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## Synthesis and Complete Stereochemical Assignment of Psymberin/ Irciniastatin A

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In 2004, two groups led by Pettit and Crews independently disclosed the isolation of constitutionally identical cytotoxins, irciniastatin A<sup>1</sup> and psymberin<sup>2</sup> from the marine sponges Ircinia ramose and Psammocinia sp., respectively. NMR and chiroptical data substantiated the assigned relative and absolute configuration for psymberin shown in 1, save for the undefined configuration at  $C_{4}$ <sup>2</sup> The relative stereochemistry of irciniastatin A (2) was only resolved for the  $C_8-C_{13}$  aminal fragment.<sup>1</sup> Interestingly, the  $C_8$ aminal configuration in irciniastatin A was opposite to the corresponding center assigned for psymberin.<sup>3</sup> Psymberin/irciniastatin most closely resemble the pederin family of natural products (e.g., 3 and 4, see Figure 1).4,5 However, a constellation of unique structural attributes (dihydroisocoumarin and acyclic left half)<sup>6</sup> and unprecedented tumor cell selectivity<sup>1,2</sup> indicate that 1/2 might be functionally distinct from the pederin family of protein synthesis inhibitors. Herein, we communicate a short, highly convergent synthesis of 1/2 that (1) resolves the stereochemical ambiguities and (2) provides material and synthetic avenues for future biochemical and preclinical investigation.



Figure 1. Psymberin, irciniastatins, and related natural products.

Our approach to 1/2 envisioned the coupling of fragments 6-7 via carbon-bond formation to control stereochemistry of the C<sub>15</sub>-C<sub>17</sub> stereotriad, followed by appending carboxylic acid **5**. Given the unknown stereochemistry at C<sub>4</sub>, we prepared both *anti*- and *syn*-**5** (Scheme 1A).<sup>7</sup> Asymmetric methallylation<sup>8</sup> of aldehyde **8** followed by methylation and acetonide hydrolysis provided diol **9**, to be converted to benzoate **10** via silylation, benzoylation, and desilylation. The relative stereochemistry was confirmed through <sup>1</sup>H NMR analysis of acetal **11**. Finally, a two-step oxidation of alcohol **10** yielded *anti*-**5** (8 steps, 49% from **8**). *Syn*-**5** was prepared from **8**, starting with antipodal methallyl borane reagent.

The aryl fragment 6 was obtained in 7 steps (41% overall yield, Scheme 1B) from known aldehyde  $12^9$  via: (1) oxidation/amidation



<sup>*a*</sup> Reagents and conditions: (a) (-)-(Ipc)<sub>2</sub>BOMe for the *anti*-**5** series and (+)-(Ipc)<sub>2</sub>BOMe for the *syn*-**5** series, CH<sub>2</sub>CMeCH<sub>2</sub>Li, Et<sub>2</sub>O, -78 °C; (b) NaH, MeI, THF; (c) PPTS, MeOH/H<sub>2</sub>O, 50 °C; (d) TBSCl, imid, CH<sub>2</sub>Cl<sub>2</sub>; (e) BzCl, py; (f) aq 3 N HCl; (g) Dess-Martin periodinane, CH<sub>2</sub>Cl<sub>2</sub>; (h) NaH<sub>2</sub>PO<sub>4</sub>, NaClO<sub>2</sub>, 2-methyl-2-butene, *t*-BuOH/H<sub>2</sub>O; (i) O<sub>3</sub>, CH<sub>2</sub>Cl<sub>2</sub>; Me<sub>2</sub>S; (j) TsOH, CH(OMe)<sub>3</sub>, MeOH; (k) SOCl<sub>2</sub>, benzene; Et<sub>2</sub>NH; (l) *sec*-BuLi, CuBr·SMe<sub>2</sub>, allylBr, THF, -78 °C; (m) BBr<sub>3</sub>, CH<sub>2</sub>Cl<sub>2</sub>,  $-78 \rightarrow 25$  °C; (n) Me<sub>3</sub>OBF<sub>4</sub>, CH<sub>2</sub>Cl<sub>2</sub>; Na<sub>2</sub>CO<sub>3</sub>, MeOH; (o) PMBCl, Bu<sub>4</sub>NI, K<sub>2</sub>CO<sub>3</sub>, DMF, 80 °C; (p) cat. OsO<sub>4</sub>, NMO, THF/H<sub>2</sub>O; NaIO<sub>4</sub>, aq MeOH (q) **15**, PhMe, -15 °C; (r) TBSOTf, 2,6-lutidine, CH<sub>2</sub>Cl<sub>2</sub>, 0 °C; (s) O<sub>3</sub>, CH<sub>2</sub>Cl<sub>2</sub>; Ph<sub>3</sub>P; (t) Ac<sub>2</sub>O, Et<sub>3</sub>N, DMAP, CH<sub>2</sub>Cl<sub>2</sub>, 0 °C; (u) *N,N'*-(1*R*,2*R*-cyclohexane-1,2-diylbis(trifluoromethanesulfonamide), Ti(O'Pr)<sub>4</sub>, Et<sub>2</sub>Zn, PhMe, -15 °C; (v) TMSCN, ZnI<sub>2</sub>, MeCN, 0 °C; aq 1 N HCl.

