Natural Products (1)

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Toward the Total Synthesis of Spirastrellolide A. Part 1: Strategic Considerations and Preparation of the Southern Domain**

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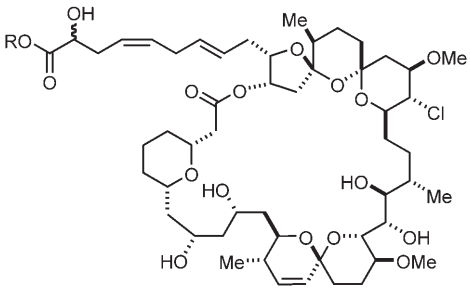
As part of a program aimed at the discovery of new antimitotic natural products, Andersen and co-workers recently isolated spirastrellolide A (**1**; Scheme 1) from the



1 (R = H)

Scheme 1. One of the 16 possible stereostructures that might represent spirastrellolide A.

Caribbean sponge *Spirastrella coccinea*.[1] Unlike many other antimitotic macrolides of marine origin, **1** does not affect tubulin polymerization in vitro but was shown to be a very potent ($IC_{50} = 1$ nM) and surprisingly selective inhibitor of protein phosphatase PP2A, with the ability to drive cells directly from the S phase into mitosis before causing cell-cycle arrest.[1,2] In view of the central regulatory role of PP2A, spirastrellolide A represents a potential lead for the development of novel therapeutic agents for the treatment of cancer as well as various neurological and metabolic disorders.[3]

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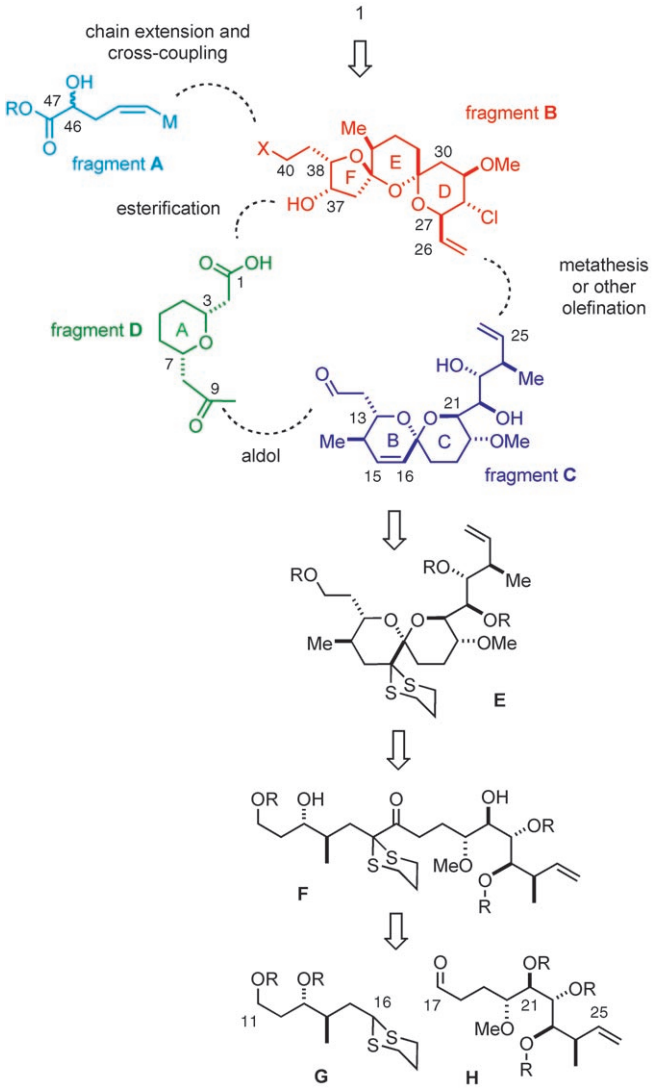
The initial assignment[1] of this intriguing natural product, based on extensive NMR studies of its methyl ester derivative **1a** (R = Me), was corrected shortly after publication.[2] Even the revised structure **1** remains tentative; although it certainly depicts the correct constitution of spirastrellolide A and the proper relative stereochemistry within the individual domains embedded into the complex macrocylic frame, it must be emphasized that the stereochemical relationships between the segments color-coded in Scheme 2 have yet to be determined. Moreover, the absolute stereochemistry of **1** is still unknown.[2]



