Toward the total synthesis of spirastrellolide A. Part 3: Intelligence gathering and preparation of a ring-expanded analogue†

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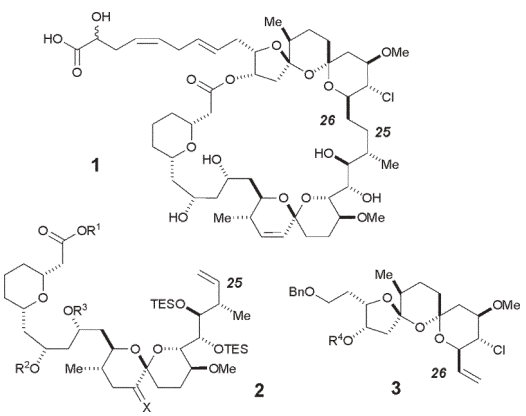
Different methods for the formation of the C.25–C.26 bond of spirastrellolide A (1) are evaluated that might qualify for the end game of the projected total synthesis, with emphasis on metathetic ways to forge the macrocyclic frame.

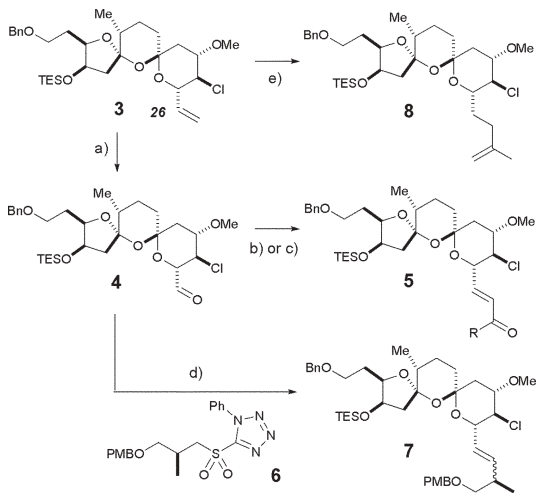
Spirastrellolide A (**1**), a potent and selective inhibitor of protein phosphatase 2A isolated from the Caribbean sponge *Spirastrella coccinea*, elicits considerable interest due to its captivating molecular architecture and promising antimitotic activity.[1,2] In this context, we have recently described concise entries into the 'southern' (**2**) as well as the 'northern' domains (**3**) of this 38-membered macrolide,[3] and now wish to present preliminary investigations concerning the fusion of these segments. Since these studies had been initiated before the stereostructure of **1** was fully unravelled,[1a] they address, in part, the enantiomer or diastereomers of the natural product.



The incomplete structural information available at the outset of the project[1b,c] enforced an overall synthesis plan dissecting **1** into regions of known relative stereochemistry. One such site is the non-stereogenic C.25–C.26 bond to be forged by methodology that makes proficient use of the olefinic termini of **2** and **3**.[3] In an attempt to explore different options, compound **3** (R^4 = TES) was converted into aldehyde **4** by dihydroxylation and subsequent oxidative cleavage of the resulting diol with $Pb(OAc)_4$; although **4** turned out to be exceptionally sensitive, it underwent productive Wittig and Horner–Emmons reactions (Scheme 1); a related Julia olefination[4] could also be achieved, although product **7** was obtained as an inseparable mixture of isomers. Moreover, hydroboration of the terminal olefin in **3** (R^4 = TES) with 9-BBN followed by a Suzuki reaction[5] of the resulting alkylborane with 2-bromopropene as a model electrophile was successful (**3** → **8**). This result holds considerable promise for an endgame based on cross coupling methodology.

It is obvious, however, that olefin metathesis constitutes a more direct means to form the C.25–C.26 bond.[6] Despite considerable experimentation, however, all attempts to engage dienes of type **9** in RCM-based macrocyclizations were unsuccessful, either leading to no reaction or resulting in partial olefin isomerization and/or incorporation of the =CHPh unit of the catalyst, when more forcing conditions were employed. As evident from the representative examples depicted in Scheme 2, this outcome was largely independent of the chosen protecting group pattern and the absence or presence of the dithiane moiety at C.16.[7]

This failure is likely caused by the massive chlorinated bis-spiroketal unit flanking the 'northern' olefin, which not only renders its conversion into a ruthenium carbene difficult but even prevents metal carbenes from approaching to this particular site in a productive manner.[8] In line with this notion, the detached



Scheme 1 *Reagents and conditions*: (a) (i) OsO_4 (2 mol%), NMO, tBuOH; (ii) $Pb(OAc)_4$, CH_2Cl_2; (b) Ph_3P=CHCOOMe, THF, 44% (R = OMe, over three steps); (c) $(MeO)_2P(O)CH_2C(O)Me$, $Ba(OH)_2 \cdot 8H_2O$, THF, 85% (R = Me); (d) LiHMDS, THF, −78 °C → RT%; (e) (i) 9-BBN, THF; (ii) 2-bromopropene, $(dppf)PdCl_2$, (10 mol%), $AsPh_3$ (20 mol%), Cs_2CO_3, DMF, 65 °C, 41%.

