ORGANIC LETTERS

2011
Vol. 13, No. 12
3246–3249

Synthesis of Key Fragments of Leiodelide A

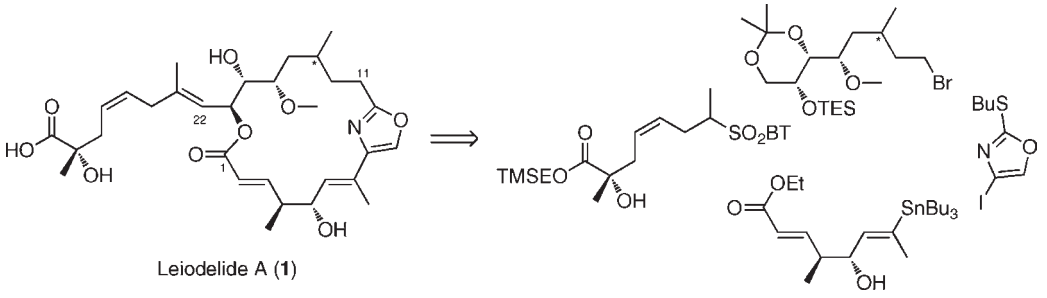
Mathieu F. Chellat, Nicolas Proust, Matthew G. Lauer, and James P. Stambuli*

Department of Chemistry, The Ohio State University, 100 West 18th Avenue, Columbus, Ohio 43210, United States

stambuli@chemistry.ohio-state.edu

Received May 4, 2011

ABSTRACT



The synthesis of all key fragments of the marine macrolide leiodelide A is described. The polyoxygenated northern subunit is derived from D-xylose, while the southern subunit is rapidly assembled via an aldol reaction and Horner–Wadsworth–Emmons olefination. This highly convergent approach will allow for rapid modification and assembly of several isomers of leiodelide A, which may be necessary considering the assignment of leiodelide B has been previously shown to be incorrect.

The leiodelides are a family of biologically active macrolides produced by the deep-water marine sponge *Leiodermatium* and first isolated by Fenical and co-workers (Figure 1).[1] Structures of these two 19-membered macrolides were proposed as **1** and **2** based on spectral analysis, and both currently have at least one unassigned stereogenic center. Recently, Fürstner et al. published the synthesis of the proposed structure of leiodelide B (**2**) along with three diastereomers and concluded that none of these isomers matched the reported spectroscopic data enough to claim identity.[2]

Leiodelide A (**1**) exhibits cytotoxic activity against HL-60 leukemia and OVCAR-3 ovarian cancer cell lines. It features an oxazole-containing 19-membered macrolide, seven stereocenters, and a 10-carbon side chain with an α,α-disubstituted carboxylic acid terminus similar to that of okadaic acid.[3] The combined factors of low natural supply, biological activity, and unusual structure made it an attractive target for total synthesis. Moreover, a total synthesis and absolute configuration determination of

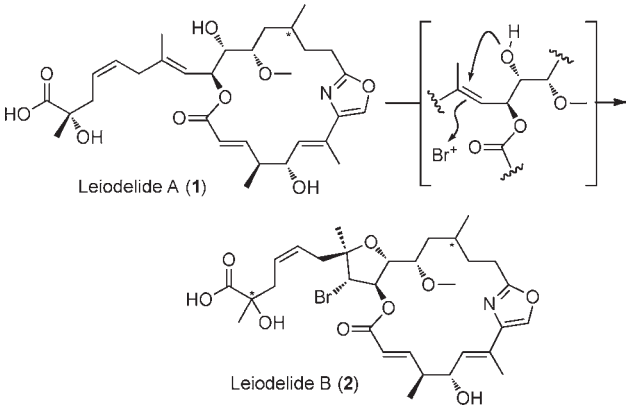


Figure 1. Proposed structures of and biosynthetic relationship between leiodelide A (**1**) and leiodelide B (**2**).

(1) Sandler, J. S.; Colin, P. L.; Kelly, M.; Fenical, W. *J. Org. Chem.* **2006**, *71*, 7245.

