ORGANIC LETTERS

2012
Vol. 14, No. 17
4350–4353

Total Synthesis of (−)-Irciniastatin B and Structural Confirmation via Chemical Conversion to (+)-Irciniastatin A (Psymberin)

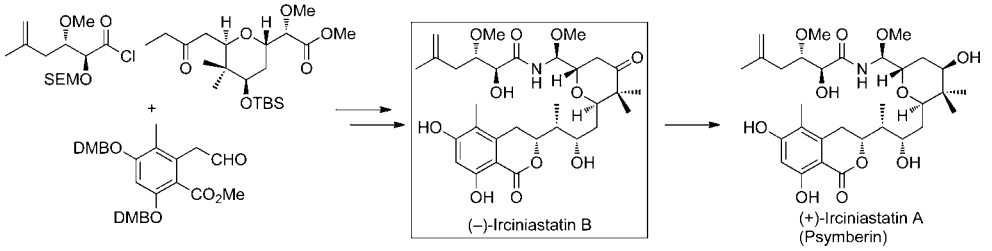
Chihui An, Adam T. Hoye, and Amos B. Smith III*

Department of Chemistry, Laboratory for Research on the Structure of Matter and Monell Chemical Senses Center, University of Pennsylvania, Philadelphia, Pennsylvania 19104, United States

smithab@sas.upenn.edu

Received June 28, 2012

ABSTRACT



The total synthesis and structural confirmation of the marine sponge cytotoxin (−)-irciniastatin B has been achieved via a unified strategy employing a late-stage, selective deprotection/oxidation sequence that provides access to both (+)-irciniastatin A (psymberin) and (−)-irciniastatin B.

In 2004, Pettit and co-workers reported the isolation of (+)-irciniastatin A (**1**) and (−)-irciniastatin B (**2**) from the Indo-Pacific marine sponge *Ircinia ramosa* (Figure 1).[1] Months later, Crews et al. independently reported the isolation of (+)-psymberin from the marine sponge *Psammocinia*.[2] Initial reports suggested that all three metabolites possessed structures with notable architectural features including a substituted *trans*-2,6-tetrahydropyran core, a dihydroisocoumarin, and an *N*,*O*-hemiaminal moiety. (+)-Irciniastatin A (**1**) and (−)-irciniastatin B (**2**) differed only in the oxidation state at C(11), while (+)-irciniastatin A (**1**) and (+)-psymberin appeared to be possible diastereomers. The C(4) stereogenicity, however, remained undefined with opposite stereochemical assignments reported for C(8). In 2005, De Brabander and colleagues reported the first total synthesis of (+)-irciniastatin A (**1**) that established the complete structure including the absolute configuration and confirmed that both (+)-irciniastatin A (**1**) and (+)-psymberin were identical.[3]

From a biomedical perspective, both (+)-irciniastatin A (**1**) and (−)-irciniastatin B (**2**) possess selective tumor cell growth inhibition (0.004−0.0005 μg/mL).[1] Interestingly, although structurally almost identical, (−)-irciniastatin B (**2**) was reported to be almost 10-fold more potent than (+)-irciniastatin A (**1**) against human pancreas (BXPC-3), breast (MCF-7), and central nervous system (SF268) cell lines. Recent studies by Usui and co-workers determined that the cytotoxicity of (+)-irciniastatin A (**1**) derives from activation of stress-activated protein kinases such as JNK and p38.[4] In addition, analogue studies by the Schering-Plough group revealed that the C(11) hydroxyl group was not necessary for biological activity; in particular, the (+)-C(11)-deoxy analogue possesses a 3−10 fold increase

(1) Pettit, G. R.; Xu, J. P.; Chapuis, J. C.; Pettit, R. K.; Tackett, L. P.; Doubek, D. L.; Hooper, J. N. A.; Schmidt, J. M. *J. Med. Chem.* **2004**, *47*, 1149.

(2) Cichewicz, R. H.; Valeriote, F. A.; Crews, P. *Org. Lett.* **2004**, *6*, 1951.

(3) Jiang, X.; García-Fortanet, J.; DeBrabander, J. K. *J. Am. Chem. Soc.* **2005**, *127*, 11254.

(4) Chinen, T.; Nagumo, Y.; Watanabe, T.; Imaizumi, T.; Shibuya, M.; Kataoka, T.; Kanoh, N.; Iwabuchi, Y.; Usui, T. *Toxicol. Lett.* **2010**, *199*, 341.