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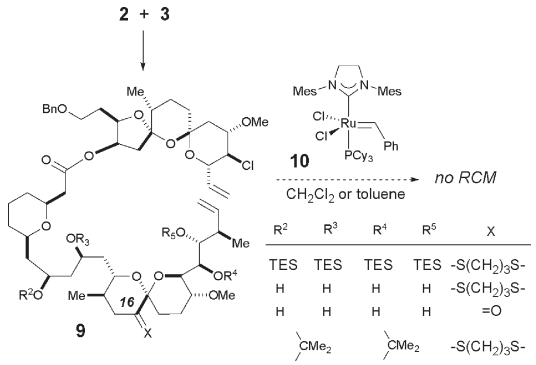
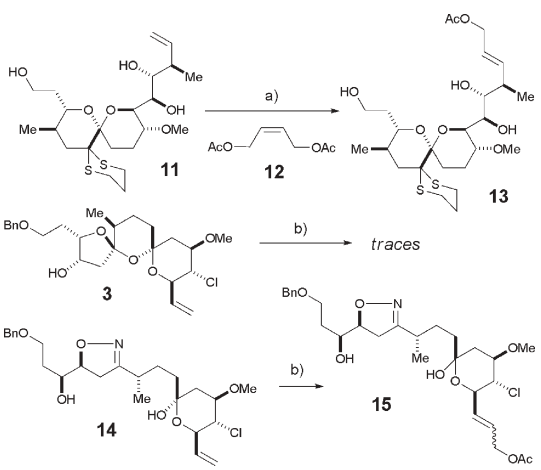


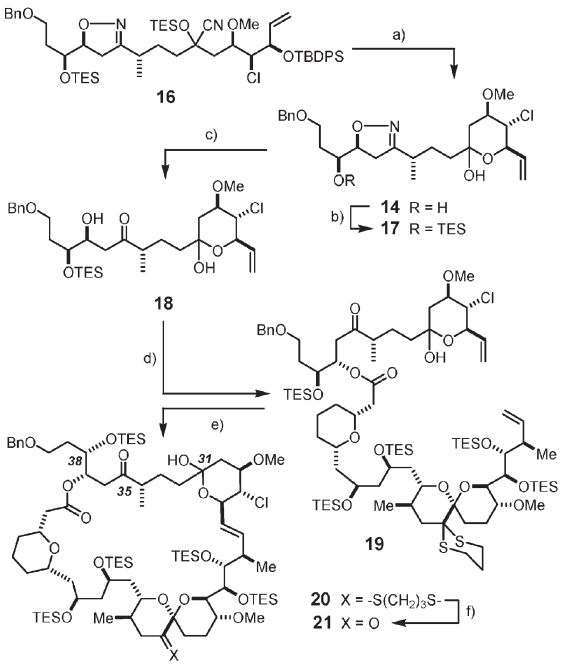
Scheme 2 Attempted cyclizations by RCM.

'southern' spiroacetal segment **11** *per se* underwent effective cross-metathesis, whereas the 'northern' domain **3** essentially failed to react under otherwise identical conditions (Scheme 3). Partial unfolding of the bis-spiroacetal, as manifested in isoxazoline **14**,[3b] however, restores some of the reactivity and hence corroborates the view that mainly steric factors account for the unsuccessful attempts to cyclize dienes of type **9**.

As a consequence, it was envisaged to effect macrocyclization by RCM *prior* to the elaboration of the bis-spiroketal. To this end, treatment of compound **16**[3] with $[(Me_2N)_3S][Me_3SiF_2]$ (TASF)[9] in aqueous DMF afforded hemiketal **14** upon release of the carbonyl from the cyanohydrin and concomitant cleavage of the silyl ethers (Scheme 4). Reprotection of the remaining hydroxyl group (**14** → **17**) followed by reductive cleavage of the N–O-bond with $Mo(CO)_6$[10] gave aldol **18**, which was acylated with carboxylic acid **2** under Yamaguchi conditions.[11] Gratifyingly, the resulting diene **19** converted into cycloalkene **20** on treatment with the 'second-generation' Grubbs carbene **10**[12] in toluene at 60 °C; yet, this transformation denotes a present limit of metathesis, as it required 2.5 equivalents of the "catalyst", added in several portions, to reach complete conversion. After oxidative hydrolysis of the dithioacetal with $NCS/AgNO_3$,[13] product **21** could be separated from traces of isomeric compounds by routine flash chromatography. This macrocyclic compound exists as a mixture of slowly interconverting conformers in solution which cause



Scheme 3 *Reagents and conditions*: **12** (10 eq.), complex **10** (10 mol%): (a) CH_2Cl_2, reflux, 65% (**13**); (b) toluene, 80 °C, 48% (**15**).

