Pure Appl. Chem., Vol. 79, No. 4, pp. 667–676, 2007.
doi:10.1351/pac200779040667

Progress toward a total synthesis of spirastrellolide A*

Ian Paterson‡, Edward A. Anderson, Stephen M. Dalby, Jong Ho Lim, Olivier Loiseleur, Philip Maltas, and Christian Moessner

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

Abstract: Progress toward a total synthesis of spirastrellolide A, a 38-membered marine macrolide, is reported. Syntheses of two diastereomers of the C1–C25 region, and an evolving Sharpless dihydroxylation strategy toward a C26–C40 fragment, are described. The syntheses exploit boron-mediated aldol chemistry to install key stereocenters, and feature late-stage thermodynamically controlled spiroacetalizations.

Keywords: natural products; macrolides; anticancer; stereocontrolled synthesis; spiroacetal; aldol.

INTRODUCTION

Marine organisms, particularly sponge invertebrates and associated bacteria, are a prolific source of novel biologically active compounds with unusual, and often complex, structures [1]. The harsh environment that marine sponges inhabit, together with their lack of physical defenses, requires that these organisms develop chemical deterrents to aid their survival. As a result, many of their associated secondary metabolites exhibit exceptional levels of biological activity, often combined with unique modes of action. However, the potential therapeutic utility of marine-derived natural products is hampered not only by the limited supply, but often also by their incomplete stereochemical assignment. In both these respects, total synthesis can provide a powerful solution [2].

Within our group, the development of practical methods for stereochemical control and the efficient total synthesis of bioactive natural products and structural analogs are underlying research themes. For example, our synthetic work on discodermolide [3] (**1**, Fig. 1) has aided the development of an industrially viable route [4], whereby multi-gram quantities of this promising anticancer agent, isolated originally from the deep-sea sponge *Discodermia dissoluta*, were produced for clinical trials (by Novartis Pharma AG).

With regard to the issue of stereochemical determination, total or partial synthesis can also provide essential structural information. Our recent total synthesis of dictyostatin [5], a novel microtubule-stabilizing anticancer agent that previously was only available in microscopic quantities from its sponge source, validated its full configurational assignment as **2** [6]. A second case where synthetic efforts have formed the cornerstone of structural assignment is that of the reidispongiolide family of actin-binding natural products; the stereodefined synthesis of small libraries of degradation fragments of reidispongiolide A, in combination with NMR analysis, made possible the complete assignment of the configuration as shown in structure **3** [7]. We now review our work-in-progress

Pure Appl. Chem. **79**, 467–823 (2007). An issue of reviews and research papers based on lectures presented at the 25th International Symposium on Chemistry of Natural Products (ISCNP-25) and 5th International Conference on Biodiversity (ICOB-5), held jointly in Kyoto, Japan, 23–28 July 2006, on the theme of natural products.
‡Corresponding author

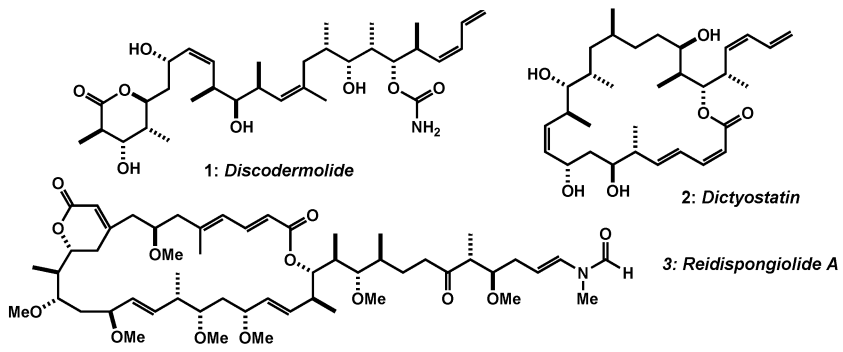


Fig. 1

directed toward the stereochemical assignment and total synthesis of spirastrellolide A, a structurally intriguing antimitotic polyketide obtained from a marine sponge.

