* aldol addition of the kinetically generated (*E*)-boron enolate (*c*-Hex_2BCl, Me_2NEt) with a solution of freshly prepared aldehyde **9** gave the expected β-hydroxy ketone **10**,[11,12] as essentially a single isomer (97:3 dr, 91%). Formation of the PMB ether of aldol adduct **10** [PMBTCA, cat. $Sc(OTf)_3$] was followed by cleavage of the auxiliary under standard conditions[9b] to deliver aldehyde **11** in 72% yield. Corey–Fuchs[13] homologation of **11** to the vinyl dibromide then proceeded smoothly (98%) to install the latent terminal alkyne moiety. Finally, a Wacker oxidation[14] provided the required methyl ketone **4** (41% from **8**).

Efficient access to the C_1–C_9 subunit **5**, containing the *trans*-disubstituted tetrahydropyran, was achieved in four steps from the known[15] dihydropyranone **12** (Scheme 2). Luche reduction of **12**, followed by acetylation, gave the Ferrier rearrangement substrate **13** cleanly (94%). Following previous work within our group,[16] treatment of ac-

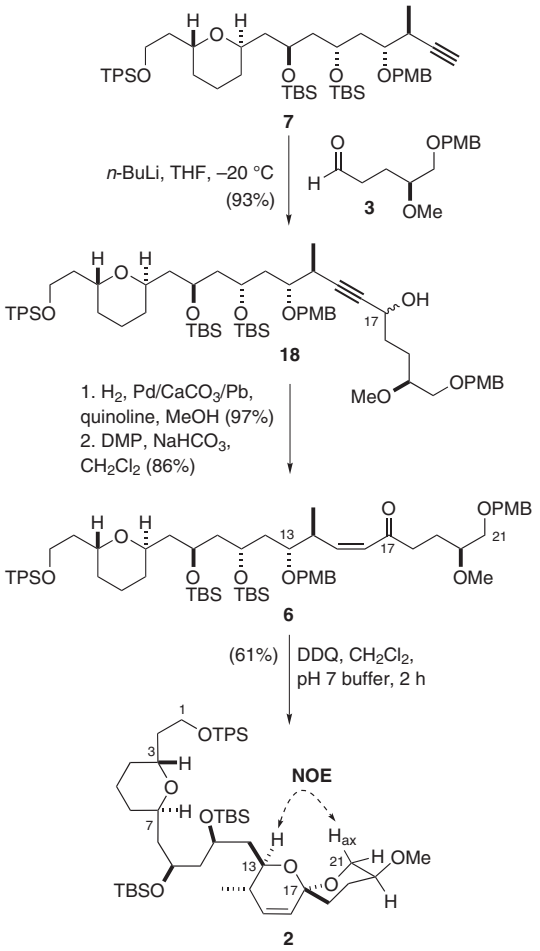


Scheme 2 Asymmetric synthesis of the three key subunits **3**, **4** and **5**.



Scheme 3 Aldol coupling of **4** and **5** followed by elaboration to alkyne **7**.

etate **13** with $(i\text{-PrO})_2TiCl_2$ and TBSOCH=CH_2 gave the 2,6-*trans*-dihydropyran **14** as a single isomer, which was followed by hydrogenation of the alkene to provide aldehyde **5**. The remaining C_{17}–C_{21} subunit **3** was accessed (73%, 3 steps) from the PMB ether **15** of (*S*)-glycidol (Scheme 2). This involved copper-promoted epoxide opening with allylmagnesium bromide followed by methyl ether formation and oxidative cleavage of the alkene using $OsO_4/NaIO_4$ to deliver the aldehyde **3**.



Scheme 4 Coupling of **7** and **3** followed by elaboration into tricyclic C_1–C_{21} subunit **2**.

