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Aust. J. Chem. **2004**, *57*, 669–672

Asymmetric Synthesis of (−)-Swainsonine†

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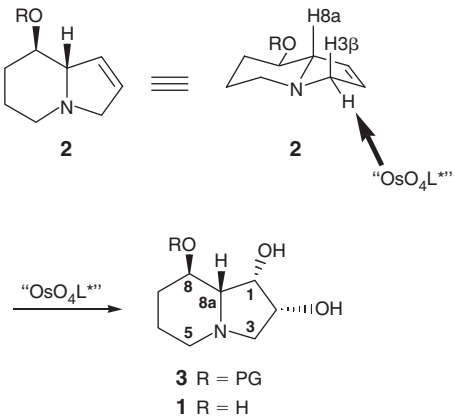
This paper describes a new synthesis of (−)-swainsonine via the ring-closing metathesis reaction of a substituted 3-allyl-4-vinyloxazolindin-2-one and subsequent diastereoselective *syn*-dihydroxylation of the resulting pyrrolo-[1,2-*c*]oxazol-3-one.

Manuscript received: 15 January 2004.
Final version: 3 March 2004.

While numerous total syntheses of naturally occurring (−)-swainsonine **1**[1] and its non-natural enantiomer (+)-swainsonine[2–4] have been reported, these molecules and their analogues are still popular targets to develop new synthetic strategies and methodologies. This is partially driven by the ability of (−)-swainsonine to inhibit Golgi α-mannosidase II, an enzyme involved in the processing of glycoproteins on the surface of cancer cells. This process has been associated with cancer metastasis, and thus (−)-swainsonine and analogues are potentially useful anti-metastasis drugs for the treatment of cancer.[5,6] Unfortunately, (−)-swainsonine is not selective for Golgi α-mannosidase II over other α-mannosidases (e.g. lysosomal α-mannosidase)[7] resulting in undesired side effects (e.g. inhibition of the catabolism of oligosaccharides), and thus creating the need for more potent and selective (−)-swainsonine analogues. A comprehensive review of the synthesis of swainsonine and its analogues was published in 2000 by Nemr.[1] Since this review, seven total syntheses of (−)-swainsonine have been reported[8–14] along with several papers describing the synthesis of analogues.[14–21]

Blechert,[12] Carretero,[13] and Pyne[14] have each reported a synthesis of (−)-swainsonine via the *syn*-dihydroxylation (DH) of the indolizidine derivative **2** (Scheme 1).

Syn-dihydroxylation of racemic **2** (R = TBS) using catalytic osmium tetraoxide/stoichiometric *N*-methylmorpholine oxide (NMO) has been reported[22] to give an 88 : 12 mixture of diols in favour of the desired diastereomer **3** (Scheme 1). Blechert,[12] however, found that this method using enantiomerically pure **2** (R = TBS) gave an almost equal mixture of the two diastereomers. However, the use of the Sharpless asymmetric dihydroxylation (AD) reaction conditions[23] using AD-mix-α gave a 20 : 1 mixture of diols in favour of the desired diol **3** (R = TBS). Independently, we[14] also found that the use of either AD-mix-α or AD-mix-β on the *O*-benzyl



Scheme 1.

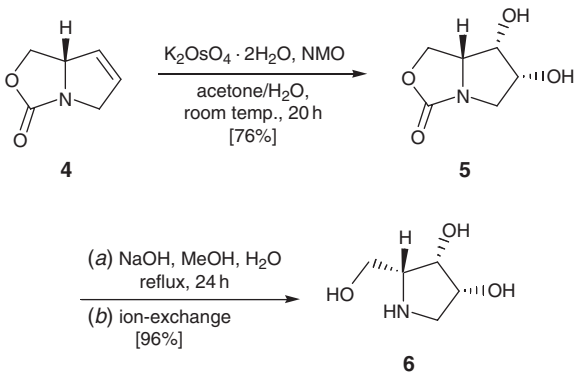
analogue of **2** gave the desired diol **3** (R = Bn) in excellent diastereomeric ratios (*d.r.* 95 : 5 to 98 : 2). The stereochemical outcomes for these reactions were consistent with addition of the osmium reagent to the less hindered α-face of **2**,[14,22] approach to the β-face being hindered by the pseudo-axial protons H8a and H3β (Scheme 1).