SPIRASTRELLOLIDE A

In 2003, Andersen and coworkers reported the isolation of spirastrellolide A from the Caribbean sponge *Spirastrella coccinea* [8a]. This highly oxygenated 38-membered macrolide, initially assigned as structure **4** (Fig. 2) from NMR and mass spectroscopic analysis of its methyl ester derivative, exhibited potent antimitotic activity at the low nanomolar level. Further structural investigations by the Andersen group revealed several inconsistencies in their original assignment, which led in mid-2004 to the reassignment of structures **5** and **6** for spirastrellolide A and its methyl ester, respectively [8b]. The complete stereochemistry could not be determined, such that this depiction represents 1 of 16 possible stereoisomers. Further biological testing revealed that spirastrellolide A is a potent and selective inhibitor of protein phosphatase 2A (PP2A) [8b], with a similar mode of action to other Ser/Thr phosphatase inhibitors such as fostriecin and the calyculins, which also cause premature cell entry into mitosis [9]. Consequently, spirastrellolide represents a potential candidate for the development of antitumor therapeutic agents and, given the central regulatory role of PP2A in the cell, it may also have value as a lead in the treatment of neurological and metabolic disorders.

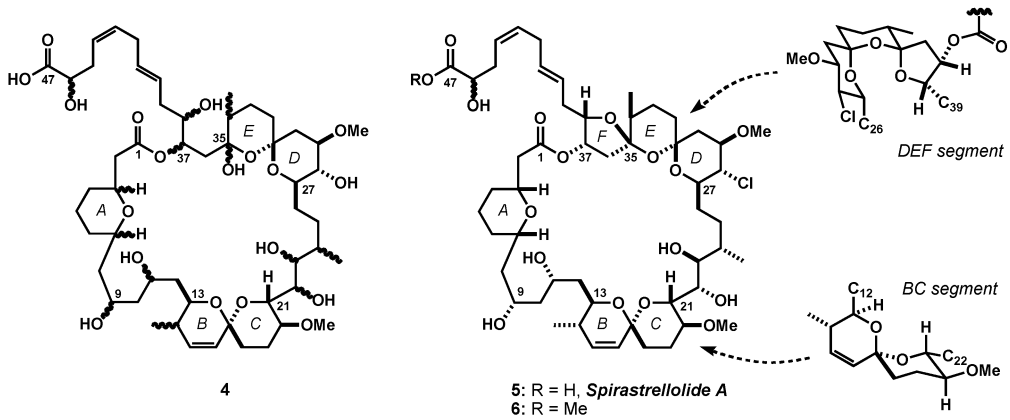
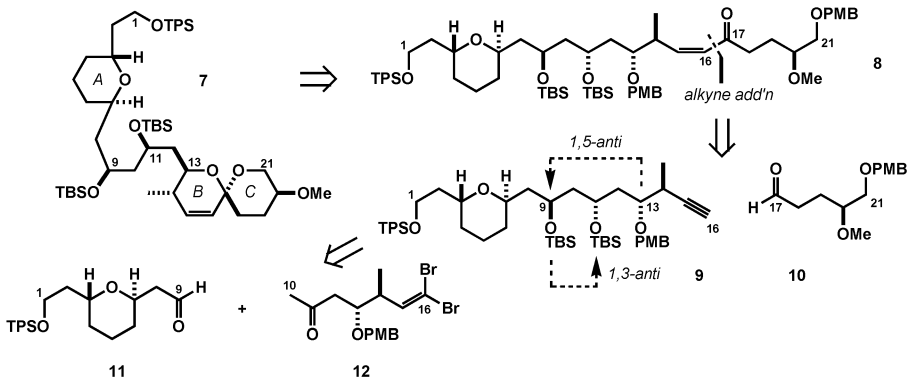


