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Toward the Synthesis of Spirastrellolide A: Construction of Two C_1–C_{25} Diastereomers Containing the BC–Spiroacetal

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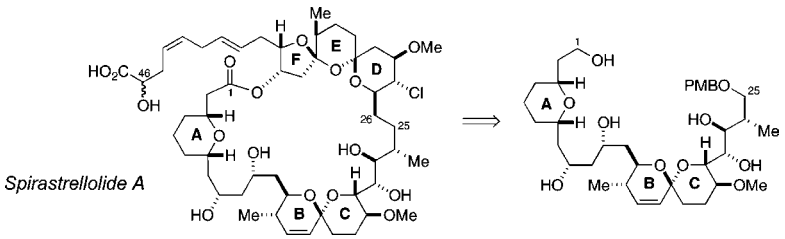
ABSTRACT



Stereocontrolled syntheses of two possible C_1–C_{25} diastereomers of spirastrellolide A containing the cis-disubstituted tetrahydropyran and [6,6]-spiroacetal are reported, exploiting boron-mediated asymmetric aldol and allylation methodology.

Spirastrellolide A (**1**, Scheme 1) is a novel antimitotic macrolide isolated by Andersen and co-workers from the Caribbean sponge *Spirastrella coccinea*,[1] which represents a potent and selective inhibitor of protein phosphatase 2A. In the preceding communication,[2] we describe a stereocontrolled synthesis of the C_{26}−C_{40} subunit **3**, corresponding to the fully functionalized [5,6,6]-bis-spiroacetal (DEF rings) of spirastrellolide A. We report herein the construction of two possible diastereomers of the C_1−C_{25} southern hemisphere of spirastrellolide, containing the C_3−C_7 cis-disubstituted tetrahydropyan (A ring), the [6,6]-spiroacetal (BC rings), and the challenging C_{20}−C_{24} stereopentad.[3]

Our proposed retrosynthesis of spirastrellolide is outlined in Scheme 1. As indicated previously,[2] we envisaged initial disconnections of spirastrellolide that would isolate subunits **3** and **4** from the C_1−C_{25} southern hemisphere. Mindful of the need to maintain a flexible synthetic strategy with respect to the unknown relative stereochemistry between C_3−C_7 and C_9−C_{24}, we targeted the two diastereomeric spiroacetals **5** and **6** (which differ in configuration at C_3 and C_7) as suitable fragments for eventual coupling with the northern hemisphere subunit **3**. Spiroacetals **5** and **6** might arise through thermodynamically controlled spiroacetalization of the respective open-chain precursors **7** and **8** following deprotection. These *cis*-enones could themselves be derived from the coupling of the lithiated alkynes **9** and **10** with aldehyde **11**, followed by reoxidation at C_{17} and Lindlar reduction. Alkynes **9** and **10** might be prepared, in turn, from a common tetrahydropyran **12**, while aldehyde **11** could arise from the tartrate-derived aldehyde **13**. Our selected routes to both these fragments exploit a combination of boron-mediated asymmetric allylation and aldol methodology.

(1) (a) Williams, D. E.; Roberge, M.; Van Soest, R.; Andersen, R. J. *J. Am Chem. Soc.* **2003**, *125*, 5296. (b) Williams, D. E.; Lapawa, M.; Feng, X.; Tarling, T.; Roberge, M.; Andersen, R. *J. Org. Lett.* **2004**, *6*, 2607.

(2) Paterson, I.; Anderson, E. A.; Dalby, S. M.; Loiseleur, O. *Org. Lett.* **2005**, *7*, 4121.

(3) For other synthetic studies, see: (a) Liu, J.; Hsung, R. P. *Org. Lett.* **2005**, *7*, 2273. (b) Paterson, I.; Anderson, E. A.; Dalby, S. M.; Loiseleur, O. *Abstracts of Papers*, 229th National Meeting of the American Chemical Society, San Diego, Mar 13−17, 2005; American Chemical Society: Washington, DC, 2005; ORGN-331. (c) Wang, C.; Forsyth, C. J. *Abstracts of Papers*, 229th National Meeting of the American Chemical Society, San Diego, Mar 13−17, 2005; American Chemical Society: Washington, DC, 2005; ORGN-414.