While the Sharpless AD reagents allowed us access to the desired diol **3** (R = Bn), the yields for these reactions were disappointingly low (44–49%).[14] We suspect that this low yield was due to a competing oxidation reaction occurring at the tertiary nitrogen atom of **2** (R = Bn) or **3** (R = Bn). In view of this difficulty, we have recently examined pyrrolo[1,2-*c*]oxazol-3-ones (e.g. **4**) as more suitable bicyclic substrates to control the DH of substituted pyrrolidines and to simultaneously protect the nitrogen atom from oxidation.[24,25] For example, the unsubstituted pyrrolo[1,2-*c*]oxazol-3-one **4** underwent DH with catalytic osmium tetraoxide to give exclusively the diol **5** in good yield (Scheme 2). This diol resulted from attack of the oxidizing agent from the

† Dedicated to Professor Lew Mander on the occasion of his 65th birthday. Lew, thanks for teaching me carbocyclic chemistry. I will never forget the structure of gibberellic acid (GA_3).

10.1071/CH04009 0004-9425/04/070669

concave face of the molecule (Fig. 1) due to the pseudo-axial protons H5β and H7a that sterically hinder the β-face to attack by the osmium reagent (Fig. 1).[24] This argument is similar to that proposed to account for the facial selectivity of DH reactions on the related indolizines **2** (Scheme 1). This methodology allowed the diastereoselective synthesis of the triol **6** having the desired relative stereochemistry required for the synthesis of swainsonine.[24] In this paper, we report the application of this methodology to the synthesis of (−)-swainsonine **1** (Schemes 3 and 5).



4 **5** **6**

Scheme 2.

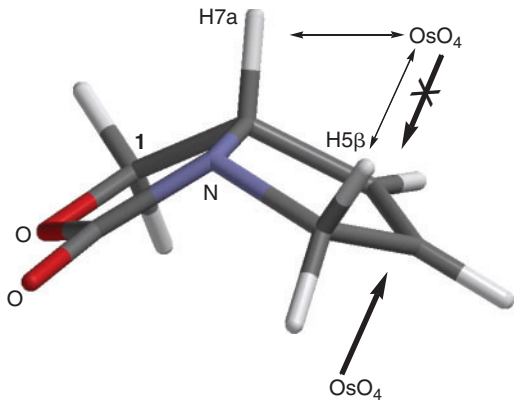
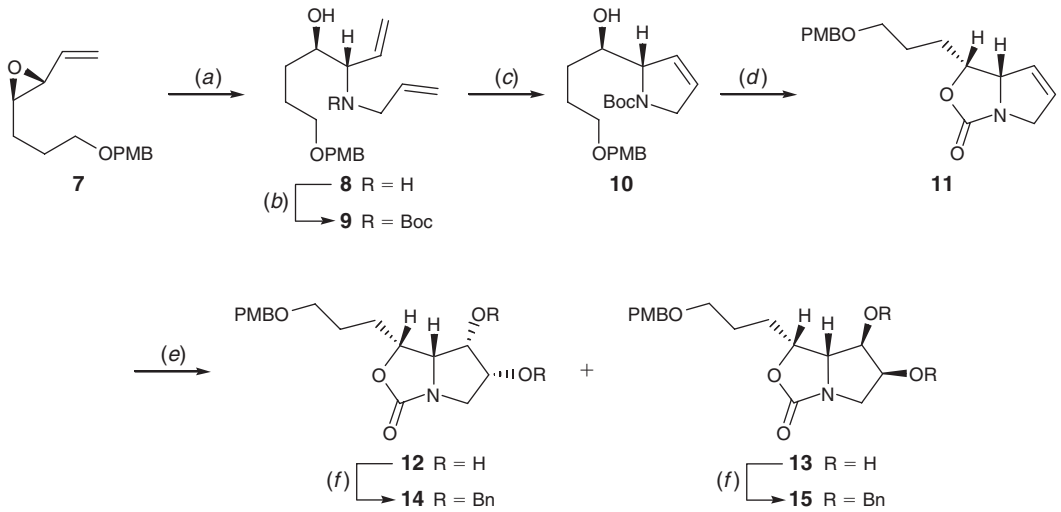


