A Convenient Approach to (–)-8-*epi*-Swainsonine

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Abstract: A novel and efficient synthesis of (–)-8-*epi*-swainsonine (**2**) is reported. Face-selective diol formation from the bicyclic alkene **3** followed by a stereoselective vinylation of the aldehyde and ring-closing metathesis gave the indolizidine ring system, which was converted into (–)-8-*epi*-swainsonine (**2**).

Key words: stereoselective, indolizidine synthesis, metathesis, stereoelectronic

The synthesis of indolizidine alkaloids has been the subject of intense research due to their interesting chemical structures and variable and potent biological properties.[1] Swainsonine (**1**), which has been isolated from the fungus *Rhizoctonia leguminicola*[2] and was later isolated from other fungal[3] and plant sources,[4] possesses a range of interesting biological properties which include the inhibition of both lysosomal α-mannosidase[5] and mannosidase II.[6] It is clear that the indolizidine alkaloids are an important class of compounds in biological terms but that they are often difficult to make on a scale which would permit extensive biological evaluation.[7] We have developed a synthesis of (–)-8-*epi*-swainsonine (**2**) that will also allow the simple construction of other members of this important class of compounds (Figure 1).

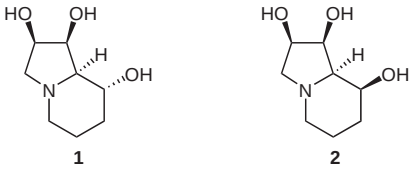
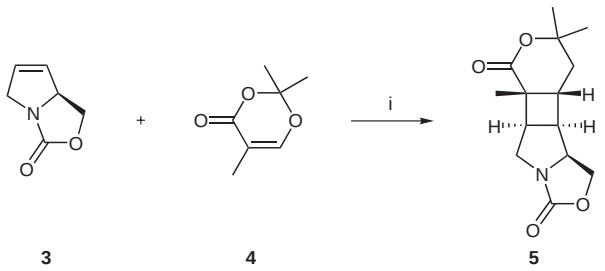


Figure 1

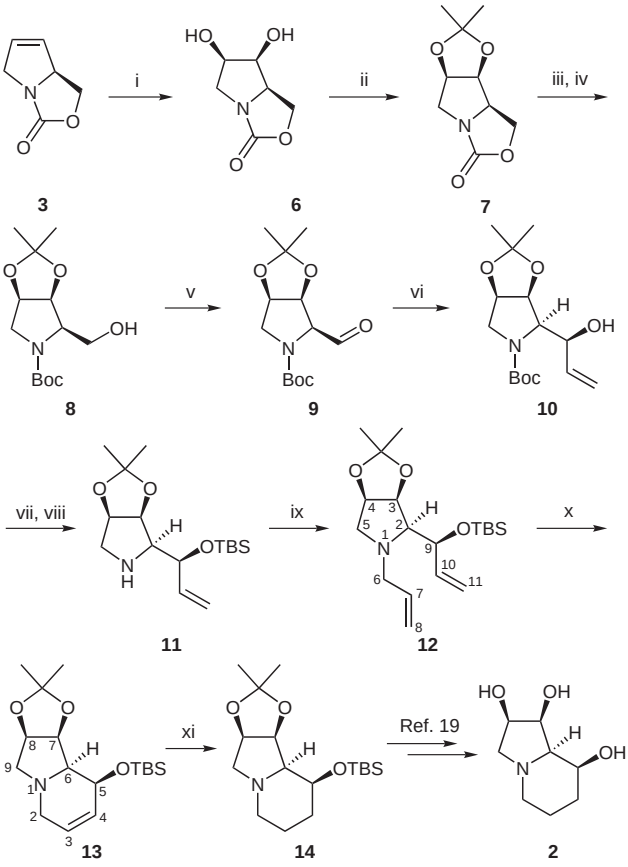
We have recently discovered and reported that oxazolidinone **3** undergoes facile and unexpected addition reactions (Scheme 1).[8]

Calculations from our laboratory[9] have shown that the HOMO reveals an unsymmetrical π-bond with a higher electronic density on the *endo*-face of the bicyclic system **3**. These data led us to devise new and efficient routes to the indolizidine alkaloids including (–)-8-*epi*-swainsonine (**2**).[7]

The synthetic route to (–)-8-*epi*-swainsonine (**2**) is shown in Scheme 2.