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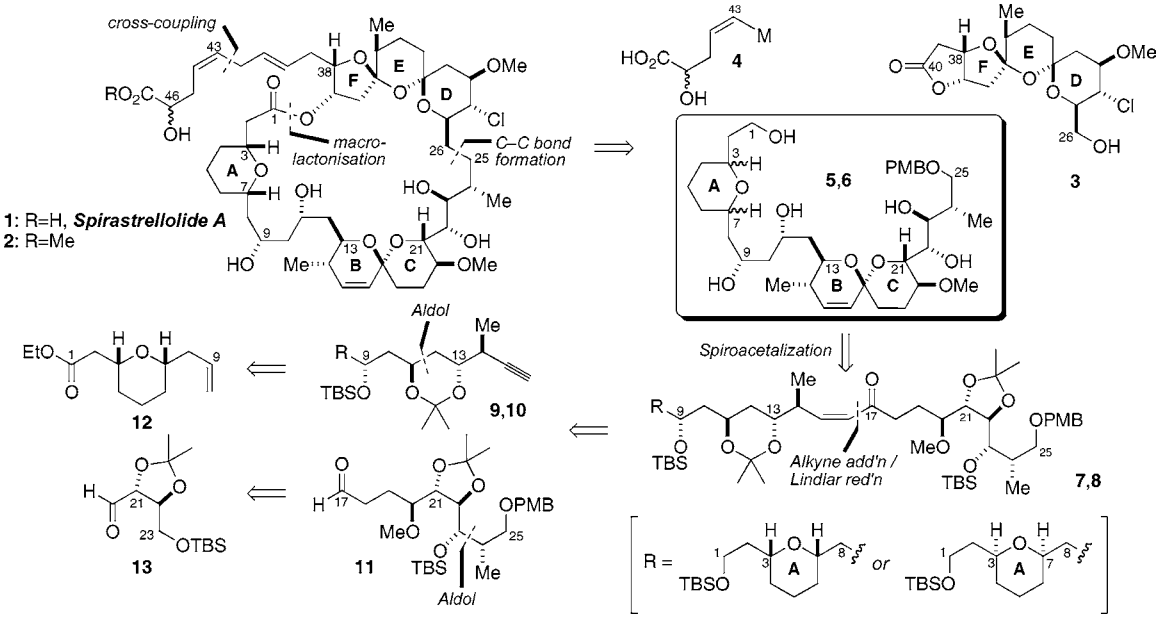
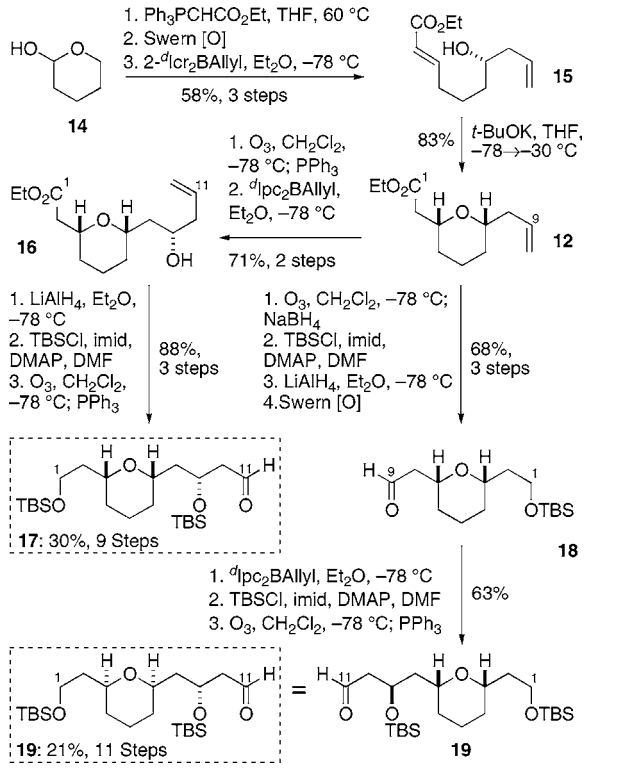
Scheme 1. Retrosynthetic Analysis of Spirastrellolide A



The synthesis of the C_3,C_7-epimeric alkynes **9** and **10** utilizes the pseudo-S_2 symmetry of the tetrahydropyran **12** (Scheme 2). This pyran could be conveniently derived from

Scheme 2



lactol **14**.[4] Thus, a Wittig reaction of lactol **14** was followed by Swern oxidation and a Brown allylation using *B*-methoxy-bis(2-isocaranyl)borane (three steps, 58%, 90% ee).[5] Exposure of the resulting allylic alcohol **15**[6] to potassium *tert*-butoxide effected a smooth hetero-Michael cyclization under thermodynamic conditions to provide exclusively the 2,6-*cis*-tetrahydropyran **12** (83%). Subsequent ozonolysis of **12** and Brown asymmetric allylboration[7] provided alcohol **16** with high stereoselectivity (dr > 95:5, 71%, two steps). Reduction of the ester with $LiAlH_4$, followed by bis-TBS protection, and a second ozonolysis, delivered aldehyde **17** in 88% yield (three steps).

