

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

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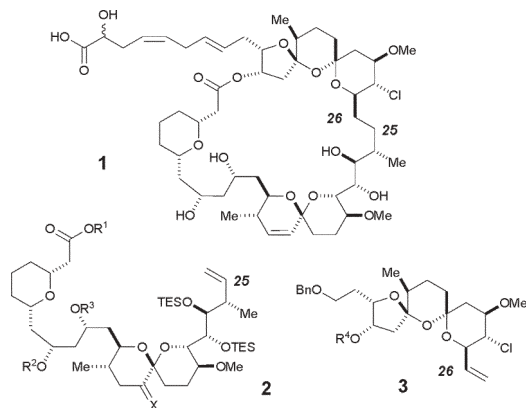
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Different methods for the formation of the C.25–C.26 bond of spirastrellolide A (**1**) are evaluated that might qualify for the end game of the projected total synthesis, with emphasis on metathetic ways to forge the macrocyclic frame.

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.

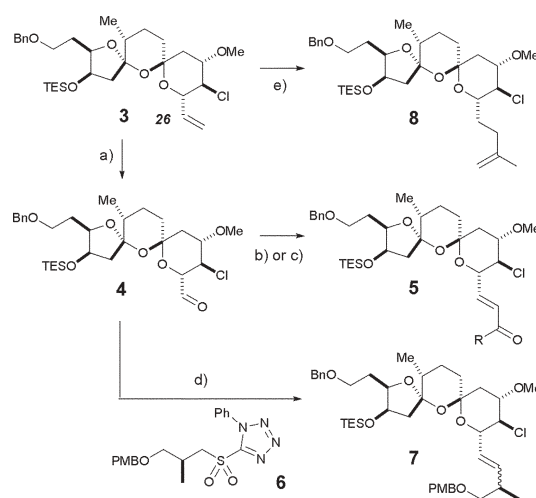


The incomplete structural information available at the outset of the project^{1b,c} enforced an overall synthesis plan dissecting **1** into regions of known relative stereochemistry. One such site is the non-stereogenic C.25–C.26 bond to be forged by methodology that makes proficient use of the olefinic termini of **2** and **3**.³ In an attempt to explore different options, compound **3** ($R^4 = \text{TES}$) was converted into aldehyde **4** by dihydroxylation and subsequent oxidative cleavage of the resulting diol with $\text{Pb}(\text{OAc})_4$; although **4** turned out to be exceptionally sensitive, it underwent productive

Wittig and Horner–Emmons reactions (Scheme 1); a related Julia olefination⁴ could also be achieved, although product **7** was obtained as an inseparable mixture of isomers. Moreover, hydroboration of the terminal olefin in **3** ($R^4 = \text{TES}$) with 9-BBN followed by a Suzuki reaction⁵ of the resulting alkylborane with 2-bromopropene as a model electrophile was successful (**3** \rightarrow **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 $=\text{CHPh}$ 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

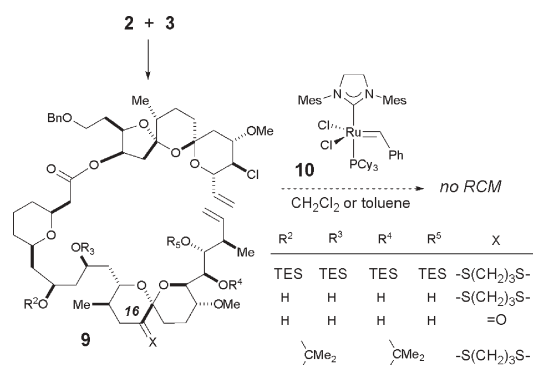
This failure is likely caused by the massive chlorinated bis-spiroketal unit flanking the 'northern' olefin, which not only renders its conversion into a ruthenium carbene difficult but even prevents metal carbenes from approaching to this particular site in a productive manner.⁸ In line with this notion,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



Scheme 1 Reagents and conditions: (a) (i) OsO_4 (2 mol%), NMO, tBuOH ; (ii) $\text{Pb}(\text{OAc})_4$, CH_2Cl_2 ; (b) $\text{Ph}_3\text{P}=\text{CHCOOMe}$, THF, 44% ($R = \text{OMe}$, over three steps); (c) $(\text{MeO})_2\text{P}(\text{O})\text{CH}_2\text{C}(\text{O})\text{Me}$, $\text{Ba}(\text{OH})_2 \cdot 8\text{H}_2\text{O}$, THF, 85% ($R = \text{Me}$); (d) LiHMDS , THF, $-78^\circ\text{C} \rightarrow \text{RT}$; (e) (i) 9-BBN, THF; (ii) 2-bromopropene, $(\text{dppf})\text{PdCl}_2$ (10 mol%), AsPh_3 (20 mol%), Cs_2CO_3 , DMF, 65°C , 41%.

