

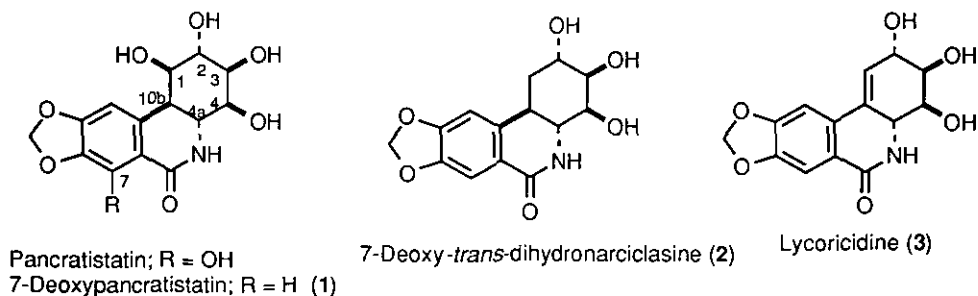
TOTAL SYNTHESIS OF (+)-7-DEOXYPANCRATISTATIN AND  
(+)-7-DEOXY-*trans*-DIHYDRONARCICLASINE

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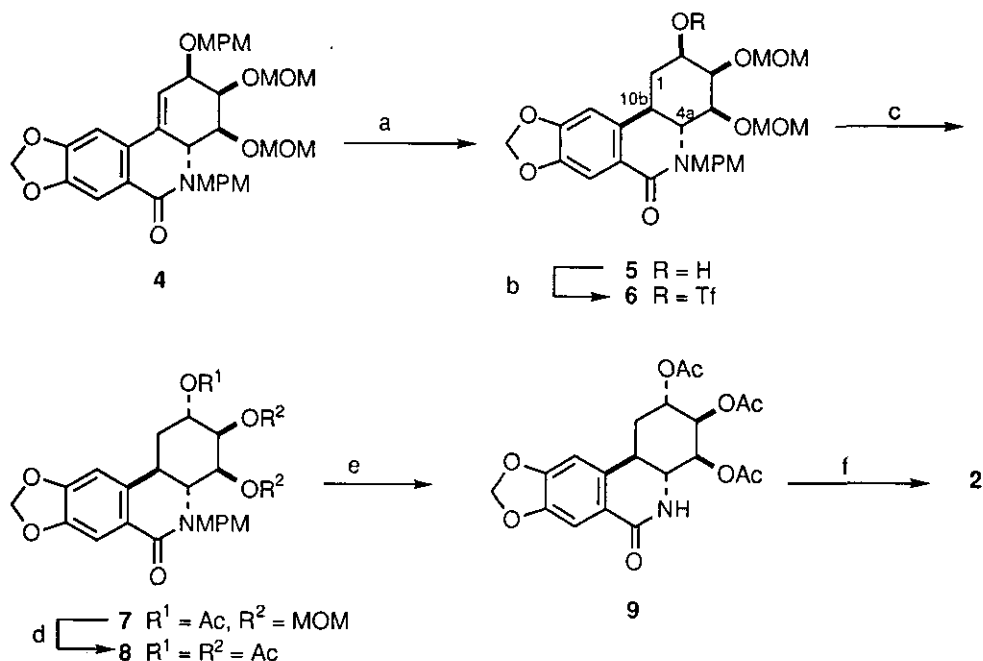
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**Abstract-** The chiral and stereoselective synthesis of antimitotic phenanthridone alkaloids, (+)-7-deoxypancratistatin (**1**) and (+)-7-deoxy-*trans*-dihydronarciclasine (**2**) is described. Both natural products were synthesized from the common compound (**4**), which had been prepared from D-glucose and employed for the synthesis of lycoricidine (**3**).

The highly oxygenated phenanthridone alkaloids,<sup>1</sup> represented by pancratistatin,<sup>2a</sup> 7-deoxypancratistatin (**1**),<sup>2b</sup> 7-deoxy-*trans*-dihydronarciclasine (**2**),<sup>2c</sup> and lycoricidine (**3**)<sup>2d</sup> isolated from *Amaryllidaceae* plants are known to show wide range of biological activities such as antineoplastic,<sup>2c</sup> antiviral<sup>3</sup> and plant growth regulatory activities.<sup>2b</sup> Their interesting biological activity as well as challenging structures which embody four to six contiguous chiral centers on the cyclohexane ring attracted much attention, and a number of synthetic study of these alkaloids have appeared to date.<sup>4,5</sup> Very recently, asymmetric total syntheses of pancratistatin<sup>5b</sup> and 7-deoxypancratistatin<sup>5e,f</sup> have been reported. In this communication, we describe the chiral and stereoselective total synthesis of (+)-7-deoxypancratistatin (**1**) and (+)-7-deoxy-*trans*-dihydronarciclasine (**2**). Our synthetic tactic for the synthesis of **1** and **2** is based on the utilization of the common precursor (**4**), which had been effectively prepared from D-glucose and served as the key intermediate in our previous total synthesis of lycoricidine (**3**).<sup>5g</sup> Hydrogenation of **4**, which was prepared in an optically pure form from D-glucose<sup>5g</sup> using Ferrier's carbocyclization reaction<sup>6</sup> and palladium catalyzed cyclization as the key steps, in the presence of Pd on