10.1021/ol301783p
Published on Web 08/14/2012

in activity against all cancer cell lines tested compared to (+)-irciniastatin A (**1**).[5]

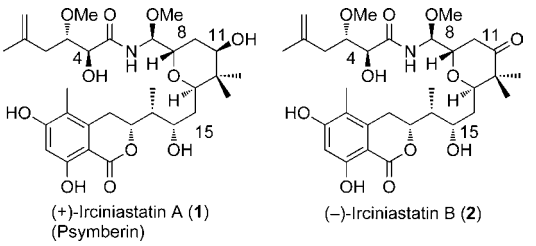
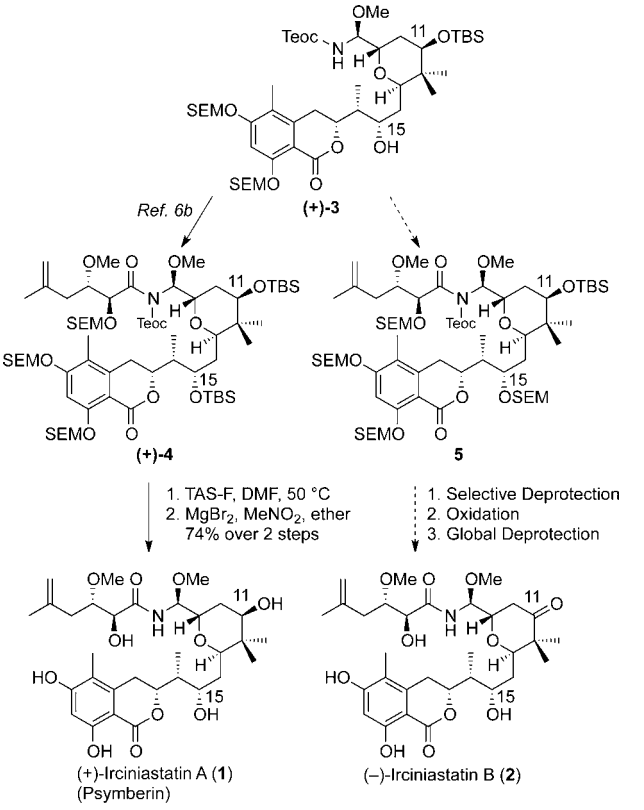


Figure 1

Given the biological profile and limited abundance of both **1** and **2**, significant interest has arisen within the synthetic community. To date, seven total syntheses have been reported for (+)-irciniastatin A,[3,6] including one report from our laboratory.[6b] To the best of our knowledge, the total synthesis of (−)-irciniastatin B has yet to be reported. Due to the greatly enhanced cytotoxic activity of (−)-irciniastatin B (**2**) compared to (+)-irciniastatin A (**1**) in several cancer cell lines, we set out to develop a unified synthetic strategy to access both natural products as well as analogues varying in substitution at C(11). Herein, we report the first total synthesis of (−)-irciniastatin B (**2**) that includes structural confirmation via chemical conversion to (+)-irciniastatin A (**1**).

Our synthetic strategy for the synthesis of (−)-irciniastatin B (**2**) is based on our previous route to (+)-irciniastatin A (**1**) (Scheme 1).[6b] In order to introduce the requisite oxidation at C(11), we selected advanced intermediate (+)-**3**[6b] for the orthogonal protection at C(15) (Scheme 1). However, careful attention to the selection of a suitable protecting group at C(15) would clearly be required. Initially, the SEM group (cf. **5**) was selected with the expectation of selective removal of the sterically hindered TBS protecting group at the C(11) position. Oxidation of the resultant alcohol and global deprotection was then envisioned to provide (−)-irciniastatin B (**2**). The advantage of this approach compared to our orginal strategy for (+)-irciniastatin A (**1**) would be ready access to a late-stage intermediate [i.e., (+)-**3**] en route to both (+)-irciniastatin A (**1**) and (−)-irciniastatin B (**2**). Additionally, chemical modification of both the C(11) alcohol or ketone in late stage intermediates would permit access to analogues varying at the C(11) stereogenic center, thus permitting further exploration of the irciniastatin chemotype as a potent therapeutic lead.

Scheme 1



Having accessed advanced Teoc carbamate (+)-**3** via our published route,[6b] we were surprised that all attempts to protect (+)-**3** as the SEM ether at C(15) resulted in the unforeseen loss of the phenolic SEM ethers during workup and purification steps.[7] Moreover, reprotection to introduce the phenolic SEM ethers proved to be ineffective even at elevated temperatures. After considerable experimentation, we discovered that the phenolic 3,4-dimethoxybenzyl group (DMB) could be easily removed under standard oxidative conditions in model studies while at the same time be suitable for the orthogonal TBS ether removal.