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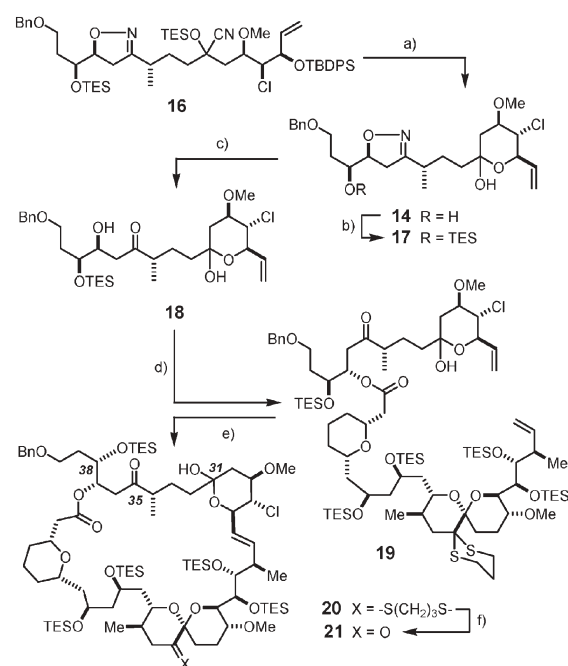
† Electronic supplementary information (ESI) available: Experimental section including spectroscopic data and spectra of all new compounds. See DOI: 10.1039/b707835h



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 [(Me₂N)₃S][Me₃SiF₂] (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)₆¹⁰ 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/AgNO₃,¹³ 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

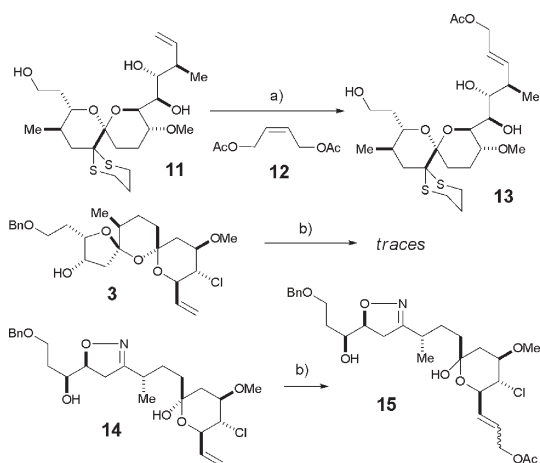


Scheme 4 Reagents and conditions: (a) TASF, aq. DMF, 97%; (b) TESOTf, 2,6-lutidine, CH₂Cl₂, –78 °C, 76%; (c) Mo(CO)₆, MeCN–H₂O, 90 °C, 92%; (d) compound **2** (R¹ = H, R² = R³ = TES, X = –S(CH₂)₃S–), 2,4,6-trichlorobenzoyl chloride, Et₃N, DMAP cat., toluene, 50%; (e) complex **10** (250 mol%), toluene, 60 °C; (f) NCS, AgNO₃, 2,6-lutidine, MeCN–H₂O, 49% (over two steps).