Fig. 2

From a synthetic perspective, spirastrellolide is a formidable target. It contains several challenging and appealing structural features, including some 21 stereocenters, of which 20 are embedded in a 38-membered macrolactone ring, and a 9-carbon side chain featuring a (*Z*,*E*)-1,4-diene, while the macrocycle contains a tetrahydropyran (A ring), a bicyclic 6,6- (BC rings), and a tricyclic 5,6,6-spiroacetal (DEF rings), with the latter substituted with a chlorine atom at C28. Significantly, both of these spiroacetal motifs benefit from stabilization by a double-anomeric effect. Importantly, several stereochemical ambiguities remain which must be addressed in any synthesis plan. In addition to the unknown configuration at the isolated C46 alcohol, spirastrellolide may be divided into three regions of known *relative* stereochemistry: the tetrahydropyran ring, C3–C7; the spiroacetal-containing region, C9–C24; and the chlorinated *bis*-spiroacetal, C27–C38. However, the relationship between these stereoclusters, together with the absolute configuration, is undefined. Our approach aimed to isolate these regions of known relative stereochemistry, such that we would benefit from maximum flexibility in terms of fragment coupling, and thus enable the synthesis of any of the 16 possible stereoisomers of spirastrellolide [10,11].

Initial synthetic endeavors: C1–C21 of the originally assigned structure

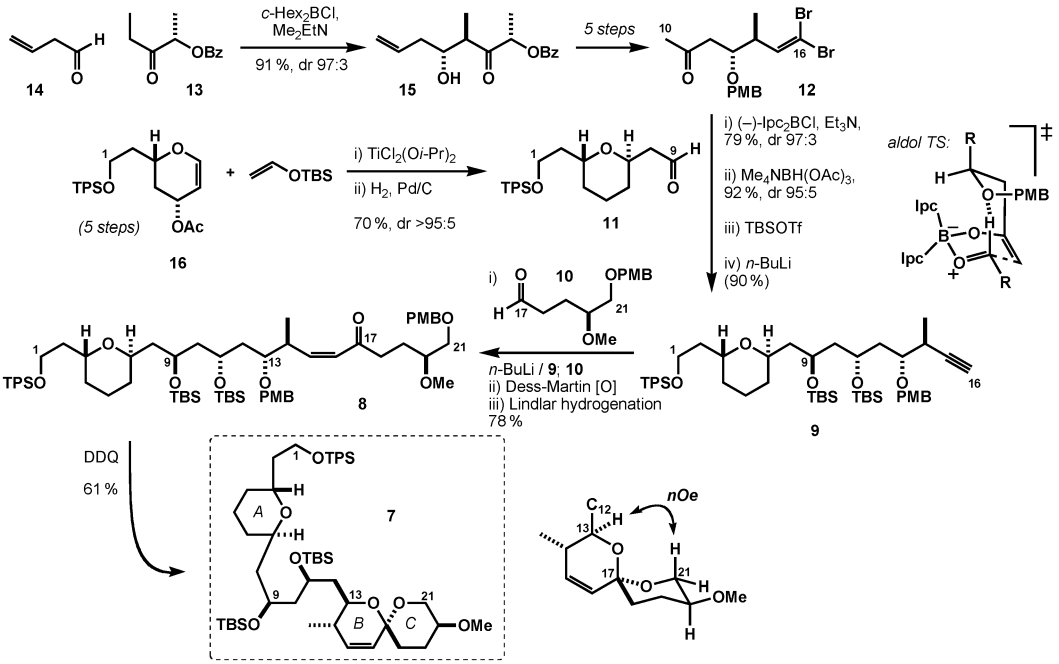
With the first report of spirastrellolide A in 2003, we embarked upon our synthetic endeavors [8a]. Mindful of the array of unknown stereochemistry in the originally assigned structure **4**, we needed to consider many possible permutations. At the outset, we elected to target the candidate structure **7** corresponding to the C1–C21 region, incorporating the ABC rings and having an *anti* relationship between C9 and C11 (Scheme 1). A thermodynamically controlled spirocyclization was anticipated to configure the BC ring system from the linear precursor **8**, which itself could be disassembled into alkyne **9** and aldehyde **10**. This flexible coupling strategy benefits from the possibility of a union of alkyne **9** with *any* suitable aldehyde, enabling access to other stereoisomers and more elaborate fragments. The C1–C16 alkyne **9** with its characteristic 1,5-*anti*/1,3-*syn* stereotriad was viewed as being amenable to synthesis using a boron aldol/directed reduction sequence, employing aldehyde **11** and methyl ketone **12**, containing a latent alkyne in the form of a vinyl dibromide [12].



