ORGANIC LETTERS

2005
Vol. 7, No. 11
2273−2276

Synthesis of the C11–C23 Fragment of Spirastrellolide A. A Ketal-Tethered RCM Approach to the Construction of Spiroketals

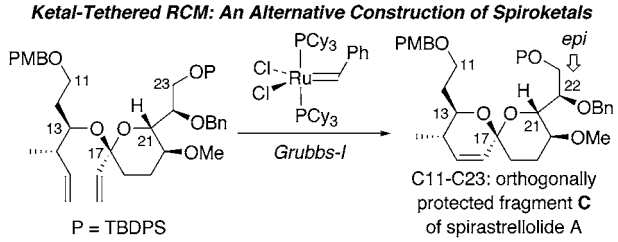
Jia Liu and Richard P. Hsung*

Department of Chemistry, University of Minnesota, Minneapolis, Minnesota 55455

hsung@chem.umn.edu

Received March 27, 2005

ABSTRACT



The synthesis of the C11–C23 fragment in spirastrellolide A is described here featuring a ketal-tethered RCM as an alternative approach to the construction of spiroketals.

Roberge and Andersen et al. reported in 2003 the isolation of spirastrellolide A, a novel macrolide from marine sponge *Spirastrellolide coccinea*,[1a] and recently, the structure of spirastrellolide A was revised as shown in Figure 1.[1b] In addition to its ability to cause untimely mitotic arrest in cells, spirastrellolide A was shown to exhibit potent inhibitory activity against protein phosphatase 2A ($IC_{50} = 1$ nM) along with a good selectivity for PP2A over PP1 (ratio of IC_{50} values 1:50).[1,2] We became interested in spirastrellolide A as a result of our recent interest and efforts in developing an unconventional approach to the synthesis of spiroketals.[3] Specifically, we have been developing ketal-tethered reactions such as IMDA[4] and RCM[5] using cyclic ketals **1** to construct spiroketals **2** (Scheme 1), which are among the most prevalent structural motifs in natural products.

This seldom-employed approach is in distinct contrast with the classical internal ketalization using keto diols **3**. By

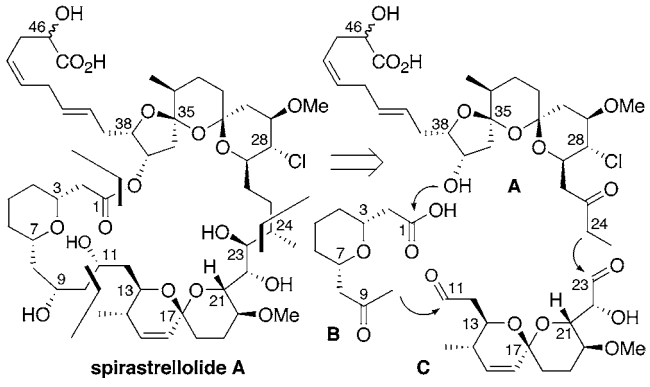


Figure 1.

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

(2) Roberge, M.; Cinel, B.; Anderson, H. J.; Lim, L.; Jiang, X.; Xu, L.; Kelly, M. T.; Andersen, R. J. *Cancer Res.* **2000**, *60*, 5052.

(3) For reviews, see: (a) Mead, K. T.; Brewer, B. N. *Curr. Org. Chem.* **2003**, *7*, 227. (b) Perron, F.; Albizati, K. F. *Chem. Rev.* **1989**, *89*, 1617.

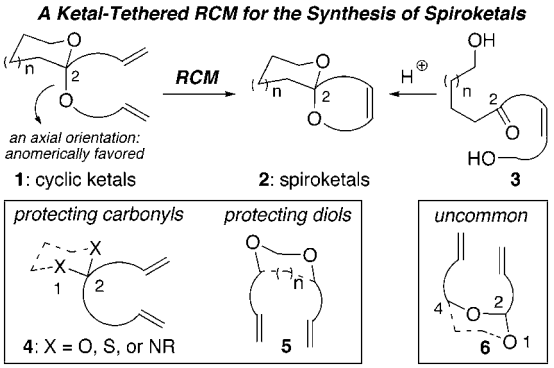
(4) Wang, J.; Hsung, R. P.; Ghosh, S. K. *Org. Lett.* **2004**, *6*, 1939.