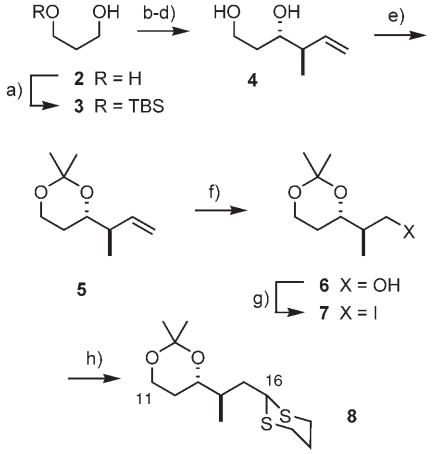
Scheme 2. Retrosynthetic analysis of spirastrellolide based on disconnections into four stereoclusters of known relative configuration and further analysis of the spiroacetal fragment **C**.

In view of the 16 possible combinations of these stereoclusters, any investigation directed toward this complex natural product, which contains no less than 21 chiral centers, a 38-membered macrolactone, a skipped diene, five pyranose rings, and a tetrahydrofuran moiety which flanks a chlorinated [5,6,6]-bis-spiroacetal entity faces considerable chal-

lenges.[4] Only a convergent, flexible, and modular approach might eventually be successful; however, any such plot is confined to disconnections at or close to the boundaries of the individual stereoclusters as long as the internal relationship between them has not been established. This notion is reflected in our global retrosynthetic plan depicted in Scheme 2, which envisages cross-coupling, metathesis[5] (or alternative alkene formations), aldol, and esterification transformations for the deconvolution of the target into fragments **A**–**D**. Outlined below is our approach to the fully functional southern C1–C25 domain of spirastrellolide A, whereas the accompanying Communication reports the conquest of the complementary northern hemisphere.[6]

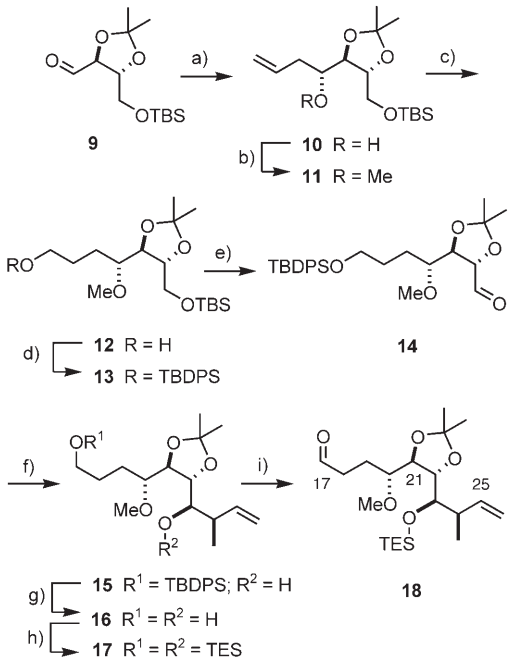
As indicated in Scheme 2, the preparation of the spiroketal segment **C** envisaged a thermodynamic acetalization of a dihydroxyketone precursor **F**. Although it was tempting to have the *Z* alkene at C15/C16 in place at that stage, we opted against this possibility for strategic reasons;[7] rather, we chose to encode this future olefin as a protected carbonyl group (**E**), which in turn facilitates the assembly of the carbon backbone of the spirocyclization precursor **F** from segments **G** and **H**.

