ORGANIC LETTERS

2008
Vol. 10, No. 6
1083−1086

Toward the Synthesis of Spirastrellolide B: A Synthesis of the C1–C23 Subunit

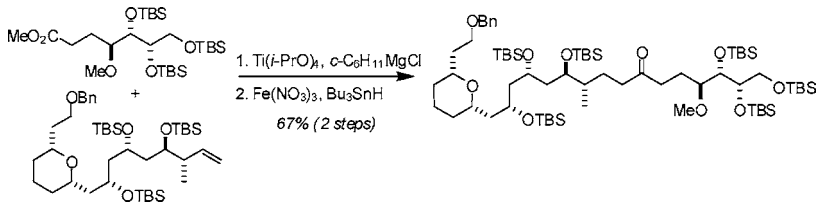
Katie A. Keaton and Andrew J. Phillips*

Department of Chemistry and Biochemistry, University of Colorado at Boulder, Boulder, Colorado 80309-0215

andrew.phillips@colorado.edu

Received December 6, 2007

ABSTRACT



A synthesis of the C1–C23 subunit of spirastrellolide B is described. The synthesis features two applications of a Kulinkovich-cyclopropanol ring-opening strategy for the coupling of esters with olefins to produce ketones.

Spirastrellolide A and B (**1** and **2**, Figure 1) are two closely related polyketides that were isolated by Anderson and coworkers from the marine sponge *Spirastrella coccinea*. The key elements of the structure of spirastrellolide A were first disclosed in 2003[1] and were followed by a report describing a structure revision and the inhibition of PP2A.[2] Subsequent cleavage of the $\Delta^{40,41}$ olefin and derivitization of spirastrellolide B produced a compound suitable for X-ray analysis[3] and revealed the complete relative and absolute stereochemistry of the macrolide core. Recently, Anderson and coworkers have reported that the C46 alcohol is of (*R*) configuration and also described the isolation of a further 5 congeners (spirastrellolides C to G).[4]

The spirastrellolides have generated substantial interest from the synthesis community, and although no total synthesis has yet been described, a number of papers describe the synthesis of fragments.[5−10] In this communication, we report our preliminary studies that have led to a synthesis of the C1−C23 domain.

As shown in Figure 1, our overall plan consists of the assembly of two large domains (**3** and **4**) by a combination of Nozaki−Hiyama−Kishi reaction and an esterification or lactonization. Further dissection of the C1−C23 subunit **4** led to three fragments of similar complexity: pyran-containing methyl ketone **5**, known aldehyde **6**,[5b] and methyl ester **7**. In the forward direction, we planned to couple these fragments by a combination of aldol reaction and our recently described Kulinkovich-cyclopropanol opening strategy.[11]