(5) Ghosh, S. K.; Hsung, R. P.; Wang, J. *Tetrahedron Lett.* **2004**, *45*, 5505.

10.1021/ol050653q CCC: $30.25
Published on Web 05/06/2005

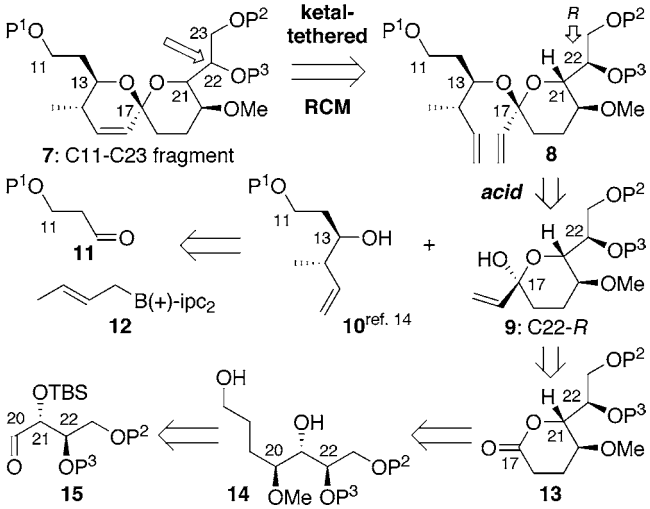
utilizing a cyclic ketal as a template for synthesis, an anomeric effect of 1.5 kcal mol^{-1}, such as shown with the axially oriented C2-oxygen substituent in **1**,[3a,6] could be advantageous in either promoting reactivities[4] or controlling remote stereochemistry[7] away from the pending spiro center at C2. This lack of development is likely because ketals are mostly regarded as protecting groups (see **4** and **5**). Although there are limited reports featuring reactions of **1**[8] and **6**,[9] this approach to spiroketal construction has been largely underappreciated.[10,11] Given the synthetic prowess of RCM,[12] we have been pursuing applications in natural product synthesis to feature the ketal-tethered RCM (Scheme 1). We communicate here our efforts in the synthesis of the C11−C23 fragment of spirastrellolide A.[13]

Scheme 1



Retrosynthetically, the synthesis of the C11−C23 fragment (**7**) would feature the ketal-tethered RCM of cyclic ketal **8** (Scheme 2). We note here that the relative stereochemistry at C22 (see the arrow) was not unambiguously assigned when we began our study.[1a] We elected to go with C22 being *R* because of its availability. After C22 was assigned as *S*,[1b] we continued our efforts with the C22-*R* stereochemistry to focus on establishing the feasibility of the ketal-tethered RCM approach.

Scheme 2



Cyclic ketal **8** can be envisioned from an acid-promoted ketal formation through substitution at the C17 anomeric position of lactol **9** with the known alcohol **10** (**11** + **12**).[14] Lactol **9** can be attained from a vinyl Grignard addition to lactone **13**, which can be prepared from aldehyde **15** through diol **14**. The stereochemistry at C20 will be set using a known allylation protocol,[15] and stereocenters at C21 and C22-*R* could be borrowed from D-glucose.[16]

Our synthetic efforts commenced with transforming D-glucose (**16**) to the vinyl alcohol **17** in three steps using reported procedures (Scheme 3).[16] Protection of C22−OH in **17** as a benzyl ether followed by hydrolysis of benzylidene acetal gave **18**[17] in 82% yield over two steps. A double silylation using TBSCl capped both C21 and C23 hydroxyl groups, and an oxidative cleavage sequence led to aldehyde **15** in 74% overall yield from **18**. With aldehyde **15** in hand, a $BF_3{\cdot}Et_2O$-promoted allylation[15] was accomplished to afford

(6) For reviews on the anomeric effect related to carbohydrate chemistry, see; (a) Postema, M. H. D. *C-Glycoside Synthesis*; CRC Press: Ann Arbor, MI, 1995. Also see: (b) Woods, R. J.; Andrews, C. W.; Bowen, J. P. *J. Am. Chem. Soc.* **1992**, *114*, 859. (c) Miljkovic, M.; Yeagley, D.; Deslongchamps, P.; Dory, Y. L. *J. Org. Chem.* **1997**, *62*, 7597.