carbon proceeded in a highly stereoselective manner and gave the desired product, 4a–10b *trans* isomer (5)<sup>7</sup> as the sole product in 87% yield (Scheme 1). The observed coupling constants in 5 ( $J_{1,10b} = 12.1$ ,  $J_{4a,10b} = 10.4$  Hz) clearly showed that the addition of hydrogen to the double bond took place from the less hindered  $\alpha$ -face, exclusively. The *O*-MPM group was simultaneously deprotected under this reaction condition.

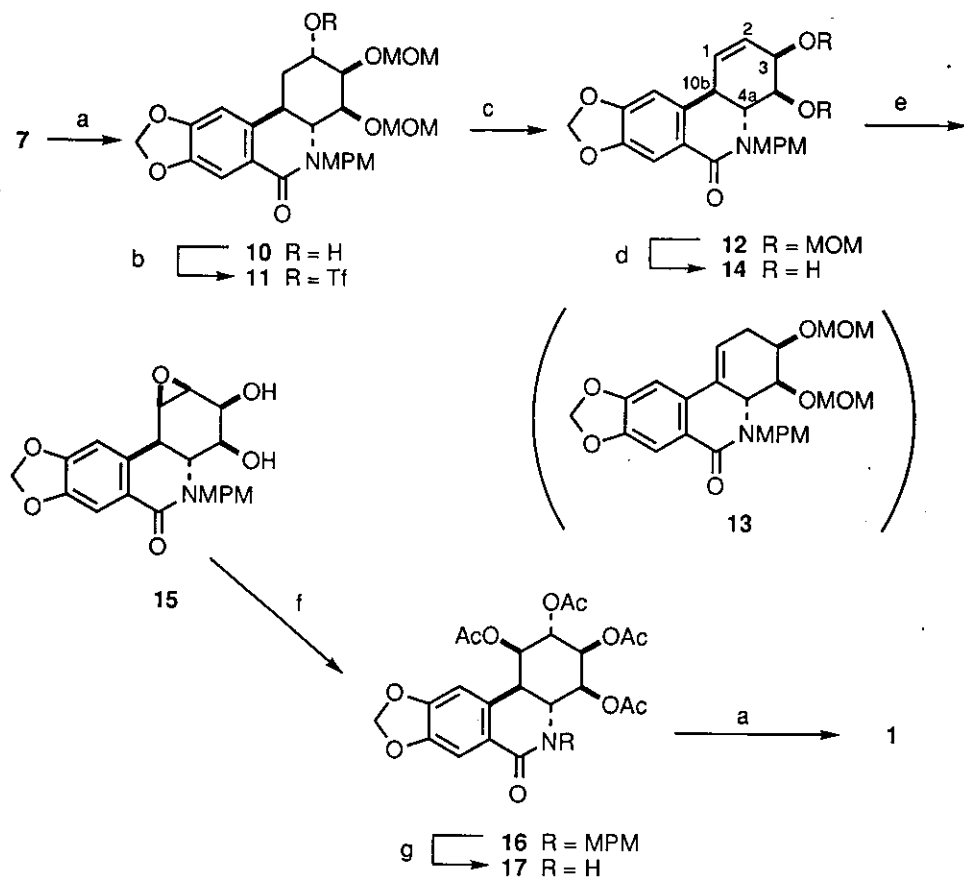


**Scheme 1.** MPM =  $-\text{CH}_2\text{C}_6\text{H}_4(p\text{-OMe})$ , MOM =  $-\text{CH}_2\text{OMe}$ , Tf =  $-\text{SO}_2\text{CF}_3$ . Reagents and conditions: a,  $\text{H}_2$ , 5% Pd on carbon, EtOH–EtOAc (14:1), room temperature; b,  $\text{Ti}_2\text{O}$ , pyridine,  $\text{CH}_2\text{Cl}_2$ , 0 °C; c, KOAc (5 equiv.), 18-crown-6 (2 equiv.), benzene, room temperature; d, tetrahydrofuran–1 N aq. HCl (1:1), 50 °C, then  $\text{Ac}_2\text{O}$ , pyridine, room temperature; e, TFA– $\text{CHCl}_3$  (1:1), room temperature; f, MeONa, MeOH, 0 °C.