(2) Larivée, A.; Unger, J., B.; Thomas, M.; Wirtz, C.; Dubost, C.; Handa, S.; Fürstner, A. *Angew. Chem., Int. Ed.* **2011**, *50*, 304.

(3) (a) Tachibana, K.; Scheuer, P. J.; Tsukitani, Y.; Kikuchi, H.; Van Engen, D.; Clardy, J.; Gopichand, Y.; Schmitz, F. J. *J. Am. Chem. Soc.* **1981**, *103*, 2469. (b) Forsyth, C. J.; Sabes, S. F.; Urbanek, R. A. *J. Am. Chem. Soc.* **1997**, *119*, 8381.

10.1021/ol201183f
Published on Web 05/25/2011

leiodelide A would hopefully help resolve the "leiodelide B puzzle".[2]

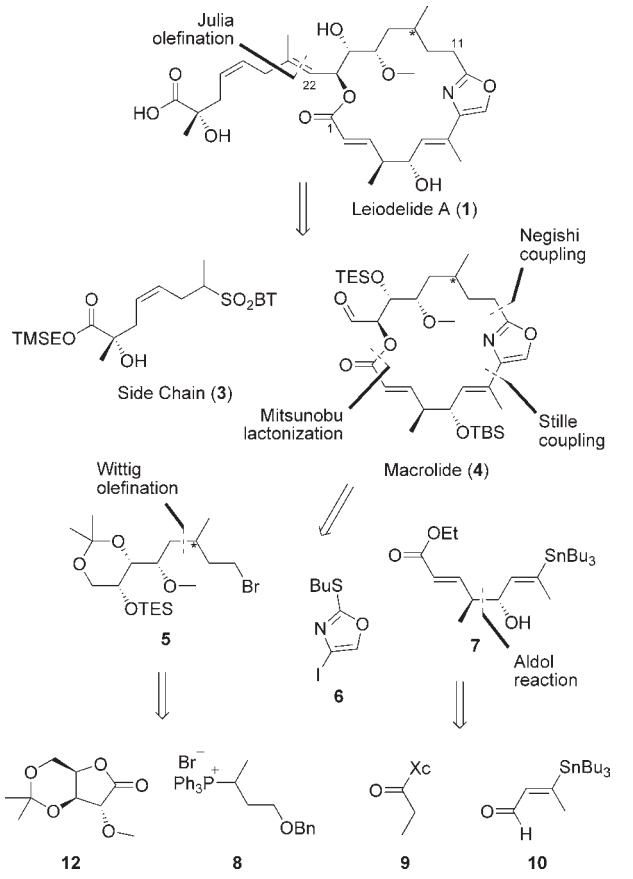
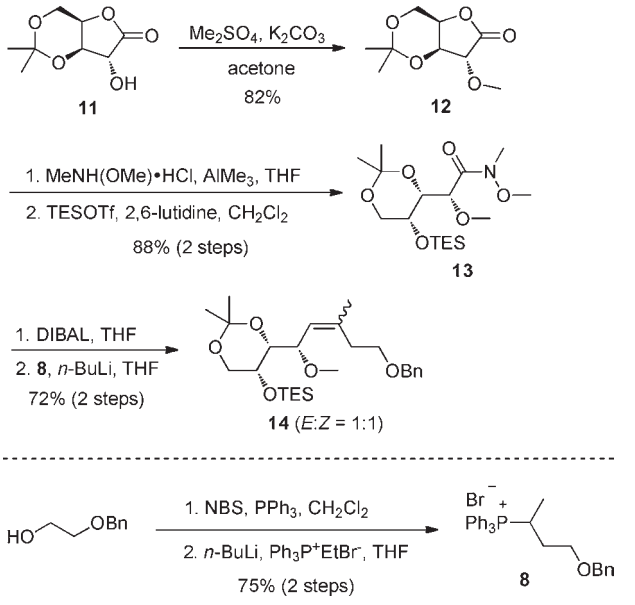


Figure 2. Retrosynthetic analysis of leiodelide A (**1**).

