Organic & Biomolecular Chemistry

PAPER

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Cite this: DOI: 10.1039/c6ob00531d

Epimerization of C5 of an *N*-hydroxypyrrolidine in the synthesis of swainsonine related iminosugars†

Bao-Chen Qian,[a,e] Akiko Kamori,[b] Kyoko Kinami,[b] Atsushi Kato,*[b] Yi-Xian Li,[a] George W. J. Fleet[c,d] and Chu-Yi Yu*[a,d]

Received 10th March 2016,
Accepted 14th April 2016

DOI: 10.1039/c6ob00531d

www.rsc.org/obc

Epimerization of C5 of an *N*-hydroxypyrrolidine ring by regioselective oxidation to a nitrone followed by diastereoselective reduction provides a new approach to the synthesis of swainsonine and related compounds. The only protection in the synthesis of the potent mannosidase inhibitor DIM (1,4-dideoxy-1,4-imino-D-mannitol) was the acetonation of D-mannose.

Introduction

The biological properties of iminosugars, especially their glycosidase inhibition, make them attractive synthetic targets.[1] Mannosidase inhibitors have potential in the treatment of many diseases, including cancer, HCV and HIV.[2] Polyhydroxylated indolizidine alkaloids, conformationally restricted pyrrolidine equivalents of furanoses, are a subclass of iminosugars.[3] Swainsonine (**1**) (Fig. 1), first isolated from the fungal plant pathogen *Rhizoctonia leguminicola*[4] in 1973 and later from *Swainsona canescens*[5] and other sources,[6] is a potent inhibitor of lysosomal α-mannosidase[4b,7] and Golgi mannosidase II,[8] and may be useful in the treatment of cancer and other diseases.[9] There are many syntheses of swainsonine(**1**)[10] and its analogues[11] such as 8a-*epi*-swainsonine (**2**)[10e,12] (Fig. 1). 1,4-Dideoxy-1,4-imino-D-mannitol (DIM, **3**),[13] the pyrrolidine equivalent of mannofuranose, is almost as potent an inhibitor of α-mannosidase as is swainsonine. The synthesis of swainsonine from mannose requires the introduction of nitrogen with *retention* at C4 of mannose; in all previous syntheses, this has been done *before* the formation of the pyrrolidine ring. In the context of our interest in iminosugars,[14] we have developed a novel approach which provides the first example in which the stereochemistry is adjusted *after* the formation of the pyrrolidine ring. In particular, this provides a short synthesis of DIM with only acetonide protection; subsequent manipulation allows access to other targets. There are many advantages in the use of sugar-derived cyclic nitrones as starting materials for the aim of developing an efficient and flexible synthesis of DIM (**3**), swainsonine (**1**) and related compounds.

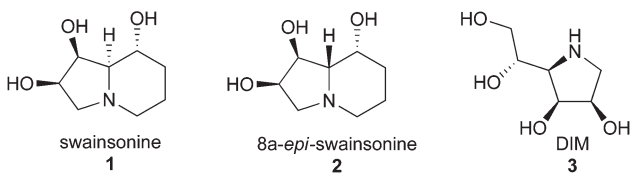


Fig. 1 Swainsonine and related compounds.

The synthesis of swainsonine (**1**) and DIM (**3**) is outlined in Fig. 2. The pyrrolidine ring in the cyclic nitrone **10**, available on a large scale in 43% yield from D-mannose, requires inversion at C5 for the construction of swainsonineand DIM. Replacement of **10** with cyclic nitrones derived from various other sugars as starting materials would provide a diverse synthesis of iminosugars *via* similiar synthetic routes. Sugar-derived cyclic nitrones can be prepared on multi-gram scales from almost any aldose and have proven to be effective building blocks for the synthesis of iminosugars.[14a–c,15] Furthermore, the nitrone functionality in the pyrrolidine ring can undergo a variety of chemical reactions which provides the possibility of diverse construction of the pyrrolidine ring with various substituents and stereochemistries.

The key steps of the synthesis involve epimerization of C5 of the nitrone **10**: (i) regioselective oxidation of *N*-hydroxypyrrolidine (**9**) to nitrone (**8**), followed by (ii) diastereoselective reduction of nitrone (**8**) to *N*-hydroxypyrrolidine (**7**).[16]

[a]*Beijing National Laboratory for Molecular Science (BNLMS), CAS Key Laboratory of Molecular Recognition and Function, Institute of Chemistry, Chinese Academy of Sciences, Beijing 100190, China. E-mail: yucy@iccas.ac.cn*
[b]*Department of Hospital Pharmacy, University of Toyama, 2630 Sugitani, Toyama 930-0194, Japan. E-mail: kato@med.u-toyama.ac.jp*
[c]*Chemistry Research Laboratory, Department of Chemistry, University of Oxford, Mansfield Road, Oxford, OX1 3TA, UK*
[d]*National Engineering Research Center for Carbohydrate Synthesis, Jiangxi Normal University, Nanchang 330022, PR China*
[e]*University of Chinese Academy of Sciences, Beijing 100049, China*
† Electronic supplementary information (ESI) available: Copies of ^{1}H, ^{13}C and 2D NMR spectra, data of crystal structure and results of the bioassay. CCDC 1455389. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c6ob00531d

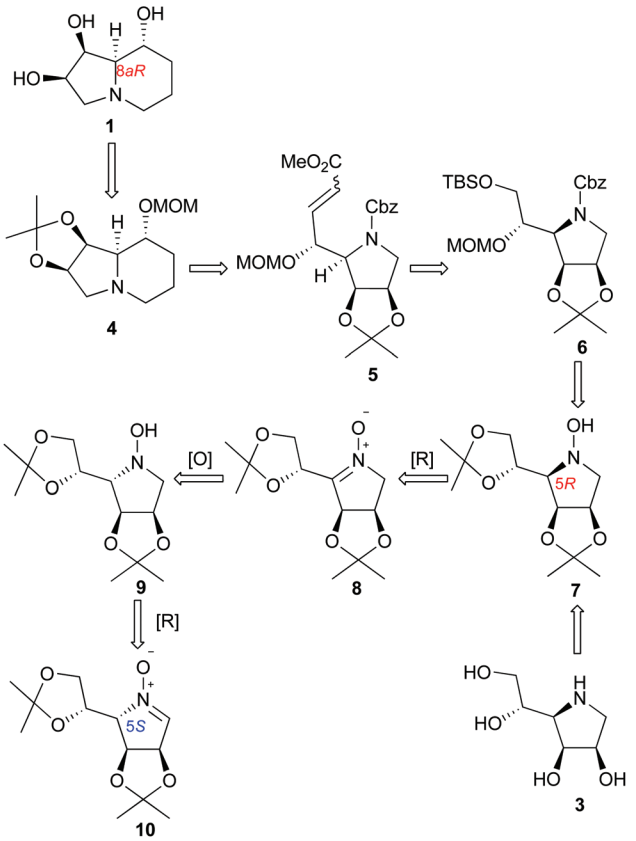
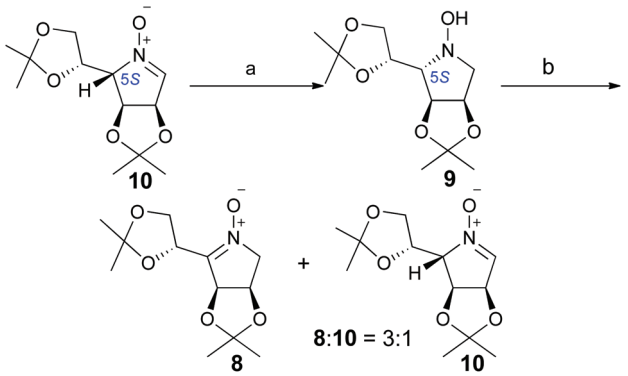


Fig. 2 Retrosynthesis of swainsonine.

Reduction of 7 followed by deprotection gives DIM (3) in which the only protecting step was the acetonation of mannose. Selective deprotection and homologation of the side chain of the pyrrolidine **6**, and subsequent chemical manipulations provide access to swainsonine. The syntheses of 8a-*epi*-swainsonine (**2**) and its equivalent monocyclic pyrrolidine analogue **22** are also reported. The side-by-side comparison of glycosidase inhibition of swainsonine (**1**) and its epimer **2** with those of their monocyclic equivalents, DIM (**3**) and its epimer **22**, was studied.

