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Asymmetric Synthesis of (-)-Swainsonine†

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

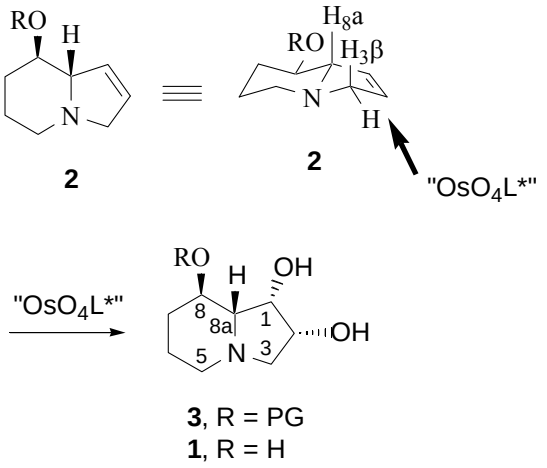
Key words: swainsonine, ring-closing metathesis, dihydroxylation, oxazolidinone

†Dedicated to Prof. 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).

Introduction

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).

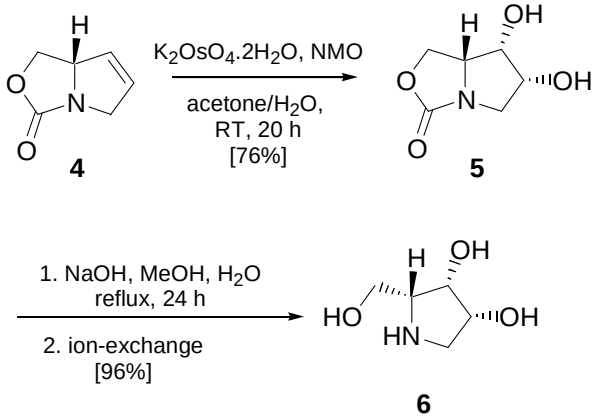


Scheme 1

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 2 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 analogue of **2** gave the desired diol **3** (R = Bn) in excellent diastereomeric ratios (dr 95 : 5 –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 concave face of the molecule (Figure 1) due to the pseudo-axial protons H5β and H7a that sterically hinder the β-face to attack by the osmium reagent (Figure 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).



Scheme 2

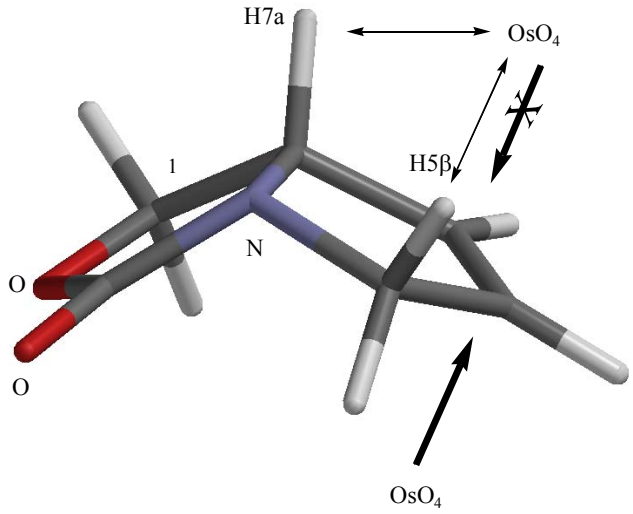


Figure 1. Stereochemical model of **4** (Spartan PC AM1).

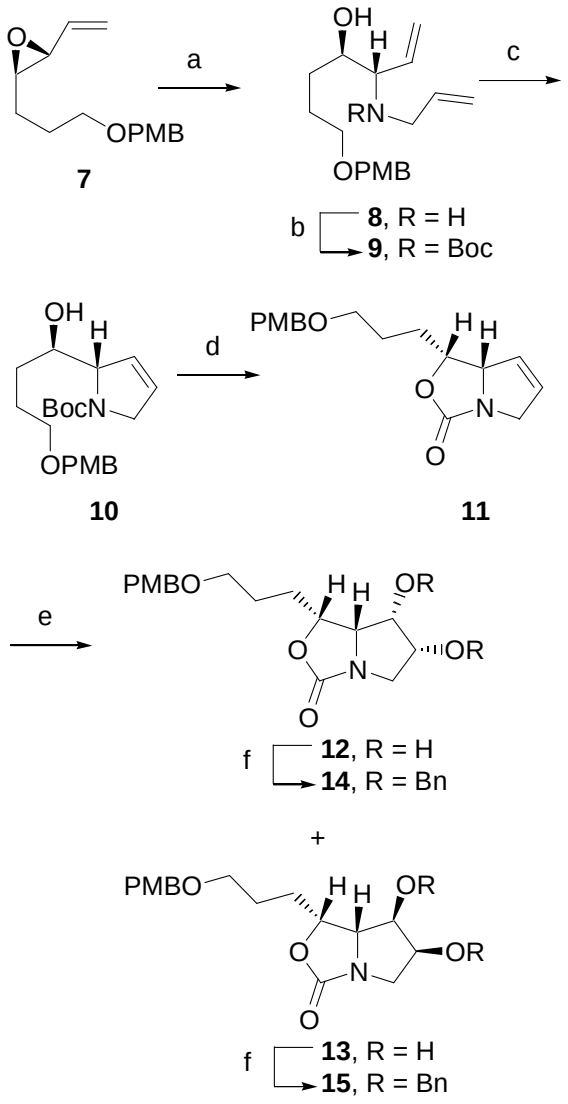
Results and Discussion

The requist pyrrolo[1,2-*c*]oxazol-3-one **11** was prepared according to Scheme 3 from the vinyl epoxide (*R*, *S*)-**7** (ee 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 using 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 to 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 to 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 THF and 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