The C_3,C_7-epimeric aldehyde **19** could be accessed efficiently via a similar route. A four-step sequence, which converted the common pyran **12** into aldehyde **18** (68%), was followed by an allylboration,[7] which again proceeded with excellent stereocontrol (dr > 95:5), to install the C_9 hydroxyl-bearing stereocenter. Finally, conversion of this allylation product into aldehyde **19** was achieved by TBS protection and ozonolysis (63%, three steps).

Transformation of the aldehydes **17** and **19** to alkynes **9** and **10** is shown in Scheme 3. The required 11,14-syn relationship was established through application of our boron-mediated aldol methodology employing methyl ketone **20**.[8] Enolization of **20** with (−)-Ipc_2BCl followed by addition of aldehyde **17** afforded aldol adduct **21** in excellent yield and selectivity (87%, dr > 20:1). A highly selective 1,3-anti reduction,[9] followed by acetonide formation, delivered **23**

(4) De Brabander has described a similar sequence to deliver the corresponding enantiomeric methyl ester of **12**, see: (a) Bhattacharjee, A.; Soltani, O.; De Brabander, J. K. *Org. Lett.* **2002**, *4*, 481. (b) Evans, D. A.; Carreira, E. M. *Tetrahedron Lett.* **1990**, *31*, 4703.

(5) Brown, H. C.; Randad, R. S.; Bhat, K. S.; Zaidlewicz, M.; Racherla, U. S. *J. Am. Chem. Soc.* **1990**, *112*, 2389.

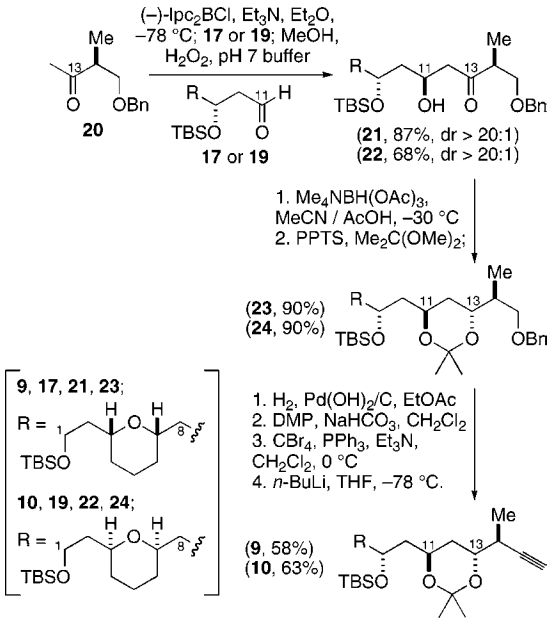
(6) See Supporting Information for proof of stereochemistry of novel compounds.

(7) Jadhav, P. K.; Bhat, K. S.; Perumal, T.; Brown, H. C. *J. Org. Chem.* **1986**, *51*, 432.

(8) (a) Paterson, I.; Goodman, J. M.; Isaka, M. *Tetrahedron Lett.* **1989**, *30*, 7121. (b) Paterson, I.; Oballa, R. M. *Tetrahedron Lett.* **1997**, *38*, 8241.

as a single isomer (90%, two steps). This acetonide was then converted into alkyne **9** by hydrogenolysis of the benzyl group, Dess−Martin oxidation and Corey−Fuchs alkynylation (58%, four steps).[10]

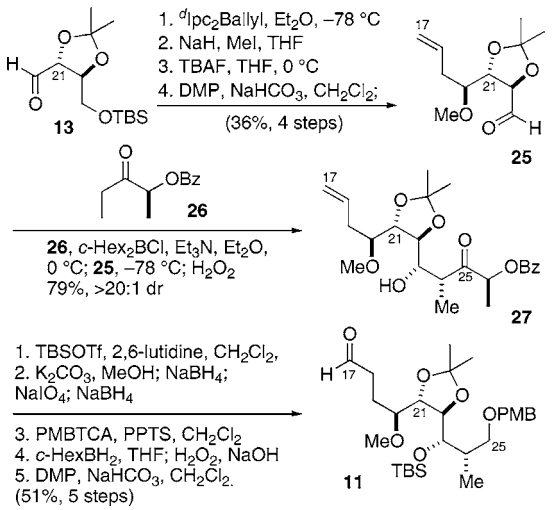
Scheme 3



Application of this reaction sequence to the diastereomeric aldehyde **19** proved to be equally efficient. Aldol coupling proceeded selectively for the desired adduct **22** (68%, dr > 20:1), and an analogous six-step sequence enabled the completion of alkyne **10** (57%).[5]

