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

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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 coworkers 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*-hemaminal 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 2007, 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 to 0.0005 $\mu\text{g/mL}$).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 coworkers 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 in activity against all cancer cell lines tested compared to (+)-irciniastatin A (**1**).⁵

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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>.

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 earlier 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, SEM group (cf. **5**) was selected with the expectation of selective removal of the sterically hindered TBS protecting group at 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 original 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.

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-dimethoxy-benzyl 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 base to furnish the desired *syn*-aldol product (+)-**9**, achieved in 70% yield with excellent selectivity (>20:1).⁹ A chelation-controlled reduction protocol¹⁰ 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 work-up led to the desired acid (+)-**12** in 69% yield for the two steps (Scheme 3). The acidic work-up 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 (+)-zampanolide¹¹ and (+)-irciniastatin A^{6b} to install the *N,O*-aminal moiety with complete stereoselectivity. 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*-Pr₂NEt. 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 coworkers,^{6c} specifically acid chloride **16** in conjunction 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**) in tact, 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 periodinane¹² 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 epimerizing¹³ the C(9) stereogenic center of the tetrahydropyran core, while acidic conditions lead to hydrolysis of the *N,O*-acetal.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 MgBr₂, *n*-butanethiol, and nitromethane¹⁵ in Et₂O removed the SEM ethers to furnish (–)-irciniastatin B (**2**) in 78% yield over two steps. The spectral data of synthetic (–)-irciniastatin B (**2**) was identical in all respects with the spectral data kindly provided to us by Pettit and coworkers.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 NaBH₄ 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, ¹³C 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).

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 (–)-irciniastatin B (**2**), as well as to *epi*-C(11)-irciniastatin A (**18**) and potential future analogues. Development of a more efficient strategy towards (–)-**17**, in conjunction with the synthesis of analogues for biological evaluation continue in our Laboratory.

Supplementary Material

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Acknowledgments

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Figure 1.

Scheme 1.

Scheme 2.

Scheme 3.

Scheme 4.