Scheme 1 *Reagents and conditions*: i) hν, EtOAc (38%).



Scheme 2 *Reagents and conditions*: i) OsO_4, NMO, $(CH_3)_2CO$–H_2O (1:1, 85%); ii) $(CH_3O)_2C(CH_3)_2$, PPTS, $(CH_3)_2CO$, Δ, (95%); iii) LiOH, EtOH, Δ; iv) $(Boc)_2O$, Et_3N, MeCN (85% over two steps); v) TPAP, 4 Å MS, NMO, CH_2Cl_2, (88%); vi) CH_2=CHMgBr, THF, (85%); vii) TBSOTf, Et_3N, CH_2Cl_2, (98%); viii) $ZnBr_2$, CH_2Cl_2 (81%); ix) CH_2CHCH_2Br, K_2CO_3, THF, Δ (91%); x) Grubbs' 2nd-generation catalyst (20 mol%), CH_2Cl_2, Δ (70%); xi) 10% Pd/C, H_2, EtOAc (54%).

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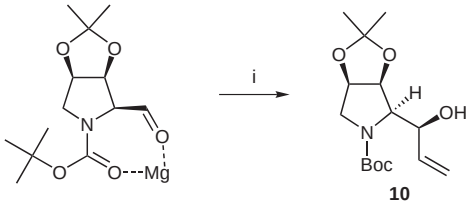
Treatment of the readily available alkene **3**[8] with osmium tetroxide in the presence of *N*-methylmorpholine-*N*-oxide[10] gave the diol **6** in high (85%) yield.[9] The diol **6** was smoothly converted into the acetal **7** with 2,2-dimethoxypropane in the presence of PPTS.[11] Lithium hydroxide mediated hydrolysis of **7** followed by the addition of di-*tert*-butyl dicarbonate gave the alcohol **8** (85%). Conversion of the alcohol **7** into the aldehyde **9** was achieved using TPAP (88%).[12] Addition of vinylmagnesium bromide to a solution of the aldehyde **9** in tetrahydrofuran gave the allylic alcohol **10** as the exclusive product. The addition of vinylmagnesium bromide to the aldehyde **9** was conducted over a range of temperatures (–78 °C to r.t.) and no change in stereoselectivity was observed. We further investigated the addition of vinyllithium in conjunction with DMPU in an attempt to reverse the selectivity of addition as detailed by Donohoe in a related system.[13] We found, however, that no reversal of stereochemistry occurred. We believe that this interesting result could be due to prior chelation of the aldehyde carbonyl group to magnesium and the Boc protecting group (Scheme 3).



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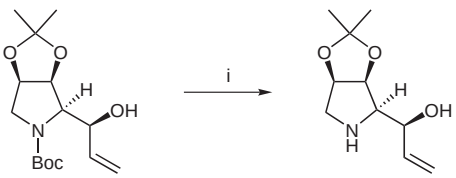
Scheme 3 *Reagents and conditions*: i) CH_2=CHMgBr, THF, then NH_4Cl, H_2O (85%).

Removal of the *N*-Boc protecting group was achieved using zinc bromide[14] after prior protection of the alcohol **10** as its *tert*-butyldimethylsilyl ether. The aforementioned deprotection requires mild conditions and we found that absorption of the allylic alcohol **10** onto silica followed by microwave assisted irradiation at 140 °C also removed the Boc protecting group (Scheme 4).[15] *N*-Allylation of **11** was achieved using allyl bromide in the presence of potassium carbonate[16] to afford the alkene **12**.[17]



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Scheme 4 *Reagents and conditions*: i) SiO_2, MW 200 °C, 4 min (41%).