Results and discussion

The starting polyhydroxylated cyclic nitrone **10** was prepared according to the reported method from D-mannose in six steps with an overall yield of 43%.[17] In comparison with swainsonine (**1**), it can be seen that nitrone **10** bears all stereocenters of swainsonine (**1**) except that at C5 position, which is correlated to the C8a position of swainsonine. Therefore, inversion of the configuration at C5 of nitrone **10** is necessary for the construction of the bicyclic indolizidine skeleton of swainsonine (**1**) with the correct C8a configuration. The synthesis started with the reduction of nitrone **10** (Scheme 1). Reduction of nitrone **10** with $NaBH_4$ at 0 °C in methanol resulted in the formation of hydroxylamine **9** in 89% yield. With the hydroxylamine in hand, we explored an efficient and regioselective oxidation method for the transformation of **9** to the desired cyclic nitrone **8**. After several attempts with different oxidation methods and conditions, oxidation of **9** with MnO_2 at room temperature was optimal, yielding the expected nitrone **8** together with nitrone **10** in high total yield (95%) with acceptable regioselectivity (a ratio of **8**/**10** = 3 : 1).[14c,18]

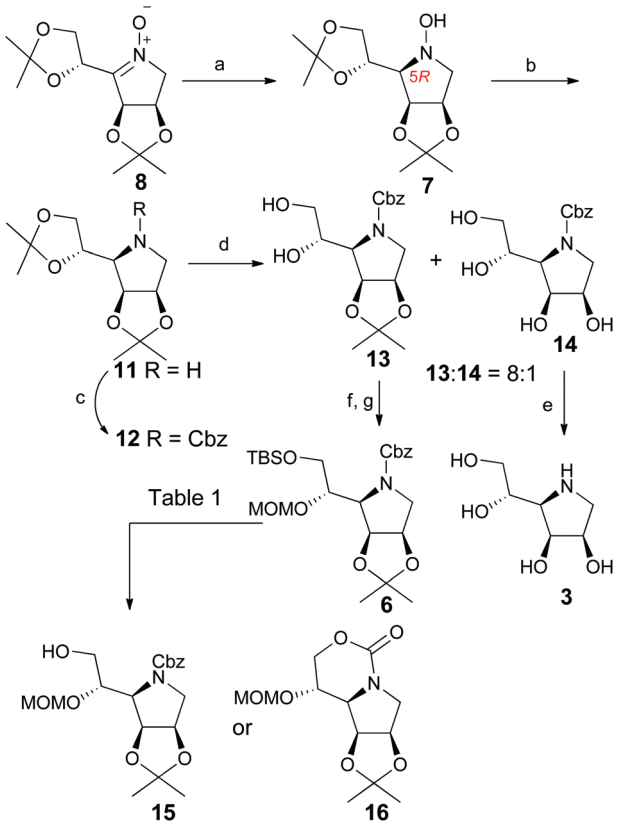


Scheme 1 Reagents and conditions: (a) $NaBH_4$, MeOH, 0 °C, 89%; (b) MnO_2, CH_2Cl_2, rt, 95% total yield.

The next task was the reduction of nitrone **8** into the desired pyrrolidine. Catalytic hydrogenation was first attempted for the reduction of nitrone **8** and was expected to give the pyrrolidine **11** smoothly. However, Pd-catalyzed hydrogenation of **8** unexpectedly resulted in a complicated mixture of products, especially when the reaction was conducted on gram-scale. Accordingly nitrone **8** was treated with $NaBH_4$ in methanol at 0 °C, which afforded *manno*-pyrrolidine hydroxylamine **7** in excellent yield (94%) and high diastereoselectivity. *Manno*-**7** was the only product; none of the epimeric *talo*-**9** was formed (Scheme 2).

Reduction of **7** with zinc powder and $Cu(OAc)_2$ in acetic acid and subsequent installation of Cbz protecting group gave the fully protected pyrrolidine **12** in good total yield (89%). Selective cleavage of the side-chain acetonide (Scheme 2) exposed the 6,7-diol for further regio-selective modification. The acetonide on the side-chain was selectively removed by 1% H_2SO_4-MeOH system[19] at room temperature to afford diol **13**[20] together with tetrahydroxylated pyrrolidine **14** in moderate yield (52% and 6.5%, respectively). The structure of **14** was confirmed by X-ray crystallographic analysis (Fig. 3, and ESI†).[21] Finally, Pd-catalyzed hydrogenation of **14** produced DIM (**3**) in 88% yield.

Homologation of the side-chain of diol **13** required the selective exposure of the primary hydroxyl group (Scheme 2). Thus, the primary hydroxyl group was first selectively protected by TBS group and then the secondary hydroxyl group was etherified with chloromethylmethylether to give **6** in good yield (76% in two steps). Selective cleavage of the TBS protecting group gave the free primary alcohol **15**. The usual methods, *i.e.* TBAF and KF, for the selective removal of TBS protection resulted in the formation of bicyclic compound **16** (Table 1). The unexpectedly easy formation of the bicyclic



Scheme 2 Reagents and conditions: (a) $NaBH_4$, MeOH, 0 °C, 94%; (b) Zn, $Cu(OAc)_2$, AcOH, rt; (c) CbzCl, $NaHCO_3$, $THF–H_2O$ (20 : 1), 89% for 2 steps; (d) 1% H_2SO_4(w/w), MeOH, rt, 52% for **13**; (e) Pd/C, H_2, MeOH, 88%; (f) TBSCl, Et_3N, CH_2Cl_2; (g) MOMCl, DIPEA, CH_2Cl_2, 0 °C to rt, 76% in 2 steps.

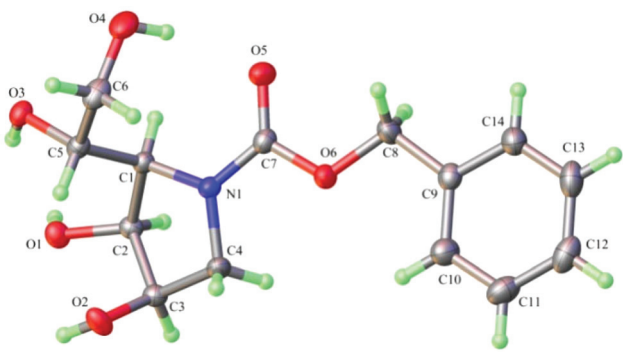


Fig. 3 X-Ray crystal structure of **14**.

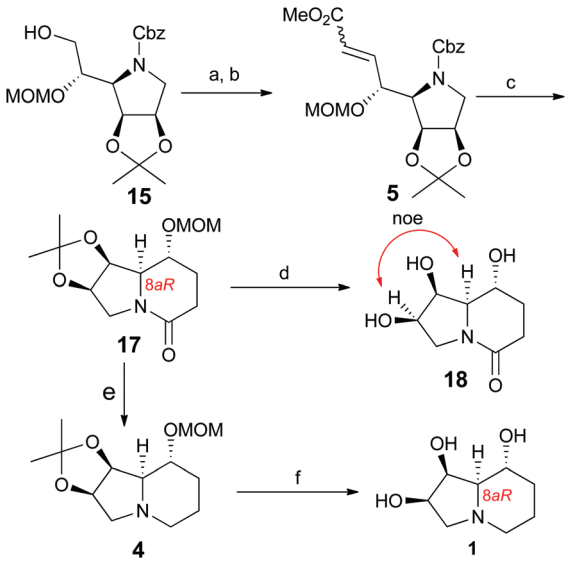
Table 1 Conditions for selective deprotection of **6**

Reagent	Temperature (°C)	Product	Yield (%)
TBAF	0	**16**	97
TBAF	rt	**16**	92
KF	0	**16**	86
Olah's reagent[a]	rt	**15**	91

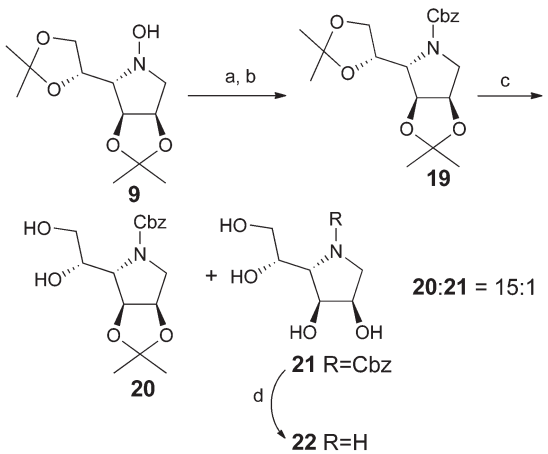
[a] Olah's reagent = pyridinium poly(hydrogen fluoride).

compound **16** may be due to the relatively strong basic reaction conditions. It was necessary to use neutral or weak acidic reagents. Olah's reagent [pyridinium poly(hydrogen fluoride)] with **6** gave the desired alcohol **15** in good yield.[22]

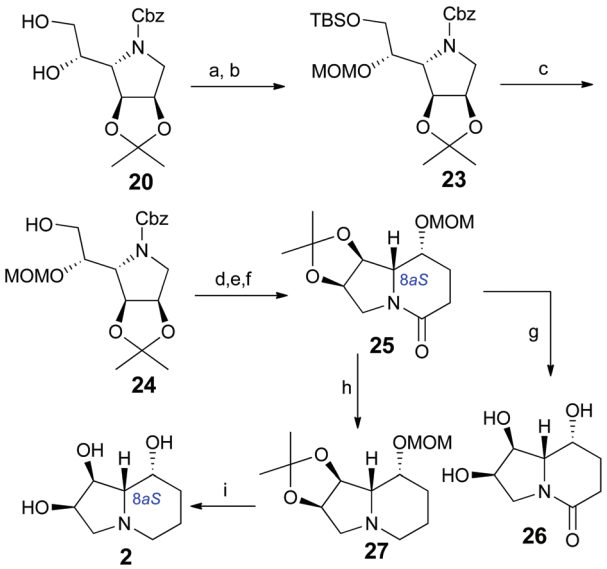
Subsequent oxidation of the alcohol **15** with Dess–Martin periodinane gave the aldehyde which was used directly in the Wittig olefination with methyl 2-(triphenylphosphoranylidene) acetate to afford the unsaturated ester **5**. After being separated from triphenylphosphine oxide by recrystallization, crude **5** was used in the next step without further purification. The catalytic hydrogenation and cyclization of **5** were performed in a one-pot reaction; the cyclization gave the δ-lactam **17** after



Scheme 3 Reagents and conditions: (a) DMP (Dess–Martin periodinane), $NaHCO_3$, CH_2Cl_2, rt; (b) Ph_3P = $CHCO_2Me$, toluene, reflux; (c) Pd/C, H_2, MeOH then K_2CO_3, 79% in 3 steps; (d) 3 N HCl, MeOH, 97%; (e) $LiAlH_4$, THF, reflux; (f) 3 N HCl, MeOH, 74% in 2 steps.