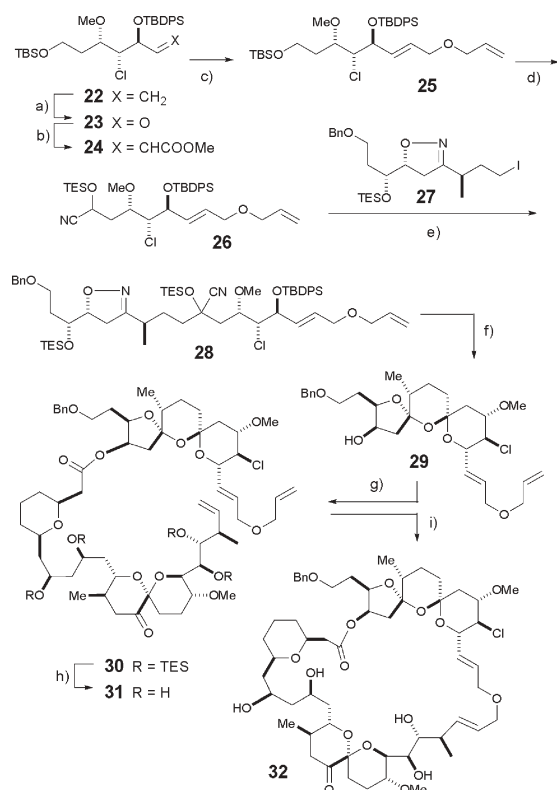
considerable line broadening in the NMR spectra. Preliminary attempts to engender formation of the conspicuous bis-spiroacetal subunit by acid catalyzed cyclization of the linear C.31–C.38 chain in **21** onto the pre-existing hemiacetal met with failure. It remains to be seen however, if application 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 Ph₃P=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 CH₂Cl₂ 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 3 Reagents and conditions: **12** (10 eq.), complex **10** (10 mol%); (a) CH₂Cl₂, reflux, 65% (**13**); (b) toluene, 80 °C, 48% (**15**).



Scheme 5 Reagents and conditions: (a) O_3 , CH_2Cl_2 , -78°C , then Me_2S , 95%; (b) $\text{Ph}_3\text{P}=\text{CHCOOMe}$, THF, $0^\circ\text{C} \rightarrow \text{RT}$, 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 , $-78^\circ\text{C} \rightarrow \text{RT}$; (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) $\text{Mo}(\text{CO})_6$, MeCN– H_2O , 90°C ; (ii) TASF, aq. DMF; (iii) PPTS cat., CH_2Cl_2 , 45% (over three steps); (g) compound **2** ($\text{R}^1 = \text{H}$, $\text{R}^2 = \text{R}^3 = \text{TES}$, $\text{X} = \text{O}$), 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 spirostrelolid analogues with enlarged backbones.¹⁵ The evaluation of their phosphatase inhibitory activity¹⁶ as well as further studies toward **1** are underway and will be disclosed in due course.

