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A New Approach to Indolizidine Alkaloids: Asymmetric Formal Total Synthesis of (-)-Swainsonine

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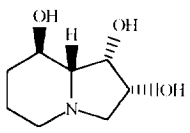
Abstract: *A concise, noncarbohydrate-based approach to (-)-Swainsonine (1) has been achieved by utilizing the kinetic resolution of the α-furfuryl amide 4 and the Sharpless ADH reaction as key steps.*

Polyhydroxylated indolizidine alkaloids, typified by Swainsonine (**1**),[1] Castanospermine (**2**),[2] Lentiginosine (**3**)[3] and their derivatives are of considerable importance due to their potent activities as inhibitors of glycosidase and glycoprotein processing[4]. These compounds have also exhibited interesting activities in anticancer, antiviral, antiretroviral and immunoregulatory.[5] Consequently, much attention has been devoted to the synthesis of Swainsonine (**1**) over the past decade.[6-18] Most of the previous methodologies utilized carbohydrates as starting material.[6-13] Others used R-glutamic acid[14], D-tartaric acid,[15] D-malic acid,[16] and D-iso ascorbic acid[17] as the chiral precursors. However, to the best of our knowledge, only one approach to the target compound **1** was reported[18], starting from a racemic allylic alcohol derivative instead of the above mentioned chiral pool.



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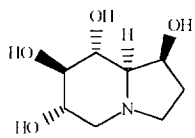

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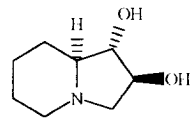

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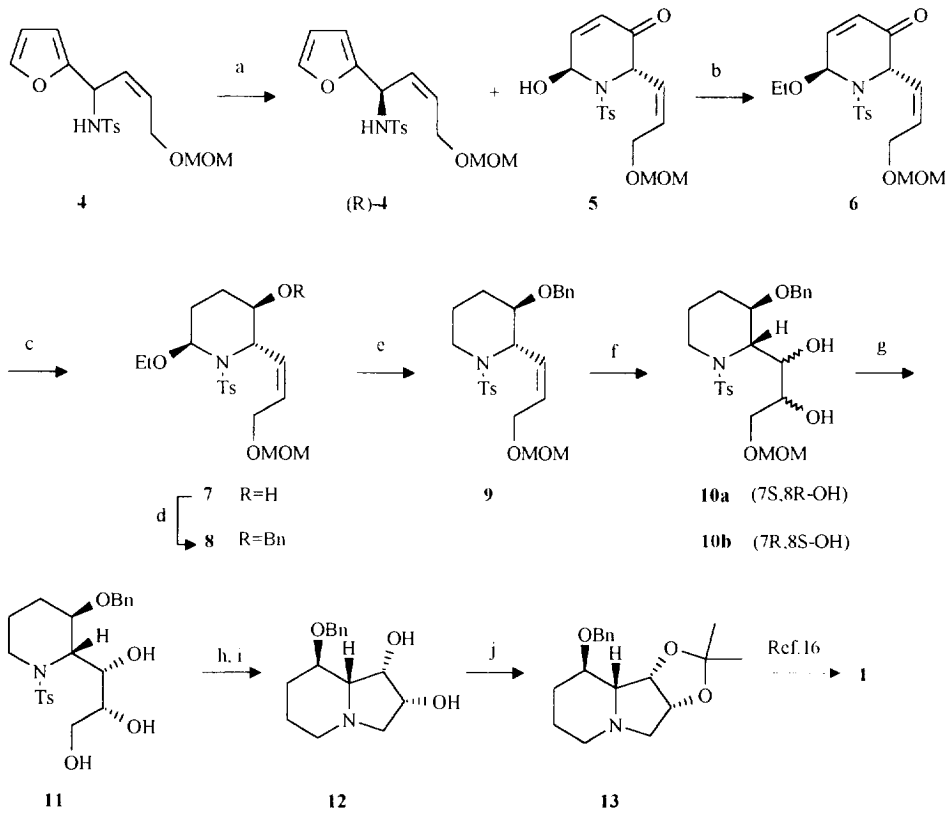
Notwithstanding this plethora of methods, interest in the synthesis of Swainsonine and its analogues remains undiminished. Development of general methods which could have flexibility for the construction of these compounds and analogues continues to be important to probe structure-activity relationship. We have previously developed an efficient method for the kinetic resolution of α-furfuryl amide by using the modified Sharpless asymmetric epoxidation reagent.[19] This reaction afforded two versatile chiral building blocks, both of them are very suitable to be used for elaboration of the skeleton of many types of alkaloids.[20] As part of a program designed to develop a new general strategy for the enantioselective synthesis of biologically active

alkaloids and explore the use of the reaction in alkaloid synthesis, we undertook a synthesis of (-)-Swainsonine (**1**), utilizing the α-furfurylamide **4** as the starting material.