Scheme 4 Reagents and Conditions (a) Zn, $Cu(OAc)_2$, AcOH, rt; (b) CbzCl, $NaHCO_3$, $THF–H_2O$ (20 : 1), 87% in 2 steps; (c) 1% H_2SO_4(w/w), MeOH, rt, 69% for **20**; (d) Pd/C, H_2, MeOH, 81%.



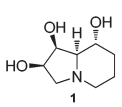
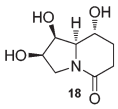
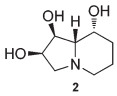
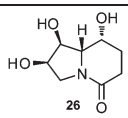
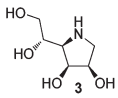
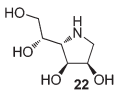
Scheme 5 Reagents and Conditions: (a) TBSCl, Et_3N, CH_2Cl_2; (b) MOMCl, DIPEA, CH_2Cl_2, 0 °C to rt, 79% in 2 steps; (c) TBAF, THF, 97%; (d) DMP, $NaHCO_3$, CH_2Cl_2, rt; (e) Ph_3P = $CHCO_2Me$, toluene, reflux; (f) Pd/C, H_2, MeOH, 63% in 3 steps; (g) 3 N HCl, MeOH, 99%; (h) $LiAlH_4$, THF, reflux, 92%; (i) 3 N HCl, MeOH, 94%.

the addition of potassium carbonate in excellent total yield (79% in three steps). Removal of the acetonide and methoxymethyl protecting groups provided the polyhydroxylated δ-lactam **18** in 97% yield. Then, reduction of δ-lactam **17** with $LiAlH_4$ yielded the tertiary amine **4** together with impurities which were difficult to remove. Accordingly, crude **4** was treated directly with HCl–MeOH solution to give the target final product swainsonine (**1**). Purification of the crude product with acidic ion exchange resin produced pure swainsonine (**1**) in 74% yield in two steps. Thus, swainsonine (**1**) was synthesized starting from cyclic nitrone **10** with an overall yield of 12.5%. The structure of swainsonine (**1**) was confirmed by spectroscopic data and its relative configuration was further confirmed by NOESY experiment of **18** (see ESI†) (Scheme 3).

The synthesis of 8a-*epi*-swainsonine (**2**) was achieved *via* a similar route (Scheme 4). Hydroxylamine **9**, obtained from the reduction of nitrone **10**, was treated with zinc powder and cupric acetate monohydrate to give secondary cyclic amine, which was then protected with Cbz group to give **19** in 87% yield (two steps). Selective cleavage of the side-chain acetonide afforded 5,6-diol **20** in 69% yield together with the by-product **21** (with a ratio of **20**/**21** = 15 : 1). Removal of protecting group of **21** gave pyrrolidine iminosugar **22**,[23] the C5-*talo* epimer of DIM.

Diol **20** was selectively protected with TBS and MOM groups respectively to yield **23** in 79% total yield in two steps

Table 2 The glycosidase inhibition of swainsonine (**1**), DIM (**3**) and related compounds (**2**, **18**, **22** and **26**)

Enzyme	IC_{50} (μM)					
	 **1**	 **18**	 **2**	 **26**	 **3**	 **22**
α-Glucosidase						
Yeast	NI[a] (0.3%)[b]	NI (5.4%)	NI (13.4%)	NI (5.6%)	68	NI (4.9%)
Rice	NI (45.3%)	NI (0%)	NI (3.7%)	NI (3.4%)	NI (38.7%)	NI (17%)
Rat intestinal maltase	NI (42.9%)	NI (6.8%)	NI (17.4%)	NI (4.2%)	NI (31.6%)	NI (28.1%)
β-Glucosidase						
Almond	NI (1.2%)	NI (6.6%)	NI (0%)	NI (6.2%)	NI (20.2%)	NI (40.8%)
Bovine liver	NI (30.3%)	595	NI (36.8%)	NI (0%)	NI (20.5%)	NI (37.2%)
α-Galactosidase						
Coffee beans	NI (1.8%)	NI (0%)	NI (0%)	NI (0%)	NI (35.7%)	NI (7.4%)
β-Galactosidase						
Bovine liver	546	491	1000	NI (17.9%)	NI (46.8%)	NI (14.6%)
α-Mannosidase						
Jack bean	0.73	NI (3.8%)	71	625	3.9	213
β-Mannosidase						
Snail	NI (0%)	NI (0%)	NI (0%)	NI (2.2%)	NI (6.4%)	NI (1.2%)
α-L-Fucosidase						
Bovine kidney	NI (0%)	NI (2.4%)	NI (16.3%)	NI (8.3%)	NI (33.2%)	NI (29.4%)
α,α-Trehalase						
Porcine kidney	NI (4.3%)	NI (2.9%)	NI (4.8%)	NI (3.9%)	NI (2.8%)	NI (9.6%)
Amyloglucosidase						
Aspergillus niger	NI (9.3%)	NI (0%)	NI (0%)	NI (0%)	NI (0%)	NI (3.8%)
α-L-Rhamnosidase						
Penicillium decumbens	NI (4.9%)	NI (0%)	NI (26.1%)	NI (3.6%)	NI (19.1%)	NI (1.6%)
β-Glucuronidase						
E. coli	NI (0.7%)	NI (11.5%)	NI (17.7%)	NI (0.4%)	542	NI (0%)
Bovine liver	NI (6.5%)	NI (0%)	NI (0%)	NI (13.8%)	NI (22.3%)	NI (23.8%)

[a] NI: no inhibition (less than 50% inhibition at 1000 μM). [b] ( ): inhibition at 1000 μM.

(Scheme 5). As in the synthesis of swainsonine (**1**), cleavage of TBS group was then performed. In contrast to the synthesis of swainsonine (**1**), the TBS group was removed easily with TBAF to give the alcohol **24** in 97% yield; base induced closure to a lactam did not occur in the epimeric series.

Homologation of the side-chain of **24** and the subsequent hydrogenation gave the key intermediate **25** in 63% yield (three steps). Treatment of **25** with HCl–MeOH solution produced polyhydroxylated δ-lactam **26** in quantitative yield. The reduction of **25** with $LiAlH_4$ gave the precursor of 8a-*epi*-swainsonine **27** in 92% yield. The indolizidine **27** could be purified easily. Finally, acidic hydrolysis of **27** with HCl–MeOH solution provided 8a-*epi*-swainsonine (**2**) as a white solid in 94% yield.

The fully-deprotected iminosugars prepared were evaluated against a number of glycosidases (Table 2, for complete results of bioassay, see ESI†). For the first time a side by side comparison of swainsonine (**1**) and its 8a-epimer **2** and of each with their pyrrolidine equivalents of the parent *manno*- and *talo*-furanoses is presented. 8a-*epi*-Swainsonine (**2**) is also α-mannosidase inhibitor, though the inhibition potency was about 100-fold lower than that of swainsonine (**1**). DIM (**3**) is comparable potent inhibitor against Jack bean mannosidase (IC_{50} = 3.9 μM), whereas it also showed moderate inhibition against yeast α-glucosidase and *E. coli* β-glucuronidase, with IC_{50} values 68 and 542 μM, respectively. 4-*epi*-DIM (**22**) is a much weaker inhibitor of Jack bean mannosidase (IC_{50} = 213 μM) than DIM (**3**).[24] Amide **18** showed no inhibition of α-mannosidase but was a weak inhibition of bovine liver β-glucosidase (IC_{50} = 595 μM) and β-galactosidase (IC_{50} = 491 μM). In contrast, **26** did not show inhibition against these enzymes but showed weak inhibition against Jack bean mannosidase (IC_{50} = 625 μM).

Conclusions

In summary, inversion of C5 in a pyrrolidine provides a new strategy for the synthesis of iminosugars such as swainsonine (**1**) starting from sugar-derived cyclic nitrone **10**. Swainsonine (**1**) was synthesized in 12 steps with overall yield of 12.5%. Additionally, swainsonine related compounds (**2**, **3**, **18**, **22** and **26**) were also synthesized. This synthetic approach provides a versatile approach to the synthesis of compounds related to swainsonine (**1**), which will be valuable for future study of the structure–activity relationship (SAR) of swainsonine-related compounds.