(7) Ghosh, S. K.; Hsung, R. P.; Liu, J. Submitted for publication in *J. Am. Chem. Soc*.

(8) (a) van Hooft, P. A. V.; Leeuwenburgh, M. A.; Overkleeft, H. A.; van der Marel, G. A.; van Boeckel, C. A. A.; van Boom, J. H. *Tetrahedron Lett.* **1998**, *39*, 6061. (b) Leeuwenburgh, M. A.; Appeldoorn, C. C. M.; van Hooft, P. A. V.; Overkleeft, H. A.; van der Marel, G. A.; van Boom, J. H. *Eur. J. Org. Chem.* **2000**, 837. (c) Bassindale, M. J.; Hamley, P.; Leitner, A.; Harrity, J. P. A. *Tetrahedron Lett.* **1999**, *40*, 3247.

(9) (a) Hansen, E. C.; Lee, D. *J. Am. Chem. Soc.* **2004**, 126, 15074. (b) Hansen, E. C.; Lee, D. *J. Am. Chem. Soc.* **2003**, *125*, 9582. (c) Keller, V. A.; Martinellie, J. R.; Strieter, E. R.; Burke, S. D. *Org. Lett.* **2002**, *4*, 467. (d) Voight, E. A.; Rein, C.; Burke, S. D. *J. Org. Chem.* **2002**, *67*, 8489 and references cited therein. (e) Scholl, M.; Grubbs, R. H. *Tetrahedron Lett.* **1999**, *40*, 1425.

(10) Kinderman, S. S.; Doodeman, R.; van Beijma, J. W.; Russcher, J. C.; Tjen, K. C. M. F.; Kooistra, T. M.; Mohaselzadeh, H.; van Maarseveen, J. H.; Hiemstra, H.; Schoemaker, H. E.; Rutjes, F. P. J. T. *Adv. Synth. Catal.* **2002**, *344*, 736.

(11) For some examples of ketal-tethered reactions, see: (a) Roush, W. R.; Barba, D. A. *Tetrahedron Lett.* **1997**, *38*, 8781. (b) Wong, T.; Wilson, P. D.; Woo, S.; Fallis, A. G. *Tetrahedron Lett.* **1997**, *38*, 7045. (c) Ainsworth, P. J.; Craig, D.; White, A. J. P.; Williams, D. J. *Tetrahedron* **1996**, *52*, 8937. (d) Boeckman, R. K., Jr.; Estep, K. G.; Nelson, S. G.; Walters, M. A. *Tetrahedron Lett.* **1991**, *32*, 4095. (e) Jung, M. E.; Street, L. J. *J. Am. Chem. Soc.* **1984**, *106*, 8327.

(12) For reviews on metathesis, see: (a) Grubbs, R. H.; Miller, S. J.; Fu, G. C. *Acc. Chem. Res.* **1995**, *28*, 446. (b) Schrock, R. R. *Tetrahedron* **1999**, *55*, 8141. (c) Mori, M. In *Topics in Organometallic Chemistry*; Fürstner, A., Ed.; Springer-Verlag: Berlin, Heidelberg, Germany, 1998; Vol. 1, p 133. (d) Fürstner, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3012. (e) Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res*. **2001**, *34*, 18.

(13) For recent synthetic efforts toward spirastrellolide A, see: (a) Dalby, S. M.; Loiseleur, O.; Paterson, I. *Abstracts of Papers*, 229th National Meeting of the American Chemical Society, San Diego, CA, Spring 2005; American Chemical Society: Washington, DC, 2005; ORGN-331. (b) Wang, C.; Forsyth, C. J. *Abstracts of Papers*, 229th National Meeting of the American Chemical Society, San Diego, CA, Spring 2005; American Chemical Society: Washington, DC, 2005; ORGN-414.