Scheme 1

Following our standard conditions, the C10–C16 methyl ketone **12** (destined for coupling with aldehyde **11**) was assembled using a boron-mediated *anti* aldol reaction between lactate-derived ethyl ketone **13** and enal **14** (Scheme 2) [13]. The aldehyde partner **11** was prepared using chemistry previously developed within the group, via a Ferrier rearrangement (>95:5 dr) of dihydropyran **16** (itself originating from Jacobsen HDA technology) followed by alkene hydrogenation [14]. These fragments were readily coupled under well-precedented 1,5-*anti* aldol conditions [13], for which there is strong

evidence that the remote stereoinduction arises from a hydrogen bond between the formyl proton and the C13 PMB ether oxygen in a bicyclic transition state [15]. The high dr of this aldol reaction (97:3) was mirrored by the similarly high selectivity for the ensuing 1,3-*anti* reduction (95:5) [16], which completed the installation of the stereochemistry of this segment. Alkyne **9** could be obtained in two further transformations.



Scheme 2

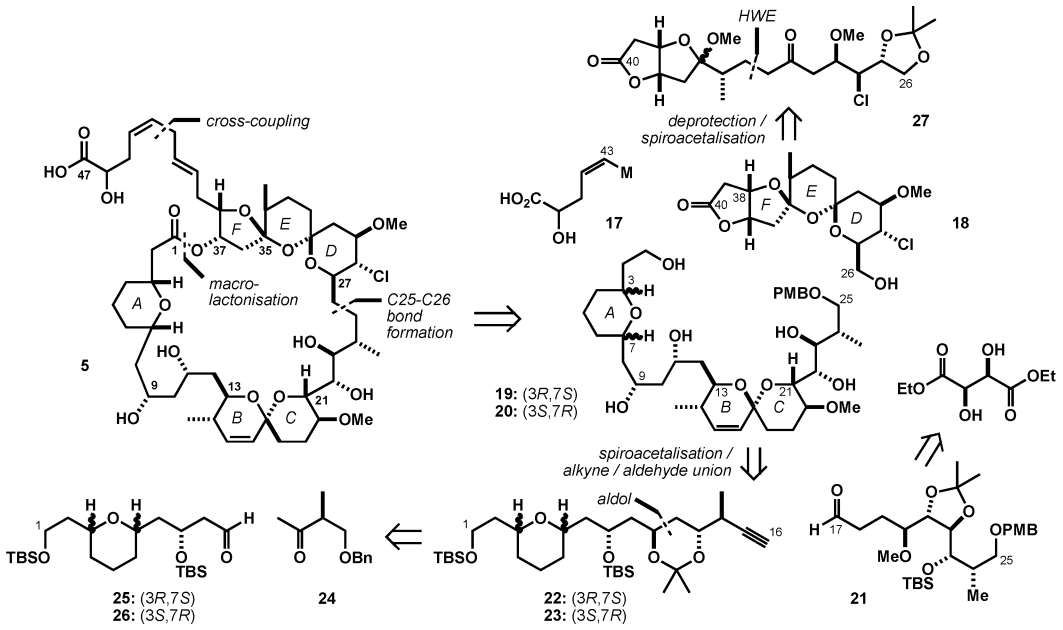
Lithiation of **9**, followed by addition of the glycidol-derived aldehyde **10**, gave a mixture of alcohols which were readily converted to the *cis*-enone **8**. We expected treatment of **8** with dichlorodicyano-*p*-benzoquinone (DDQ) to effect *p*-methoxybenzyl (PMB) deprotection, and even spirocyclization, but were especially pleased to observe in situ isomerization of a mixture of two products to a single compound, spiroacetal **7** [10c].

^{1}H NMR comparison of our synthetic ABC segment **7** with spirastrellolide methyl ester showed a close correlation in the BC spiroacetal region. Our confidence in the stereochemical assignment was reinforced by the observation of a nuclear Overhauser effect (NOE) enhancement between H13 and $H21_{ax}$, as had been observed in the natural product. However, significant NMR discrepancies in the C1–C11 region caused us to question the validity of this initial candidate structure. Shortly after we had completed this work, a structural reassignment of spirastrellolide was published [8b].