The synthesis of (−)-irciniastatin B (**2**) began with bis-DMB aryl fragment **7**, which was obtained by protection of known bis-phenol **6**[8] followed by chemoselective reduction to aldehyde **7** (Scheme 2). From here, the synthetic route employed a similar sequence as applied in our earlier synthesis of (+)-irciniastatin A (**1**).[6b] Pleasingly, union between aldehyde **7** and known ketone (+)-**8**[6b] was achieved by employing dichlorophenylborane and Hünig's

(5) Huang, X.; Shao, N.; Huryk, R.; Palani, A.; Aslanian, R.; Seidel-Dugan, C. *Org. Lett.* **2009**, *11*, 867.

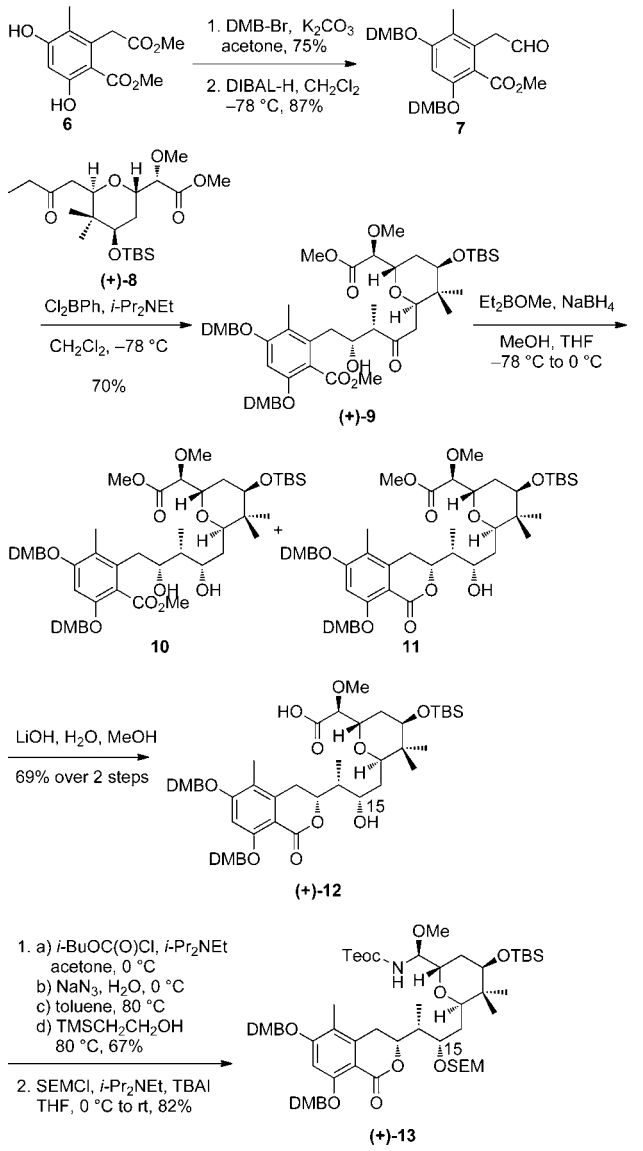
(6) (a) Huang, X.; Shao, N.; Palani, A.; Aslanian, R.; Buevich, A. *Org. Lett.* **2007**, *9*, 2597. (b) Smith, A. B., III; Jurica, J. A.; Walsh, S. P. *Org. Lett.* **2008**, *10*, 5625. (c) Crimmins, M. T.; Stevens, J. M.; Schaaf, G. M. *Org. Lett.* **2009**, *11*, 3994. (d) Watanabe, T.; Imaizumi, T.; Chinen, T.; Nagumo, Y.; Shibuya, M.; Usui, T.; Kanoh, N.; Iwabuchi, Y. *Org. Lett.* **2010**, *12*, 1040. (e) Wan, S.; Wu, F.; Rech, J. C.; Green, M. E.; Balachandran, R.; Horne, W. S.; Day, B. W.; Floreancig, P. E. *J. Am. Chem. Soc.* **2011**, *133*, 16668. (f) Byeon, S. R.; Park, H.; Kim, H.; Hong, J. *Org. Lett.* **2011**, *13*, 5816.

(7) While particularly deleterious at this point in the synthesis, the loss of phenloic SEM ethers had plagued the route at various stages and contributed to our decision to identfiy an alternative protecting group strategy.

(8) Langer, P.; Kracke, B. *Tetrahedron Lett.* **2000**, *41*, 4545.

(9) Hamana, H.; Sasakura, K.; Sugasawa, T. *Chem. Lett.* **1984**, *13*, 1729.

