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

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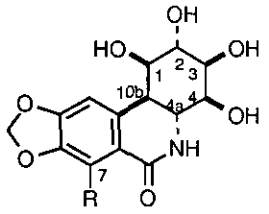
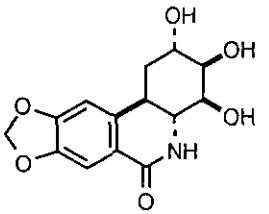
Abstract- The chiral and stereoselective synthesis of antimitotic phenanthridone alkaloids, (+)-7-deoxypancratistatin (**1**) and (+)-7-deoxy-*trans*-dihydronarciclasine (**2**) is described. Both natural products were synthesized from the common compound (**4**), which had been prepared from D-glucose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

The highly oxygenated phenanthridone alkaloids,[1] represented by pancratistatin,[2a] 7-deoxypancratistatin (**1**),[2b] 7-deoxy-*trans*-dihydronarciclasine (**2**),[2c] and lycoricidine (**3**)[2d] isolated from *Amaryllidaceae* plants are known to show wide range of biological activities such as antineoplastic,[2c] antivirus[3] and plant growth regulatory activities.[2b] 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.[4,5] Very recently, asymmetric total syntheses of pancratistatin[5b] and 7-deoxypancratistatin[5e,f] 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**).[5g]

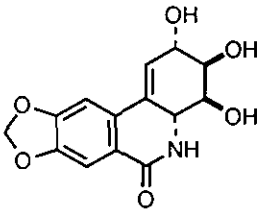
Hydrogenation of **4**, which was prepared in an optically pure form from D-glucose[5g] using Ferrier's carbocyclization reaction[6] and palladium catalyzed cyclization as the key steps, in the presence of Pd on



Pancratistatin; R = OH
7-Deoxypancratistatin; R = H (1)

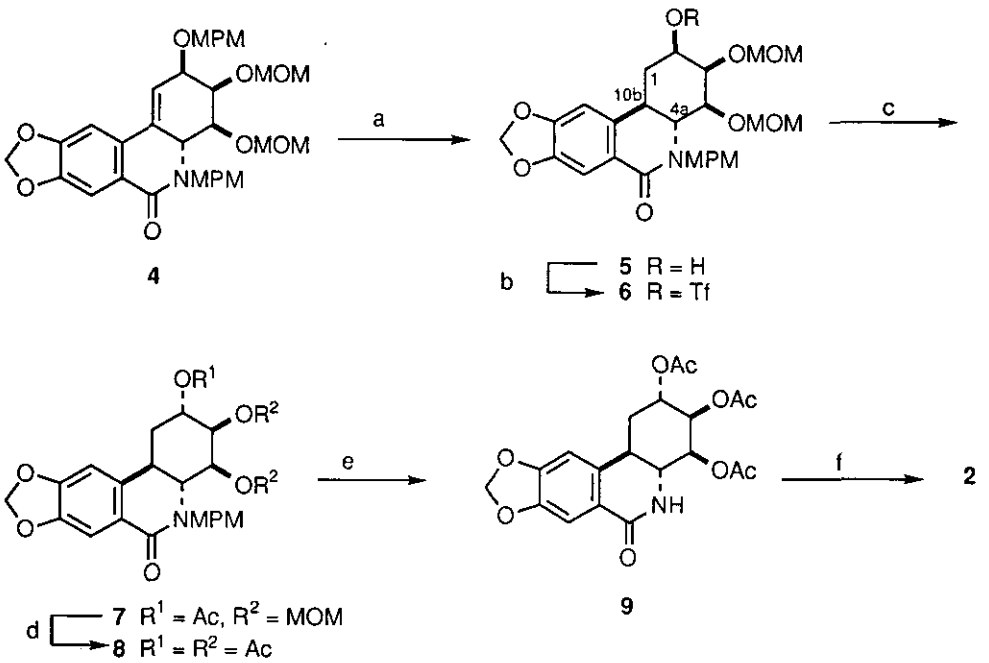


7-Deoxy-*trans*-dihydronarciclasine (2)



Lycoricidine (3)

carbon proceeded in a highly stereoselective manner and gave the desired product, 4a–10b trans isomer (**5**)[7] 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 α-face, exclusively. The *O*-MPM group was simultaneously deprotected under this reaction condition.