A new strategy: Structural revision of spirastrellolide

The substantial structural reassignment of spirastrellolide as **5** allowed us to consider in more detail our overall strategy toward the natural product (Scheme 3). Conscious of the need to segment the molecule into its constituent regions of known stereochemistry, we decided on initial disconnections that would isolate the C46-stereocenter (**17**), the DEF *bis*-spiroacetal northern hemisphere (**18**), and the ABC southern hemisphere. The latter spiroacetal still contains stereochemical uncertainty in the form of the *cis*-fused tetrahydropyran A ring, and as such we chose to target both diastereomers of the pyran (at C3

and C7, relative to C9–C24) in the form of the polyols **19** (3*R*,7*S*) and **20** (3*S*,7*R*). The inversion of stereochemistry at C9 and C11 of spirastrellolide relative to our previous ABC candidate **7** necessitated a revision of our approach to the C1–C25 region; our retrosynthesis (of **19** and **20**) maintained the successful key late-stage spiroacetalization and alkyne/aldehyde union strategy, but required an alternative source of these compounds. The more elaborate C17–C25 aldehyde **21** was now envisioned to derive from diethyl tartrate, whilst the new route to alkynes **22** and **23** required complete revision. The use of other group methodology, namely, a ligand-enhanced 1,4-*syn* boron aldol reaction between methyl ketone **24** and either isomer of C1–C9 pyran aldehyde (**25**/**26**) [17], would provide access to either of the possible diastereomers of the C1–C16 alkyne (**22**/**23**), and therefore also of the complete C1–C25 region. In a similar fashion, the C26–C40 *bis*-spiroacetal **18** could arise from spirocyclization of an appropriately protected polyol **27**, which itself could be conveniently constructed using a Horner–Wadsworth–Emmons (HWE) strategy.