(1) Williams, D. E.; Roberge, M.; Van Soest, R.; Andersen, R. J. *J. Am. Chem. Soc.* **2003**, *125*, 5296.
(2) Williams, D. E.; Lapawa, M.; Feng, X.; Tarling, T.; Roberge, M.; Andersen, R. J. *Org. Lett.* **2004**, *6*, 2607.
(3) Warabi, K.; Williams, D. E.; Patrick, B. O.; Roberge, M.; Andersen, R. J. *J. Am. Chem. Soc.* **2007**, *129*, 508.
(4) Williams, D. E.; Keyzers, R. A.; Warabi, K.; Desjardine, K.; Riffell, J. L.; Roberge, M.; Andersen, R. J. *J. Org. Chem.* **2007**, *72*, 9842.
(5) Liu, J.; Hsung, R. P. *Org. Lett.* **2005**, *7*, 2273. (b) Liu, J.; Yang, J. H.; Ko, C.; Hsung, R. P. *Tetrahedron Lett.* **2006**, *47*, 6121. (c) Ghosh, S. K.; Ko, C.; Liu, J.; Wang, J.; Hsung, R. P. *Tetrahedron* **2006**, *62*, 10485.
(6) (a) Paterson, I.; Anderson, E. A.; Dalby, S. M.; Loiseleur, O. *Org. Lett.* **2005**, *7*, 4125. (b) Paterson, I.; Anderson, E. A.; Dalby, S. M.; Loiseleur, O. *Org. Lett.* **2005**, *7*, 4121. (c) Paterson, I.; Anderson, E. A.; Dalby, S. M.; Lim, J. H.; Maltas, P.; Moessner, C. *Chem. Commun.* **2006**, 4186. (d) Paterson, I.; Anderson, E. A.; Dalby, S. M.; Genovino, J.; Lim, J. H.; Moessner, C. *Chem. Commun.* **2007**, 1852.
(7) (a) Furstner, A.; Fenster, M. D. B.; Fasching, B.; Godbout, C.; Radkowski, K. *Angew. Chem., Int. Ed.* **2006**, *45*, 5506. (b) Furstner, A.; Fenster, M. D. B.; Fasching, B.; Godbout, C.; Radkowski, K. *Angew. Chem., Int. Ed.* **2006**, *45*, 5510. (c) Furstner, A.; Fasching, B.; O'Neil, G. W.; Fenster, M. D. B.; Godbout, C.; Ceccon, J. *Chem. Commun.* **2007**, 3045.
(8) Pan, Y.; De Brabander, J. K. *Synlett* **2006**, 853.
(9) (a) Wang, C.; Forsyth, C. J. *Org. Lett.* **2006**, *8*, 2997. (b) Wang, C.; Forsyth, C. J. *Heterocycles* **2007**, *72*, 621.
(10) Smith, A. B., III; Kim, D.-S. *Org. Lett.* **2007**, *9*, 3311.
(11) Keaton, K. A.; Phillips, A. J. *Org. Lett.* **2007**, *9*, 2717.

10.1021/ol702955m CCC: $40.75
Published on Web 02/15/2008

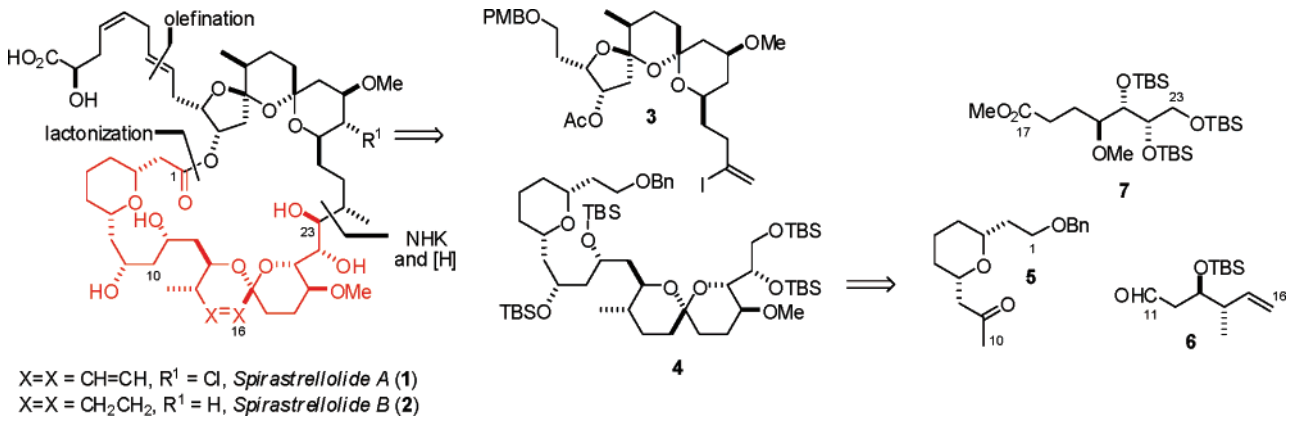
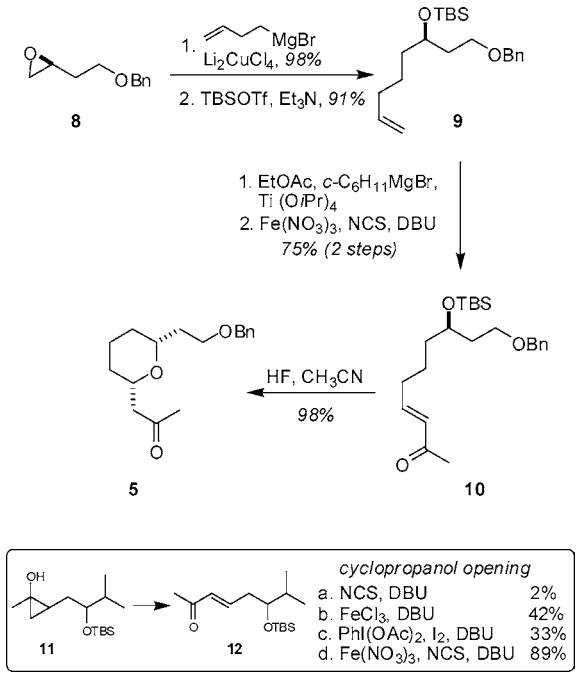