To this end, preparation of the required dithiane commenced with monoprotection of 1,3-propanediol **2** followed by oxidation of the resulting product **3** to the corresponding aldehyde (Scheme 3). Brown crotylation[8] and deprotection of the TBS group then gave the known diol **4**[9] (93% *ee*), which was elaborated into acetonide **5** prior to ozonolysis of the double bond followed by reductive work-up with excess $NaBH_4$. The resulting alcohol **6** was converted into iodide **7**, which could be alkylated with lithio-1,3-dithiane at low temperature. To obtain high yields, however, syringe-pump addition of **7** was necessary to minimize elimination of HI. Under these conditions, the route summarized in Scheme 3 was amenable to scale-up and afforded multigram quantities of **8** in high overall yield.



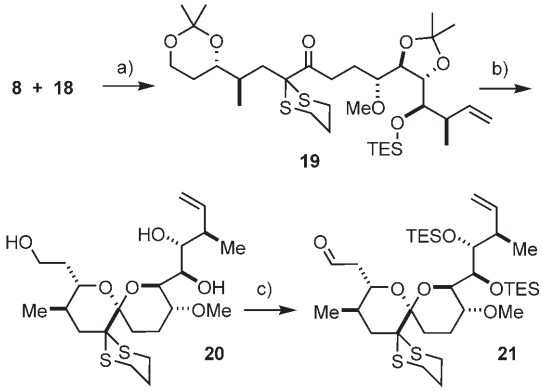
Scheme 3. Preparation of the required dithiane unit. Reagents and conditions: a) TBSCl, Et_3N, CH_2Cl_2 (97%); b) SO_3·pyridine, DMSO, Et_3N, CH_2Cl_2, −78→0°C (95%); c) (+)-[(*E*)-crotyl]B(ipc)$_2$, THF, −78°C (80%; 93% *ee*); d) TBAF, THF (94%); e) 2,2-dimethoxypropane, CSA cat., acetone, MS 4 Å (92%); f) O_3, CH_2Cl_2/MeOH, −78°C, then $NaBH_4$, RT (97%); g) I_2, PPh_3, imidazole, THF, 0°C (97%); h) 1,3-dithiane, *t*BuLi, −78°C, THF/DMPU (10% v/v; 91%). CSA = camphorsulfonic acid, DMPU = 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone, DMSO = dimethyl sulfoxide, IPC = isopinocampheyl, MS = molecular sieves, TBS = *tert*-butyldimethylsilyl.

The tartrate-derived aldehyde **9**[10] served as a convenient starting material for the preparation of the C17–C25(26) segment through a "two-directional" synthetic strategy (Scheme 4).[11] A reagent-controlled allylation set the *R* configured secondary alcohol that resides at C20; of the many procedures surveyed, we settled on the classical Brown protocol,[12] which was the only method that reliably gave **10** as a single diastereomer in consistently high yields of up to 81% on a 20-g scale. The symmetry-related chain extension at the C23 terminus of aldehyde **14** derived from **10** by standard protecting-group and oxidation-state management was analogously performed by Brown crotylation,[8] which was once more superior to alternative procedures in terms of scalability and stereoinduction. The terminal TBDPS ether in product **15** thus formed was then cleaved with TBAF; however, all attempts at a selective oxidation of the primary alcohol in the resulting diol **16** remained unsuccessful. Therefore, **16** was bis-silylated with TESCl/imidazole to give **17**, which served as the substrate for a subsequent oxidation with PDC, which nicely remedied the selectivity issue, thus converting only the primary TES ether into the desired aldehyde. Overall, this unambiguous route establishes the challenging stereopentad that extends from C20–C24 and was successful in providing multigram amounts of building block **18**.



