

## Asymmetric Total Synthesis of (+)-7-Deoxypancratistatin

Xinrong Tian, Rakesh Maurya, Kurt Königsberger and Tomas Hudlicky\*<sup>1</sup>

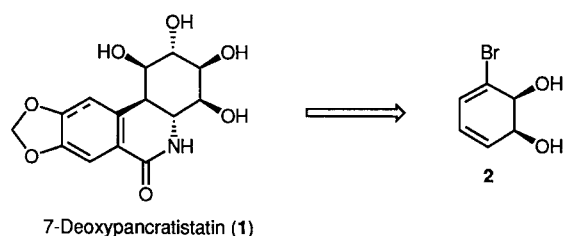
Department of Chemistry, University of Florida, Gainesville, FL32611, USA.

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**Abstract:** An asymmetric synthesis of 7-deoxypancratistatin **1** has been accomplished starting from diol **2** via two pathways in overall yields of 2.6 and 3.0%, respectively. The key step involved the regioselective ring opening of tosylaziridine **3** or the new carbomethoxyaziridine **15** with a higher-order cuprate and the cyclization of urethane **11**.

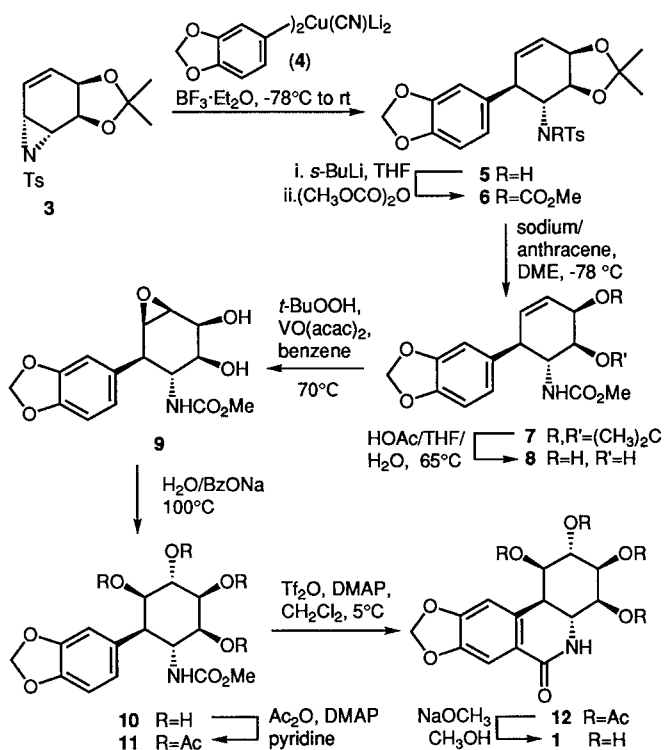
The title alkaloid was isolated in 1989 from *Haemanthus kalmeyeri* by Ghosal<sup>2</sup> and coworkers and has been shown to have a promising therapeutic index in *in vitro* antitumor screening.<sup>3</sup> Synthetic ventures aimed at the efficient preparation of **14** and its congeners, pancratistatin,<sup>5</sup> lycoricidine,<sup>6</sup> and narciclasine<sup>7</sup> abound in the chemical literature, with the most recent synthesis of **1** reported by Keck<sup>4b</sup> and the first asymmetric synthesis of pancratistatin published by our group.<sup>5b</sup>

In this communication we report a short approach to **1** that may be amenable to a large scale preparation of this alkaloid as well as its congeners.