Ring-closing metathesis was attempted initially with first generation Grubbs' catalyst[18] to no effect; however, the second generation catalyst[19] reacted with the alkene **12** to afford the bicyclic amine **13** in respectable yield.[20] Hydrogenation of **13** using hydrogen and palladium on charcoal gave the fully protected indolizidine ring system **14** which is the direct precursor of (–)-8-*epi*-swainsonine (**2**).[21]

It has come to our attention that Battacharjya and co-workers have prepared epi-swainsonine triacetate using ring-closing metathesis.[22]

The synthesis of (–)-8-*epi*-swainsonine **2** reported here is highly efficient and robust and can be tailored to the preparation of a range of indolizidine alkaloids. Pyne and his co-workers have also published work on the synthesis of polyfunctionalised pyrrolidines, but seem to have overlooked our original work in this area.[23]

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(17) **Data for Compound 12.**
Colourless oil; R_f = 0.66 (30% Et_2O–PE); $[\alpha]_D^{28}$ –50.5 (*c* 2.2, $CHCl_3$). IR (film): 3080, 2956, 2931, 2858, 2792, 1644, 1473, 1463, 1420, 1403, 1379, 1369, 1277, 1255, 1210, 1169, 1139, 1112, 1092, 1019, 1005, 926, 873, 838, 777, 676 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 0.03 and 0.08 [6 H, 2 × s, $SiC(CH_3)_2$], 0.90 [9 H, s, $SiC(CH_3)_3$], 1.28 and 1.53 [6

H, 2 × s, $C(CH_3)_2$], 2.02 (1<H, dd, *J* = 3.7, 11.5 Hz, 5-H), 2.11 (1 H, dd, *J* = 3.4, 7.8 Hz, 2-H), 2.63 (1 H, dd, *J* = 7.7, 14.0 Hz, 6-H), 3.22 (1 H, d, *J* = 11.5 Hz, 5-H), 4.03 (1 H, m, 6-H), 4.49–4.56 (3 H, m, 3-H, 4-H, 9-H), 5.03–5.18 (3 H, m, 8-H, 11-H), 5.30 (1 H, d, *J* = 17.2 Hz, 11-H), 5.87 (1 H, m, 7-H), 6.15 (1 H, ddd, *J* = 5.9, 10.8, 17.2 Hz, 10-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = –4.7 and –4.0 [$Si(CH_3)_2$], 18.2 [$SiC(CH_3)_3$], 25.5 [$C(CH_3)_2$], 26.0 [$SiC(CH_3)_3$], 26.3 [$C(CH_3)_2$], 58.1 (C-6), 60.5 (C-5), 71.6 (C-2), 74.4, 77.3 and 81.5 (C-3, C-4, C-9), 110.8 [$C(CH_3)_2$], 115.1 (C-11), 116.2 (C-8), 135.9 (C-7), 139.6 (C-10). HRMS (ESI): *m*/*z* calcd for $C_{19}H_{36}NO_3Si$ [M + H]$^+$: 354.2459; found: 354.2448.

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(20) **Data for Compound 13.**
Colourless oil; R_f = 0.40 (75% Et_2O–PE); $[\alpha]_D^{28}$ 19.6 (*c* 1.5 in $CHCl_3$). IR (film): 3037, 2952, 2928, 2856 2781, 1719, 1660, 1461, 1379, 1253, 1207, 1167, 1150, 1119, 1045, 1011, 961, 938, 901, 860, 836, 775, 653 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.11 and 0.13 [6 H, s, $Si(CH_3)_2$], 0.91 [9 H, s, $SiC(CH_3)_3$], 1.29 and 1.51 [6 H, s, $C(CH_3)_2$], 2.10–2.11 (1 H, m, 6-H), 2.14 (1 H, dd, *J* = 5.7, 11.4 Hz, 2-H), 2.59 (1 H, d, *J* = 17.1 Hz, 9-H), 3.33 (1 H, d, *J* = 11.4, 2-H), 3.60–3.67 (1 H, m, 9-H), 4.50 (1 H, m, 5-H), 4.62 (1 H, dd, app. t, *J* = 6.0 Hz, 7-H), 4.69 (1 H, dd, *J* = 3.8, 6.0 Hz, 8-H), 5.77–5.79 (2 H, m, 3-H, 4-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = –5.3 and –4.4 [$Si(CH_3)_2$], 18.8 [$SiC(CH_3)_3$], 24.2 [$C(CH_3)_2$], 26.1 [$SiC(CH_3)_3$], 26.5 [$C(CH_3)_2$], 53.3 (C-9), 61.9 (C-2), 65.3 (C-5), 67.2 (C-6), 77.8 (C-7), 80.8 (C-8), 111.2 [$C(CH_3)_2$], 126.8 and 127.5 (C-3 and C-4). HRMS (ESI): *m*/*z* calcd for $C_{17}H_{32}NO_3Si$ [M + H]$^+$: 326.2146; found: 326.2138.

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