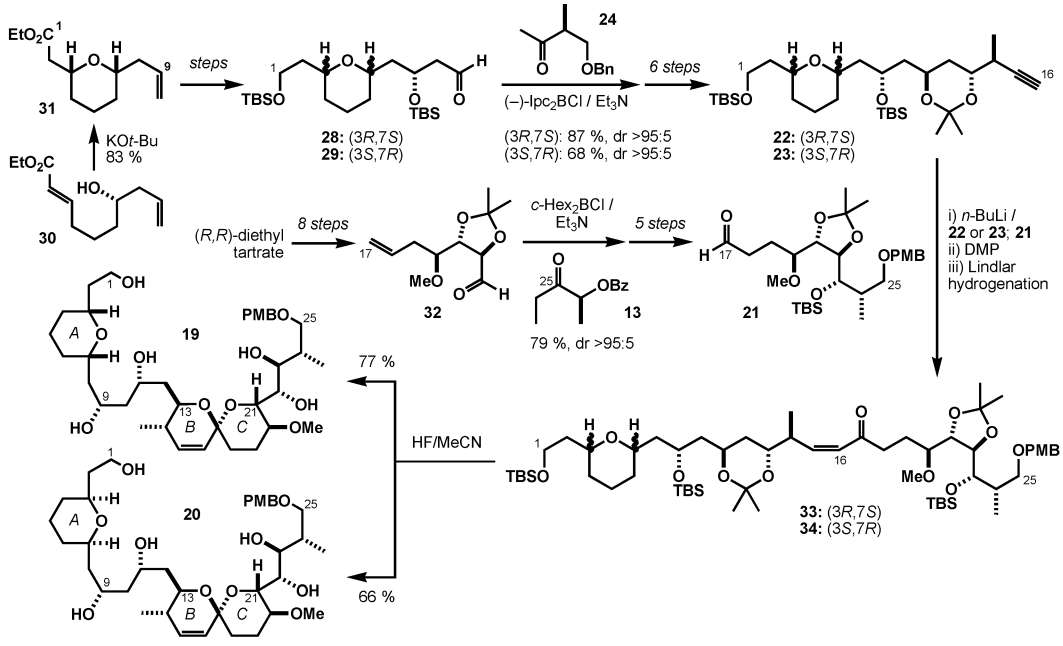


Scheme 3

Synthesis of two diastereomeric C1–C25 spiroacetal subunits

With the majority of the stereochemistry of the C1–C25 region now known, we had elected to pursue a route toward both possible *cis*-tetrahydropyran isomers (3*R*,7*S*–**19** and 3*S*,7*R*–**20**) of this segment of the natural product, with the hope of solving the stereoconundrum posed by this region. To this end, diastereomeric pyran aldehydes **28** and **29** were assembled using a Michael cyclization of **30** as the key pyran-forming reaction (Scheme 4).

The ligand-enhanced 1,4-*syn* aldol reactions of these aldehydes with methyl ketone **24** proceeded smoothly and with good selectivity in both cases; the aldol adducts were then advanced using standard chemistry (including selective 1,3-*anti* reductions [16]) to the diastereomeric alkynes **22** and **23**, in readiness for coupling with aldehyde **21**. The preparation of this aldehyde utilized diethyl tartrate as a convenient starting material, which was advanced to aldehyde **32**. A second boron aldol reaction was now used to install the *anti* relationship between the C23 hydroxyl and C24 methyl substituents [13]; further manipulation gave the targeted aldehyde **21**.



Scheme 4

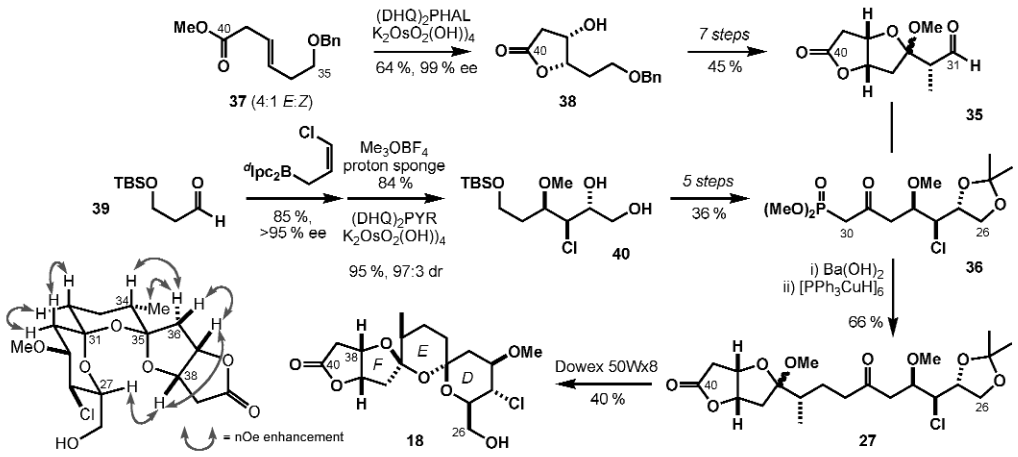
Fragment union of the diastereomeric alkynes with aldehyde **21** proved successful, with an alcohol oxidation/alkyne reduction sequence providing the linear spiroacetal precursors **33** and **34**. At this point, all that was required to complete the ABC subunit synthesis was acetonide removal and spirocyclization. However, under a wide range of conditions, the five-membered C21–22 acetonide proved particularly resistant to deprotection. Side reactions were observed leading to the formation of complex product mixtures, possibly due to competitive Michael cyclization of the C11 hydroxyl. Finally, it was found that the use of aqueous HF in acetonitrile could remove both acetonides and effect cyclization (to spiroacetals **19** and **20**). Whilst these successful conditions also resulted in deprotection of all the silyl ethers, isolation of these spiroacetals enabled extensive comparison of NMR data of **19** and **20** with that of the natural product. A close correlation between the synthetic and natural compounds was observed in the A ring and the BC spiroacetal region. Unfortunately, ambiguity still remained around C7–C9, in both the acetals **19** and **20**, and also their corresponding peracetates and acetonides, preventing a definitive stereochemical assignment of the southern hemisphere of spirastrellolide [10b].