As outlined in Figure 2, our retrosynthetic strategy started by disconnection at C22 to reveal macrolide **4** and side chain **3**. Macrolide **4** could be accessed from simplified fragments **5**, **6**, and **7**. First, the northern subunit **5**, with its three contiguous oxygenated chiral centers, was envisioned to originate from the opening of chiral lactone **12** (derived from D-xylose) followed by Wittig olefination with phosphonium bromide **8**. Second, the α,β-unsaturated ester **7** could be generated from an Evans aldol reaction between acylated oxazolidinone **9** and aldehyde **10** followed by a Horner–Wadsworth–Emmons olefination reaction to install the ester moiety. Finally, oxazole **6** can be obtained in three steps from known 2-thiooxazole.[4] The key steps of the synthesis would be the appending of the northern and southern fragments onto the oxazole via metal-catalyzed cross-coupling reactions.[4] This highly convergent strategy would provide a great deal of flexibility when it comes to derivatization and SAR studies. It would also provide us with easy access to multiple diastereomers in the event of discrepancies between the synthetic and natural products.

The synthesis of bromide **5** commenced with the formation of olefin **14** (Scheme 1). Starting from known alcohol **11**,[5] methylation provided lactone **12**, which was then opened to the corresponding Weinreb amide. Since the chromatographic purification of the amide on silica gel resulted in recyclization to **12**, immediate conversion to the triethylsilyl ether **13** was performed.

Scheme 1. Synthesis of the Northern Subunit Precursor **14**



Reduction of amide **13** to the corresponding aldehyde using DIBAL set the stage for the Wittig olefination. The coupling partner, phosphonium bromide **8**, was prepared in two steps: bromination of 2-(benzyloxy)ethanol[6] followed by treatment with ethyltriphenylphosphonium bromide in the presence of *n*-BuLi.[7] The Wittig reaction resulted in an inconsequential 1:1 mixture of *E*- and *Z*-olefins **14**, which were separated for analytical purposes.

The reduction/deprotection sequence proved to be more difficult than expected and required some optimization. Treatment of unsaturated benzyl ether **14** with various sources of palladium all led to hydrogenolysis of the benzyl ether to alkane **15** (Scheme 2). This product is presumably formed via an olefin migration/palladium π-allyl formation/elimination mechanism. Palladium is known to have a high isomerization activity,[8] and this type of reaction has been previously reported with both homoallylic

(4) Counceller, C. M.; Eichman, C. C.; Proust, N.; Stambuli, J. P. *Adv. Synth. Catal.* **2011**, *353*, 79.

(5) Han, S.-Y.; Joullié, M. M.; Fokin, V. V.; Petasis, N. A. *Tetrahedron: Asymmetry* **1994**, *5*, 2535.

(6) Hammerschmidt, F.; Kaehlig, H. *J. Org. Chem.* **1991**, *56*, 2364.

(7) Marinier, A.; Deslongchamps, P. *Can. J. Chem.* **1992**, *70*, 2350.

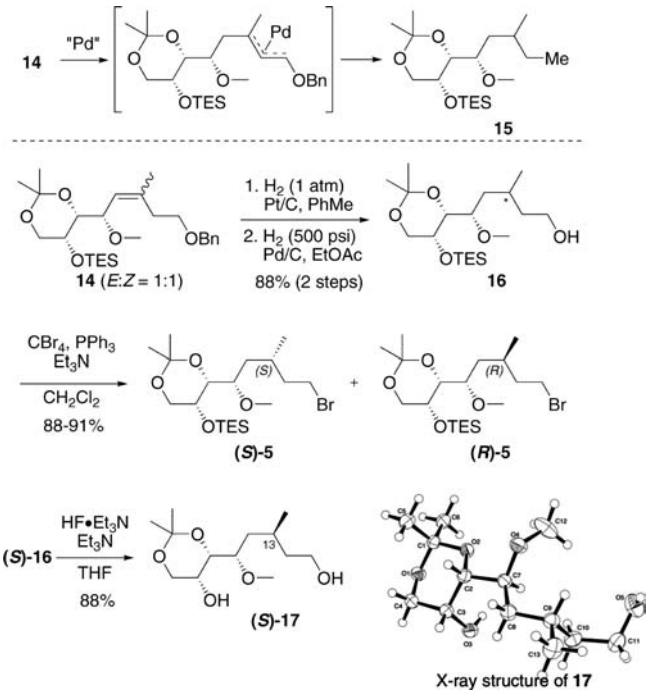
(8) Rylander, P. N. *Hydrogenation Methods*; Academic Press: London; Orlando, FL, 1985; pp 31–36.

