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Original article

A concise formal stereoselective total synthesis of (−)-swainsonine

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ABSTRACT

A short formal stereoselective synthesis of (−)-swainsonine (**1**) is described. Our synthesis started with the versatile building block (*R*)-3-benzyloxyglutarimide **5**. Through controlled regioselective reduction, Ley's-sulfone chemistry (*N*-α-sulfonylation and $ZnCl_2$-catalyzed *N*-α-amidovinylation), an RCM reaction, and an amide reduction, the synthesis of unsaturated indolizidine (8*R*,8a*S*)-**3** has been achieved in five steps. The indolizidine (8*R*,8a*S*)-**3** is an advanced intermediate toward the synthesis of (−)-swainsonine (**1**).

1. Introduction

(−)-Swainsonine (Fig. 1) is an indolizidine alkaloid that is also classified as an azasugar (imino sugar) [1] due to the presence of three hydroxyl groups in the molecule. After its first isolation in 1973 from the fungus *Rhizoctomia leguminicola* [2a], it has also been extracted from diverse fungi and numerous species of flowering plants [2b,1a]. As an azasugar, (−)-swainsonine exhibits lysosomal α-mannosidase and mannosidase II inhibitory properties. Although the pharmacological properties of this product have not been fully investigated, it has been tested as a treatment for cancer [3], HIV, and immunological disorders [1,4a]. The important biological properties of swainsonine have attracted the interest of many synthetic and medicinal chemists. Numerous methods have been developed for the stereoselective synthesis of swainsonine and its diastereomers [4–7]. In connection with a general program on the development of efficient and general methodologies for the synthesis of *N*-containing bioactive compounds and alkaloids [8], we became interested in the stereoselective synthesis of (−)-swainsonine, and have recently reported the synthesis of two diastereomers of (−)-swainsonine [9]. We now report a short formal stereoselective synthesis of (−)-swainsonine.

A survey of literature revealed that among the many approaches to swainsonine [4–7], the unsaturated indolizidine derivatives **2** [5], **3** [6a], and **4** [6b] proved to be reliable advanced intermediates for the synthesis of swainsonine (Scheme 1). Since indolizidine **2** is a silica gel sensitive compound [5d], we chose the unsaturated indolizidine **3** as our target in view of developing a short formal stereoselective synthesis of (−)-swainsonine.

2. Experimental

2.1. (5R,6R/S)-1-Allyl-5-(benzyloxy)-6-vinylpiperidin-2-one (7)

To a solution of anhydrous zinc chloride (1.0 mol/L in diethyl ether, 3.6 mL. 3.6 mmol) in dichloromethane (0.5 mL) was added dropwise an Et_2O solution of vinylmagnesium bromide (1.0 mol/L in diethyl ether, 6.0 mL, 6.0 mmol). The mixture was stirred at room temperature under nitrogen for 30 min. A solution of a diastereomeric mixture of sulfone **8** (1.16 g, 3.01 mmol) in anhydrous dichloromethane (8 mL) was added and the mixture was stirred at room temperature for 14–16 h. The reaction was quenched with a saturated aqueous NH_4Cl and the resulting mixture was extracted with dichloromethane (3× 25 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (eluent: EtOAc/PE = 1/4) to give an inseparable diastereomeric mixture of *trans*-**7** and *cis*-**7** as a colorless oil (612 mg, combined yield: 75%, *trans*/*cis* = 6/1). IR (film, cm^{-1}): ν_{max} 2925, 1723, 1652, 1457, 1403, 1358, 1266, 1076, 922, 730, 698; ^1H NMR (400 MHz, $CDCl_3$): δ (data of the

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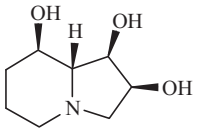


Fig. 1. The structure of (−)-swainsonine (**1**).

major diastereomer read from the spectrum of the diastereomeric mixture) 1.96 (dt, 2H, *J* = 8.8, 4.4 Hz), 2.35 (dt, 1H, *J* = 18.0, 4.4 Hz), 2.65 (dt, 1H, *J* = 18.0, 9.6 Hz), 3.18 (dd, 1H, *J* = 15.6, 7.2 Hz), 3.65 (dd, 1H, *J* = 5.6, 2.8 Hz), 4.11 (d, 1H, *J* = 5.6 Hz), 4.56 (d, 1H, *J* = 12.8 Hz), 4.60 (d, 1H, *J* = 12.8 Hz), 4.77 (dt, 1H, *J* = 15.6, 2.0 Hz), 5.11–5.29 (m, 4H), 5.61–5.79 (m, 1H), 7.26–7.35 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 21.4, 27.1, 47.1, 62.2, 70.3, 73.9, 116.9, 118.2, 127.4 (2C), 127.7, 128.4 (2C), 132.9, 135.8, 138.0, 169.6; HRESIMS calcd. for $[C_{17}H_{21}NNaO_2]^+$ (M+Na$^+$): 294.1465; found: 294.1470.