Synthesis of a C26–C40 tetracyclic bis-spiroacetal

Our approach to the C26–C40 DEF spiroacetal required the construction of linear precursor **27** via HWE reaction of aldehyde **35** and phosphonate **36** (Scheme 5). The aldehyde **35** was prepared using a Sharpless AD/lactonization of β,γ-unsaturated ester **37** (synthesized by olefin cross-metathesis as a 4:1 *E*:*Z* mixture of alkenes) to differentiate the vicinal oxygenation at C37 and C38 [18]; this lactone (**38**) was advanced to the aldehyde **35** using standard chemistry, including a Brown crotylation to install the C34-methyl group. Synthesis of the phosphonate partner **36** for the HWE reaction relied on Oehlschlager's asymmetric chloroallylation methodology to construct the *syn* relationship between the C29-methoxy and C28-chloro substituents [19].

HWE union of the aldehyde **35** and phosphonate **36**, followed by conjugate reduction, gave linear substrate **27** [20]. Investigation of spirocyclization conditions revealed that, as with the C1–C25

southern hemisphere, acetonide deprotection was rather problematic. The strongly acidic conditions required to remove this protecting group also led to competing elimination of the F ring to an aromatic furan. Our optimized conditions (Dowex 50Wx8, MeCN, 80 °C) gave at best a 40 % yield of the C26–C40 subunit. ^{1}H NMR comparison of this fragment with spirastrellolide again showed excellent agreement, with diagnostic NOE enhancements confirming the *bis*-spiroacetal stereochemistry [10a].



Scheme 5

Strategy evolution: Improved syntheses of C26–C40 bis-spiroacetal subunits

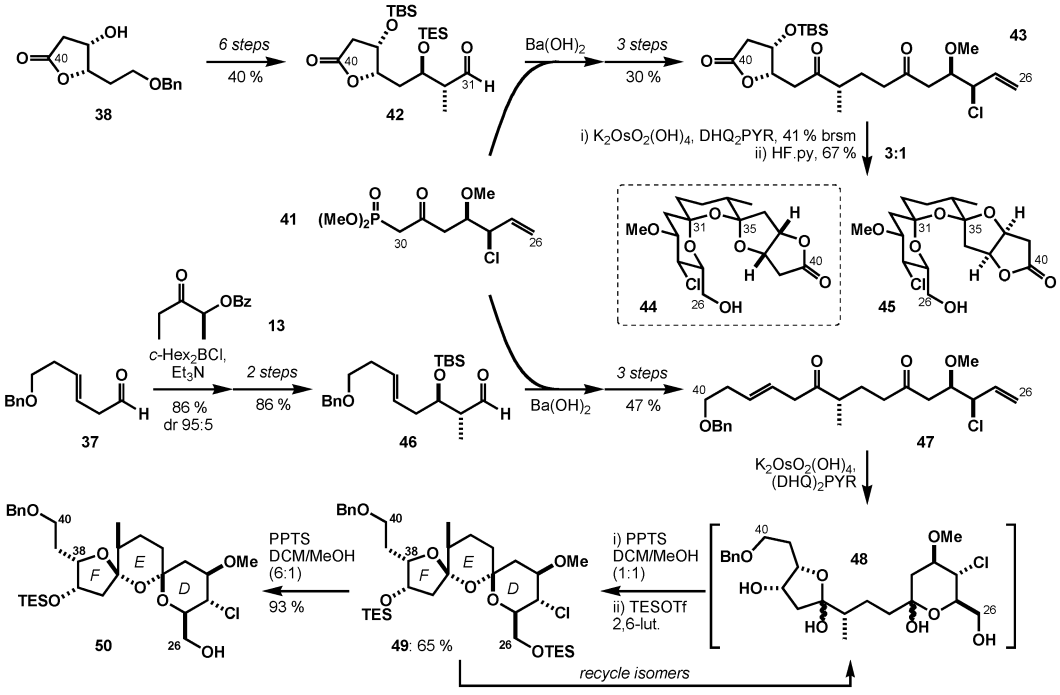
Although our route to the C26–C40 segment **18** had proved successful, we were not satisfied with the modest yield and capricious nature of the final deprotection/cyclization. It was apparent that any conditions that would allow deprotection of the C26/27 acetonide could also effect elimination of the F ring. Extended reaction times caused product degradation, and isomerization of any isomers formed was also not possible without competing furan formation.