The resulting alcohol (**5**) was converted into triflate (**6**), which, without isolation, was reacted with KOAc in benzene to provide inverted acetate (**7**) in 81% yield from **5**. Removal of the *O*-MOM group followed by acetylation afforded triacetate (**8**) in 93% yield. The *N*-MPM group in **8** was cleanly deprotected by the action of trifluoroacetic acid (TFA) to give **9** (85% yield), whose *O*-acetyl group was detached to provide 7-deoxy-*trans*-dihydronarciclasine (**2**) in 83% yield. The physical {mp 298-303 °C;  $[\alpha]_D^{23} +125$  (*c* 0.8, DMSO); lit.,<sup>2c</sup> mp 303-304 °C;  $[\alpha]_D^{25} +138$  (*c* 0.8, DMSO)} and <sup>1</sup>H nmr spectral data of synthetic **2** showed good accord with those reported for the natural product.<sup>2c</sup>

Having achieved the stereoselective construction of the C-10b stereocenter, which culminated in the synthesis of **2**, we then turned to the total synthesis of **1** via **7** (Scheme 2). Treatment of **7** with sodium methoxide gave **10** (98% yield), which was converted into triflate (**11**). When compound (**11**) was treated with organic base (1,8-diazabicycloundecene or triethylamine), formation of the C-10b epimer of compound (**12**) and conjugated olefin (**13**) (30-45% combined yield) was observed and the desired **12** was isolated in low yield (less than 6%). However, reaction of **11** with KOAc in benzene in the presence of 18-crown-6 afforded olefin (**12**) in 81% yield from **10**.<sup>8</sup> The *O*-MOM group in **12** was removed by acidic hydrolysis to give diol (**14**) in 92% yield. Epoxidation of **14** with *m*-chloroperbenzoic acid (mCPBA) in CH<sub>2</sub>Cl<sub>2</sub>-phosphate buffer<sup>9</sup> (pH 8) generated single epoxide (**15**)<sup>10</sup> (46% yield). Reaction of **15** with sodium acetate in DMF caused the *trans* diaxial opening of the epoxide ring with acetate anion and provided **16** as the sole product in 51% yield after acid catalyzed *O*-acetylation.<sup>11</sup> Removal of the *N*-MPM group was achieved by hydrogenolysis in acidic media to afford tetra-*O*-acetyl-7-deoxypancratistatin (**17**) in 83% yield. The spectral (<sup>1</sup>H and <sup>13</sup>C nmr) property of **17** was fully identical with those reported for the authentic sample,<sup>5d</sup> and the specific rotational value of **17** { $[\alpha]_D^{21} +66$  (*c* 0.26, CHCl<sub>3</sub>); lit.,<sup>5d</sup>  $[\alpha]_D^{20} +68.4$  (*c* 1.0, CHCl<sub>3</sub>)} was also in good agreement with the reported value. Finally, basic methanolysis of **17** provided 7-deoxypancratistatin (**1**) in 85% yield. Again, physical { $[\alpha]_D^{19} +80$  (*c* 0.18, DMF); lit.,  $[\alpha]_D^{20} +82.6$  (*c* 1.1, DMF),<sup>5d</sup>  $+78.5$  (*c* 0.75, DMF)<sup>5f</sup>} and <sup>13</sup>C nmr spectral data (in DMSO-*d*<sub>6</sub>) of synthetic **1** showed a good accord with those reported for the authentic compound.<sup>5d</sup>

In summary, stereoselective synthetic pathway to **1** and **2** has been established. This work revealed that compound **4**, derived from D-glucose, should be an effective common precursor for the chiral synthesis of a variety of natural phenanthridone alkaloids.



**Scheme 2.** *Reagents and conditions:* a, MeONa, MeOH, 0 °C.; b, Tf<sub>2</sub>O, pyridine, CH<sub>2</sub>Cl<sub>2</sub>, 0 °C.; c, KOAc (5 equiv.), 18-crown-6 (2 equiv.), benzene, room temperature; d, tetrahydrofuran–1 N aq. HCl (1:1), 50 °C; e, mCPBA, (ClCH<sub>2</sub>)<sub>2</sub>–phosphate buffer (1 M, pH 8) (1:1), 50 °C; f, NaOAc (3 equiv.), DMF–H<sub>2</sub>O (4:1), 60 °C, then Ac<sub>2</sub>O, ZnCl<sub>2</sub>, room temperature; g, H<sub>2</sub>, 5% Pd on carbon, catalytic amount of 1 N aq. HCl, EtOH, room temperature.

## ACKNOWLEDGMENT

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  7. All new compounds described were characterized by 270 MHz  $^1\text{H}$  nmr, ir and mass spectrometric and/or elemental analyses.
  8. Attempts to convert **5** or **6** into **12** were unsuccessful. For example, base treatment of **6** gave  $\Delta^{2,3}$  isomer of compound **12**.
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  10. The configuration of the epoxide ring in **15** is not determined but has been tentatively assigned to be  $\beta$  as depicted in Scheme 2, on consideration of the directive effect of the C-3 hydroxy group.
  11. When *O*-acetylation was carried out with acetic anhydride-pyridine, significant amount of eliminated product (*N*-MPM lycoricidine triacetate) was formed.

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