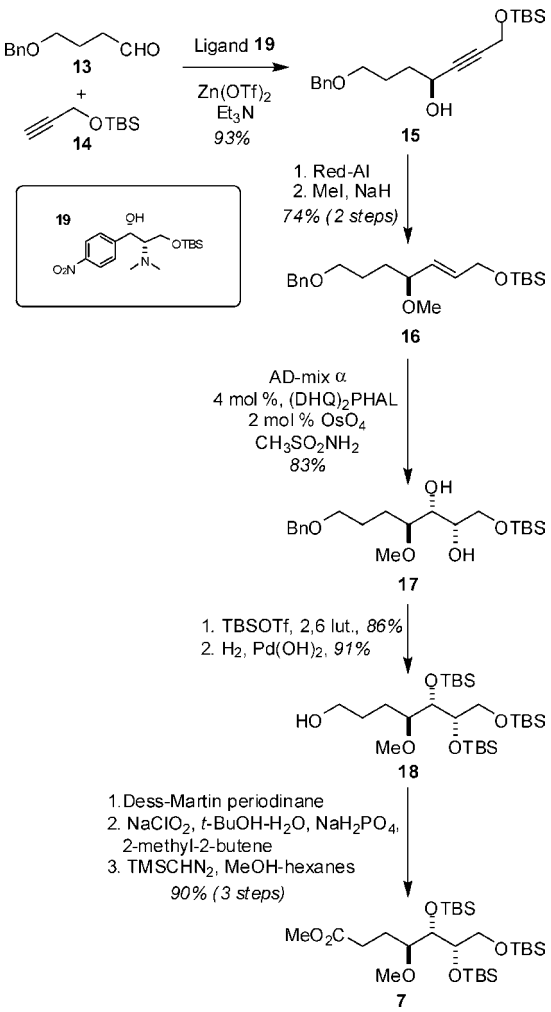
Figure 1. Structures of spirastrellolides A and B, overall synthesis plan, and key building blocks for C1−C23 of spirastrellolide B.

The synthesis of pyran **5** commences with known epoxide **7**, which is readily available by application of Jacobsen's hydrolytic kinetic resolution to racemic starting material (see Scheme 1).[12] Opening with 3-butenylmagnesium bromide in the presence of Kochi's catalyst[13] and subsequent silylation of the secondary alcohol with TBSOTf provided **8** in 72% yield for the two steps. Reaction of **8** with ethyl acetate in the presence of cyclohexylmagnesium bromide and Ti(*i*-PrO)$_4$ gave the expected intermediate cyclopropanol. A brief survey of conditions for the opening of cyclopropanol **11** to the enone[14,15] **12** showed NCS in the presence of Fe(NO$_3$)$_3$ and DBU to be most effective. Application of these conditions to the system at hand produced enone **10** in 75% yield for the two steps. Removal of the TBS protecting group