2.2. (8R,8aS/R)-8-Benzyloxy-6,7,8,8a-tetrahydroindolizin-5(3H)-one (**6**)

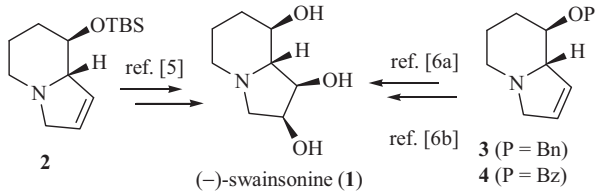
A solution of a diastereomeric mixture of 6-vinylpiperidin-2-one **7** (116.7 mg, 0.43 mmol) in degassed CH_2Cl_2 (8 mL) containing Grubbs second generation catalyst **10** (36 mg, 0.043 mmol) was stirred for 12 h at refluxing. The solution was concentrated and the resulting residue was purified by flash chromatography on silica gel (eluent: EtOAc/PE = 1/3) to give *trans*-**6** (83 mg, yield: 80%) and *cis*-**6** (14 mg, yield: 13%).

trans-**6**: colorless oil. $[\alpha]_D^{20}$ −110.1 (*c* 0.33, $CHCl_3$); IR (film, cm^{-1}): ν_{max} 2925, 2847, 1648, 1611, 1441, 1407, 1096, 1063, 740, 698; ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 1.78–1.88 (m, 1H), 2.17–2.23 (m, 1H), 2.40 (dt, 1H, *J* = 17.6, 8.0 Hz), 2.62 (ddd, 1H, 17.6, 8.0, 4.8 Hz), 3.41 (ddd, 1H, *J* = 14.4, 9.2, 5.6 Hz), 4.04 (d, 1H, *J* = 16.0 Hz), 4.27–4.28 (m, 1H), 4.44 (dt, 1H, *J* = 16.0, 2.2 Hz), 4.52 (d, 1H, *J* = 11.6 Hz), 4.68 (d, 1H, *J* = 11.6 Hz), 5.88–5.93 (m, 1 H), 6.01–6.05 (m, 1H), 7.28–7.38 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 26.4, 29.7, 52.9, 67.4, 71.3, 77.1, 126.9, 127.7 (2C), 127.9, 128.3, 128.5 (2C), 137.9, 168.7; HRESIMS calcd. for $[C_{15}H_{17}NNaO_2]^+$ (M+Na$^+$): 266.11515; found: 266.11514.

cis-**6**: colorless oil. $[\alpha]_D^{20}$ −8.5 (*c* 0.8, $CHCl_3$) {$[\alpha]_D^{20}$ −8.4 (*c* 1.31, $CHCl_3$) [14]}; ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 1.77–1.98 (m, 1H), 2.09–2.26 (m, 1H), 2.44–2.57 (m, 2H), 3.93–3.98 (m, 1H), 4.05 (d, 1H, *J* = 16.0 Hz), 4.39–4.45 (m, 1H), 4.49 (d, 1H, *J* = 12.4 Hz), 4.59 (dt, 1H, *J* = 16.0, 2.4 Hz), 4.60 (d, 1H, *J* = 12.4 Hz), 5.76–5.81 (m, 1H), 5.93–5.98 (m, 1H), 7.25–7.36 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 24.8, 27.0, 53.0, 68.0, 70.5, 70.7, 127.0, 127.3, 127.4 (2C), 127.7, 128.4 (2C), 138.3, 169.1; HRESIMS calcd. for $[C_{15}H_{17}NNaO_2]^+$ (M+Na$^+$): 266.11515; found: 266.11515.

