Synthetic Studies on Poison-Frog Alkaloid 261C

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Abstract: The synthesis of highly substituted indolizidine core for the synthesis of poison-frog alkaloid **261C** has been achieved.

Key words: poison-frog alkaloid **261C**, *Mantella betsileo*, 6,5,5-tricyclic ring system, α7 nicotinic acetylcholine receptors, highly substituted indolizidine core

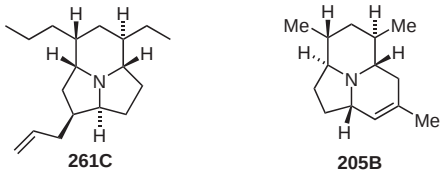
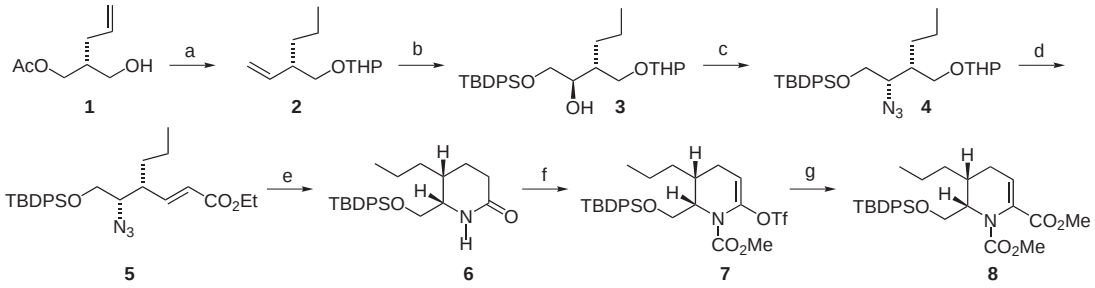


Figure 1

The alkaloid **261C** (Figure 1), isolated from skin extracts of a Madagascan poison frog *Mantella betsileo*, possesses the unique 6,5,5-tricyclic ring system with six asymmetric centers.[1] The gross structure of this alkaloid was determined on the basis of CIMS, GC-FTIR, and extensive NMR studies.[1] Since a structurally related tricyclic poison frog alkaloid **205B**[2] has been found to possess a selective inhibition of α7 nicotinic acetylcholine receptors over α4β2 or α3β4 receptors,[3] the alkaloid **261C** is expected to have similar activity. However, only 0.9 mg of this alkaloid was isolated from skins of 43 frogs, which hindered further studies. Consequently, a total synthesis of this natural product is required. In this communication, we would like to report the synthesis of highly substituted indolizidine core **14** for the synthesis of **261C**.

The key enaminoester **8** was prepared from known alcohol **1** (Scheme 1).[4] The enantiopure alcohol **1** was converted to terminal olefin **2**, which was subjected to the $(DHQD)_2PYR$ ligand-induced Sharpless asymmetric dihydroxylation reaction[5] to afford the corresponding diol **3** as a mixture of diastereoisomers. The primary hydroxyl group in **3** was protected as a TBDPS ether followed by mesylation of the secondary hydroxyl and a substitution reaction of the resulting mesylate with NaN_3 to provide the azide **4**. Removal of the THP group in **4** with acid, and Swern oxidation followed by a Horner–Emmons reaction gave the unsaturated ester **5**. Hydrogenation of **5** over 10% Pd/C gave rise to the pure piperidone **6** in 60% isolated yield. The piperidone **6** was converted to a methyl urethane, which was treated with LiHMDS followed by 2-[*N*,*N*-Bis(trifluoromethylsulfonyl)amino]-5-chloropyridine (Comins' reagent)[6] to afford the enol triflate **7**. A palladium-catalyzed CO insertion reaction under Cacchi's conditions[7] furnished **8**.



Scheme 1 *Reagents and conditions*: a) 1. dihydropyran, PPTS, CH_2Cl_2, r.t.; 2. K_2CO_3, MeOH, r.t.; 3. 10% Pd/C, H_2, EtOAc, 1 atm (60%); 4. Swern oxidation, then *n*-BuLi, $Ph_3P^+CH_3Br^-$; THF. 0 °C to r.t. (70%); b) 1. $(DHQD)_2PYR$, K_2OsO_4, $K_3Fe(CN)_6$, K_2CO_3, H_2O*t*-BuOH, 0 °C (74%); 2. TBDPSCl, Et_3N, DMAP, CH_2Cl_2, 0 °C to r.t. (99%); c) 1. MsCl, Et_3N, CH_2Cl_2, 0 °C; 2. NaN_3, DMF, 80 °C (80%); d) 1. PPTS, EtOH, 60 °C; 2. Swern oxidation, then $(EtO)_2P(O)CH_2CO_2Et$, NaH, THF, 0 °C to r.t. (95%); e) 10% Pd/C, H_2, EtOAc, 1 atm. (60%); f) 1. *n*-BuLi, $ClCO_2Me$, THF, –78 °C to 0 °C (97%); 2. LiHMDS, 2-[*N*,*N*-bis(trifluoromethylsulfonyl)amino]-5-chloropyridine (Comins' reagent), THF, –78 °C to –40 °C (94%); g) $Pd(Ph_3P)_4$, CO, MeOH, Et_3N, DMF, 75 °C (81%).