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Notes and references

- (a) K. Warabi, D. E. Williams, B. O. Patrick, M. Roberge and R. J. Andersen, *J. Am. Chem. Soc.*, 2007, **129**, 508; (b) D. E. Williams, M. Lapawa, X. Feng, T. Tarling, M. Roberge and R. J. Andersen, *Org. Lett.*, 2004, **6**, 2607; (c) D. E. Williams, M. Roberge, R. Van Soest and R. J. Andersen, *J. Am. Chem. Soc.*, 2003, **125**, 5296.
- For synthetic studies toward **1**, see ref. 3 and the following: (a) I. Paterson, E. A. Anderson, S. M. Dalby and O. Loiseleur, *Org. Lett.*, 2005, **7**, 4121; (b) I. Paterson, E. A. Anderson, S. M. Dalby and O. Loiseleur, *Org. Lett.*, 2005, **7**, 4125; (c) I. Paterson, E. A. Anderson, S. M. Dalby, J. H. Lim, P. Maltas and C. Moessner, *Chem. Commun.*, 2006, 4186; (d) J. Liu and R. P. Hsung, *Org. Lett.*, 2005, **7**, 2273; (e) Y. Pan and J. K. De Brabander, *Synlett*, 2006, 853; (f) J. Liu, J. H. Yang, C. Ko and R. Hsung, *Tetrahedron Lett.*, 2006, **47**, 6121; (g) C. Wang and C. J. Forsyth, *Org. Lett.*, 2006, **8**, 2997; (h) C. Wang and C. J. Forsyth, *Heterocycles*, 2007, **72**, 621; (i) I. Paterson, E. A. Anderson, S. M. Dalby, J. Genovino, J. H. Lim and C. Moessner, *Chem. Commun.*, 2007, 1852.
- (a) A. Fürstner, M. D. B. Fenster, B. Fasching, C. Godbout and K. Radkowski, *Angew. Chem., Int. Ed.*, 2006, **45**, 5506; (b) A. Fürstner, M. D. B. Fenster, B. Fasching, C. Godbout and K. Radkowski, *Angew. Chem., Int. Ed.*, 2006, **45**, 5510.
- Review: P. R. Blakemore, *J. Chem. Soc., Perkin Trans. 1*, 2002, 2563.
- (a) A. Suzuki, *J. Organomet. Chem.*, 1999, **576**, 147; (b) for a review on alkyl-Suzuki reactions, see: S. R. Chemler, D. Trauner and S. J. Danishefsky, *Angew. Chem., Int. Ed.*, 2001, **40**, 4544.
- Selected reviews: (a) T. M. Trnka and R. H. Grubbs, *Acc. Chem. Res.*, 2001, **34**, 18; (b) A. Fürstner, *Angew. Chem., Int. Ed.*, 2000, **39**, 3013; (c) K. C. Nicolaou, P. G. Bulger and D. Sarlah, *Angew. Chem., Int. Ed.*, 2005, **44**, 4490.
- Dithianes can potentially interfere with productive RCM, likely by coordination to the soft ruthenium centre of the catalyst, cf. A. Fürstner, G. Seidel and N. Kindler, *Tetrahedron*, 1999, **55**, 8215.
- Attempts to engage vinyl groups displayed on related tetrahydropyran templates in RCM-based macrocyclizations have previously met with considerable difficulties or even led to failures, cf. M. Ball, B. J. Bradshaw, R. Dumeunier, T. J. Gregson, S. MacCormick, H. Omori and E. J. Thomas, *Tetrahedron Lett.*, 2006, **47**, 2223.
- (a) K. A. Scheidt, H. Chen, B. C. Follows, S. R. Chemler, D. S. Coffey and W. R. Roush, *J. Org. Chem.*, 1998, **63**, 6436; (b) recent applications: C. Aïssa, R. Riveiros, J. Ragot and A. Fürstner, *J. Am. Chem. Soc.*, 2003, **125**, 15512; (c) A. Fürstner and T. Nagano, *J. Am. Chem. Soc.*, 2007, **129**, 1906.
- (a) A. Guarna, A. Guidi, A. Goti, A. Brandi and F. De Sarlo, *Synthesis*, 1989, 175; (b) P. G. Baraldi, A. Barco, S. Benetti, S. Manfredini and D. Simoni, *Synthesis*, 1987, 276.
- (a) J. Inanaga, K. Hirata, H. Saeki, T. Katsuki and M. Yamaguchi, *Bull. Chem. Soc. Jpn.*, 1979, **52**, 1989; (b) M. Hikota, Y. Sakurai, K. Horita and O. Yonemitsu, *Tetrahedron Lett.*, 1990, **31**, 6367; (c) recent applications: A. Fürstner, E. Kattig and O. Lepage, *J. Am. Chem. Soc.*, 2006, **128**, 9194; (d) J. Mlynarski, J. Ruiz-Caro and A. Fürstner, *Chem.–Eur. J.*, 2004, **10**, 2214.
- M. Scholl, S. Ding, C. W. Lee and R. H. Grubbs, *Org. Lett.*, 1999, **1**, 953.
- E. J. Corey and B. W. Erickson, *J. Org. Chem.*, 1971, **36**, 3553.
- T. R. Hoye, C. S. Jeffrey, M. A. Tennakoon, J. Wang and H. Zhao, *J. Am. Chem. Soc.*, 2004, **126**, 10210.
- A similar observation was recently made during an attempted synthesis of bryostatin, in which application of the 'relay' trigger methodology also led to a ring expanded analogue only, cf. B. M. Trost, H. Yang, O. R. Thiel, A. J. Frontier and C. S. Brindle, *J. Am. Chem. Soc.*, 2007, **129**, 2206.
- For previous syntheses and biological evaluations of phosphatase inhibitors from this laboratory, see: (a) A. Fürstner, F. Feyen, H. Prinz and H. Waldmann, *Angew. Chem., Int. Ed.*, 2003, **42**, 5361; (b) A. Fürstner, F. Feyen, H. Prinz and H. Waldmann, *Tetrahedron*, 2004, **60**, 9543; (c) A. Fürstner, J. Ruiz-Caro, H. Prinz and H. Waldmann, *J. Org. Chem.*, 2004, **69**, 459; (d) A. Fürstner, K. Reinecke, H. Prinz and H. Waldmann, *ChemBioChem*, 2004, **5**, 1575; (e) M. Manger, M. Scheck, H. Prinz, J. P. von Kries, T. Langer, K. Saxena, H. Schwalbe, A. Fürstner, J. Rademann and H. Waldmann, *ChemBioChem*, 2005, **6**, 1749.