The synthesis sets out from the enantiopure diol **2**<sup>8</sup> prepared from bromobenzene by toluene dioxygenase-mediated whole cell fermentation as previously disclosed.<sup>9</sup> Its conversion to tosylaziridine **3** in three steps was recently reported.<sup>5b</sup> To circumvent the problems associated with the manipulations of benzamide, which plagued our first generation effort toward pancratistatin,<sup>5b</sup> we decided to introduce the amide in **1** as a last step. Addition of higher-order cuprate **4** derived from 6-bromo-1,3-benzodioxol to aziridine **3** provided the crucial *trans*-substituted tosylamide **5** ( $\text{BF}_3 \cdot \text{Et}_2\text{O}$ ,  $-78^\circ\text{C}$  to rt, 32%). The low yield of this coupling may be due to the low stability of the organolithium compound and the corresponding cuprate, compared to the ortho-amide stabilized organolithium compounds and derived higher order cuprates previously employed in this reaction.<sup>5b</sup> Acylation with dimethyl pyrocarbonate gave the urethane **6** (76%) which was reduced to **7** (73%), Scheme 1. Deprotection to the free diol **8** (98%) followed by epoxidation to **9** (50%) and stereoselective ring opening of the epoxide with water in the presence of a catalytic amount of sodium benzoate provided the aryl aminocyclitol **10** in 82% yield. After peracetylation, furnishing the cyclization precursor **11** (84%), we chose the conditions reported by Banwell for the Bischler-Napieralski type cyclization.<sup>10</sup> Exposure of **11** to  $\text{TiF}_4/\text{DMAP}$  gave tetraacetate **12** (61%), which was isolated and proved identical to the compound prepared by Keck ( $[\alpha]_{\text{D}}^{25} = +78.5^\circ$  (c 0.75, DMF); lit.<sup>4a</sup>  $[\alpha]_{\text{D}}^{20} = +82.6^\circ$  (c 1.1, DMF)).

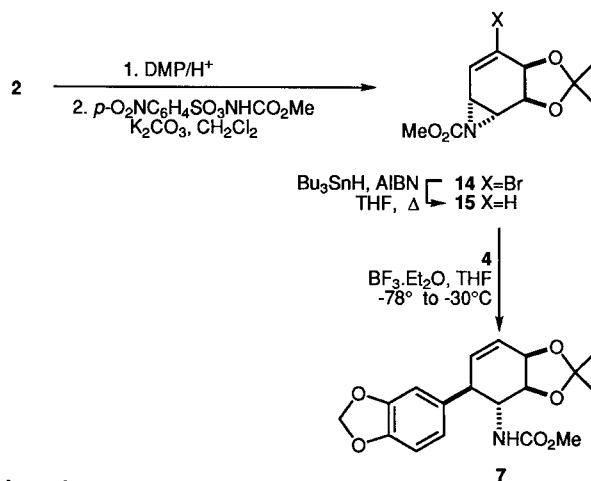
The synthesis of **1** was thus accomplished in nine steps from aziridine **3** (twelve steps from bromobenzene diol **2**) in an overall yield of 2.6 % from **2**. This approach solved adequately the problem of benzamide manipulation encountered during our previous synthesis of pancratistatin.<sup>5b</sup> However, the second problem, manipulation of the tosyl group or its replacement with the carbamate necessary for the cyclization remained.



Scheme 1

To reduce the number of functional group interconversions we prepared the new aziridine **14**, as shown in scheme 2, by adaption of a procedure used for the carboethoxyaziridination of simple olefins.<sup>11</sup> Thus, after protection of **2** as the acetone (2,2-dimethoxypropane, *p*-TSA) aziridine **14** was obtained in 80 % yield with methyl *p*-nitrophenylsulfonyloxycarbamate<sup>12</sup> /  $\text{K}_2\text{CO}_3$  and reduced to **15** with  $\text{Bu}_3\text{SnH}/\text{AIBN}$  in 54% yield. Addition of the organocuprate **4** in the presence of  $\text{BF}_3 \cdot \text{Et}_2\text{O}$  gave **7** in 34% yield and four steps from **2** overall.

In conclusion, the second generation approach to **1** addressed the major problems encountered in the synthesis of pancratistatin.<sup>5b</sup> 7-



Scheme 2

Deoxypancratistatin has been made in 12 steps via tosylamide **3** (2.6% overall yield) and in 10 steps via the new aziridine **15** (3.0% unoptimized overall yield). Applications of this protocol to the efforts aimed at an improved practical synthesis of pancratistatin and its congeners are ongoing and will be reported in due course.

#### Selected Experimental Procedures:

##### N-[(3a*S*,4*R*,5*R*,7a*R*)-5-(1,3-Benzodioxol-5-yl)-2,2-dimethyl-3a,4,5,7a-tetrahydrobenzodioxol-4-yl]-4-methylbenzenesulfonamide (**5**).