Scheme 2



base to furnish the desired *syn*-aldol product (+)-**9**, achieved in 70% yield with excellent selectivity (>20:1).[9] A chelation-controlled reduction protocol[10] next furnished a mixture of the desired *syn*-diol **10** and lactone **11** (ca. 8:1), which upon treatment with LiOH followed by an acid workup led to the desired acid (+)-**12** in 69% yield for the two steps (Scheme 3). The acidic workup was required after saponification to achieve lactonization of the undesired bis-acid byproduct.

We next turned to the required installation of the *N*,*O*-aminal functionality via a stereoretentive Curtius rearrangement (Scheme 2), a tactic successfully utilized earlier in our synthesis of (+)-zampanolide[11] and (+)-irciniastatin A[6b] to install the *N*,*O*-aminal moiety with complete stereoselectively. To this end, thermal rearrangement of the acyl azide derived from (+)-**12**, followed by treatment with 2-trimethylsilylethanol to intercept the isocyanate, led to the Teoc-protected *N*,*O*-aminal in 67% yield, again with complete retention of stereochemical configuration. Protection of the C(15) alcohol was then achieved in 82% yield upon treatment with SEMCl, TBAI, and *i*-Pr_2NEt. Gratifyingly, the resulting SEM ether (+)-**13** proved to be much more stable than other congeners such as the tris-SEM ether and thus could be isolated without decomposition following workup and purification.

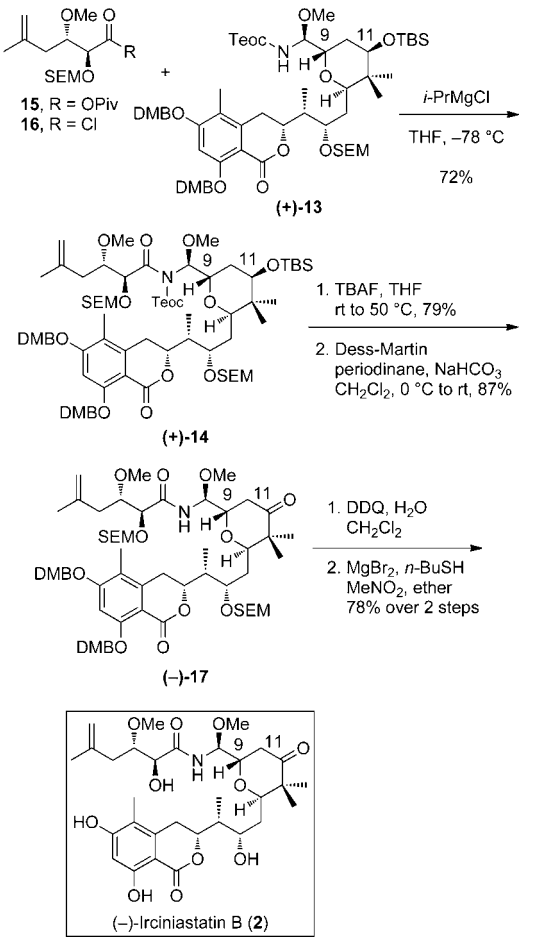
Initial attempts to append the side chain to provide (+)-**14** proved difficult (Scheme 3). The original optimized conditions employed in our (+)-irciniastatin A synthesis, which called for treatment with LiHMDS and the mixed pivalate anhydride **15**,[6b] proved to be ineffective, furnishing the desired (+)-**14** in only a poor yield (ca. 15%). After considerable screening, the conditions established by Crimmins and co-workers,[6c] specifically acid chloride **16** in conjuction with *i*-PrMgCl, furnished amide (+)-**14** in 72% yield. It is interesting to note that slight differences in molecular structure, even in regions distal to the reactive site, seem to play a significant role in the successful construction of this challenging amide bond.

With the full carbon skeleton of (−)-irciniastatin B (**2**) intact, we next explored the selective removal of the hindered neopentyl C(11) TBS group. Treatment of (+)-**14** with TBAF at room temperature initially removed the Teoc carbamate group. The reaction mixture was then warmed to 50 °C, and over the course of 42 h, the C(11) TBS ether underwent clean hydrolysis in good yield (79%). Oxidation of the resulting secondary alcohol to ketone (−)-**17** was then achieved by treatment with Dess−Martin periodinane[12] in 87% yield.