Experimental

General methods

All reagents were obtained commercially or prepared as described in the literature. Reactions sensitive to moisture were carried out under an inert atmosphere (Ar). Reactions were stirred using Teflon-coated magnetic stirring bars. Analytical TLC was performed with 0.20 mm silica gel 60F plates with 254 nm fluorescent indicator. TLC plates were visualized by ultraviolet light or by treatment with a spray of Pancaldi reagent {$(NH_4)_6MoO_4$, $Ce(SO_4)_2$, H_2SO_4, H_2O}. Chromatographic purification of products was carried out by flash column chromatography on silica gel (230–400 mesh). Acidic ion exchange chromatography was performed on Amberlite IR-120 (H^+) or Dowex 50 W × 8–400, H^+ form. Melting points were determined using an electrothermal melting point apparatus. Infrared spectra were recorded on an FT-IR spectrometer. NMR spectra were recorded on magnetic resonance spectrometers (^1H at 300 MHz, 400 MHz or 500 MHz, ^{13}C at 75 MHz, 100 MHz or 125 MHz) in $CDCl_3$ (with TMS as internal standard), D_2O or CD_3OD. Chemical shifts (δ) are reported in ppm, and coupling constants (J) are in Hz. High resolution mass spectra (HRMS) were recorded on an LTQ/FT linear ion trap mass spectrometer. Polarimetry measurements were made at the sodium D-line with a 0.5 dm path length cell. Concentrations (c) are given in gram per 100 mL.

***N*-Hydroxyl-2,3,5,6-di-*O*-isopropylidene-1,4-dideoxy-1,4-imino-D-talitol (9).** Sodium borohydride (3.1 g, 80 mmol) was added to a solution of nitrone **10** (5 g, 20 mmol) in methanol in small portions at 0 °C. The mixture was stirred for 2 hours at the same temperature then the reaction was quenched with saturated NH_4Cl and the methanol was removed *in vacuo*. The residue was redissolved in water (15 mL) and extracted with EtOAc (10 mL × 3). The combined organic layers were dried with $MgSO_4$ and concentrated. The white crystalline product (4.3 g, 89%) was then employed for the next step without further purification **9**: m.p. 83–85 °C: $[\alpha]_D^{20}$ = −29 (c = 1.0, CH_2Cl_2); IR (thin film, cm^{-1}) 3419, 2986, 2938, 1373, 1210, 1059, 850; ^1H NMR (300 MHz, $CDCl_3$) δ 4.75 (q, J = 5.9 Hz, 1H), 4.43 (dd, J = 6.7, 5.4 Hz, 1H), 4.30 (q, J = 6.5 Hz, 1H), 4.10 (dd, J = 8.4, 6.5 Hz, 1H), 3.94 (dd, J = 8.4, 6.4 Hz, 1H), 3.62 (dd, J = 11.9, 5.9 Hz, 1H), 3.18–3.13 (m, 2H), 1.67 (br, 1H), 1.53 (s, 3H), 1.46 (s, 3H), 1.37 (s, 3H), 1.32 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 114.1, 109.6, 80.8, 78.5, 75.5, 75.2, 66.3, 63.7, 27.2, 26.6, 25.3, 24.8; HRMS calcd for $[C_{12}H_{21}NO_5H^+]$ 260.1492, found 260.1491.

(3*R*,4*S*)-5-((*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl)-3,4-*O*-isopropylidene-3,4-dihydroxy-3,4-dihydro-2*H*-pyrrole 1-oxide (8). Active manganese dioxide (2.4 g, 28 mmol) was added to a solution of **9** (3.5 g, 13.5 mmol) in CH_2Cl_2 (30 mL). The suspension liquid was stirred for 48 hours at room temperature. Then the mixture was filtered through a celite pad and the residue was washed with CH_2Cl_2. The eluent was concentrated and the residue was purified by column chromatography with CH_2Cl_2 to give **8** (2.5 g, 72%) and EtOAc/petroleum ether (1 : 1) to give **10** (0.8g, 23%)as white crystals. **8**: m.p. 92–95 °C; $[\alpha]_D^{20}$ = +16 (c = 0.5, CH_2Cl_2); IR (thin film, cm^{-1}) 2988, 2350, 1599, 1374, 1207, 1038, 852, 699; ^1H NMR (300 MHz, $CDCl_3$) δ 5.37 (d, J = 6.5 Hz, 1H), 5.16–5.11 (m, 1H), 4.88–4.84 (m, 1H), 4.45 (dd, J = 9.0, 7.2 Hz, 1H), 4.21–4.14 (m, 2H), 4.11–4.05 (m, 1H), 1.51 (s, 3H), 1.48 (s, 3H), 1.4 3 (s, 3H), 1.41 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.0, 112.3, 110.4, 81.0, 71.8, 71.3, 68.3, 66.8, 27.1,

26.0, 25.5, 24.8; HRMS calcd for $[C_{12}H_{19}NO_5Na^+]$ 280.1155, found 280.1151.

***N*-Hydroxyl-2,3,5,6-di-*O*-isopropylidene-1,4-dideoxy-1,4-imino-D-mannitol (7).** Sodium borohydride (1.1 g, 29 mmol) was added to a solution of **8** (1.8 g, 0.7 mmol) in methanol in small portions at 0 °C. The mixture was stirred for 2 hours at the same temperature, then the reaction was quenched with saturated NH_4Cl and the methanol was removed *in vacuo*. The residue was redissolved in water (5 mL) and extracted with EtOAc (5 mL × 3). The combined organic layers were dried with $MgSO_4$ and concentrated. The product (1.7 g, 94%) was employed for the next step without further purification as white crystal.**7**: m.p. 79–83 °C; $[\alpha]_D^{20} = -70$ (c = 1.0, CH_2Cl_2); IR (thin film, cm^{-1}) 3183, 2988, 2939, 2877, 1701, 1380, 1211, 1104, 1064, 849; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.22 (s, 1H), 4.72 (dd, J = 6.6, 5.2 Hz, 1H), 4.64 (dd, J = 6.6, 4.8 Hz, 1H), 4.39 (q, J = 6.4 Hz, 1H), 4.20 (dd, J = 8.5, 6.5 Hz, 1H), 4.11 (dd, J = 8.5, 6.1 Hz, 1H), 3.52 (d, J = 11.1 Hz, 1H), 2.75 (dd, J = 11.3, 4.8 Hz, 1H), 2.71 (dd, J = 7.8, 5.1 Hz, 1H), 1.45 (s, 3H), 1.44 (s, 3H), 1.41 (s, 3H), 1.30 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 110.5, 108.3, 77.7, 74.9, 74.3, 72.0, 67.7, 63.3, 26.8, 25.6, 25.5, 23.9; HRMS calcd for $[C_{12}H_{21}NO_5H^+]$ 260.1492, found 260.1492.

***N*-Benzyloxycarbonyl-2,3,5,6-di-*O*-isopropylidene-1,4-dideoxy-1,4-imino-D-mannitol (12).** Zinc powder (15.6 g, 23.4 mol) and cupric acetate monohydrate (0.38 g, 23.4 mmol) were added to acetic acid (15 mL); the reaction mixture was stirred for 15 min at room temperature and turned brown. Then the substrate **7** (3.9 g, 14.4 mmol) in acetic acid was added and the mixture was stirred overnight at room temperature. The acetic acid was removed *in vacuo* and the residue was washed with EtOAc (10 mL × 3). Then the eluent was washed with aqueous $NaHCO_3$ solution and the water phase was extracted with EtOAc (5 mL × 3). The combined organic layers were dried with $MgSO_4$ and concentrated. The residue was redissolved in THF (25 mL) and water (1 mL). To the mixture was added $NaHCO_3$ (2.2 g, 25.9 mmol) at room temperature, then CbzCl (3.1 mL, 22 mmol) was added slowly. The mixture was stirred overnight. The reaction was quenched with saturated NH_4Cl and extracted with EtOAc (10 mL × 3). The combined organic layers were dried with $MgSO_4$ and concentrated. The residue was purified by column chromatography with EtOAc/petroleum ether (1 : 20) to give **12** (5.1 g, 89%) as clear oil. **12**: $[\alpha]_D^{20} = -26$ (c = 1.0, CH_2Cl_2); IR (thin film, cm^{-1}) 2986, 1707, 1412, 1370, 1211, 1060, 858; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37–7.26 (m, 5H), 5.13 (d, J = 12.3 Hz, 1H), 5.08 (d, J = 12.3 Hz, 1H), 4.78 (dd, J = 6.1 Hz, 1H), 4.66 (ddd, J = 10.6 6.4, 4.0 Hz, 1H), 4.59–4.52 (m, 1H), 4.09 (dd, J = 8.8, 6.1 Hz, 1H), 4.01–3.94 (m, 2H), 3.77 (dd, J = 12.6, 6.1 Hz, 1H), 3.50 (dd, J = 12.7, 3.7 Hz, 1H), 1.48 (s, 3H), 1.40 (s, 3H), 1.37 (s, 3H), 1.35 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.1, 136.3, 128.5, 128.1, 128.0, 113.1, 109.0, 80.0, 77.9, 74.4, 67.8, 67.3, 62.7, 52.1, 26.8, 26.5, 25.4, 24.9; HRMS calcd for $[C_{20}H_{27}NO_6Na^+]$ 400.1731, found 400.1727.