*n*-BuLi (1.94 M in hexane, 10 mL) was added to a solution of 5-bromo-1,3-benzodioxol (16.6 mmol) in THF (65 mL) at -78 °C. The reaction mixture was stirred for 40 min at -78 °C and CuCN (744 mg, 8.3 mmol) was added. After stirring at -78 °C for 1h, a solution of aziridine **3** (1.27g, 3.95 mmol) in THF (10 mL) was added, followed by BF<sub>3</sub>·Et<sub>2</sub>O (0.40 mL). The reaction mixture was allowed to warm slowly to room temperature while stirring. After addition of saturated aqueous NH<sub>4</sub>Cl solution (10 mL), the organic layer was separated and the aqueous phase was extracted with ethyl acetate (4x10 mL). The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, CH<sub>2</sub>Cl<sub>2</sub>/acetone, 12:1) to give tosylamide **5** (552 mg, 32%) as a white solid: mp 75-76 °C; [ $\alpha$ ]<sub>D</sub><sup>22</sup> +44.6° (c 1.16, CHCl<sub>3</sub>); <sup>1</sup>H NMR (200 MHz, CHCl<sub>3</sub>)  $\delta$  7.43 (d, *J*=8.2 Hz, 2H), 7.09 (d, *J*=8.2 Hz, 2H), 6.49 (m, 3H), 5.95 (m, 3H), 5.76 (dd, *J*=9.9, 1.6 Hz, 1H), 5.34 (d, *J*=8.5 Hz, 1H), 4.61(t, *J*=4.46 Hz, 1H), 4.13(dd, *J*=9.1, 6.0 Hz, 1H), 3.51(q, *J*=9.2 Hz, 1H), 3.13 (bd, *J*=9.8 Hz, 1H), 2.38 (s, 3H), 1.50 (s, 3H), 1.35 (s, 3H); <sup>13</sup>C NMR (50 MHz, C<sub>6</sub>D<sub>6</sub>)  $\delta$  147.9 (C), 146.9 (C), 141.6 (C), 140.6 (C), 135.1 (CH), 135.0 (C), 129.0 (CH), 126.9 (CH), 124.3 (CH), 122.3 (CH), 109.9 (C), 109.2 (CH), 108.4 (CH), 100.7 (CH<sub>2</sub>), 78.2 (CH), 72.7 (CH), 59.6 (CH), 47.5 (CH), 28.3 (CH<sub>3</sub>), 26.3 (CH<sub>3</sub>), 21.1 (CH<sub>3</sub>); HRMS: calcd for C<sub>23</sub>H<sub>25</sub>O<sub>6</sub>NS 443.1403, found 443.1416.

##### Methyl (1*R*,4*S*,5*S*,6*R*)-3-bromo-4,5-isopropylidenedioxy-7-azabicyclo[4.1.0]hept-2-ene-7-carboxylate (**14**).

To (1*S*,2*S*)-3-Bromocyclohexa-3,5-diene-1,2-diol (0.50 g, 2.16 mmol) in dry dichloromethane (20 mL) were added 2,2-dimethoxypropane (0.50 g, 4.8 mmol) and *p*-TsOH (10 mg). After stirring for 60 min. at room temperature, the turbid solution was washed with 1N NaOH (2 x 10 ml) and brine (10 ml). The solution was dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated in vacuo to afford the pure acetonide. Potassium carbonate (1.79g, 13.0 mmol) was added to a solution of methyl *p*-nitrophenylsulfonyloxycarbamate (3.59g, 13.0 mmol) and the freshly prepared acetonide in dry dichloromethane (20 mL) and stirred vigorously for 4 hours at rt. After filtration and concentration in vacuo, chromatographic purification (silica gel, hexane/EtOAc, 80:20) afforded 530 mg (80.5%) of colorless oil: <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  6.48 (dd, *J*=1.4, 5.0 Hz, 1H), 4.90 (ddd, *J*=6.1, 1.9, 0.8 Hz, 1H), 4.48 (dd, *J*=6.3, 1.4 Hz, 1H), 3.75 (s, 3H), 3.20 (dd, *J*=5.8, 1.6 Hz, 1H), 2.98 (t, *J*=4.9 Hz, 1H), 1.45 (s, 3H), 1.42 (s, 3H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>)  $\delta$  161.9, 128.3, 125.7, 111.2, 73.8, 72.2, 53.9, 35.3, 34.9, 27.5, 26.1; HRMS calcd for C<sub>11</sub>H<sub>15</sub>NBrO<sub>4</sub> 304.0184, found 304.0185; Anal. calcd for C<sub>11</sub>H<sub>15</sub>NBrO<sub>4</sub> C 43.44%, H 4.63%, N 4.60%, found C 43.64%, H 4.73%, N 4.55%.

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