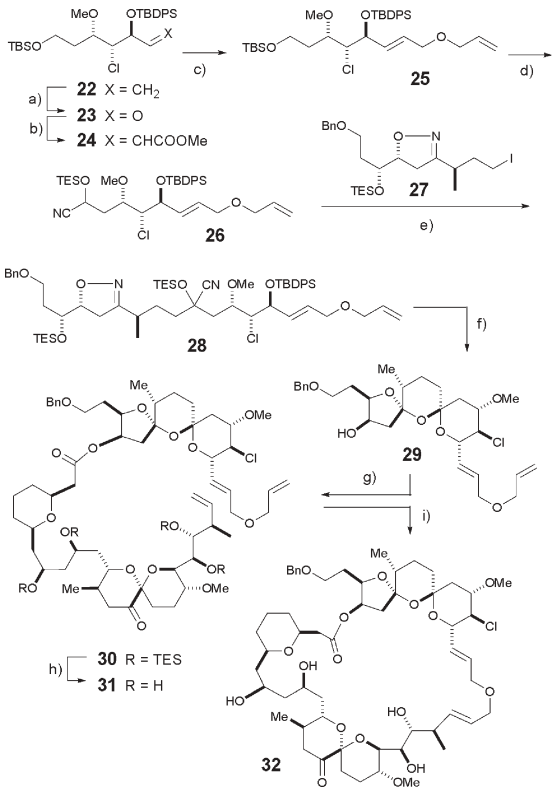


Scheme 4 *Reagents and conditions*: (a) TASF, aq. DMF, 97%; (b) TESOTf, 2,6-lutidine, CH_2Cl_2, −78 °C, 76%; (c) $Mo(CO)_6$, $MeCN–H_2O$, 90 °C, 92%; (d) compound **2** (R^1 = H, R^2 = R^3 = TES, X = $–S(CH_2)_3S–$), 2,4,6-trichlorobenzoyl chloride, Et_3N, DMAP cat., toluene, 50%; (e) complex **10** (250 mol%), toluene, 60 °C; (f) NCS, $AgNO_3$, 2,6-lutidine, $MeCN–H_2O$, 49% (over two steps).

considerable line broadening in the NMR spectra. Preliminary attempts to engender formation of the conspicuous bis-spiroacetal subunit by acid catalyzed cyclization of the linear C.31–C.38 chain in **21** onto the pre-existing hemiacetal met with failure. It remains to be seen however, if application of this strategy to the correct diastereomeric series and/or spirocyclization after saturation of the C.25–C.26 double bond might eventually open a viable route to spirastrellolide A.

A possible alternative means to overcome the deleterious steric effects of the bis-spiroketal makes use of a suitable 'relay' trigger.[14] The preparation of an adequate substrate was readily achieved by adaptation of the route leading to fragment **3**[3] and is depicted in Scheme 5. Specifically, ozonolysis of **22**[3] followed by Wittig olefination of the resulting fragile aldehyde **23** with Ph_3P=CHCOOMe gave **24** in excellent yield, which was converted into the bis-allyl ether **25** prior to elaboration of the TES-protected cyanohydrin at the other terminus. Deprotonation of **26** using LDA followed by alkylation of the resulting anion with the known iodide **27**[3] gave product **28**, which was subjected to N–O-bond cleavage and spirocyclization according to the established protocol.[3]

The chain-extended building block **29** was then linked to the southern domain **2** by means of a Yamaguchi esterification,[11] which, after cleavage of the silyl groups, delivered compound **31** qualifying for metathetic 'relay ring closure'.[14] Exposure of this substrate to catalytic amounts of carbene **10** in refluxing CH_2Cl_2 resulted in a clean conversion but gave the ring expanded macrocycle **32** as the only detectable product in 64% yield. This outcome highlights once again the exceptional reluctance of the olefin adjacent to the chlorinated bis-spiroketal unit to undergo



Scheme 5 *Reagents and conditions*: (a) O_3, CH_2Cl_2, −78 °C, then Me_2S, 95%; (b) Ph_3P=CHCOOMe, THF, 0 °C → RT, 91%; (c) (i) Dibal-H, CH_2Cl_2; (ii) allyl bromide, NaH, DMF, 97% (over both steps); (d) (i) PPTS (1.2 eq.), MeOH, 82%; (ii) DMSO, oxalyl chloride, Et_3N, −78 °C → RT; (iii) KCN, Dowex® resin, MeCN–H_2O; (iv) TESOTf, 2,6-lutidine, CH_2Cl_2, 73% (over three steps); (e) LDA, THF, −78 °C, 48%; (f) (i) $Mo(CO)_6$, MeCN–H_2O, 90 °C; (ii) TASF, aq. DMF; (iii) PPTS cat., CH_2Cl_2, 45% (over three steps); (g) compound **2** (R^1 = H, R^2 = R^3 = TES, X = O), 2,4,6-trichlorobenzoyl chloride, Et_3N, DMAP cat., toluene, 82%; (h) PPTS cat., MeOH, Et_2O–H_2O, 64%; (i) complex **10** (10 mol%), CH_2Cl_2, reflux, 64%.

productive metathesis yet outlines a convenient entry into spirastrellolide analogues with enlarged backbones.[15] The evaluation of their phosphatase inhibitory activity[16] as well as further studies toward **1** are underway and will be disclosed in due course.

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