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Stereoselective Total Synthesis of (+)-Lycoricidine

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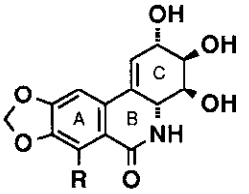
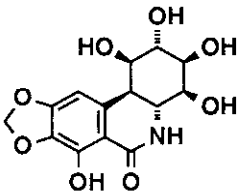
Abstract: *The stereoselective total synthesis of the title compound starting from D-glucose is described. The key steps in this synthesis are Ferrier rearrangement to construct the optically active cyclohexenone (C-ring), and Pd-catalyzed intramolecular Heck reaction to build the phenanthridone skeleton.*

The phenanthridone alkaloid family, (+)-lycoricidine (**1**)[1], narciclasine[2], and pancratistatin[3], attracted the attention because of their powerful antimitotic and cytotoxic activities. (+)-Lycoricidine triacetate (**17**) is also reported to possess antiviral activity.[4] The structures of these compounds which include the phenanthridone skeleton with four or six contiguous asymmetric centers are synthetically interesting and challenging, therefore, several reports concerning the total syntheses[5] and synthetic approaches[6] have appeared so far. In this communication, we wish to report the stereoselective total synthesis of (+)-lycoricidine (**1**) starting from D-glucose.



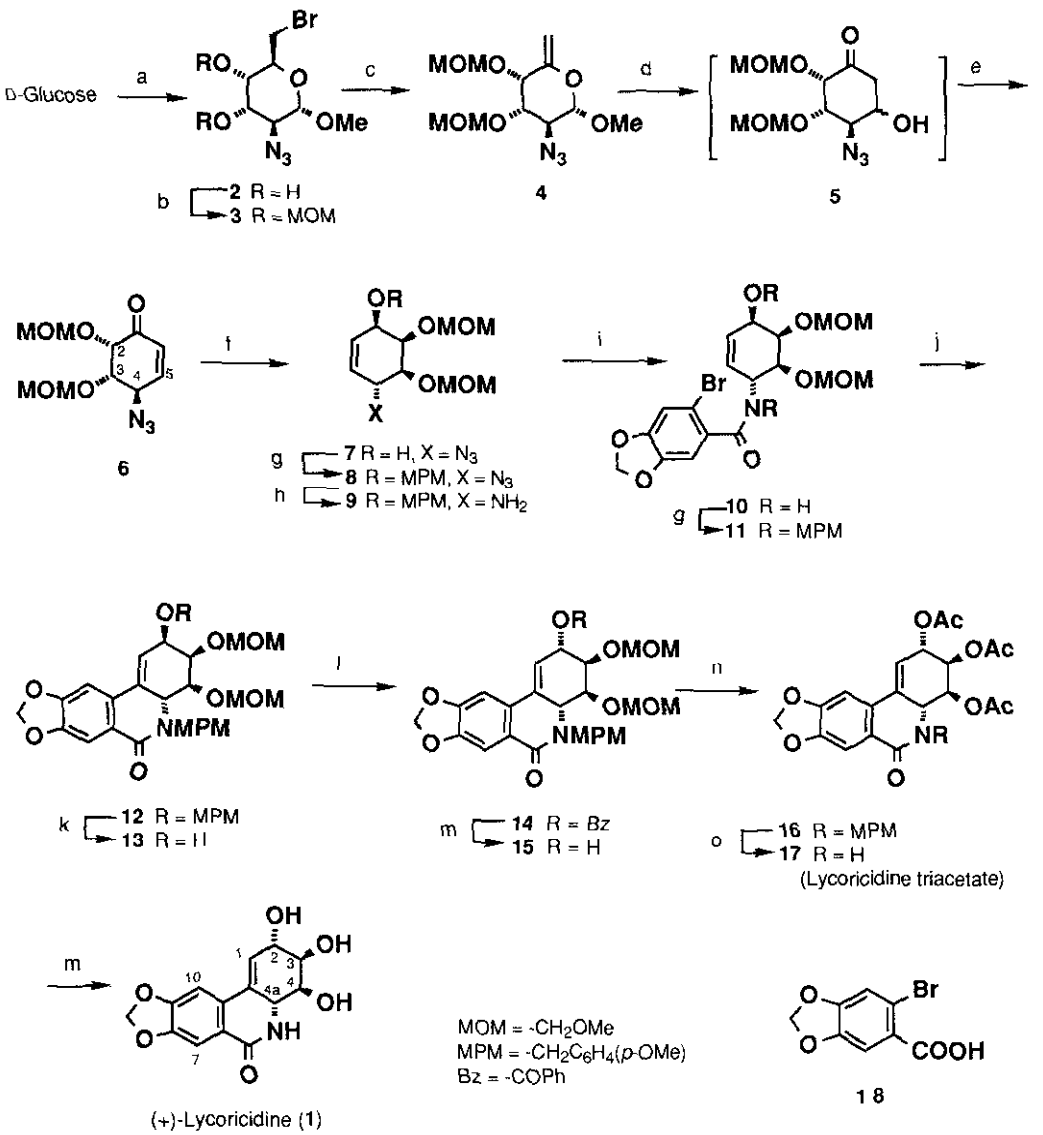
R = H: (+)-Lycoricidine (**1**)
R = OH: Narciclasine