Scheme 4. Preparation of the C17–C25(26) segment through a "two-directional" synthetic strategy. Reagents and conditions: a) (+)-Ipc$_2$B-(allyl), Et_2O, −100°C (81%); b) NaH, MeI, THF; c) BH_3·THF, THF, then H_2O_2; d) TBDPSCl, imidazole, CH_2Cl_2 (78%; 3 steps); e) 1. CSA cat., MeOH; 2. SO_3·pyridine, Et_3N, DMSO, CH_2Cl_2; f) (+)-[(*E*)-crotyl]B-(ipc)$_2$, THF, −78°C (56%; 3 steps); g) TBAF, THF; h) TESCl, imidazole, CH_2Cl_2; i) PDC, CH_2Cl_2, 0°C→RT (80%; 3 steps). TBAF = tetra-*n*-butylammonium fluoride, TBDPSCl = *tert*-butyldiphenylsilyl chloride, TES = triethylsilyl, PDC = pyridinium dichromate.

Envisaging the use of the dithiane ring as a linchpin, **8** was deprotonated with the aid of a mixed organometallic reagent formed from *n*BuLi and $(n\text{Bu})_2\text{Mg}$ in THF.[13] The addition of aldehyde **18** to the resulting anion followed by a Dess–Martin oxidation[14] furnished ketone **19** (Scheme 5). Gratifyingly,

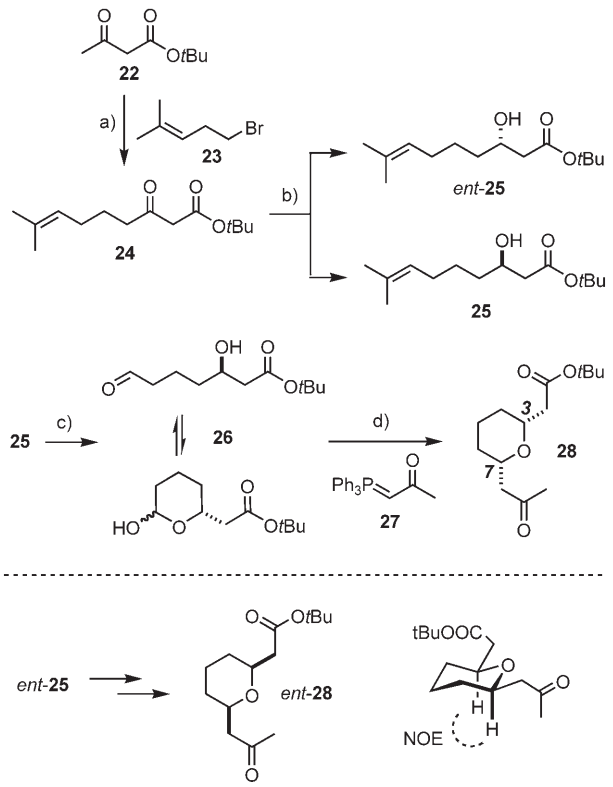


Scheme 5. Preparation of the polyfunctional fragment **21**. Reagents and conditions: a) 1. *n*BuLi/$(n\text{Bu})_2\text{Mg}$ (4:1), THF, RT, then aldehyde **18**, −78 °C; 2. Dess–Martin periodinane, CH_2Cl_2 (69%; 2 steps); b) PTSA (1 equiv), MeOH (87%); c) 1. TESOTf, 2,6-lutidine, CH_2Cl_2; 2. DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2, −40 °C (96%; 2 steps). OTf = triflate, PTSA = *p*-toluenesulfonic acid.

treatment of this compound with PTSA in MeOH engendered cleavage of the isopropylidene acetals followed by spontaneous formation of spiroacetal **20**, which was obtained as a single diastereomer in 87% yield of the isolated product. Extensive 1D and 2D NMR spectroscopic investigations unequivocally established the constitution and stereochemistry of this intricate product, which could be elaborated into aldehyde **21** by the convenient persilylation/selective monooxidation tandem process mentioned above. In this particular case, recourse to Swern oxidation[15] proved optimal, thus delivering the polyfunctional fragment **21** in virtually quantitative yield.