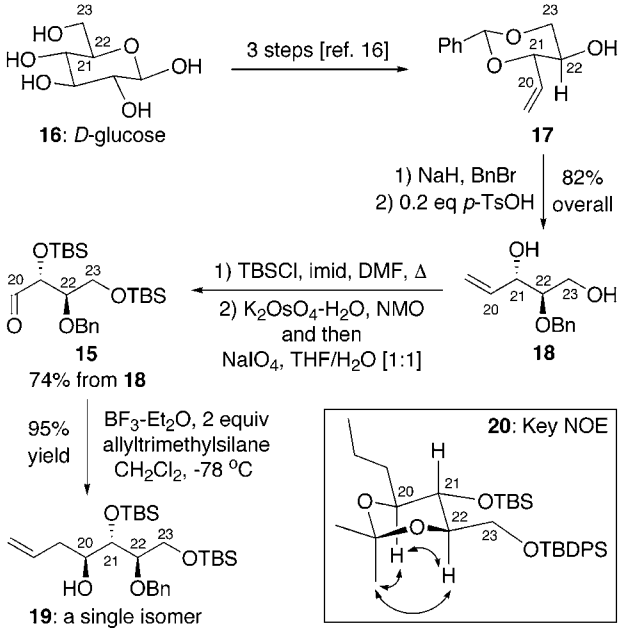
(14) For the synthesis of **10**, see: (a) Zampella, A.; Sepe, V.; D'Orsi, R.; Bifulco, G.; Bassarello, C.; D'Auria, M. V. *Tetrahedron: Asymmetry* **2003**, *14*, 1787. (b) Brown, H. C.; Bhat, K. S. *J. Am. Chem. Soc.* **1986**, *108*, 5919.

(15) Keck, G. E.; Boden, E. P. *Tetrahedron Lett.* **1984**, *25*, 265.

(16) For the synthesis of **17**, see: (a) Paquette, L. A.; Zeng, Q.; Tsui, H.-C.; Johnston, J. N. *J. Org. Chem.* **1998**, *63*, 8491. (b) Baker, S. R.; Clissold, D. W.; McKillop, A. *Tetrahedron Lett.* **1988**, *29*, 991.

(17) See the Supporting Information for procedures and characterization data for all new compounds.

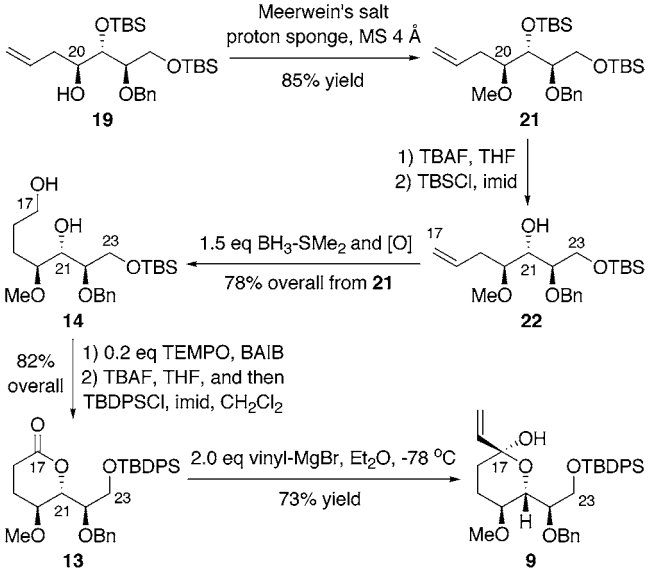
Scheme 3



the Felkin−Anh product **19** as a single diastereomer in 95% yield. The relative stereochemistry at C20 was further confirmed via NOE of acetonide **20** prepared from **19**.[17]