Scheme 1. Synthesis of the C1−C10 Subunit, **5**



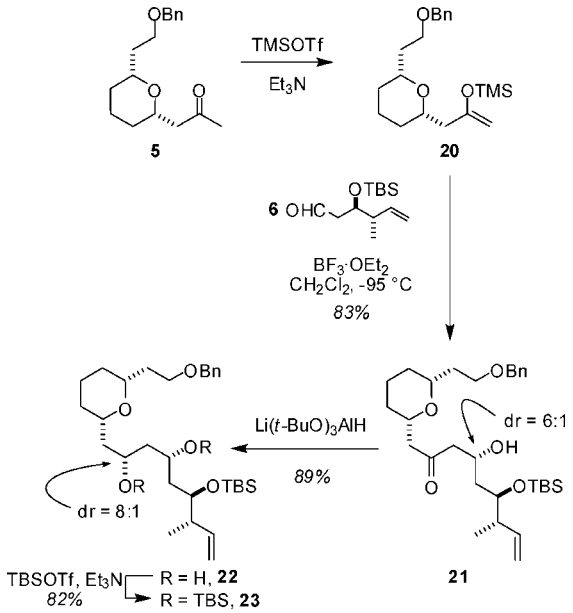
Scheme 2. Synthesis of Ester **7**



(12) Schaus, S. E.; Brandes, B. D.; Larrow, J. F.; Tokunaga, M.; Hansen, K. B.; Gould, A. E.; Furrow, M. E.; Jacobsen, E. *J. Am. Chem. Soc.* **2002**, *124*, 1307.

(13) Tamura M.; Kochi J. *Synthesis* **1971**, 303.

Scheme 3. 1,3-Anti Aldol Reaction and Reduction to Give the C1−C16 Domain, **23**



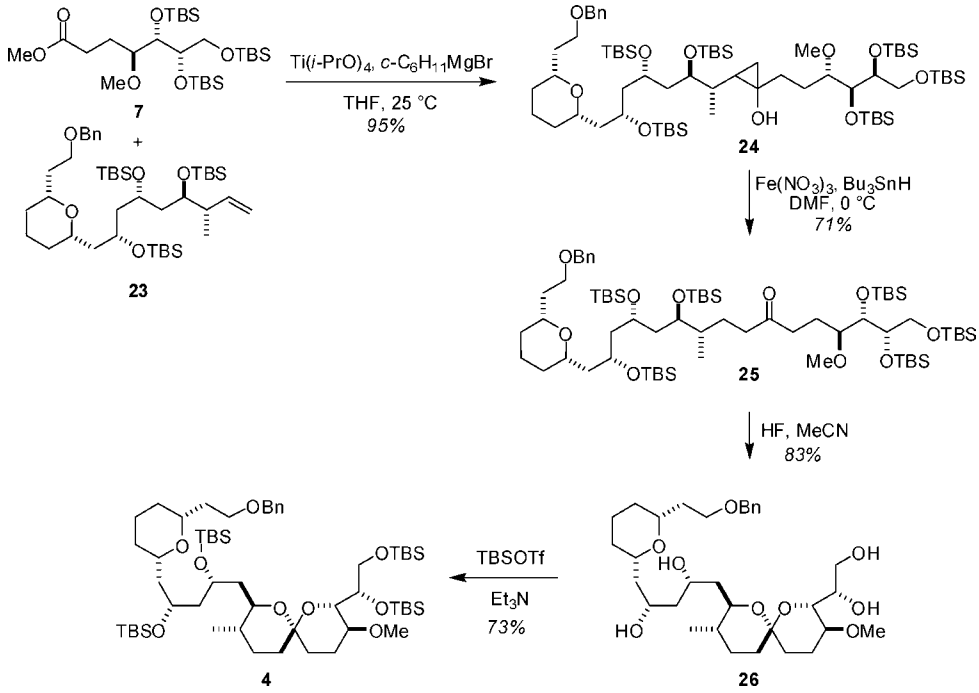
with HF and concomitant cyclization produced the pyran **5** in 98% yield and completed the synthesis of the C1−C10 domain.

The synthesis of methyl ester **7** commenced with the asymmetric alkynylation of 4-(benzyloxy)butanal **13** with TBS-protected propargyl alcohol **14** in the presence of amino alcohol **19**[16] to yield **15** in 93% yield. Propargyl alcohol **15** was reduced to the (*E*)-allylic alcohol using Red-Al[17] and was subsequently methylated to give **16** in 74% yield over the two steps. Sharpless asymmetric dihydroxylation of this compound with AD-mix alpha supplemented with $(DHQ)_2PHAL$ and OsO_4 produced diol **17** in 83% yield as a single diastereoisomer. Silylation of the alcohols (TBSOTf, Et_3N, 86%) and then hydrogenolysis of the benzyl group in the presence of Pearlman's catalyst gave primary alcohol **18** in 91% yield. A standard sequence of Dess−Martin periodinane oxidation, Lindgren−Pinnick oxidation, and methylation with trimethylsilyldiazomethane gave the targeted ester **7** (90% over 3 steps, see Scheme 2).