The synthesis of the tetrahydropyran fragment **D** relied on an asymmetric hydrogenation followed by an intramolecular Michael addition to set the two stereocenters at C3 and C7 (Scheme 6). Weiler dianion alkylation[16] of **22** with bromide **23** was followed by a Noyori reduction of the resulting ketoester **24**,[17] which had to be performed in the presence of a catalytic amount of HCl at moderate temperature and hydrogen pressure (5 bar, 40 °C).[18,19] Under these conditions, product **25** was obtained in an almost quantitative yield and excellent optical purity (≥98% *ee*), without any hydrogenation of the trisubstituted olefin or cleavage of the *tert*-butyl ester interfering.

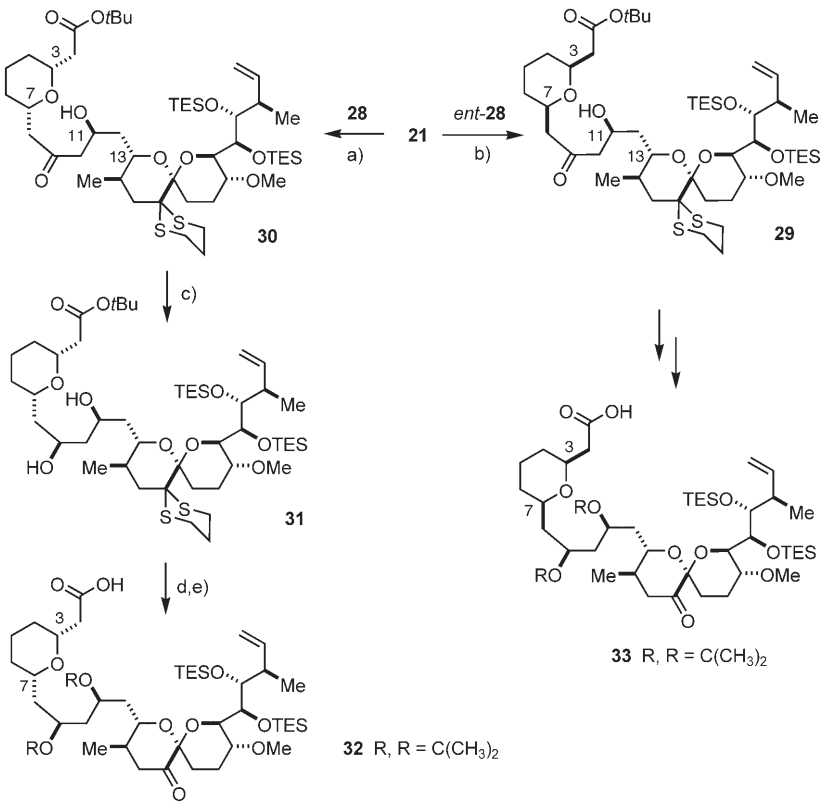
Ozonolysis of the alkene group in **25** and reaction of aldehyde **26** thus formed with the stabilized ylide **27** followed by exposure of the resulting enone to catalytic amounts of CSA in CH_2Cl_2 afforded the Michael addition product **28** in 78% yield over three steps. Compound **28** was readily separated from its C7 isomer (d.r. = 8.5:1), which could be re-equilibrated to give a second crop of **28**. Apprehensive that a similar acid-catalyzed retro-Michael/Michael manifold at



Scheme 6. Preparation of segment **D**. Reagents and conditions: a) NaH, *n*BuLi, then bromide **23**, THF/HMPA (81%); b) $[RuCl_2(\text{binap})]_2{\cdot}NEt_3$ (1 mol%), HCl (2 mol%), H_2 (5 bar), MeOH, 40 °C (95%; 98% *ee*); c) O_3, MeOH, then Me_2S, −78 °C → RT; d) 1. ylide **27**, toluene, reflux; 2. CSA cat., CH_2Cl_2 (78%; 3 steps; d.r. = 8.5:1). binap = (1,1′-binaphthalene)-2,2′-diylbis(diphenylphosphine), HMPA = hexamethyl phosphoramide.