Capping the C20−OH in **19** with Meerwein's salt gave methyl ether **21** in 85% yield (Scheme 4). Removal of both

Scheme 4

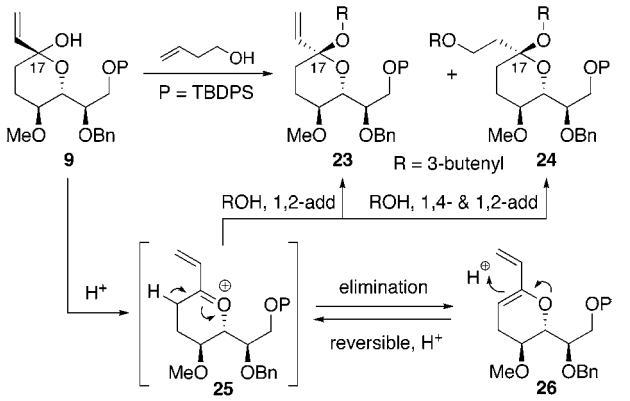


C21− and C23−TBS groups using TBAF and subsequent monoprotection of C23−OH using TBSCl gave **22**.[18] A standard BH_3·SMe_2 hydroboration−oxidation yielded diol **14** in 78% overall yield from **21**. The utility of 9-BBN was also feasible but required a large excess.

The preparation of lactone **13** experienced some problems, but ultimately TEMPO oxidation of diol **14** led to the desired lactone intermediate. Removal of the C23 TBS group in this lactone intermediate using TBAF followed by reprotection of C23−OH with TBDPSCl gave lactone **13** in 82% overall yield (Scheme 4). This latter exchange of the protecting group was pursued because the C23 TBS ether did not survive the cyclic ketal formation later under the acidic conditions. Thus, we had to return to this stage and buttress the choice of protecting groups for C23−OH. Addition of vinylmagnesium bromide to **13** gave the desired lactol **9** in 73% yield as a single diastereomer.

Despite having protocols that we have developed in the ketal formation using simple pyranyl systems[4,5,7] and those reported for more robust carbohydrate based systems,[8a,b] the cyclic ketal formation using lactol **9**, which contains the anomeric vinyl group at C17, proved to be a major challenge. A partial summary of acids examined to achieve an efficient cyclic ketal formation is shown in Table 1.

Table 1.



entry	acid	amt, equiv	solvent	temp, °C	time	product (yield, %)
1	BF_3·Et_2O	1.0	CH_2Cl_2	−78	100 min	**24** (82)
2	TMSOTf	1.0	CH_2Cl_2	0	15 min	**24** (88)
3	K-10	1.2−2.5	benzene	room temp−reflux	5−15 h	**24** (89)
4	CSA or PPTS	0.5−1.0	CH_2Cl_2	room temp−reflux	1−15 h	no reacn
5	Tf_2NH	1.0	CH_2Cl_2	−78	5 min	**23** (89)

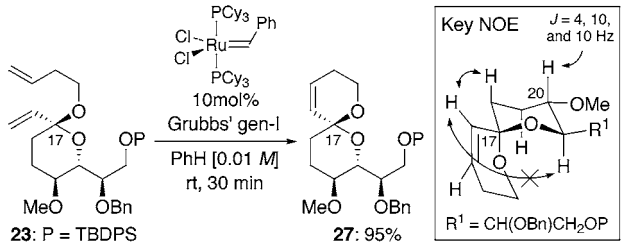
The problem involved competing pathways. In addition to the 1,2-addition of 3-buten-1-ol to oxocarbenium ion **25** (Table 1), which should lead to the desired cyclic ketal **23**, we found over additions that proceeded through 1,4- and then 1,2-additions to oxocarbenium ion **25** to give **24**. In some cases, we also observed an elimination of a proton from **25** to give **26**, which appeared to be a nonproductive pathway, although the elimination is likely reversible via reprotonation of enol ether **26**.

(18) This excessive manipulation occurred because we had to abandon earlier plans on the synthesis of lactone **13** in which the bis-TBS ether **21** would have been feasible.