With the various subunits in hand, we were now ready to tackle the fragment coupling steps. We began by exploring the aldol coupling of methyl ketone **4** with aldehyde **5**, involving the installation of the C_9 stereocentre (Scheme 3). Initially, treatment of aldehyde **5** with the dicyclohexylboron enolate of **4** (*c*-Hex_2BCl, Et_3N) led to moderate selectivity (3:1 dr) in favour of the expected[6] 1,5-*anti* adduct **16**. However, this substrate induction could be significantly enhanced through reagent control, employing the matched diisopinocampheylboron enolate of **4** [(–)-Ipc_2BCl, Et_3N], to deliver adduct **16** as essentially a single isomer (>97:3 dr) in 79% yield. The stereochemical information at C_9 could now be relayed to C_{11} via an Evans–Saksena reduction.[17] Thus, treatment of β-hydroxy ketone **16** with $Me_4NBH(OAc)_3$ in MeCN–AcOH (3:1) gave the 1,3-*anti* diol **17** (95:5 dr, 92%). Completion of the C_1–C_{16} alkyne subunit **7** proceeded smoothly in 90% yield from diol **17** via *bis*-TBS ether formation (TBSOTf) and treatment with *n*-BuLi to reveal the terminal alkyne.

At this stage, the fully elaborated open-chain precursor **6** for spiroacetal formation could be generated (Scheme 4). Fragment union was achieved via lithiation of alkyne **7** using *n*-BuLi, followed by addition of aldehyde **3**, to give adduct **18**, as an epimeric mixture at C_{17}. Lindlar hydrogenation of **18** followed by Dess–Martin oxidation gave the corresponding (*Z*)-enone **6** cleanly (77%, 3 steps). Gratifyingly, treatment of **6** with DDQ in buffered CH_2Cl_2 effected clean deprotection of the PMB ethers at C_{13} and C_{21} and led initially to the in situ formation of two spiroacetals that equilibrated to a single isomer **2**, which was isolated in 61% yield. The successful formation of the desired spiroacetal stereochemistry was readily confirmed by ^1H and ^{13}C NMR analysis.[11] A strong NOE enhancement between H_{13} and H_{21ax}, also observed in the natural product, confirmed that the C_{17} acetal centre of **2** possessed the desired configuration. As shown in Figure 1, a close correlation between the ^1H NMR data for the synthetic subunit and spirastrellolide was observed within the C_{13}–C_{20} spiroacetal region. In contrast, comparison of the C_3–C_{12} region revealed substantial differences, which suggested to us that the preliminary structural assignment of spirastrellolide as **1**[5] was probably incorrect.

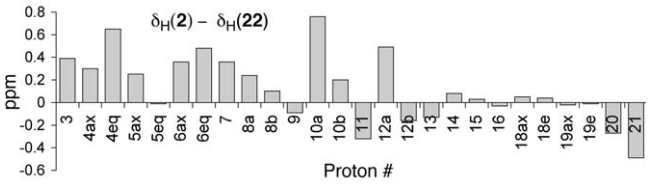


Figure 1 ^1H NMR chemical shift comparison for the C_1–C_{21} subunit **2** with spirastrellolide methyl ester **22** (Figure 2).

Around this time, the Andersen group revised the structure of spirastrellolide to **19** (Figure 2).[2] This new structure features a *cis*-disubstituted tetrahydropyran (A ring) and a [6,6]-spiroacetal (BC rings), together with additional stereochemical assignments (cf. circled carbon atoms), within the southern hemisphere. Furthermore, the northern hemisphere region was subject to more radical structural revision, now featuring a [5,6,6]-*bis*-spiroacetal (DEF rings) appended with a chlorine atom. In support of this revised structure **19** for spirastrellolide, our subsequent studies have led to the synthesis of the C_1–C_{25} subunit **20**, incorporating the appropriate stereochemical changes at C_7, C_9 and C_{11}, along with the C_{26}–C_{40} subunit **21**.[18] Both fragments now show excellent agreement with the corresponding NMR data obtained for the natural product.[19]

In summary, we have completed a highly convergent synthesis of the C_1–C_{21} spiroacetal-containing fragment **2** based on the original structural assignment of spiras-