***N*-Benzyloxycarbonyl-2,3-*O*-isopropylidene-1,4-dideoxy-1,4-imino-D-mannitol (13) and *N*-Benzyloxycarbonyl-1,4-dideoxy-1,4-imino-D-mannitol (14).** 1% (w/w) H_2SO_4 (15 mL) was added to a solution of **12** (5.1 g, 13.5 mmol) in methanol (25 mL) at room temperature, the mixture was stirred overnight. The reaction was neutralized with aqueous $NaHCO_3$ and methanol was removed *in vacuo*. The residue was extracted with EtOAc (15 mL × 3) and the combined organic layers were dried ($MgSO_4$). The residue was purified by column chromatography with EtOAc/petroleum ether (1 : 3) to give **13** (2.4 g, 52%) and **14** (0.3 g, 6.5%) as clear oil. **13** $[\alpha]_D^{20} = -30$ (c = 1.0, CH_2Cl_2); IR (thin film, cm^{-1}) 3447, 2940, 1670, 1685, 1419, 1212, 1084, 869; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39–7.28 (m, 5H), 5.14 (d, J = 12.3 Hz, 1H), 5.09 (d, J = 12.3 Hz, 1H), 4.90 (dd, J = 6.8 Hz, 1H), 4.76 (ddd, J = 11.8, 7.0, 4.7 Hz, 1H), 4.19 (dd, J = 7.5 Hz, 1H), 4.04 (dd, J = 10.7, 7.0 Hz, 1H), 3.97–3.83 (m, 1H), 3.77–3.64 (m, 2H), 3.59 (dt, J = 12.2, 3.9 Hz, 1H), 3.47 (br, 1H), 3.29 (dd, J = 12.5, 4.6 Hz, 1H), 1.54 (s, 3H), 1.35 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.6, 135.9, 128.6, 128.4, 128.2, 113.9, 80.0, 78.2, 76.7, 71.1, 67.8, 63.3, 59.9, 50.6, 26.3, 24.8; HRMS calcd for $[C_{17}H_{23}NO_6Na^+]$ 360.1418, found 360.1413; **14** $[\alpha]_D^{20} = -42$ (c = 1.0, CH_2Cl_2); IR (thin film, cm^{-1}) 3348, 2940, 1682, 1417, 1357, 1211, 1102, 890; ^{1}H NMR (400 MHz, CD_3OD) δ 7.44–7.26 (m, 5H), 5.15 (s, 2H), 4.38 (dd, J = 6.8, 4.8 Hz, 1H), 4.31–4.28 (m, 1H), 4.11 (q, J = 4.6 Hz, 1H), 4.01–3.99 (m, 1H), 3.71–3.65 (m, 3H), 3.37–3.33 (m, 1H); ^{13}C NMR (125 MHz, CD_3OD) δ 156.2, 155.7, 136.6, 128.2, 127.8, 127.5, 73.1, 72.9, 72.4, 71.9, 70.2, 69.4, 66.9, 63.4, 60.1, 59.8, 52.0, 51.5; HRMS calcd for $[C_{14}H_{19}NO_6Na^+]$ 320.1105, found 320.1100.

1,4-Dideoxy-1,4-imino-D-mannitol (3). 15 mg of 10% Pd/C was added to a solution of **14** (45 mg, 0.15 mmol) in methanol, then the mixture was stirred under the atmosphere of H_2 at room temperature for 24 hours and filtered through a celite pad. Removal of methanol gave **3** (21 mg, 88%) as yellow oil. $[\alpha]_D^{20} = -26$ (c = 1.0, CH_2Cl_2); IR (thin film, cm^{-1}) 2941, 2833, 1659, 1448, 1131, 1026; ^{1}H NMR (500 MHz, D_2O) δ 4.24 (dt, J = 8.2, 4.2 Hz, 1H), 4.12 (t, J = 3.8 Hz, 1H), 3.77 (ddd, J = 9.3, 6.5, 2.9 Hz, 1H), 3.66 (dd, J = 12.0, 2.9 Hz, 1H), 3.47 (dd, J = 12.0, 6.5 Hz, 1H), 3.08 (dd, J = 11.2, 8.0 Hz, 1H), 3.03 (dd, J = 9.4, 3.5 Hz, 1H), 2.68 (dd, J = 11.2, 8.5 Hz, 1H); ^{13}C NMR (125 MHz, D_2O) δ 72.1, 71.4, 70.2, 63.6, 60.7, 48.4; HRMS calcd for $[C_6H_{13}NO_4H^+]$ 164.0917, found 164.0917.

***N*-Benzyloxycarbonyl-2,3-*O*-isopropylidene-5-*O*-methoxylmethyl-6-*O*-*tert*-butyldimethylsilyl-1,4-dideoxy-1,4-imino-D-mannitol (6).** Triethylamine (2 mL, 28 mmol) and *tert*-butyldimethylsilyl chloride (3.8 g, 26 mmol) were added to a solution of **13** (4.8 g, 14.2 mmol) in CH_2Cl_2 (15 mL) in small portions. The mixture was stirred at room temperature for 7 hours. The reaction was quenched with saturated NH_4Cl and extracted with EtOAc (5 mL × 3). The combined organic layers were dried with $MgSO_4$ and concentrated. Then the residue was redissolved in dry CH_2Cl_2 To the mixture was added *N*,*N*-diisopropylethylamine (4.4 mL, 25 mmol) at 0 °C under argon, and then chloromethyl methyl ether (1.5 mL, 20 mmol) was added dropwisely. The mixture was allowed to warm to room temperature and stirred for 48 hours. The reaction was quenched with saturated NH_4Cl and extracted with EtOAc (10 mL × 3). The combined organic layers were dried with $MgSO_4$ and con-

centrated. The residue was purified by column chromatography with EtOAc/petroleum ether (1 : 10) to give **6** (5.4 g, 76%) as clear oil. $[\alpha]_D^{20} = -14$ (c = 0.5, CH_2Cl_2); IR (thin film cm^{-1}) 2932, 1706, 1417, 1251, 1212, 1089, 1038, 838; ^1H NMR (300 MHz, $CDCl_3$) δ 7.35–7.29 (m, 5H), 5.12 (s, 2H), 4.83 (t, J = 6.8 Hz, 1H), 4.71–4.62 (m, 3H), 4.22 (dd, J = 6.6, 5.3 Hz, 1H), 4.19–4.11 (m, 1H), 4.02 (dd, J = 11.7, 7.4 Hz, 1H), 3.85–3.78 (m, 2H), 3.33 (s, 3H), 3.32–3.25 (m, 1H), 1.53 (s, 3H), 1.32 (s, 3H), 0.87 (s, 9H), 0.02 (s, 6H).^{13}C NMR (75 MHz, $CDCl_3$) δ 154.8, 136.6, 128.6, 128.2, 113.8, 97.6, 80.0, 78.0, 77.8, 67.3, 64.3, 60.5, 55.8, 51.4, 26.8, 26.0, 25.2, 18.3, −5.3, −5.4; HRMS calcd for $[C_{25}H_{41}NO_7SiNa^+]$ 518.2545, found 518.2541.

***N*-Benzyloxycarbonyl-2,3-*O*-isopropylidene-5-*O*-methoxylmethyl-1,4-dideoxy-1,4-imino-D-mannitol (15).** Excess Olah's reagent was added to a solution of **6** (4 g, 8 mmol) in THF. The mixture was stirred at room temperature for 2 hours. The reaction was quenched with saturated $NaHCO_3$ and extracted with EtOAc (10 mL × 3). The combined organic layers were dried with $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography with EtOAc/petroleum ether (1 : 5) to give **15** (2.7 g, 91%) as clear oil. **15**: $[\alpha]_D^{20} = -56$ (c = 0.5, CH_2Cl_2); IR (thin film cm^{-1}) 3462, 2939, 1702, 1418, 1212, 1088, 1038, 866; ^1H NMR (300 MHz, $CDCl_3$) δ 7.75–7.09 (m, 5H), 5.14 (d, J = 12.3 Hz, 1H), 5.07 (d, J = 12.3 Hz, 1H), 4.85 (t, J = 6.6 Hz, 1H), 4.76 (dt, J = 7.01, 6.9 Hz, 1H),4.68 (d, J = 6.9 Hz, 1H), 4.63 (q, J = 6.9 Hz, 1H), 4.28 (dd, J = 8.8, 6.9 Hz, 1H), 4.11 (dd, J = 12.0, 7.5 Hz, 1H), 3.97 (s, 1H), 3.83 (dt, J = 8.9, 2.6 Hz, 1H), 3.74 (dd, J = 11.7 Hz, 1H), 3.59 (dt, J = 12.8, 3.5 Hz, 1H), 3.43 (s, 3H), 3.09 (dd, J = 12.0, 7.0 Hz, 1H), 1.50 (s, 3H), 1.32 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.9, 136.0, 128.7, 128.4, 128.2, 113.6, 97.6, 80.0, 77.9, 67.9, 62.4, 59.3, 55.9, 51.0, 27.3, 25.4; HRMS calcd for $[C_{19}H_{27}NO_7Na^+]$ 404.1680, found 404.1678.