Pancratistatin

Our synthetic analysis suggested that the phenanthridone skeleton might be effectively constructed by Pd-catalyzed cyclization (Heck reaction)[7] of bromo-olefin (**10** or **11**), and the C-ring of lycoricidine possessing four chiral centers could be prepared in a homochiral form utilizing Ferrier rearrangement[8] of 5-enopyranoside (**4**), which would be obtained stereoselectively from D-glucose.

The known diol (**2**),[9] prepared from D-glucose stereoselectively in 7 steps, was chosen as a starting material. The hydroxyl groups in **2** were protected as di-methoxymethyl ethers, and the resulting compound **3** (90% yield) was treated with DBU in refluxing toluene to afford 5-enopyranoside (**4**) in 77% yield. Catalytic Ferrier rearrangement of **4** with mercuric trifluoroacetate (1 mol %) in acetone-water (r t , 20 h)[10]



Scheme. a) see ref 9; b) MOMCl, iPr_2NEt, CH_2Cl_2; c) DBU, toluene, reflux; d) $(CF_3CO_2)_2Hg$ (1 mol%), acetone-water (2:1), rt; e) MsCl, Et_3N, CH_2Cl_2; f) $NaBH_4$, $CeCl_3 \cdot 7H_2O$, MeOH; g) NaH, MPMCl, DMF; h) $LiAlH_4$, ether; i) 6-bromopiperonylic acid (**18**), $(EtO)_2P(O)CN$, Et_3N, DMF; j) $Pd(OAc)_2$ (20 mol%), DIPHOS (40 mol%), TlOAc (2 mol. equiv.), DMF, 140 °C; k) DDQ, CH_2Cl_2-H_2O (19:1); l) Ph_3P, diethyl azodicarboxylate, benzoic acid, THF; m) MeONa, MeOH, rt; n) 1M HCl aq-THF (1:1), 50 °C, then Ac_2O, pyridine; o) CF_3COOH-$CHCl_3$ (1:1), rt 2 h.

provided a cyclohexanone derivative (**5**). Without purification, compound **5** was dehydrated by the action of methanesulfonyl chloride and triethylamine to give the cyclohexenone (**6**), which embodies three contiguous chiral centers corresponding to C-3, 4 and 4a of lycoricidine, in 69% yield from **4**. Reduction of the carbonyl group in **6** with $NaBH_4$-$CeCl_3$[11] in MeOH proceeded highly stereoselectively, and compound **7**

was obtained as a single product in 86% yield. The hydroxyl group in **7** was protected as a *p*-methoxybenzyl ether to give **8** in 60% yield. Reduction of the azido group in **8** with $LiAlH_4$ provided an amine (**9**), which was then condensed with 6-bromopiperonylic acid (**18**)[12] under the conditions of Shioiri's protocol[13] to give an amide (**10**) in 89% overall yield from **8**. With the bromo-olefin (**10**) in hand, Pd-catalyzed cyclization of **10** was attempted [$Pd(OAc)_2$ (20 mol%), Ph_3P (50 mol%), Et_3N (2 equiv), Ag_2CO_3 (2 equiv) CH_3CN, reflux],[14] however, no desired product was obtained. The unidentified aromatized products and the starting material were isolated. We then turned to try the cyclization reaction with the *N*-protected derivative (**11**). The amide nitrogen in **10** was alkylated with *p*-methoxybenzyl chloride in the presence of NaH to give the fully protected amide (**11**),[15] quantitatively. The crucial cyclization reaction of **11** proceeded successfully under the similar conditions of modified Heck reaction recently reported by Grigg and co-workers.[16] Thus, treatment of compound **11** with $Pd(OAc)_2$ (20 mol %), 1,2-bis(diphenylphosphino)ethane (DIPHOS) (40 mol%), and Tl(OAc) (2 equiv.) in DMF at 140 °C for 48 h afforded the product possessing the phenanthridone skeleton (**12**) in 68 % yield.[15,17] No other diastereoisomers could be found in the reaction mixture. Removal of the *O*-MPM group in **12** (DDQ, wet CH_2Cl_2)[18] afforded the allyl alcohol (**13**) in 53% yield. Mitsunobu reaction[19] of **13** with benzoic acid generated the benzoate (**14**), possessing the correct stereochemistry for (+)-lycoricidine in 68% yield. The *O*-benzoyl group in **14** was deprotected to give the allyl alcohol (**15**). Acid hydrolysis of *O*-MOM group in **15** (THF-aqueous HCl), followed by conventional acetylation (Ac_2O, pyridine) afforded the triacetate (**16**)[15] in 49% yield from compound **14**. Exposure of **16** to trifluoroacetic acid in $CHCl_3$[20] (rt, 2 h) removed the *N*-MPM group to afford (+)-lycoricidine triacetate (**17**) in 53% yield. The spectral (^1H and ^{13}C NMR) and physical properties {mp 233-235 °C, $[\alpha]_D^{24}$ +238 ° ($CHCl_3$)} of synthetic **17** were in good accordance with those reported by Paulsen[5c] {mp 236-237 °C, $[\alpha]_D^{20}$ + 214 ° ($CHCl_3$)}. Finally, *O*-acetyl group was removed by the treatment with MeONa in MeOH to generate (+)-lycoricidine (**1**), quantitatively. Again, the spectral (^1H and ^{13}C NMR) and physical data of the synthetic specimen {mp 217-221 °C (dec), $[\alpha]_D^{23}$ +199 ° (pyridine)} showed a good accordance with those reported for the authentic compound {mp 214.5-215.5 °C (dec),[1] 224-226 °C (dec),[5c] $[\alpha]_D^{20}$ + 180 ° (pyridine)[5c]}.