the "ester end" of **28** would engender an erosion in the optical purity of this building block, the enantiomeric excess of **28** was carefully checked but found to be unaltered (98% ee, determined by HPLC). Moreover, the *cis* relationship between C3 and C7 was confirmed by NOE interaction experiments (Scheme 6). Repeating this route with (*S*)-BINAP rather than (*R*)-BINAP as the ligand during the β-ketoester reduction also provided us with multigram quantities of *ent*-**28** in a respectable 60% yield over four readily scalable operations.

Stereoselective aldol reactions of either enantiomer with aldehyde **21** established the required 1,3-*anti* relationship between C13 and C11, as found in the natural product (Scheme 7). Satisfactory solutions for this critical segment coupling were secured when isomer *ent*-**28** was treated with **21** under modified Mukaiyama conditions[20] with $BF_3{\cdot}Et_2O$ as the optimal promoter. $BF_3{\cdot}Et_2O$ should be added slowly to the reaction mixture to avoid complications with the acid-sensitive groups in both reaction partners. This reliable protocol afforded product **29** in 62% yield as a single isomer. In contrast, the reaction that employed the enantiomeric ketone **28** was carried out using the boron–enolate methodology,[21] thus delivering the diastereomeric *anti*-aldol **30** together with its separable C11 isomer in 94% yield of the combined products and a diastereomeric ratio of 4:1.[22]



Scheme 7. Preparation of two possible diastereomers of the southern hemisphere of spirastrellolide A. Reagents and conditions: a) Cy_2BCl, $(iPr)_2NEt$, CH_2Cl_2, −78 °C (94%; d.r. = 4:1); b) TMSOTf, $(iPr)_2NEt$, CH_2Cl_2, then $BF_3{\cdot}Et_2O$, −78 °C (62%); c) $Me_4NBH(OAc)_3$, MeCN, HOAc, −25 → 0 °C (85%); d) $(CH_3)_2C(OMe)_2$, acetone, PPTS cat. (87%); e) 1. dibal-H, CH_2Cl_2, −78 °C; 2. $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, *t*BuOH/H_2O (69%; 2 steps). Cy = cyclohexyl, dibal-H = diisobutylaluminum hydride, PPTS = pyridinium *p*-toluenesulfonate, TMS = trimethylsilyl.

The major products of either series were then subjected to a 1,3-*anti* reduction with $Me_4NHB(OAc)_3$ to set the proper stereochemistry at C9 (**30** → **31**),[23] followed by acetonide formation and conversion of the ester terminus into the required acid function by reduction/oxidation (Scheme 7). Not unexpectedly,[24] the dithiane moiety in **31** was concomitantly cleaved by the excess of $NaClO_2$ used in the latter step. This practical maneuver afforded product **32**, which constitutes the properly functionalized southern domain of **1**, in high overall yield. The equally conceivable isomer **33**, characterized by a different internal stereochemical relationship between the A ring and the BC stereocluster, was formed analogously from aldol **29**. Detailed spectroscopic analyses confirmed the structures of these advanced compounds, with the NOE interaction patterns and the acetal resonances in the ^{13}C NMR spectra being particularly diagnostic.[22,25]

In summary, we have devised a concise, efficient, and scalable route to the southern C1–C25 domain of spirastrellolide A (**1**), which was prepared in two possible stereochemical formats. Together with the conquest of the northern hemisphere reported in the accompanying Communication,[6] we are now in a position to tackle the final assembly of this intricate natural product with the hope of unraveling its stereostructure by total synthesis of various conceivable isomers. Progress along these lines will be reported in due course.

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