Scheme: **Reagents and conditioins**: a. $Ti(O^iPr)_4$, D-(-)-DIPT, TBHP, SiO_2, CaH_2, CH_2Cl_2, 25 °C, 2 days; b. $HC(OEt)_3$, $BF_3.Et_2O$, 4A Ms, Et_2O, r.t.; c. $NaBH_4$, MeOH, -40- -30 °C; d. BnBr, NaH, $Bu_4N^+I^-$ (Cat.),THF; e. $NaBH_4$, HCO_2H, 0°C; f. OsO_4 (Cat.), NMMO, DHQN-CLB, tracc $CH_3SO_2NH_2$, acetone-H_2O, ultrasonication; g. *p*-TsOH, ^tBuOH, reflux; h. Na/naphthalene, DME, -60 °C; i. Ph_3P, CCl_4, Et_3N, DMF; j. $CH_3C(OCH_3)_2CH_3$, *p*-TsOH, CH_2Cl_2.

The synthesis of (-)-Swainsonine (**1**) is depicted in Scheme. Kinetic resolution of α-furfuryl amide **4** under the reported procedure[19] yielded the (2S,6S)-dihydropyridinone **5** in 42% yield.[21] Preliminary attempts to reach **9** in two steps by directly exposure **5** to a solution of sodium borohydride in formic acid[22] followed by benzylation of the resulting alcohol was unsuccessful. The reduction of **5** gave a complex mixture. Therefore, we circumvented this problem by first treatment of **5** with triethyl orthoformate in Et_2O in the presence of a catalytic amount of $BF_3.Et_2O$ to give **6** in 92% yield. Next, reduction of **6** with sodium borohydride in methanol at -40 °C to -30 °C afforded solely the alcohol **7** in 88% yield, with the desired sense of stereochemistry.[23] Subsequent benzylation of the alcohol **7**, followed by reduction with sodium borohydride in formic acid at 0 °C furnished **9** in 80% yield.

Having the pivotal intermediate **9** in hand, we next tried to convert **9** into the desired diol **10a**. Thus, the Sharpless asymmetric dihydroxylation reagent(DHQN-CLB as chiral ligand)[24] was tried out on **9**, however, no reaction occurred. Fortunately, we eventually found that performance of the reaction in an ultrasonic cleaner, proceeded smoothly to form a separable mixture of the desired diol **10a**[21] and its epimer **10b** in a ratio of 10:1 respectively in 80% combined yield. The stereochemical assignments for these products were based on the Sharpless' empirical rule and the major isomer **10a** was judged to have the desired 7S,8R configuration. Further confirmation of this assignment was provided by transformation of **10a** to a known compound, *vide infra*. In contrast, the use of DHQD-CLB instead of DHQN-CLB as ligand resulted in an opposite and somewhat lower diastereoselectivity (**10a**:**10b** 1:4). The inherent diastereoselectivity of the olefin **9** was 2.5:1 in favor of **10a** as observed from dihydroxylation with OsO_4-NMMO. Removal of the MOM group in **10a** by treatment with *p*-TsOH gave the triol **11** in 90% yield. Deprotection of **11** by sodium naphthalide and without purification direct treatment of the crude product with Ph_3P, CCl_4, Et_3N in DMF underwent cyclization to afford the 8-benzyloxy Swainsonine (**12**)[21] in 50% overall yield from **11**. Attempts to obtain Swainsonine by debenzylation of **11** was not successful, mainly due to the unfeasibility of isolation. To fulfill a formal synthesis of the target molecule, the diol **12** was converted into the known acetonide **13**[16,21] by treatment with dimethoxypropane in the presence of a catalytic amount of *p*-TsOH in 94% yield, which would deliver **1** by sequential hydrogenolysis and acidic hydrolysis, according to the results of C.Kibayashi.[16]

In summary, we have developed an efficient method for preparing polyhydroxylated indolizidine alkaloids by employing the kinetic resolution of α-furfuryl amide. The synthesis of the other structure related polyhydroxylated indolizidine alkaloid, castanospermine (**2**) is currently under investigation.