Silylation of methyl ketone **5** with TMSOTf in the presence of Et_3N gave silyl enol ether **20**, which was used immediately in the subsequent Mukaiyama aldol reaction (Scheme 3). To this end, reaction of **20** with aldehyde **6** in the presence of $BF_3{\cdot}OEt_2$ at −95 °C gave the expected product **21** in 83% yield. The reaction provided a 6:1 ratio of diastereoisomers, and the stereochemistry C11 for the major diastereoisomer was determined to be as desired by Mosher's ester analysis. Diastereoselective reduction of the ketone with Li(*t*-BuO)$_3$AlH gave **22** in 89% yield [dr = 8:1], and subsequent silylation of the alcohols with TBSOTf and Et_3N gave the complete C1−C16 domain **23** in 82% yield.

At this juncture, it was possible to examine the key subunit coupling of alkene **23** and ester **7**. Subjecting a mixture of these two compounds to Ti(*i*-OPr)$_4$ and cyclohexylmagnesium bromide[18] at room temperature in THF resulted in clean coupling to yield cyclopropanol **24** in 95% yield. Exposure of this compound to $Fe(NO_3)_3$ and Bu_3SnH resulted in ring opening to give ketone **25** in 71% yield (this represents a

Scheme 4. Subunit Coupling by Kulinkovich-Cyclopropanol Opening (**7**+**23**→**24**→**25**) and Assembly of the Complete C1−C23 Domain **4**



67% yield for the two steps). Subsequent removal of the protecting groups with HF in MeCN also resulted in cyclization to give the desired spiroketal **26** (83% yield), and reprotection of the alcohols gave the targeted compound **4** in 73% yield. The structure and stereochemistry of **4** was established by a combination of 2D-NMR experiments (HSQC, HMBC) and NOESY (see Scheme 4).

In conclusion, we have described a concise 14-step sequence to the full C1−C23 domain of spirastrellolide B. A key feature of the synthesis is the use of a Kulinkovich-cyclopropanol opening strategy to couple together two complex subunits (**7**+**23**→**24**→**25**). Further studies on the utility of this strategy for complex molecule synthesis, as well as progress toward spirastrellolide B, will be reported in due course.

Acknowledgment. We thank Eli Lilly and Company, the AP Sloan Foundation, and the National Institutes of Health (NCI CA110246) for support of this research.

Supporting Information Available: Procedures for the synthesis of all new compounds, along with characterization data, and spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

OL702955M

(14) For pioneering studies on the opening of cyclopropanols with Fe(III) species to give β-chloroketones, see: (a) Schaafsma, S. E.; Steinberg, H.; De Boer, Th. J. *Recl. Trav. Chim. Pays-Bas* **1966**, *85*, 73. (b) Schaafsma, S. E.; Steinberg, H.; De Boer, Th. J. *Recl. Trav. Chim. Pays-Bas* **1966**, *85*, 70.

(15) Booker-Milburn has also observed β-chloroesters as products in the opening of cyclopropenone acetals with Fe(III): Booker-Milburn, K. I.; Cox, B.; Mansley, T. E. *Chem. Commun*. **1996**, 2577.

(16) Jiang, B.; Chen, Z.; Xiong, W. *Chem. Commun.* **2002**, 1524.

(17) (a) Chan, K.; Cohen, N.; DeNoble, J. P.; Specian, A. C.; Saucy, G. *J. Org. Chem.* **1976**, *41*, 3497. (b) Denmark, S. E.; Jones, T. K. *J. Org. Chem.* **1982**, *47*, 4595.

(18) For the initial report describing these conditions for Kulinkovich, cyclopropanation, see: Lee, J.; Kim, H.; Cha, J. K. *J. Am. Chem. Soc.* **1996**, *118*, 4198.