(9) Cocker, W.; Shannon, P. V. R.; Staniland, P. A. *J. Chem. Soc. C* **1966**, 41.

(10) Nishimura, S.; Uramoto, M.; Watanabe, T. *Bull. Chem. Soc. Jpn.* **1972**, *45*, 216.

cyclopropanes[9] and homoallylic ethyl ethers.[10] Switching to platinum or rhodium at high pressures or in polar solvents led to reduction of the phenyl ring. Finally, it was found that a two-step platinum/palladium reaction with adequate solvents and pressures afforded the desired saturated alcohols **16** in 88% yield. This strategy has recently been used by Nicolaou et al. for the synthesis of englerin A.[11] At this point, the two epimeric alcohols were separated by column chromatography and were both carried on to their respective bromides in nearly quantitative yield. This late stage formation of the unassigned C13 stereocenter will give us rapid access to both epimers of the macrolide and hopefully allow us to attribute stereochemistry by comparison of spectroscopic data.

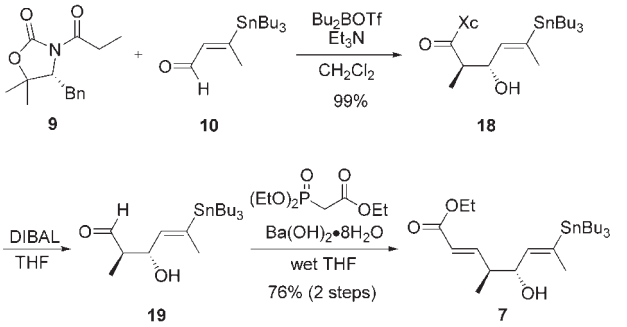
Scheme 2. Synthesis of the Northern Subunit **5**



In order to determine the absolute stereochemistry at C13, the triethylsilyl group was removed from one of the epimeric alcohols (**16**) and an X-ray structure of **17** was obtained on the resulting crystalline solid.

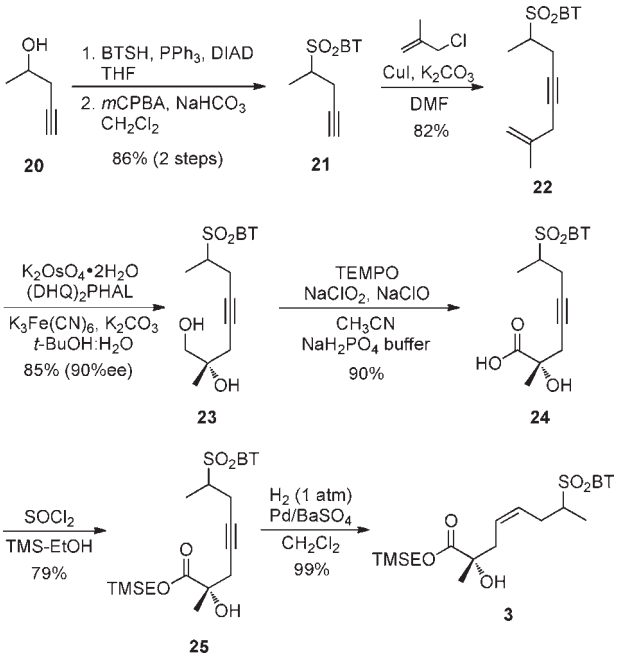
The southern fragment was first envisioned to come from a late stage hydrometalation of the corresponding alkyne to form alkenylstannane **7**. After extensive screening it became obvious that this strategy would not be viable for steric reasons or due to side reactions with the unsaturated ester. We therefore envisioned a route where the organotin would be attached early on in the sequence (Scheme 3).