A range of acids as well as solvents and temperatures were screened, and surprisingly, while most frequently used Lewis acids and Brønsted acids in anomeric substitutions[6] led to the overaddition product **24**, Tf_2NH[19] (entry 5) proved to be an excellent Brønsted acid at −78 °C, leading to **23** as the sole product in 89% yield as a single diastereomer with the oxo-butenyl group (OR) being axial (see below).

The ensuing RCM of **23** gave spiroketal **27** in 95% yield using Grubbs' generation I Ru catalyst[12] (Scheme 5). Selected

Scheme 5

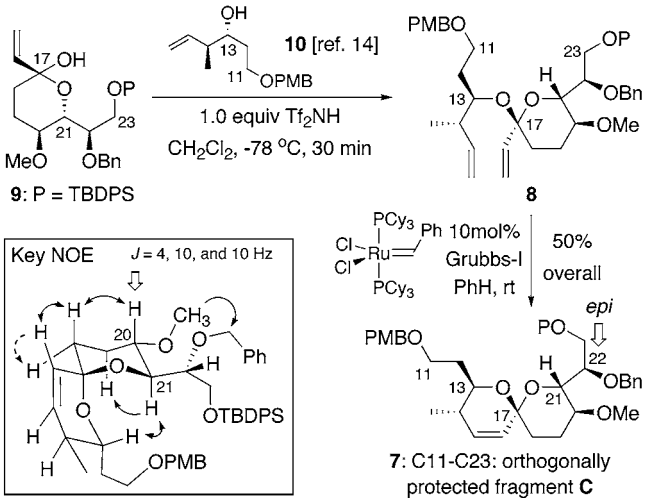


NOE experiments of **27** revealed that the C17 spiro center possesses the desired relative stereochemistry, thereby confirming that the addition of 3-buten-1-ol (ROH in Table 1) to oxocarbenium ion **25** had occurred from an anomerically favored axial trajectory. In addition, due to the conformational rigidity of this spiroketal, coupling constants of C20−H are 4, 10, and 10 Hz, thereby suggesting two vicinal di-axial couplings similar to those reported for the methyl ester of spirastrellolide A.[1]

Success in this model system allowed us to complete the synthesis of the fragment C in spirastrellolide A. As shown in Scheme 6, the known chiral alcohol **10** was prepared according to literature procedures,[14] and cyclic ketal **8** was obtained[20] from lactol **9** as a single isomer under the same Tf_2NH conditions. A successful RCM was achieved to give spiroketal **7** in 50% overall yield.

It is noteworthy that most of the protons in spiroketal **7** are well resolved,[17] and thus, comprehensive NOE experi-

Scheme 6



ments in $CDCl_3$ and C_6D_6 could be obtained to confirm the key relative stereochemistry in spiroketal **7** (see the box in Scheme 6; the dashed arrow implies a relatively weak NOE). Despite being epi at the C22 stereocenter relative to the natural product, most proton chemical shifts in C_6D_6 (i.e., protons from C13−C21) along with their respective coupling constants in **7** are quite similar to those reported for the methyl ester of spirastrellolide A.[1] More importantly, the key NOE enhancements observed for **7** closely matched those reported for the same region in spirastrellolide A.[1]

We have described here a ketal-tethered RCM approach to the construction of spiroketals by featuring the synthesis of the C11−C23 fragment in spirastrellolide A. Applications of this alternative spiroketal synthesis toward completing a total synthesis of spirastrellolide A are currently ongoing.

Acknowledgment. We thank the ACS-PRF-AC for funding.

Supporting Information Available: Text and figures giving experimental procedures as well as ^1H NMR spectral and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

OL050653Q

(19) For a study on the acidity of $HNTf_2$, see: Thomazeau, C.; Olivier-Bourbigou, H.; Magna, L.; Luts, S.; Gilbert, B. *J. Am. Chem. Soc.* **2003**, *125*, 5264.

(20) On occasion, we also found diene **26**, presumably because alcohol **10** is more sterically demanding than the model system.