2.3. (8R,8aS)-8-Benzyloxy-3,5,6,7,8,8a-hexahydroindolizine (**3**)

To an ice-cooled, stirred solution of indolizidinone *trans*-**6** (25.9 mg, 0.11 mmol) in THF (2 mL) was added $LiAlH_4$ (20.0 mg, 0.53 mmol), and the mixture was stirred at room temperature for 4 h. The reaction was quenched with a saturated aqueous $NaHCO_3$ at 0 °C. The resulting slurry was filtered through a celite pad and washed with EtOAc (5 mL). The filtrate was extracted with EtOAc (3× 5 mL), and the combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (EtOAc/PE = 1/1) to give compound **3** (22 mg, yield: 89%) as a colorless oil: $[\alpha]_D^{20}$ −115 (*c* 1.0, $CHCl_3$) {$[\alpha]_D^{20}$ −115 (*c* 3.85, $CHCl_3$) [6a]}; IR (film, cm^{-1}): ν_{max} 3058, 3029, 2925, 2851, 2772, 2751, 1635, 1494, 1449, 1192, 1088, 889, 731, 694; ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 1.14–1.32 (m, 1H), 1.52–1.74 (m, 2H), 2.20 (ddd, 1H, *J* = 11.7, 7.1, 3.9 Hz), 2.43 (dt, 1H, *J* = 11.4, 3.2 Hz), 2.94 (dd, 1H, *J* = 11.4, 3.6 Hz), 2.97–3.04 (m, 1H), 3.23–3.32 (m, 2H), 3.63 (d, 1H, *J* = 13.2 Hz), 4.54 (d, 1H, *J* = 12.0 Hz), 4.66 (d, 1H, *J* = 12.0 Hz), 5.89 (ddd, 1H, *J* = 6.0, 4.0, 2.0 Hz), 6.14 (dd, 1H, *J* = 6.0, 0.8 Hz), 7.20–7.36 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 24.2, 30.4, 48.9, 57.7, 71.0, 72.1, 78.5, 127.5, 127.6 (2C), 128.4 (2C), 128.8, 131.4, 138.9; HRESIMS calcd. for $[C_{15}H_{20}NO]^+$ (M+H$^+$): 230.1539; found: 230.1540.



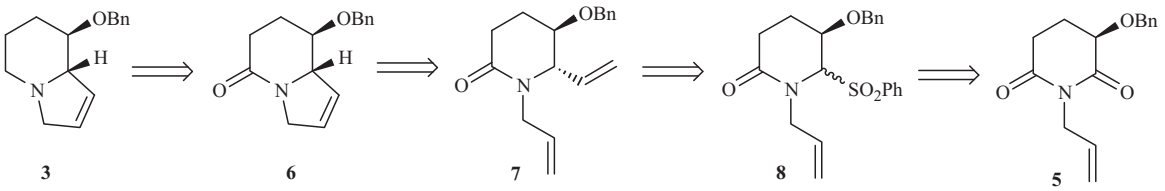
Scheme 1. Typical synthetic approaches to (−)-swainsonine based on the unsaturated indolizidines **2**–**4**.

3. Results and discussion

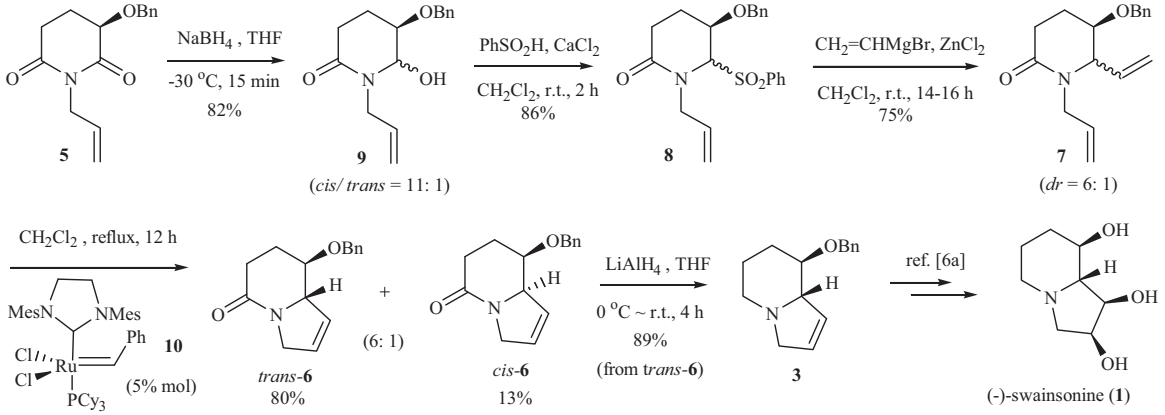
Our retrosynthetic analysis of indolizidine **3** is outlined in Scheme 2. The essential of this analysis resides on the use of (*R*)-benzyloxyglutarimide (**5**), a versatile chiral building block developed from our laboratory as a source of chirality for (−)-swainsonine [10]. Indolizidine **3** can be derived from indolizidinone **6**. The pyrroline moiety in indolizidinone **6** is accessible by the RCM reaction from diene **7** [11], and one vinyl group in **7** can be introduced by the Ley's sulfone-based chemistry [12].