Fig. 1. Stereochemical model of **4** (Spartan PC AM1).

The requisite pyrrolo[1,2-*c*]oxazol-3-one **11** was prepared according to Scheme 3 from the vinyl epoxide (*R*,*S*)-**7** (*e.e.* 92%) that was used in our earlier synthesis of (−)-swainsonine.[14] Aminolysis of **7** with allylamine in the presence of lithium triflate with microwave heating at 110°C for 1 h[26] gave the desired amino alcohol **8** in 88% yield. While this compound had been prepared previously by us by means of conventional heating in a sealed tube using acid catalysis (0.1 equiv. of *p*-TsOH, 105°C, 5 days), this method was a significant improvement in terms of reaction time. The amino alcohol **8** was converted into the *N*-Boc 2,5-dihydropyrrole **10** as described by us earlier.[14] Upon treatment with sodium hydride in toluene solution at 50°C, compound **10** was converted into the desired pyrrolo[1,2-*c*]oxazol-3-one **11** in 74% yield. Other solvents were much less effective in this transformation; for example, the use of tetrahydrofuran (THF) and dimethylformamide (DMF) resulted in very poor conversions. We suspect that the sodium *tert*-butoxide that is generated in these reactions can react reversibly with **11** giving an equilibrium mixture of **10** and **11**. In toluene, however, sodium *tert*-butoxide would be expected to be less soluble, forcing the equilibrium to favour the desired ring-closed product **11**. Alternatively, **11** could be prepared by first treatment of the amino alcohol **8** with triphosgene in the presence of base (Et_3N) to give the oxazolidinone **16** in 77% yield. Treatment of **16** with Grubbs I catalyst (benzylidene bis(tricyclohexylphosphine)dichlororuthenium)[24] in refluxing dichloromethane solution for 18 h gave **11** in 77% yield (Scheme 4).

With the pyrrolo[1,2-*c*]oxazol-3-one **11** in hand, we next examined its DH reactions; the results of this study are summarized in Table 1. To this end, **11** was treated with catalytic potassium osmate dihydrate ($K_2OsO_4 \cdot 2H_2O$) and stoichiometric NMO in acetone–water,[14] which gave a 3 : 1



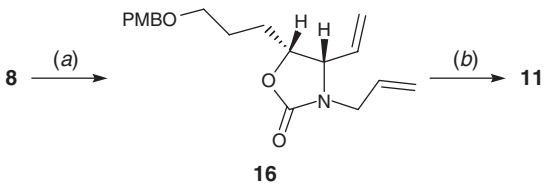
7 **8** R = H **9** R = Boc **10** **11** **12** R = H **14** R = Bn **13** R = H **15** R = Bn

Scheme 3. (*a*) $CH_2{=}CHCH_2NH_2$, LiOTf, microwave, 110°C, 1 h (88%); (*b*) Boc_2O, NEt_3, THF, room temp., 24 h (98%); (*c*) Grubbs' catalyst, CH_2Cl_2, reflux, 18 h (95%); (*d*) NaH, toluene, 50°C, 24 h (74%); (*e*) dihydroxylation (see Table 1); (*f*) NaH, BnBr, $Bu^n{}_4NI$, THF, room temp., 2 days (100%).