Scheme 3. Synthesis of the Southern Subunit **7**



The synthesis commenced with an Evans aldol reaction between Davies' SuperQuat oxazolidinone **9**[12] and known aldehyde **10**[13] to provide **18**. Evans' auxiliary commonly requires two steps to regenerate the aldehyde: cleavage to the alcohol followed by oxidation to the aldehyde.[14] In our case, oxidation of the intermediate alcohol to the aldehyde was low yielding and nonreproducible. On the other hand, the SuperQuat auxiliary afforded the desired aldehyde in one step. Therefore, DIBAL cleavage of the chiral auxiliary followed by Horner–Wadsworth–Emmons olefination gave the fully functionalized southern fragment **7** in three steps. The assignment of the stereochemistry of this southern half was described as "tenuous" by Fenical et al.,[1] which makes this short and convergent approach easily amenable to the synthesis of the other enantiomer.

Scheme 4. Synthesis of the Side Chain **3**



(11) Nicolaou, K. C.; Kang, Q.; Ng, S. Y.; Chen, D. Y. K. *J. Am. Chem. Soc.* **2010**, *132*, 8219.
(12) Bull, S. D.; Davies, S. G.; Nicholson, R. L.; Sanganee, H. J.; Smith, A. D. *Tetrahedron: Asymmetry* **2000**, *11*, 3475.
(13) Lipshutz, B. H.; Clososki, G. C.; Chrisman, W.; Chung, D. W.; Ball, D. B.; Howell, J. *Org. Lett.* **2005**, *7*, 4561.
(14) Bull, S. D.; Davies, S. G.; Nicholson, R. L.; Sanganee, H. J.; Smith, A. D. *Org. Biomol. Chem.* **2003**, *1*, 2886.
(15) Liang, Z.; Ma, S.; Yu, J.; Xu, R. *J. Org. Chem.* **2007**, *72*, 9219.

With both the northern and southern halves of the macrolide synthesized, we then concentrated on the construction of the side chain (Scheme 4). Starting from homopropargylic alcohol **20**, Mitsunobu reaction with 2-thiobenzothiazole followed by *m*-CPBA oxidation afforded sulfone **21**. Copper mediated addition onto 2-methallyl chloride[15] gave us the complete carbon skeleton in three easily scalable steps. From there, Sharpless asymmetric dihydroxylation[16] resulted in chiral diol **23** (85% yield, 90% ee) which was converted to the acid by TEMPO oxidation.[17] Finally, protection of acid **24** as the 2-(trimethylsilyl)ethyl ester[18] and subsequent palladium-catalyzed *Z*-selective reduction of the alkyne delivered the fully functionalized side chain **3**. The trimethylsilylethyl ester was chosen to allow the deprotection of all silyl groups in one final step. A potentially difficult saponification of the carboxylate of the side chain in the presence of the macrolactone would therefore be avoided.[2]

In summary, the synthesis of all the fragments of leiodelide A has been accomplished in a short and very convergent manner. Assembly of the macrolactone and completion of the synthesis are currently underway and will be reported in due time.

Acknowledgment. This work was generously supported by The Ohio State University. We thank Dr. Judith Gallucci (OSU) for the X-ray structure of **17**.

Supporting Information Available. Experimental procedures and characterization of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

(16) Jacobsen, E. N.; Marko, I.; Mungall, W. S.; Schroeder, G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1988**, *110*, 1968.

(17) Zhao, M.; Li, J.; Mano, E.; Song, Z.; Tschaen, D. M.; Grabowski, E. J. J.; Reider, P. J. *J. Org. Chem.* **1999**, *64*, 2564.

(18) Hashimoto, T.; Maruoka, K. *Synthesis* **2008**, 3703.