The synthesis of aldehyde **11** (the coupling partner for alkynes **9** and **10**) commenced with the known aldehyde **13**, which is available in four steps from (*R*,*R*)-diethyl tartrate (Scheme 4).[11] Brown allylboration[7] of **13** proceeded to install

Scheme 4



the C_{20} hydroxyl-bearing stereocenter (dr > 95:5), which was subsequently O-methylated. Desilylation with TBAF, followed by Dess−Martin oxidation, delivered aldehyde **25** (36%, four steps).

Installation of the C_{23} and C_{24} stereocenters was achieved through application of a second boron-mediated aldol reaction, in this case making use of (*S*)-ethyl lactate-derived ketone **26**. Here, reaction of aldehyde **25** with the (*E*)-boron enolate of **26** (*c*-Hex_2BCl, Et_3N) gave β-hydroxyketone **27** as a single isomer in 79% yield.[12] TBS protection was followed by efficient cleavage of the auxiliary and PMB protection of the resultant primary alcohol. Finally, the required C_{17} oxygenation was established through hydroboration/Dess−Martin oxidation to deliver aldehyde **11** (51% yield, five steps).

At this point, we were set to couple the appropriate fragments to generate the open-chain precursors for spiroacetal formation (Scheme 5). Coupling of aldehyde **11** with **9** and **10** was achieved via alkyne lithiation using *n*-BuLi, followed by addition of **11**, to furnish the desired coupled products, each being isolated as an inconsequential ca. 1:1 epimeric mixture at C_{17}. Dess−Martin oxidation followed by Lindlar hydrogenation smoothly delivered the corresponding (*Z*)-enones **7** (77%, three steps) and **8** (66%).

With the targeted enones in hand, the crucial spiroacetalization reaction was investigated. In the event, treatment of enone **7** with HF in aqueous MeCN *led to complete desilylation, and acetonide removal followed by the formation of a single spiroacetal product* **5** (55%). The diastereomeric enone **8** underwent spirocyclization (70%) under analogous conditions. The choice of HF/MeCN to mediate the cyclization reaction proved to be critical, as alternative reagents (CSA/MeOH, Dowex 50Wx8 resin, HCl/THF) led to extensive decomposition.

The successful formation of the desired spiroacetal stereochemistry could be readily confirmed by comparison of the ^1H and ^{13}C NMR data of **5** and **6** with that of the methyl ester derivative **2** of spirastrellolide.[1b,13] There was a close correlation between the NMR data for the synthetic subunit and natural product in the $C_{11}-C_{24}$ spiroacetal-containing region. The ^{13}C NMR spectra exhibited characteristic C_{17} acetal resonances at 95.1 (**5**) and 94.8 ppm (**6**), also in close agreement with that of the natural product (93.8 ppm). In addition to these similarities, diagnostic strong NOE enhancements between H_{13} and H_{21}, which had also been observed for the natural product, served to confirm that the C_{17} stereocenter of **5** and **6** possessed the desired configuration.

In contrast to these markedly similar regions of the synthetic and natural compounds, comparison of the C_7-C_9 portion of the two diastereomers revealed substantial differ-

(9) Evans, D. A.; Chapman, K. T.; Carreira, E. M. *J. Am. Chem. Soc.* **1988**, *110*, 3560.