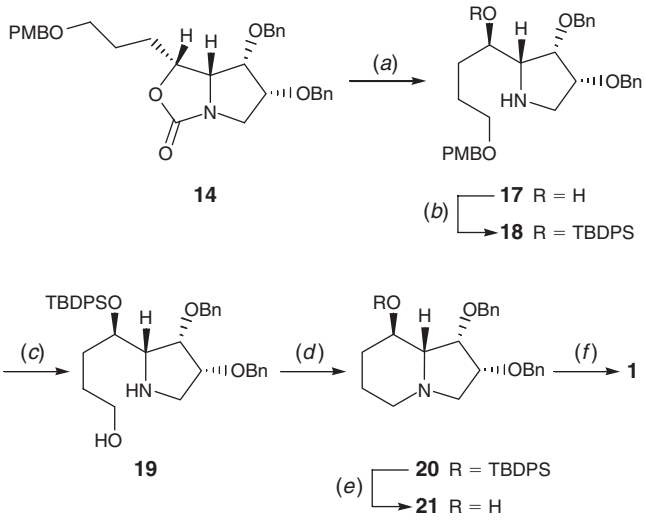
inseparable mixture of the diols **12** and **13** from ^{1}H NMR analysis (Scheme 3).[27] Complete conversion was obtained within 18 h at room temperature giving an 85% yield. A pure sample of the major diol **12** [mp 146°C, $[\alpha]_D^{25}$ −31.0 (*c* 1.77 in $CHCl_3$)] was isolated by careful crystallization from hot dichloromethane and petroleum spirit. This crystallization was not necessary, however, because benzylation of the mixture of diols gave the corresponding bis(benzyl ethers) **14** and **15** in quantitative yield, and these were readily separable by column chromatography. Conducting the same DH reaction at 0°C resulted in an improved diastereoselectivity and yield (3.5 : 1 and 92%, respectively). Thus the diastereoselectivities for the DH reaction of **11** were similar to those found for the DH reactions of indolizidine **2**. These DH reactions, however, were far less diastereoselective than those of the unsubstituted pyrrolo[1,2-*c*]oxazol-3-one **4**. The C1 α-substituent present in **11** is most likely responsible for this reduced α-face diastereoselectivity. With the aim of increasing the steric bulk of the oxidant, and perhaps the diastereoselectivity, the DH reaction was repeated in the presence of the coordinating ligand pyridine (10 equiv.). Unfortunately, the use of pyridine extended the reaction time to 7 days and resulted in a significant reduction in the diastereoselectivity to 1.5 : 1 (Table 1). When AD-mix-α was used at room temperature, the reaction did not go to completion within 6 days, and the diastereoselectivity was only slightly improved (3.7 : 1). Surprisingly, when AD-mix-β was used, a 20 : 1 ratio of diastereoisomers was obtained, albeit at low conversion after 6 days at room temperature, giving a 46% yield of product diols **14** and **15** (and 45% recovered starting material). We attribute the discrepancies between the α- and β-AD-mixes to be a result of a matched/mismatched situation.[23]