We recognized that a late-stage dihydroxylation might solve these problems, as it would eliminate the need for a (robust) diol protecting group—although it would also necessitate carrying the potentially fragile allylic chloride through a number of synthetic steps. In the event, phosphonate **41** (Scheme 6, prepared using an equivalent sequence of steps to phosphonate **36**) underwent smooth HWE olefination/conjugate reduction with aldehyde **42**, itself readily derived from lactone **38**, to give the dihydroxylation substrate **43**. Sharpless dihydroxylation of the allylic chloride using our optimized conditions led to a hemiacetal which, upon treatment with HF.py, gave the targeted DEF subunit **44**, together with its EF spiroacetal isomer (67 %, 3:1 ratio of **44**:**45**).

Once again, this isomer **45** could not be equilibrated (to **44**) without furan formation, nor could the cyclization be performed under other conditions without extensive degradation. It now seemed that the presence of the δ-lactone ring conferred additional stability on the DEF subunit with respect to isomerization, whilst promoting elimination under harshly acidic conditions. Additionally, it seemed to us that all the cyclizations investigated to this point had been achieved under kinetic control, or at least that any attempt at isomerization (i.e., exposure to "thermodynamic control" conditions) led to extensive degradation. We reasoned that deletion of the δ-lactone ring from this subunit might increase the ease of equilibration of any isomers formed under kinetic conditions; additionally, we realized that we might further streamline our synthesis of this subunit by performing *both* asymmetric dihydroxylations simultaneously, as a direct prelude to *bis*-spiroacetalization.

This revised route would still utilize phosphonate **41**, but required the preparation of the linear aldehyde **46** for HWE olefination. Our approach to this aldehyde incorporated some synthetic

improvements over our previous routes. Aldehyde **37** was no longer prepared using cross-metathesis (with its associated isomeric olefin mixture), but instead used a deconjugative Knoevenagel condensation to install the β,γ-unsaturation [21]. Additionally, the C34 methyl-bearing stereocenter could now be installed using our lactate aldol methodology [13]; olefination and subsequent manipulations delivered the key diene **47**.



Scheme 6

Exposure of this diene to the Sharpless conditions optimized for the allylic chloride olefin resulted in rapid (<1 h) dihydroxylation of the internal olefin, followed by dihydroxylation at C26–27. We found that this product (**48**) and later compounds could not be readily purified by chromatography without substantial loss of material, and the crude reaction mixture was instead exposed to PPTS in 1:1 DCM/MeOH, to effect spirocyclization to a mixture of tricyclic compounds. These diols were also not isolated, but instead converted directly to the *bis*-triethylsilyl ether **49**, together with its isomers. At this point, a reliable purification of **49** was possible; furthermore, the mixture of undesired DEF isomers finally proved susceptible to equilibration on further exposure to pyridinium *p*-toluenesulfonate (PPTS). The combined yield for this three-step process, after one recycling of undesired DEF isomers, was a pleasing 65 % (from linear diene **47**), in recognition of the fact that we had finally discovered conditions under which a thermodynamic cyclization/isomerization of the DEF subunit could occur. As a conclusion to this study, a selective deprotection of the primary TES ether (to **50**) was carried out using PPTS in 6:1 DCM/MeOH, in readiness for fragment coupling.

CONCLUSION AND OUTLOOK

Our synthetic endeavors toward spirastrellolide A have enabled the development of scaleable routes toward the northern and southern hemispheres of the natural product. It is anticipated that investigations into fragment coupling and eventual macrocyclization should provide invaluable information

concerning the precise stereochemistry of spirastrellolide, and permit a total synthesis of this potentially important molecule in the ongoing battle against cancer.

NOTE ADDED IN PROOF

Subsequent to the submission of this manuscript, Andersen reported the assignment of the relative and absolute stereochemistry of the spirastrellolide macrocycle to be that depicted in structure **5**. The stereochemistry of the remote C46 stereocenter remains undetermined [22].

ACKNOWLEDGMENTS

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

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