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21. The data of some typical intermediate are listed below: **5**. colorless oil; $[\alpha]_D^{20}$= -9.0° (c 1.0, MeOH); ^{1}H-NMR (400 MHz, $CDCl_3$): 7.71-7.28 (each *d*, *J*=*J'*=7 Hz, each 2H), 6.91 (*dd*, *J*=4.54 Hz, *J'*=5.77 Hz, 1H), 5.88 (*d*, *J*= 5.77Hz, 1H), 5.68 (*d*, *J*=4.57 Hz, 1H), 5.16 (*d*, *J*= 8.54 Hz, 1H), 4.69 (*d*, *J*=1.98 Hz, 2H), 4.44 (*dd*, *J*=6.26Hz, *J'*=7.50Hz, 1H), 4.23 (*m*, 1H), 3.97, 3.69 (each *m*, each 1H), 3.42 (*s*, 3H), 2.40 (*s*, 3H); FAB-MS(m/z): 368 (M^++1, 5%), 350 (M^++1-H_2O, 100%); Anal. Calcd. for $C_{17}H_{21}NO_6S$: C 55.57, H 5.76, N 3.81; Found: C 55.32, H 5.92, N 3.98; **10a**. crystals; m.p. 140-142 °C; $[\alpha]_D^{20}$ = -70.5° (c 1.0, MeOH); ^{1}H-NMR (400 MHz, $CDCl_3$): 7.58, 7.16 (each *d*, *J*=*J'*=8.14 Hz, each 2H), 7.39-7.28 (*m*, 5H), 4.69 (*s*, 2H), 4.51 (*d*, *J*=2.15 Hz, 2H), 4.31 (*m*, 1H), 4.02 (*m*, 1H), 4.28 (*m*, 1H), 3.93 (*m*, 1H), 3.85, 3.58 (each *m*, 2H), 3.81 (*m*, 1H), 3.40 (*s*, 3H), 3.33 (*m*, 1H), 2.39 (*s*, 3H), 2.04, 1.69 (each *m*, each 1H), 1.51, 1.05 (each *m*, each 1H); FAB-MS *m/z*: 480 (M^++1, 5%), 448 (M^++1-CH_3OH, 88%), 344 (100%); Anal. Calcd. for $C_{24}H_{33}NO_7S$: C 60.11, H 6.94, N 2.92; Found: C 60.27, H 7.16, N 2.88.; **12**. colorless oil; $[\alpha]_D^{20}$ = -79.4° (c 1.0, MeOH); ^{1}H NMR (400 MHz, CD_3OD): 7.35-7.28 (*m*, 5H), 4.69 (*s*, 2H), 4.32, 4.02 (each *m*, each 1H), 4.29 (*m*, 1H), 3.94 (*m*, 1H), 3.85, 3.59 (each *m*, each 1H), 3.81 (*m*, 1H), 3.08 (*m*, 1H), 2.05, 1.69 (each *m*, each 1H), 1.51, 1.05 (each *m*, each 1H); FAB-MS *m/z*: 264 (M^++1, 10%), 246 (M^++1-H_2O, 8%), 91 (100%); Anal. Calcd. for $C_{15}H_{21}NO_3$: C 68.40, H 8.04, N 5.34; Found: C 68.00, H 8.37, N 5.09; **13**. colorless oil; $[\alpha]_D^{20}$ -64.2° (c 0.5, $CHCl_3$) {Lit.[16] colorless oil; $[\alpha]_D^{26}$ -58.9° (c 0.27, $CHCl_3$)}; ^{1}H-NMR (400 MHz, $CDCl_3$): 7.37-7.21 (*m*, 5H), 4.68 (*dd*, *J*=3.2, *J'*=7.2 Hz, 1H), 4.61 (*s*, 2H), 4.39 (*m*, 1H), 3.51 (*m*, 1H), 3.12 (*m*, 1H), 2.44 (*dd*, *J*=3.2 Hz, *J'*=7.2 Hz, 1H), 2.32 (*t*, *J*=8.3, *J'*=10.2 Hz, 1H), 2.08 (*dbr*, *J*=14.6 Hz, 1H), 1.94 (*m*, 1H), 1.68 (*m*, 2H), 1.53 (*s*, 4H), 1.35 (*s*, 3H), 1.25 (*m*, 1H); FABMS *m/z*: 304 (M^++1, 3%), 289 (M^++1-CH_3, 7%), 214 (100%); Anal. Calcd. for $C_{18}H_{25}NO_3$: C 71.26, H 8.31, N 4.62; Found: C 70.88, H 8.52, N 4.77.
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