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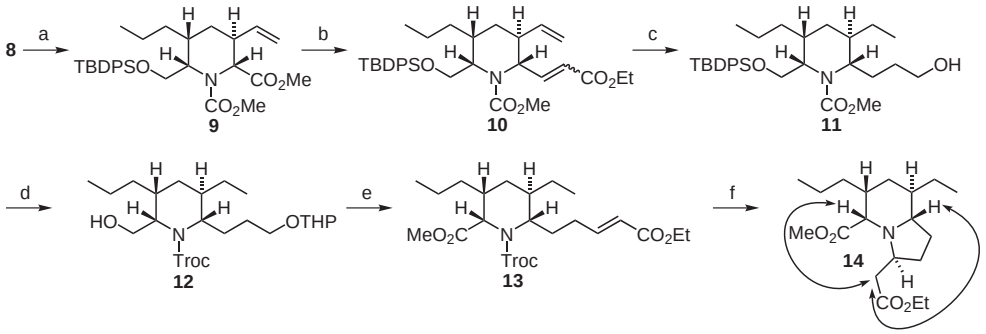

Scheme 2 *Reagents and conditions*: a) $(vinyl)_2CuLi$, Et_2O, –78 °C to –10 °C (96%); b) 1. Super-Hydride® THF, 0 °C (95%); 2. Swern oxidation, then NaH, $(EtO)_2P(O)CH_2CO_2Et$, THF, 0 °C to r.t. (93%); c) 1. 10% Pd/C, H_2 (4 atm) EtOAc; 2. Super-Hydride®, THF, 0 °C (98%); d) 1. dihydropyran, PPTS, CH_2Cl_2, r.t.; 2. 2 M KOH/*i*-PrOH, 120 °C, sealed tube, then TrocCl, K_2CO_3, CH_2Cl_2–H_2O (84%); e) 1. Swern oxidation, then $NaClO_2$, NaH_2PO_4, *t*-BuOH–H_2O; 2. CH_2N_2, EtOAc (62%); 3. PPTS, EtOH, 60 °C, then Swern oxidation, then NaH, $(EtO)_2P(O)CH_2CO_2Et$, THF, 0 °C to r.t. (85%); f) 10% Cd/Pb, 1 N NH_4OAc–THF, r.t. (70%), (7: 1).

A key Michael-type conjugate addition reaction of **8** with divinyllithium cuprate afforded the adduct **9** as a single stereoisomer.[8] Reduction of the ester moiety in **9** followed by Swern oxidation of the resulting alcohol and a Horner–Emmons olefination gave rise to the α,β-unsaturated ester **10** as a mixture of *E*- and *Z*-olefin isomers. Hydrogenation of both isomers of **10** and reduction of the resulting ester with Super-Hydride® provided the alcohol **11**. Protection of the hydroxyl group in **11** with dihydropyran under acidic conditions followed by hydrolysis of the methyl urethane moiety afforded an amino alcohol, which was treated with TrocCl to give **12**. A two-step oxidation of **12** and esterification using diazomethane provided the methyl ester, whose side chain at the other α-position was modified to give rise to the α,β-unsaturated ester **13**. With the requisite **13** in hand, the stage was now set for the key Michael-type cyclization reaction to afford the indolizidine **14**. Thus, treatment of **13** with 10% Cd/Pb under Ciufolini's conditions[9] gave the cyclized product as a 7:1 mixture of the diastereomers, with the major product **14** being isolated in 70% yield. The stereochemistry of **14** was determined to be the desired indolizidine for the synthesis of **261C** by the NOE experiments shown in Scheme 2.

In summary, we achieved the construction of the indolizidine core **14** possessing the desired stereochemistry for our planned synthesis of the unique tricyclic poison-frog alkaloid **261C**. Further studies toward the completion of total synthesis of **261C** are now in progress.

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