(CHO  $\rightarrow$  CONEt<sub>2</sub>); (2) *ortho*-metalation/allylation ( $\rightarrow$  **13**);<sup>10</sup> (3) BBr<sub>3</sub>-mediated methyl ether deprotection; (4) methyl ester formation using a protocol reported by Keck;<sup>11</sup> (5) phenol protection; and (6) oxidative double bond cleavage ( $\rightarrow$  **6**).

The synthesis of central fragment **7** commences with the preparation of  $C_2$ -symmetrical diol **17** via allylation of monoprotected dialdehyde **14**<sup>12</sup> using Leighton's silane reagent **15**,<sup>13</sup> followed by a second allylation of aldehyde **16**, which was unmasked during the workup (Scheme 1C). Monosilylation (**18**) and ozonolysis destroys the symmetry and provides a lactol (trapped as acetate **19**) that differentiates the chain termini. Addition of diethylzinc using conditions reported by Kobayashi<sup>14</sup> gave a secondary alcohol, which was oxidized to ketone **7** after acetate displacement with TMSCN (8 steps, 30% from **14**).<sup>5f</sup>

Scheme 2. Synthesis of 4 Psymberin/Irciniastatin Diastereomers<sup>a</sup>



<sup>*a*</sup> Reagents and conditions: (a) PhBCl<sub>2</sub>, DIPEA, CH<sub>2</sub>Cl<sub>2</sub>, -78 °C; (b) catecholborane, THF, 0 °C; aq 2 N NaOH; (c) TBAF, THF; (d) cat. [PtH(PMe<sub>2</sub>OH)(PMe<sub>2</sub>O)<sub>2</sub>H], EtOH/H<sub>2</sub>O, 80 °C; (e) 10% Pd/C, H<sub>2</sub>, EtOH; (f) Ac<sub>2</sub>O, py; (g) Me<sub>3</sub>OBF<sub>4</sub>, polyvinylpyridine, CH<sub>2</sub>Cl<sub>2</sub>; filter; (h) *anti-* or *syn-***27**, <sup>*i*</sup>Pr<sub>2</sub>NEt, PhMe, 40 °C; then add NaBH<sub>4</sub>, EtOH, 0 °C; (i) LiOH, MeOH.

With the three fragments in hand, the foundation was laid to explore their union via a double convergent coupling strategy (Scheme 2). Treatment of the (*Z*)-chlorophenylboryl enolate derived from **7** with aldehyde **6** yielded one major *syn*-aldol product **20** predicted from enolate facial bias imposed by the  $\beta$ -alkoxy substituent.<sup>15</sup> Reduction of **20** with catecholborane provided lactone **21** directly after basic workup,<sup>16,17</sup> followed by silyl deprotection to alcohol **22**. Crystallographic analysis of crystals obtained from benzyl ether **22a** fully confirmed the assigned structure and relative stereochemistry.<sup>18</sup> Hydrolysis of the nitrile group in **22** with the platinum(II) catalyst of Ghaffar and Parkins<sup>19</sup> yielded amide **23** in >95% yield. Hydrogenolysis (**24**) and peracetylation furnished tetraacetate **25** (>90%, 2 steps).

We had planned to acylate imidate 26 and intercept the incipient acylimidate with a reducing agent but were unable to prepare and handle imidates related to and including 26 using Me<sub>3</sub>OBF<sub>4</sub> as reported.<sup>20</sup> Extensive experimentation identified a uniquely beneficial effect of adding polyvinylpyridine during the imidate formation with Me<sub>3</sub>OBF<sub>4</sub> (soluble pyridine or other amine bases could not substitute for immobilized pyridine). After TLC analysis indicated complete conversion, the reaction mixture was filtered and concentrated, followed by dissolving the crude imidate 26 in toluene and addition of Hunig's base and acid chloride 27 (from 5 with (COCl)<sub>2</sub>). The mixture was heated to 40 °C for 2 h, cooled to 0 °C, and treated with an ethanolic sodium borohydride solution. After workup, the crude compounds were saponified to afford a separable mixture of 28 and epi-28 (71:29 ratio) with acid chloride anti-27 (56% from 25), or an inseparable mixture of 29 and epi-29 (75:25 ratio) with syn-27 (50%). Of the four diastereomers, only spectral data (1H, 13C) recorded for 28 corresponded exactly with those of psymberin<sup>2</sup> (CD<sub>3</sub>OD) and irciniastatin A<sup>1</sup> (CDCl<sub>3</sub>). The

rotation of synthetic **28** ( $[\alpha]_D = +25.2$ , *c* 0.11, MeOH) agreed with those reported for psymberin ( $[\alpha]_D = +29$ , *c* 0.02, MeOH)<sup>2</sup> and irciniastatin A ( $[\alpha]_D = +24.4$ , *c* 0.55, MeOH).<sup>1</sup>

In summary, we prepared compounds with structures relevant to those proposed for psymberin/irciniastatin, leading to a complete stereochemical assignment and the notion that psymberin and irciniastatin A are identical compounds represented by **28**. Starting from fragments 5-7 (7–8 steps each, 30–49% overall yield) the synthesis of **28** was completed in an additional 9 steps and 30% yield (17 steps, 8.9% overall from **14**).

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**Supporting Information Available:** Experimental procedures, characterization data, copies of NMR spectra, and X-ray crystal structure data for compound **22a** (PDF, CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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