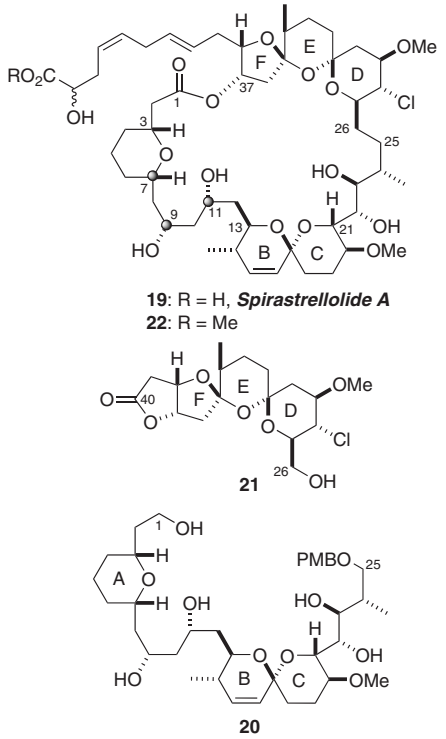


Figure 2 Revised structural assignment of spirastrellolide[2] and synthetic fragments prepared.[18]

trellolide A (16% yield over the longest linear sequence of 14 steps). Key features include the use of asymmetric boron aldol reactions to configure several stereocentres, along with the mild and selective conditions employed for spiroacetalisation. In more recent efforts directed towards the total synthesis of spirastrellolide A (**19**), this preliminary work has already helped guide our strategy for the construction of the stereochemically revised C_1–C_{25} subunit **20**.

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(11) All new compounds gave spectroscopic data in agreement with the assigned structures. Compound **2** had $[\alpha]_D^{22}$ = +34.5 (*c* 0.80, $CHCl_3$); ^{1}H NMR (500 MHz, C_6D_6): δ = 7.78–7.83 (m, 4 H, ArH), 7.22–7.29 (m, 6 H, ArH), 5.60 (dd, *J* = 9.9, 2.4 Hz, 1 H, H_{15}), 5.51 (dd, *J* = 9.9, 1.7 Hz, 1 H, H_{16}), 4.38 (m, 1 H, H_{11}), 4.22 (m, 1 H, H_9), 4.07 (m, 1 H, H_3), 4.03 (m, 1 H, H_7), 3.94 (m, 1 H, $H_{21eq.}$), 3.88 (m, 3 H, 2 × H_1, $H_{21ax.}$), 3.81 (m, 1 H, H_{13}), 3.15 (m, 1 H, H_{20}), 3.10 (s, 3 H, OMe), 2.12 (m, 1 H, H_8), 2.10 (m, 1 H, H_2), 2.09 (1H, m, H_{10}), 2.04 (m, 1 H, H_{10}), 2.02 (m, 1 H, H_{14}), 1.97 (m, 1 H, $H_{19ax.}$), 1.93 (m, 2 H, 2 × H_{12}), 1.84 (m, 1 H, $H_{18eq.}$, $H_{19eq.}$), 1.82 (m, 1 H, H_2), 1.76 (m, 1 H, H_8), 1.65 (m, 1 H, $H_{6eq.}$), 1.58 (m, 1 H, $H_{4eq.}$), 1.50 (m, 1 H, $H_{18ax.}$), 1.49 (m, 2 H, 2 × H_5), 1.36 (m, 1 H, $H_{6ax.}$), 1.25 (m, 1 H, $H_{4ax.}$), 1.19 (s, 9 H, Si^{t}Bu), 1.05 (s, 9 H, Si^{t}Bu), 1.03 (s, 9 H, Si^{t}Bu), 0.80 (d, *J* = 7.1 Hz, 3 H, Me_{14}), 0.26 (s, 3 H, SiMe), 0.28 (s, 3 H, SiMe), 0.24 (s, 3 H, SiMe), 0.20 (s, 3 H, SiMe); ^{13}C NMR (125 MHz, C_6D_6): δ = 135.8, 135.7, 134.2, 134.1, 134.0, 129.7, 129.4, 93.0, 74.9, 71.0, 68.4, 68.3, 67.7, 67.6, 63.7, 61.5, 55.7, 46.6, 43.0, 42.5, 36.3, 34.5, 34.3, 30.8, 29.8, 27.0, 26.1, 26.0, 25.3, 19.3, 18.8, 18.2, 18.1, 17.0, –3.5, –3.7, –3.9, –4.0; HRMS (ES+): *m/z* $[M + H]^+$ calcd for $C_{51}H_{87}O_7Si_3$: 895.5754; found: 895.5752.
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