1,2-*O*-Isopropylidene-8-*O*-methoxylmethyl-5-oxo-D-swainsonine (17). Sodium hydrogen carbonate (0.17 g, 2.34 mmol) was added to a solution of DMP (0.69 g, 1.56 mmol) in dry CH_2Cl_2. The mixture was stirred at room temperature for 15 minutes and **15** (0.3 g, 0.78 mmol) in 2 mL of dry CH_2Cl_2 was added dropwisly. The mixture was stirred at room temperature for 2 hours. The product and substrate cannot be separated by TLC. To this suspension was added 3 mL of saturated $Na_2S_2O_3$. The mixture was stirred and became clear. Then 5 mL of saturated NH_4Cl was added and the mixture was extracted with EtOAc (3 × 10 mL). The combined organic layers were dried with $MgSO_4$ and concentrated. The residue was dissovled in dry toluene (15 mL) and methyl 3-(triphenylphosphoranylidene)propanoate (0.31 g, 0.94 mmol) was added. The mixture was refluxed under argon for 1 hour. The mixture was concentrated and the residue was recrystallized with Et_2O to separate Ph_3PO. Then the solvent was removed and the residue was dissolved in MeOH. To the mixture under argon was added 30 mg of 10% Pd/C. The reaction was stirred under the atmosphere of H_2 at room temperature for 24 hours, filtered through a celite pad, and concentrated *in vacuo*. The residue was redissolved in methanol (5 mL) and K_2CO_3 (30 mg) was added. The mixture was stirred at room temperature overnight. Then the reaction was concentrated *in vacuo*, redissolved in water and extracted with EtOAc (5 mL × 3). The combined organic layers were dried with $MgSO_4$ and concentrated. The residue was purified by column chromatography with EtOAc/petroleum ether (1 : 1) to give amide **17** (135 mg, 72%) as clear oil. $[\alpha]_D^{20} = +22$ (c = 0.5, CH_2Cl_2); IR (thin film cm^{-1}) 2939, 1652, 1451, 1379, 1212, 1156, 1098; ^1H NMR (300 MHz, $CDCl_3$) δ 4.76 (d, J = 6.8 Hz, 1H), 4.74–4.65 (m, 3H), 4.16 (d, J = 13.5 Hz, 1H), 4.12–4.01 (m, 1H), 3.38 (s, 3H), 3.33 (dd, J = 7.9, 2.8 Hz, 1H), 3.05 (dd, J = 13.6, 3.7 Hz, 1H), 2.52–2.41 (m, 1H), 2.41–2.27 (m, 1H), 2.20–2.14 (m, 1H), 1.90–1.81 (m, 1H), 1.37 (s, 3H), 1.29 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.6, 112.0, 95.9, 79.8, 77.6, 70.3, 65.3, 55.6, 50.6, 29.5, 27.7, 26.6, 24.8; HRMS calcd for $[C_{13}H_{21}NO_5H^+]$ 272.1493, found 272.1488.

5-Oxo-D-swainsonine (18). Hydrochloric acid (3 N, 2 mL) was added to a solution of **17** (54 mg, 0.2 mmol) in methanol. The mixture was stirred at room temperature for 2 hours. Removal of solvent gave **18** (35 mg, 97%) as yellow gel. **18**: $[\alpha]_D^{20} = -16$ (c = 0.25, CH_2Cl_2); IR (thin film cm^{-1}) 3359, 2933, 1061, 1488, 1415, 1267, 1110, 1046, 808; ^1H NMR (500 MHz, D_2O) δ 4.47–4.43 (m, 1H), 4.27 (d, J = 2.6 Hz, 1H), 4.03–3.98 (m, 1H), 3.72 (dd, J = 11.7, 9.0 Hz, 1H), 3.45 (d, J = 9.1 Hz, 1H), 3.20 (dd, J = 11.2, 9.5 Hz, 1H), 2.52–2.38 (m, 2H), 2.12–2.09 (m, 1H), 1.87–1.78 (m, 1H). ^{13}C NMR (125 MHz, D_2O) δ 171.6, 70.3, 69.2, 65.7, 63.2, 48.3, 28.8, 28.1; HRMS calcd for $[C_8H_{13}NO_4H^+]$ 188.0917, found 188.0917.

Swainsonine (1). Lithium aluminium hydride (80 mg, 2 mmol) was added to solution of amide **18** (120 mg, 0.73 mmol) in dry THF. The reaction mixture was refluxed for 4 hours. To the mixture were subsequently added water (0.08 mL), 15% (w/w) NaOH (0.08 mL) and water (0.24 mL) and white solid occurred. The mixture was filtered to separate the solid and washed with CH_2Cl_2. The eluent was dried with $MgSO_4$ and concentrated. The residue was chromatographed on silica gel with EtOAc–PE (1 : 3) to give **4** which was then dissolved in methanol. To a solution of **4** in methanol was added 2 mL of 3 N HCl. The mixture was stirred at room temperature for 20 minutes. The reaction was concentrated and the residue was subjected to an ion exchange column (DOWEX 50 W × 8, 100–200 mesh) eluted with 6 N ammonia solution. Removal of solvent gave **1** (56 mg, 74%) as white solid. **1**: mp 141–143 °C (lit.[4b] mp 144–145 °C); $[\alpha]_D^{25} = -81.9$ (c = 1.05, MeOH) [lit.[4b] $[\alpha]_D^{20} = -87.2$ (c 2.1, MeOH)]; IR (KBr cm^{-1}) 3359, 2928, 1661, 1447, 1327, 1215, 1142, 1084, 1027; ^1H NMR (500 MHz, D_2O) δ 4.42–4.35 (m, 1H), 4.29 (dd, J = 5.7, 3.6 Hz, 1H), 3.83 (dt, J = 10.7, 4.6 Hz, 1H), 2.99–2.94 (m, 2H), 2.67 (dd, J = 10.9,8.25 Hz, 1H), 2.14–2.02 (m, 3H), 1.76 (d, J = 13.8 Hz, 1H), 1.55 (qt, J = 5.7, 3.6 Hz, 1H), 1.31–1.23 (m, 1H); [lit.[5] (90 MHz, D_2O, ref. DSS) 4.42–4.17(m, 2H), 3.79(ddd, J = 9–10, 10, 4–5 Hz, 1H), 2.85(m, 2H), 2.50 (dd, J = 11, 6 Hz, 1H), 2.13–0.94 (m, 6H); lit.[4b] (89.55 MHz, D_2O, ref. DSS) 4.44–4.18 (m, 2H), 3.80 (ddd, 1H), 2.89 (dd, 2H), 2.53 (dd, 1H), 2.14–0.98 (m, 6H)]; ^{13}C NMR (125 MHz, D_2O) δ 72.29, 69.08, 68.53, 65.66, 59.90, 51.22, 31.85, 22.54; [lit.[5] (D_2O, ref. MeOH) 72.55, 69.42, 68.74, 66.07, 60.38, 51.33, 32.16, 22.89; lit.[4b] (22.5 MHz, D_2O, ref. MeOH)

72.56, 69.42, 68.77, 66.06, 60.38, 51.38, 32.21, 22.89]; HRMS calcd for $[C_8H_{15}NO_3H^+]$ 174.1125, found 174.1127.

***N*-Benzyloxycarbonyl-2,3,5,6-di-*O*-isopropylidene-1,4-dideoxy-1,4-imino-D-talitol (19).** Zinc powder (10 g, 0.15 mmol) and cupric acetate monohydrate (0.3 g, 0.15 mmol) were added to acetic acid (15 mL), the mixture was stirred for 15 min at room temperature and turned into brown. Then the substrate **7** (4 g, 15 mmol) in acetic acid was added and the mixture was stirred overnight at room temperature. The acetic acid was removed under vacuum and the residue was washed with EtOAc (10 mL × 3). Then the eluent was washed with aqueous $NaHCO_3$ solution and the water phase was extracted with EtOAc (5 mL × 3). The combined organic layer was dried over $MgSO_4$ and concentrated. The residue was redissolved in THF (25 mL) and water (1 mL). To the mixture was added $NaHCO_3$ (2.5 g, 30 mmol) at room temperature, then CbzCl (3.1 mL, 22 mmol) was added slowly. The mixture was stirred overnight. The reaction was quenched with saturated NH_4Cl and extracted with EtOAc (10 mL × 3). The combined organic layers were dried with $MgSO_4$ and concentrated. The residue was purified by column chromatography with EtOAc/petroleum ether (1 : 20) to give **19** (4.9 g, 82%) as clear oil. $[\alpha]_D^{25}$ = +76 (*c* = 1.00, CH_2Cl_2); IR (thin film cm^{-1}) 2986, 1703, 1455, 1213, 1118, 1060, 872; ^1H NMR (300 MHz, $CDCl_3$) δ 7.38–7.29 (m, 5H), 5.23–5.10 (m, 2H), 4.80–4.70 (m, 2H), 4.32–4.17 (m, 2H), 4.06–3.99 (m, 1H), 3.95–3.86 (m, 1H), 3.76 (t, *J* = 8.3 Hz, 0.5H), 3.63–3.52 (m, 1.5H), 1.38 (s, 3H), 1.33–1.30 (m, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.0, 155.3, 136.8, 136.4, 128.5–126.9, 111.6, 109.1, 109.0, 83.4, 82.8, 80.2, 79.5, 77.7, 77.5, 67.3, 67.1, 66.0, 65.9, 63.9, 63.6, 54.4, 54.3, 26.9, 26.0, 25.5, 25.4, 24.8; HRMS calcd for $[C_{20}H_{27}NO_6Na^+]$ 400.1731, found 400.1728.