In summary, the stereoselective total synthesis of (+)-lycoricidine (**1**) starting from D-glucose has been achieved. This synthesis proceeded in 17 steps from the known compound (**2**), and revealed that Ferrier rearrangement should be very useful for chiral syntheses of natural products having substituted cyclohexane rings. This approach also proved that intramolecular Heck reaction is effective for the construction of the phenanthridone skeleton.

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15. All new compounds were characterized by 270 MHz ^{1}H NMR, IR and mass spectrometric and/or elemental analyses. Selected spectral and physical data for **11**: $[\alpha]_D^{21}$ -141 ° (c 0.25, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.40 and 7.23 (2d, each 2H, J = 8.4 Hz), 6.90 (d, 2H, J = 8.8 Hz), 6.85 (s, 2H), 6.82 (d, 2H, J = 8.8 Hz), 5.95 and 5.89 (2d, each 1H, J = 1.3 Hz), 5.62 (s, 2H), 4.93 (d, 1H, J = 15.2 Hz), 4.67 (m, 1H), 4.65 (d, 1H, J = 7.1 Hz), 4.59 (s, 2H), 4.53 (s, 2H), 4.28 (m, 1H), 4.24 (d, 1H, J = 15.2 Hz), 4.22 (d, 1H, J = 7.1 Hz), 4.04 (dd, 1H, J = 3.3 and 3.3 Hz), 3.80 and 3.80 (2s, each 3H), 3.72 (dd, 1H, J = 9.5 and 1.5 Hz), 3.41 and 3.17 (2s, each 3H). For **12**: $[\alpha]_D^{22}$ -32 ° (c 0.7, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.53 (s, 1H), 7.30 and 7.11 (2d, each 1H, J = 8.8 Hz), 6.96 (s, 1H), 6.89 and 6.80 (2d, each 1H, J = 8.8 Hz), 6.02 and 6.01 (2d, each 1H, J = 1.3 Hz), 5.99 (m, 1H), 5.19 and 4.97 (2d, each 1H, J = 16.1 Hz), 4.77 (s, 2H), 4.74 (d, 1H, J = 6.8 Hz), 4.72 (m, 1H), 4.67 and 4.59 (2d, each 1H, J = 11.7 Hz), 4.49 (d, 1H, J = 6.8 Hz), 4.37 (m, 1H), 4.14 (m, 1H), 3.99 (dd, 1H, J = 7.7 and 1.8 Hz), 3.81 , 3.76, 3.38 and 3.38 (4s, each 3H). For **16**: $[\alpha]_D^{25}$ +154 ° (c 0.64, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.62 (s, 1H), 7.17 (d, 2H, J = 8.8 Hz), 6.89 (s, 1H), 6.82 (d, 2H, J = 8.8 Hz), 6.06 and 6.05 (2d, each 1H, J = 1.3 Hz), 5.96 (dd, 1H, J = 2.9 and 1.5 Hz), 5.91 (dd, 1H, J = 4.0 and 2.6 Hz), 5.57 (ddd, 1H, J = 7.0, 2.6 and 1.5 Hz), 5.45 (d, 1H, J = 16.1 Hz), 5.12 (dd, 1H, J = 7.0 and 2.6 Hz), 4.60 (d, 1H, J = 16.1 Hz), 4.29 (ddd, 1H, J = 4.0, 1.5 and 1.5 Hz), 3.77, 2.09, 2.05 and 1.88 (4s, each 3H).
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