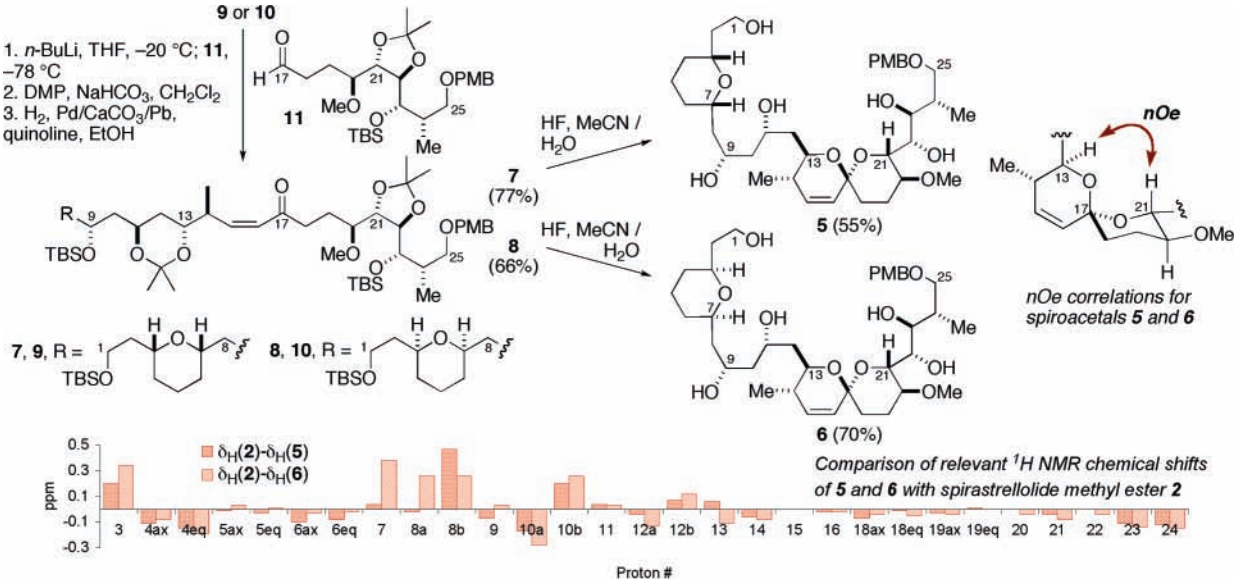
(10) Corey E. J., Fuchs, P. L. *Tetrahedron Lett.* **1972**, *13*, 3769.

(11) Taunton, J.; Collins, J. L.; Schreiber, S. L. *J. Am. Chem. Soc.* **1996**, *118*, 10412.

(12) (a) Paterson, I.; Wallace, D. J.; Velazquez, S. M. *Tetrahedron Lett.* **1994**, *35*, 9083. (b) Paterson, I.; Wallace, D. J.; Cowden, C. J. *Synthesis* **1998**, 639.

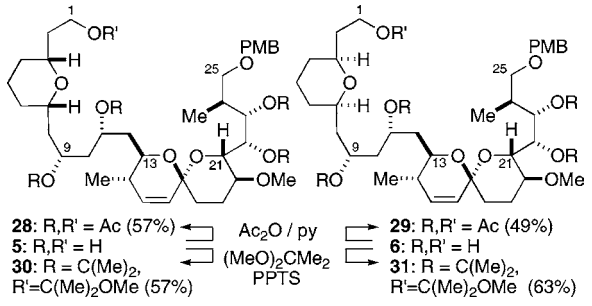
(13) See Supporting Information for full NMR comparisons.

Scheme 5



ences by NMR analysis. In terms of prediction of the relationship between the C_3-C_7 and C_9-C_{24} stereoclusters, it was anticipated that one of the isomers would correlate significantly more closely with spirastrellolide than the other, thus allowing a possible resolution of this stereochemical ambiguity. As can be seen from the chart in Scheme 5, spiroacetal **5** seems to exhibit a closer match to spirastrellolide at H_7 and H_9 than its isomer **6**, although comparison of the resonances at H_8 remains somewhat inconclusive.

Scheme 6



Finally, derivatization of the spiroacetals **5** and **6** as the pentaacetates (**28** and **29**) and peracetonides (**30** and **31**) was carried out to enable additional NMR comparisons with the equivalent natural product derivatives (Scheme 6).[1b] Again, both sets of compounds showed a similar degree of correlation with the corresponding spirastrellolide derivatives, emphasizing the need for further synthetic studies.

In summary, we have completed convergent syntheses of two diastereomers of the ABC-ring containing C_1-C_{25} region of spirastrellolide. Ongoing work into the coupling of these subunits with the $C_{26}-C_{40}$ northern hemisphere[2] should enable elucidation of the remaining unknown relative stereochemistry and ultimately a total synthesis of spirastrellolide A.

Acknowledgment. We thank the EPSRC (EP/C541677/1), Homerton College, Cambridge (Research Fellowship to E.A.A.), Syngenta Crop Protection (secondment of O.L.), and Merck for support and Professor Raymond Andersen (University of British Columbia) for helpful discussions.

Supporting Information Available: Spectroscopic data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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