***N*-Benzyloxycarbonyl-2,3,-*O*-isopropylidene-1,4-dideoxy-1,4-imino-D-talitol (20) and *N*-benzyloxycarbonyl-1,4-dideoxy-1,4-imino-D-talitol (21).** 1% (w/w) H_2SO_4 was add to a solution of **19** (3 g, 8.9 mmol) in methanol (15 mL) at room temperature, the mixture was stirred overnight. The reaction was neutralized with aqueous $NaHCO_3$ and methanol was removed *in vacuo*. The residue was extracted with EtOAc (15 mL × 3) and the combined organic layers were dried ($MgSO_4$). The residue was purified by column chromatography with EtOAc/petroleum ether (1 : 3) to give **20** (1.8 g, 69%) and **21** (0.11 g, 4.6%) as clear oil. **20**: $[\alpha]_D^{20}$ = +54 (*c* = 1.0, CH_2Cl_2); IR (thin film cm^{-1}) 3423, 2986, 2940, 1682, 1425, 1214, 1126, 1063, 699; ^1H NMR (300 MHz, $CDCl_3$) δ 7.43–7.27 (m, 5H), 5.18 (s, 2H), 4.80–4.74 (m, 2H), 4.33 (d, *J* = 1.6 Hz, 1H), 4.03–3.93 (m, 1H), 3.91 (d, *J* = 12.4 Hz, 1H), 3.70–3.65 (m, 1H), 3.58 (dd, *J* = 12.3, 4.8 Hz, 2H), 3.52–3.48 (m, 1H), 2.06 (d, *J* = 4.5 Hz, 1H), 1.41 (s, 3H), 1.31 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.8, 136.4, 128.5, 128.1, 127.5, 111.5, 83.1, 79.9, 73.5, 67.5, 65.0, 63.3, 54.3, 26.9, 24.8; HRMS calcd for $[C_{17}H_{23}NO_6Na^+]$ 360.1418, found 360.1414. **21**: $[\alpha]_D^{20}$ = +18 (*c* = 1.0, MeOH); IR (thin film cm^{-1}) 3335, 2940, 1682, 1417, 1357, 1101, 698; ^1H NMR (300 MHz, CD_3OD) δ 7.39–7.32 (m, 5H), 5.15 (m, 2H), 4.41 (dd, *J* = 10.6, 6.1 Hz, 1H), 4.16 (dd, *J* = 4.2, 2.5 Hz, 1H), 3.95–3.91 (m, 1H), 3.79 (dt, *J* = 5.9, 2.9 Hz, 1H), 3.89–3.48 (m, 4H), 3.43–3.32 (m, 1H); ^{13}C NMR (125 MHz, CD_3OD) δ 157.2, 136.7, 128.1, 127.9, 127.7, 127.5, 74.0, 72.5, 70.1, 67.1, 65.8, 63.4; HRMS calcd for $[C_{14}H_{19}NO_6Na^+]$ 320.1105, found 320.1101.

1,4-Dideoxy-1,4-imino-D-talitol (22). 10% Pd/C (15 mg) was added to a solution of **21** (25 mg, 0.08 mmol) in methanol, then the mixture was stirred under the atmosphere of H_2 at room temperature for 24 hours and filtered through a celite pad. Removal of methanol gave **22** (11 mg, 81%) as yellow oil. $[\alpha]_D^{20}$ = −54 (*c* = 0.4, CH_2Cl_2); IR (thin film cm^{-1}) 2930, 1671, 1445, 1329, 1126, 1003; ^1H NMR (400 MHz, D_2O) δ 4.14 (dd, *J* = 7.7, 4.7 Hz, 1H), 3.98 (dd, *J* = 8.2, 4.9 Hz, 1H), 3.85–3.76 (m, 1H), 3.65 (dd, *J* = 11.8, 3.9 Hz, 1H), 3.55 (dd, *J* = 11.8, 7.0 Hz, 1H), 3.21 (dd, *J* = 12.6, 4.8 Hz, 1H), 3.08 (dd, *J* = 8.2, 4.2 Hz, 1H), 2.90 (dd, *J* = 12.6, 2.8 Hz, 1H); [lit.[23e] ^1H NMR (D_2O) δ 3.95 (dt, H-2, 1H), 3.78 (dd, H-3, $J_{2,3}$ = 5.2 Hz, 1H), 3.62 (m, H-5, 1H), 3.57 (dd, H-6′, $J_{5,6'}$ = 4.1 Hz, 1H), 3.40 (dd, H-6, $J_{6,6'}$ = 11.8 Hz, $J_{5,6}$ = 7.7 Hz, 1H), 3.02 (dd, H-1′, $J_{1',2}$ = 5.1 Hz, 1H), 2.78 (dd, H-4, $J_{3,4}$ = 7.9 Hz, $J_{4,5}$ = 4.2 Hz, 1H), 2.62 (dd, H-1, $J_{1,1'}$ = 12.5 Hz, $J_{1,2}$ = 3.4 Hz, 1H)]; ^{13}C NMR (100 MHz, D_2O) δ 72.8, 70.5, 70.0, 63.7, 62.1, 50.1; HRMS calcd for $[C_6H_{13}NO_4H^+]$ 164.0917, found 164.0914.

***N*-Benzyloxycarbonyl-2,3-*O*-isopropylidene-5-*O*-methoxylmethyl-6-*O*-*tert*-butyldimethylsilyl-1,4-dideoxy-1,4-imino-D-talitol (23).** Triethylamine (3.7 mL, 26 mmol) and *tert*-butyldimethylsilyl chloride (3 g, 20 mmol) were added to a solution of **20** (4.5 g, 13 mmol) in CH_2Cl_2 (5 mL) in small portions. The mixture was stirred at room temperature for 7 hours. The reaction was quenched with saturated NH_4Cl and extracted with EtOAc (5 mL × 3). The combined organic layers were dried with $MgSO_4$ and concentrated. Then the residue was redissolved in dry CH_2Cl_2. To the mixture was added *N*,*N*-diisopropylethylamine (4.4 mL, 25 mmol) at 0 °C under argon, and then chloromethyl methyl ether (1.5 mL, 20 mmol) was added dropwisely. The mixture was allowed to warm to room temperature and stirred for 48 hours. The reaction was quenched with saturated NH_4Cl and extracted with EtOAc (10 mL × 3). The combined organic layers were dried with $MgSO_4$ and concentrated. The residue was purified by column chromatography with EtOAc/petroleum ether (1 : 10) to give **23** (5.2 g, 79%) as clear oil. **23**: $[\alpha]_D^{20}$ = +8 (*c* = 0.5, CH_2Cl_2); IR (thin film cm^{-1}) 2932, 1706, 1458, 1418, 1213, 1121, 1032, 838; ^1H NMR (300 MHz, $CDCl_3$) δ 7.35–7.26 (m, 5H), 5.14 (s, 2H), 4.91 (d, *J* = 6.0 Hz, 1H), 4.82 (d, *J* = 6.7 Hz, 0.5H), 4.76 (d, *J* = 6.8 Hz, 0.5H), 4.73 (d, *J* = 5.6 Hz, 1H), 4.66 (dd, *J* = 6.6 Hz, 0.5H), 4.60 (dd, *J* = 6.7 Hz, 0.5H), 4.28 (dd, *J* = 12.0, 4.5 Hz, 1H), 4.00–3.88 (m, 1H), 3.81–3.76 (m, 1H), 3.69 (dd, *J* = 11.4, 3.3 Hz, 1H), 3.62–3.45 (m, 2H), 3.36 (d, *J* = 13.0 Hz, 3H), 1.39 (s, 3H), 1.30 (s, 3H), 0.87 (d, *J* = 5.6 Hz, 9H), 0.07–0.01 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.2, 155.1, 136.9, 136.6, 128.5, 128.0, 127.9, 127.8, 127.7, 111.3, 111.3, 96.9, 96.5, 82.8, 82.2, 80.1, 79.4, 77.8, 76.7, 67.2, 66.9, 65.3, 65.1, 63.9, 63.4, 55.9, 55.9, 53.7, 53.5, 26.9, 26.8, 25.9, 25.8, 24.8, 24.7, 18.3, −5.4, −5.5, −5.57, −5.6; HRMS calcd for $[C_{25}H_{41}NO_7SiNa^+]$ 518.2545, found 518.2540.

***N*-Benzyloxycarbonyl-2,3-*O*-isopropylidene-5-*O*-methoxylmethyl-1,4-dideoxy-1,4-imino-D-talitol (24).** Tetrabutylammonium fluoride trihydrate (2.8 g, 8.9 mmol) was added to a solution of **23**

(4 g, 8 mmol) in THF. The mixture was stirred at room temperature for 30 minutes. The reaction was quenched with saturated NH_4Cl and extracted with EtOAc (10 mL × 3). The combined organic layers were dried with $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography with EtOAc/petroleum ether (1 : 5) to give **24** (2.9 g, 97%) as oil. $[\alpha]_D^{20}$ = +66 (*c* = 0.75, CH_2Cl_2); IR (thin film cm^{-1}) 2940, 1701, 1678, 1423, 1212, 1128, 1051, 869; ^1H NMR (300 MHz, $CDCl_3$) δ 7.42–7.27 (m, 5H), 5.23–5.14 (m, 2H), 4.79–4.72 (m, 1H), 4.70 (d, *J* = 6.0 Hz, 1H), 4.60 (dd, *J* = 11.8, 6.7 Hz, 2H), 4.49 (d, *J* = 1.9 Hz, 1H), 4.17 (dd, *J* = 9.7, 5.1 Hz, 1H), 3.89 (d, *J* = 12.4 Hz, 1H), 3.89–3.83 (m, 1H), 3.76–3.62 (m, 1H), 3.55 (dd, *J* = 12.3, 5.0 Hz, 1H), 3.46–3.36 (m, 1H), 3.35 (s, 3H), 1.40 (s, 3H), 1.31 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.7, 136.4, 128.5, 128.1, 127.6, 111.5, 96.9, 83.0, 80.9, 80.1, 67.5, 64.2, 60.7, 55.9, 54.3, 26.9, 24.8; HRMS calcd for $[C_{19}H_{27}NO_7Na^+]$ 404.1680, found 404.1677.