We next discovered, after considerable experimentation, a two-stage deprotection sequence was required to remove the two sets of orthogonal protecting groups in (−)-**17**. Interestingly, introduction of the C(11)-ketone moiety greatly increases the sensitivity of the molecule: according to the literature on similar systems, basic conditions lead to a retro-Michael/Michael sequence epimerizing[13] the C(9) stereogenic center of the tetrahydropyran core, while acidic conditions lead to hydrolysis of the *N*,*O*-aminal.[14] Pleasingly, treatment of ketone (−)-**17** with DDQ provided the desired bis-phenol without visible decomposition (Scheme 3). For removal of the remaining protecting groups, the use of TASF or TBAF in the second step proved unworkable, leading only to a complex mixture of products. Eventually, we discovered that a premixed solution of $MgBr_2$, *n*-butanethiol, and nitromethane[15] in Et_2O removed the SEM ethers to furnish (−)-irciniastatin B (**2**) in 78% yield over two steps. The spectral data of synthetic (−)-irciniastatin B (**2**) were identical

(10) Chen, K.-M.; Hardtmann, G. E.; Prasad, K.; Repic, O.; Shapiro, M. J. *Tetrahedron Lett*. **1987**, *28*, 155.
(11) Smith, A. B., III; Safonov, I. G.; Corbett, R. M. *J. Am. Chem. Soc*. **2002**, *124*, 11102.
(12) Dess, D. B.; Martin, J. C. *J. Org. Chem*. **1983**, *48*, 4155.
(13) Allevi, P.; Anastasia, M.; Ciuffreda, P.; Fiecchi, A.; Scala, A. *J. Chem. Soc., Perkins Trans. 1* **1989**, *7*, 1275.
(14) Mori, M.; Uozumi, Y.; Ban, Y. *J. Chem. Soc., Chem. Commun*. **1986**, *11*, 841.
(15) Denmark, S. E.; Kobayashi, T.; Regens, C. S. *Tetrahedron* **2010**, *66*, 4745.

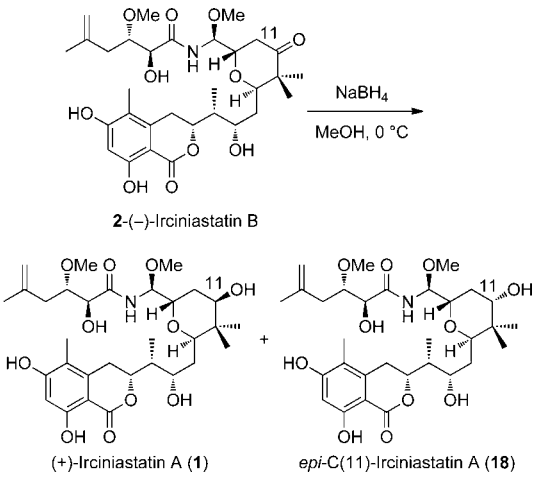
Scheme 3



in all respects with the spectral data kindly provided to us by Pettit and co-workers.[1]

To confirm the structure of (−)-irciniastatin B (**2**), the chemical conversion of (−)-irciniastatin B (**2**) to (+)-irciniastatin A (**1**) was carried out (Scheme 4). To this end, treatment of synthetic (−)-irciniastatin B (**2**) with $NaBH_4$ provided a 1:1 mixture of (+)-irciniastatin A (**1**) and *epi*-C(11)-irciniastatin A (**18**). After separation of the two diastereomers by preparatory TLC, the spectral data of the more rapidly moving congener on TLC proved identical to (+)-irciniastatin A (i.e., ^1H and ^{13}C NMR and HRMS), thus confirming that the structure of the (+)-irciniastatin A (**1**) and (−)-irciniastatin B (**2**) are identical except for the oxidation state at C(11).

Scheme 4



In summary, the first total synthesis of (−)-irciniastatin B (**2**) has been achieved. The central features of this synthetic venture entailed a modified protecting group strategy that is amenable to scalable synthesis and a late-stage selective deprotection and oxidation sequence. Importantly, the availability of ketone (−)-**17** now permits access to both (+)-irciniastatin A (**1**) and (−)-ircinaistatin B (**2**) as well as to *epi*-C(11)-irciniastatin A (**18**) and potential future analogues. Development of a more efficient strategy toward (−)-**17**, in conjunction with the synthesis of analogues for biological evaluation, continue in our laboratory.

Acknowledgment. Financial support was provided by the National Institutes of Health (National Cancer Institute) through Grant No. CA-19033. We thank Drs. George Furst and Rakesh Kohli (University of Pennsylvania) for their help in obtaining the high-resolution NMR and mass spectral data, respectively. We thank Professor G. R. Pettit (Arizona State University) for his generous help in providing the ^1H and ^{13}C NMR spectra of (−)-irciniastatin B.

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

The authors declare no competing financial interest.