The synthesis commenced with the regio- and diastereoselective reduction [10a] of the known chiral building block (*R*)-benzyloxyglutarimide **5** [10b] ($NaBH_4$, THF, −30 °C, 10 min), which produced the hemiaminal **9** as a diastereomeric mixture (dr = 11:1) in a combined yield of 82% (Scheme 3). The major diastereomer was tentatively assigned as *cis* in light of our previous results on a similar system [10a]. Without separation, the diastereomeric mixture [13,14] of **9** was treated with phenylsulfinic acid and $CaCl_2$ [12a] in CH_2Cl_2 at r.t. for 2 h to give the sulfone **8** in a yield of 86%. Although sulfone **8** was obtained as an inseparable diastereomeric mixture, the diastereomeric mixture can be used in the next step without separation. The subsequent reaction is considered to pass through an *N*-acyliminium intermediate [10,13], either diastereomer could give the same *N*-acyliminium ion. On standing at −20 °C for two weeks, the minor diastereomer in the diastereomeric mixture was epimerized gradually and completely to give the *trans*-diastereomer. This is in accordance with the phenomenon we observed previously on the corresponding 5-phenylsulfonyl-pyrrolidin-2-one homologue [12b]. Reaction of the diastereomeric mixture of 6-phenylsulfonyllactam **8** with organozinc reagent, generated *in situ* from vinylmagnesium bromide and a 1.0 mol/L solution of anhydrous $ZnCl_2$ in diethyl ether [12a], at r.t. for 14–16 h yielded 6-vinyllactam **7** in 75% yield as an inseparable 6:1 diastereomeric mixture (determined by ^{1}H NMR). The stereochemistry of the major diastereomer was tentatively deduced as *trans* based on our previous results with the pyrrolidinone homologous [12b,12d], which was confirmed by converting the diastereomeric mixture **7** into the known compounds *cis*-**6** [14] and **3** [6a], respectively.

We next investigated the RCM reaction [8b,11]. Treatment of the diastereomeric mixture of diene **7** with Grubbs second generation catalyst [15] **10** in CH_2Cl_2 at reflux produced the desired unsaturated indolizidinones *trans*-**6** and *cis*-**6** (ratio = 6:1) in a combined yield of 93%. The physical and spectral data of *cis*-**6** match those reported {$[\alpha]_D^{20}$ −8.5 (*c* 0.8, $CHCl_3$); $[\alpha]_D^{20}$ −8.4 (*c* 1.31, $CHCl_3$) [15]}. Reduction of indolizidinone *trans*-**6** with $LiAlH_4$ in



Scheme 2. Retrosynthetic analysis of indolizidine **3**.



Scheme 3. Formal stereoselective synthesis of (−)-swainsonine (**1**).

THF provided the known unsaturated (8*R*,8a*S*)-indolizidine (**3**) in an 89% yield. The physical and spectral (^{1}H NMR and ^{13}C NMR) data of the synthetic indolizidine **3** are in agreement with those reported {$[\alpha]_D^{20}$ −115 (*c* 1.0, $CHCl_3$); $[\alpha]_D^{20}$ −115 (*c* 3.85, $CHCl_3$)} [6a]. Thus, the stereochemistry assigned for *trans*-**6** and *cis*-**6** was further confirmed. Since the unsaturated indolizidine (8*R*,8a*S*)-**3** has been converted by Pyne and co-workers in four steps into (−)-swainsonine (**1**) [6a], our synthesis thus constitutes a short formal stereoselective synthesis of this alkaloid.

4. Conclusion

In summary, we have developed a five-step synthesis of the unsaturated indolizidine (8*R*,8a*S*)-**3**, and thus accomplished a short formal stereoselective synthesis of (−)-swainsonine (**1**). Through this work, we have demonstrated that a combination of the versatile building block (*R*)-**5** with the Ley's-sulfone chemistry and the RCM reaction constitutes a powerful method for a rapid access to the highly functionalized 8-oxygenated indolizidin-5-one **6**, which may be used as a versatile intermediate for the stereoselective synthesis of other hydroxylated indolizidine alkaloids.

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