1,2-*O*-Isopropylidene-8-*O*-methoxylmethyl-5-oxo-8a-*epi*-D-swainsonine (25). Sodium hydrogen carbonate was added (0.29 g, 3.5 mmol) to a solution of DMP (1.03 g, 2.3 mmol) in dry CH_2Cl_2. The mixture was stirred at room temperature for 15 minutes and **24** (0.5 g, 1.3 mmol) in 2 mL of dry CH_2Cl_2 was added dropwisly. The mixture was stirred at room temperature for 2 hours. The product and substrate cannot be separated by TLC. To this suspension was added 3 mL of saturated $Na_2S_2O_3$. The mixture was stirred and became clear. Then 5 mL of saturated NH_4Cl was added and the mixture was extracted with EtOAc (3 × 10 mL). The combined organic layers were dried with $MgSO_4$ and concentrated. The residue was redissolved in dry toluene (15 mL) and methyl 3-(triphenylphosphoranylidene)propanoate (0.5 g, 1.5 mmol) was added. The mixture was refluxed under argon for 1 hour. The mixture was concentrated and the residue was recrystallized with Et_2O to separate Ph_3PO. Then the solvent was removed and the residue was dissolved in MeOH. To the mixture under argon was added 30 mg of 10% Pd/C. The reaction was stirred under atmosphere of H_2 at room temperature for 24 hours, filtered through a celite pad, and concentrated *in vacuo*. The residue was redissolved in methanol (5 mL) and K_2CO_3 (30 mg) was added. The mixture was stirred at room temperature overnight. Then the reaction was concentrated *in vacuo*, redissolved in water and extracted with EtOAc (5 mL × 3). The combined organic layers were dried with $MgSO_4$ and concentrated. The residue was purified by column chromatography with EtOAc/petroleum ether (1 : 1) to give amide **25** (197 mg, 63%) as clear oil. $[\alpha]_D^{20}$ = −44 (*c* = 0.5, CH_2Cl_2); IR (thin film cm^{-1}) 3443, 2938, 1641, 1459, 1376, 1216, 1151, 1085, 1033; ^1H NMR (300 MHz, $CDCl_3$) δ 4.78–4.74 (m, 2H), 4.71–4.66 (m, 2H), 4.18–4.12 (m, 2H), 3.57 (dd, *J* = 6.3, 2.6 Hz, 1H), 3.48 (dd, *J* = 13.9, 1.2 Hz, 1H), 3.41 (s, 3H), 2.44–2.35 (m, 2H), 2.25–2.22 (m, 1H), 1.86–1.74 (m, 1H), 1.53 (s, 3H), 1.37 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.6, 113.3, 95.5, 79.5, 76.6, 68.0, 66.6, 56.0, 49.5, 28.0, 26.5, 25.8, 25.2; HRMS calcd for $[C_{13}H_{21}NO_5H^+]$ 272.1492, found 272.1495.

5-Oxo-8a-*epi*-D-swainsonine (26). Hydrochloric acid (3 N, 2 mL) to a solution of **25** (54 mg, 0.2 mmol) in methanol. The mixture was stirred at room temperature for 2 hours. Removal of solvent gave **26** (37 mg, 99%) as yellow gel. $[\alpha]_D^{20}$ = −56 (*c* = 0.5, MeOH); IR (thin film cm^{-1}) 3354, 2946, 1605, 1487, 1416, 1266, 1110, 1046; ^1H NMR (300 MHz, D_2O) δ 4.26–4.24 (m, 1H), 4.22 (t, *J* = 4.3 Hz, 1H), 4.02 (dd, *J* = 10.1, 4.2 Hz, 1H), 3.61–3.54 (m, 2H), 3.37 (d, *J* = 14.0 Hz, 1H), 2.37–2.32 (m, 2H), 2.08–1.96 (m, 1H), 1.95–1.84 (m, 1H). ^{13}C NMR (75 MHz, D_2O) δ 172.3, 70.5, 67.9, 62.6, 61.0, 51.5, 26.6, 25.4; HRMS calcd for $[C_8H_{13}NO_4H^+]$ 188.0917, found 188.0918.

1,2-*O*-Isopropylidene-8-*O*-methoxylmethyl-8a-*epi*-D-swainsonine (27). Lithium aluminium hydride (0.16 g, 4 mmol) was added to solution of amide **25** (0.4 g, 1.5 mmol) in dry THF. The reaction mixture was refluxed for 4 hours. To the mixture were subsequently added water (0.16 mL), 15% (w/w) NaOH and water (0.48 mL) and white solid occurred. The mixture was filtered to separate the solid and washed with CH_2Cl_2. The eluent was dried with $MgSO_4$ and concentrated. The residue was purified by column chromatography with EtOAc/petroleum ether (1 : 3) to give **27** (0.35 g, 92%) as yellow oil. $[\alpha]_D^{20}$ = −36 (*c* = 0.5, CH_2Cl_2); IR (thin film cm^{-1}) 2985, 2937, 1668, 1444, 1380, 1209, 1040; ^1H NMR (300 MHz, $CDCl_3$) δ 4.78–4.63 (m, 3H), 4.59 (t, *J* = 6.3 Hz, 1H), 3.98 (s, 1H), 3.45 (dd, *J* = 8.8, 6.3 Hz, 1H), 3.39 (s, 3H), 2.99 (d, *J* = 10.4 Hz, 1H), 2.28 (dd, *J* = 9.1, 4.5 Hz, 1H), 2.22–2.09 (m, 2H), 2.03 (d, *J* = 14.1 Hz, 1H), 1.89–1.74 (m, 1H), 1.49 (s, 3H), 1.41 (m, 2H), 1.32 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 113.8, 96.1, 79.6, 77.6, 71.4, 70.5, 60.5, 55.8, 52.4, 28.1, 27.3, 25.3, 19.7; HRMS calcd for $[C_{13}H_{23}NO_4H^+]$ 258.1700, found 258.1697.

8a-*epi*-Swainsonine (2). Hydrochloric acid (3 N, 2 mL) was added to a solution of **27** (51 mg, 0.2 mmol) in methanol. The mixture was stirred at room temperature for 20 minutes. Removal of solvent and work-up with acidic ion exchange column (DOWEX 50 W × 8, 100–200 mesh) gave 2 (32 mg, 94%) as white solid. m.p. 112–115 °C [lit.[12e] mp 117–119 °C]; $[\alpha]_D^{20}$ = −66 (*c* = 0.5, MeOH) [lit.[12e] $[\alpha]_D^{21}$ −63 (*c* 0.95, MeOH)]; IR (thin film cm-1) 3355, 2928, 1661, 1446, 1328, 1124; ^1H NMR (500 MHz, D_2O, ref. MeOH) δ 4.25–4.12 (m, 2H), 3.97 (dd, *J* = 9.4, 6.7 Hz, 1H), 3.56 (dd, *J* = 11.2, 6.7 Hz, 1H), 3.18–3.03 (m, 1H), 2.47 (d, *J* = 9.2 Hz, 1H), 2.42 (d, *J* = 5.0 Hz, 1H), 2.41–2.35 (m, 1H), 1.99–1.88 (m, 1H), 1.85–1.75 (m, 1H), 1.68–1.51 (m, 2H); [lit.[12e] (600 MHz, D_2O, ref CD_3OD) δ 4.32 (q, *J* = 6.6 Hz, 1H), 4.10 (m, 1H), 3.91 (dd, *J* = 9.0, 6.6 Hz, 1H), 3.39 (dd, *J* = 10.2, 6.6 Hz, 1H), 2.95 (dd, *J* = 10.2, 1.8 Hz, 1H), 2.14 (dd, *J* = 10.2, 6.6 Hz, 1H), 2.10 (m, 2H), 1.87–1.90 (m, 1H), 1.69–1.77 (m, 1H), 1.50–1.58 (m, 2H)]; ^{13}C NMR (125 MHz, D_2O, ref. MeOH) δ 69.2, 69.15, 66.5, 62.8, 59.9, 52.6, 29.4, 18.7; [lit.[12e] (150 MHz, D_2O, ref. CD_3OD) δ 70.7, 70.5, 67.7, 64.4, 61.4, 53.4, 30.9, 20.1]; HRMS calcd for $[C_8H_{15}NO_3H^+]$ 174.1125, found 174.1126.

Acknowledgements

We thank the Ministry of Science and Technology of P. R. China (no. 2012CB822101), the National Natural Science Foundation of China (no. 21272240, 21202173), National

Science and Technology Major Projects for "Major New Drugs Innovation and Development" (2013ZX09508104), and the Chinese Academy of Sciences for financial support. This work was supported in part by a Grant-in-Aid for Scientific Research (C) (no. 26460143) (AK) from the Japanese Society for the Promotion of Science (JSPS) and a Leverhulme research fellowship (GWJF).

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