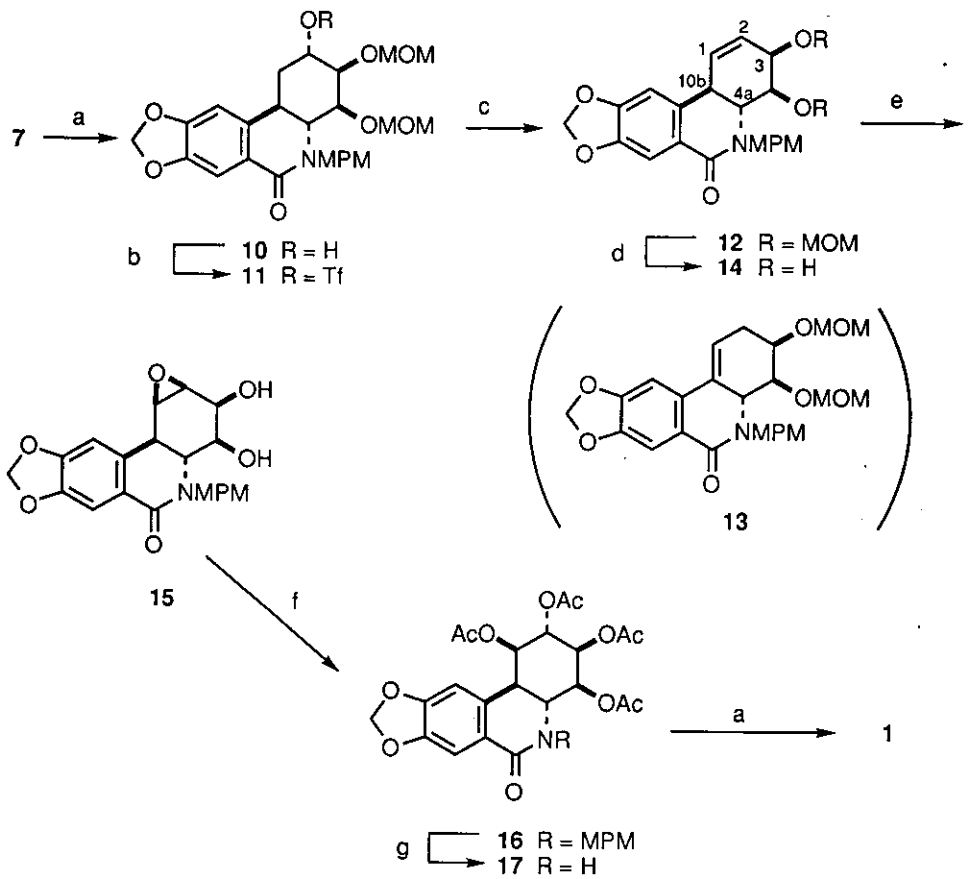


Scheme 1. MPM = -$CH_2C_6H_4$(*p*-OMe), MOM = -CH_2OMe, Tf = -SO_2CF_3. *Reagents and conditions:* a, H_2, 5% Pd on carbon, EtOH–EtOAc (14:1), room temperature; b, Tf_2O, pyridine, CH_2Cl_2, 0 °C; c, KOAc (5 equiv.), 18-crown-6 (2 equiv.), benzene, room temperature; d, tetrahydrofuran–1 N aq. HCl (1:1), 50 °C, then Ac_2O, pyridine, room temperature; e, TFA–$CHCl_3$ (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.,[2c] mp 303-304 °C; $[\alpha]_D^{25}$ +138 (*c* 0.8, DMSO)} and ^{1}H nmr spectral data of synthetic **2** showed good accord with those reported for the natural product.[2c]

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**.[8] 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_2Cl_2–phosphate buffer[9] (pH 8) generated single epoxide (**15**)[10] (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.[11] 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 (^{1}H and ^{13}C nmr) property of **17** was fully identical with those reported for the authentic sample,[5d] and the specific rotational value of **17** {$[\alpha]_D^{21}$ +66 (*c* 0.26, $CHCl_3$); lit.,[5d] $[\alpha]_D^{20}$ +68.4 (*c* 1.0, $CHCl_3$)} 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),[5d] +78.5 (c 0.75, DMF)[5f]} and ^{13}C nmr spectral data (in DMSO-d_6) of synthetic **1** showed a good accord with those reported for the authentic compound.[5d]

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_2O, pyridine, CH_2Cl_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; e, mCPBA, $(ClCH_2)_2$–phosphate buffer (1 M, pH 8) (1:1), 50 °C; f, NaOAc (3 equiv.), DMF–H_2O (4:1), 60 °C, then Ac_2O, $ZnCl_2$, room temperature; g, H_2, 5% Pd on carbon, catalytic amount of 1 N aq. HCl, EtOH, room temperature.

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7. All new compounds described were characterized by 270 MHz ^{1}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 β 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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