Conversion of **14** into (−)-swainsonine proved to be relatively straightforward (Scheme 5). Hydrolysis of the oxazolidinone with NaOH in MeOH–water[25] gave the amino alcohol **17** in good yield (84%). We thought it prudent to protect the secondary alcohol of **17**, as it might interfere with the cyclization of the piperidine ring, by providing an alternative nucleophile to the nitrogen atom. Consequently, **17** was treated with *tert*-butylchlorodiphenylsilane (TBDPSCl) and imidazole at 60°C to give the silyl ether **18** in 97% yield. Oxidative removal of the *O*-PMB (*para*-methoxybenzyl) protecting group was then conducted by reaction of **18** with ceric(IV) ammonium nitrate (CAN), giving the amino alcohol **19** in 92% yield.[14,25] Cyclization of **19** by activation of the primary hydroxyl and then intramolecular *N*-alkylation (Ph_3P, CBr_4, Et_3N)[14] gave the indolizidine derivative **20** in excellent yield (93%). Deprotection of the silyl ether by reaction with tetra-*n*-butylammonium fluoride (TBAF) was slow, requiring 5 days to complete; however, the desired alcohol **21** was obtained in 76% yield. Finally, the two benzyl ethers were removed by catalytic hydrogenolysis under acidic conditions ($PdCl_2$, H_2) and the resulting product was purified and neutralized by ion-exchange chromatography to give (−)-swainsonine **1** in excellent overall yield (93%) and purity.

This synthetic compound had identical ^{1}H and ^{13}C NMR spectra and TLC mobility to an authentic sample of (−)-swainsonine[28] and had a specific rotation, $[\alpha]_D^{26}$ −71 (*c* 0.56



Scheme 4. (*a*) triphosgene, NEt_3, CH_2Cl_2, 0°C, 2 h (77%); (*b*) Grubbs' catalyst, CH_2Cl_2, reflux, 18 h (77%).



Scheme 5. (*a*) NaOH, MeOH, H_2O, 110°C, microwave, 2 h (84%); (*b*) TBDPSCl, imidazole, 65°C, 3 days (97%); (*c*) CAN, CH_3CN, H_2O, room temp., 3 h (92%); (*d*) PPh_3, CBr_4, NEt_3, CH_2Cl_2, 0°C, 16 h (93%); (*e*) TBAF, THF, room temp., 5 days (76%); (*f*) $PdCl_2$, H_2 (1 atm), MeOH, room temp., 2 h; ion-exchange (93%).

Table 1. Summary of results for the dihydroxylation reactions of 11

Reagent used[A]	Reaction temp.[B]	Combined yield [%] of **12** and **13**	Recovered **11** [%]	Ratio of **12** to **13**	Reaction time [days]
$K_2OsO_4 \cdot 2H_2O$/NMO	RT	85	–	3 : 1	1
$K_2OsO_4 \cdot 2H_2O$/NMO	0°C	92	–	3.5 : 1	2
$K_2OsO_4 \cdot 2H_2O$/NMO, pyridine (10 equiv.)	RT	90	5	1.5 : 1	7
AD-mix-α	RT	24	56	3.7 : 1	6
AD-mix-β	RT	46	45	20 : 1	6

[A] See references [14] and [25] for general experimental procedures.
[B] RT refers to room temperature.

in MeOH) [lit.[29] −82.6 (*c* 1.03 in MeOH); lit.[8] $[\alpha]_D^{23}$ −86 (*c* 0.30 in MeOH); lit.[30] $[\alpha]_D^{23}$ −74 (*c* 0.98 in MeOH); lit.[31] $[\alpha]_D^{26}$ −85.5 (*c* 0.42 in MeOH); lit.[32] $[\alpha]_D^{23}$ −87.2 (*c* 2.1 in MeOH)], that was consistent with the enantiomeric purity of its precursor **7**.

In conclusion, an alternative synthetic strategy has been developed that allows the synthesis of (−)-swainsonine. The oxazolidinone group was found to be a useful protecting group in the ring-closing metathesis reaction and, as part of a pyrrolo[1,2-*c*]oxazol-3-one ring system, has functioned as a stereodirecting group in the *syn*-DH reaction.

Accessory Materials

General experimental details, and syntheses of compounds **1**, **11**–**15**, and **17**–**21** are available from the author or, until July 2009, the *Australian Journal of Chemistry*.

Acknowledgments

We thank the Australian Research Council for financial support and the University of Wollongong for a Ph.D. scholarship to K.B.L. We thank Dr Reg Smith from Phytex Australia for an authentic sample of (−)-swainsonine.

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