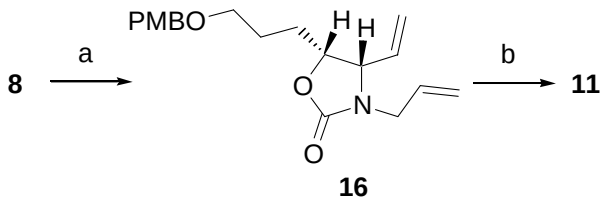
to be less soluble forcing the equilibrium to favour the desired ring-closed product **11**. Alternatively **11** could be prepared by first treatment of the amino alcohol **8** with triphosgene in the presence of base (Et_3N) to give the oxazolidinone **16** in 77% yield. Treatment of **16** with Grubbs 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 ($K_2OsO_4.2H_2O$) and stoichiometric NMO in acetone-water,[14] which gave a 3 : 1 inseparable mixture of the diols **12** and **13** from ^{1}H NMR analysis (Scheme 3).[27] Complete conversion was obtained within 18 h at RT giving an 85 % yield. A pure sample of the major diol **12** (m.p. 146 ^{o}C, $[\alpha]_D^{25}$ -31.0 (c 1.77, $CHCl_3$)) was isolated by careful crystallisation from hot dichloromethane and petroleum spirit. This crystallisation 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^{o}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 C-1 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 d and resulted in a

significant reduction in the diastereoselectivity to 1.5 : 1 (Table 1). When AD-mix-α was used at RT the reaction did not go to completion within 6 d, 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 RT, giving a 46 % yield of product diols **14** and **15** (and 45 % recovered starting material). We attribute the disparencies between the α and β AD-mixes to be a result of a matched/mismatched situation.[23]



Scheme 3. *Reagents* (a) CH_2=$CHCH_2NH_2$, LiOTf, microwave, 110 ^oC, 1 h (88 %); (b) Boc_2O, NEt_3, THF, RT, 24 h (98 %); (c) Grubbs' cat., DCM, reflux, 18 h (95 %); (d) NaH, toluene, 50^oC, 24 h (74 %); (e) dihydroxylation (see Table 1); (f) NaH, BnBr, *n*-Bu_4NI, THF, RT, 2 d (100 %).



Scheme 4. *Reagents* (a) triphosgene, NEt_3, CH_2Cl_2, 0 ^oC, 2 h (77 %); (b) Grubbs' cat., DCM, reflux, 18 h (77 %).

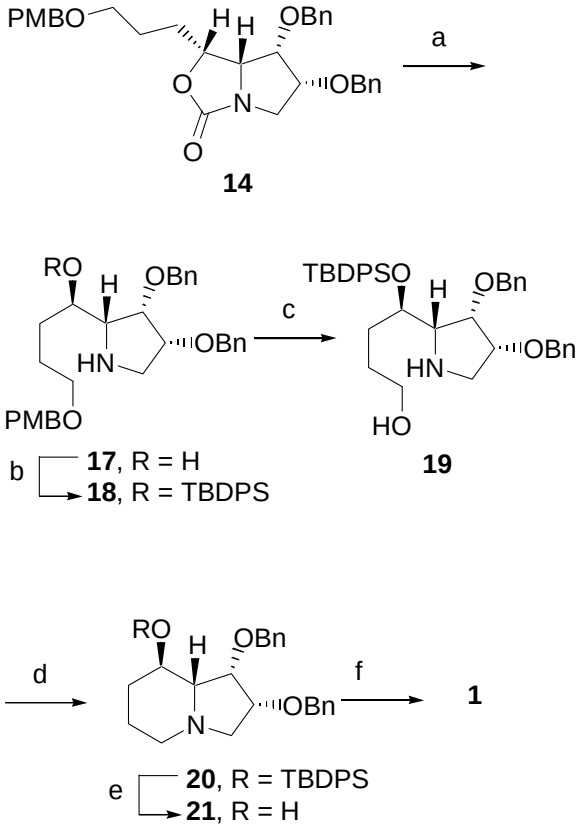
Table 1 - Summary of results for the dihydroxylation reactions of **11**.

Reagent[a]	Reaction temp. (^oC)	Combined yield (%) of **12** + **13**	Recovered **11 (%)**	Ratio **12** : **13**	Reaction time (days)
$K_2OsO_4.2H_2O$/NMO	RT	85	-	3 : 1	1
$K_2OsO_4.2H_2O$/NMO	0	92	-	3.5 : 1	2
$K_2OsO_4.2H_2O$/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

Conversion of **14** into (-)-swainsonine proved to be relatively straight forward. (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 cyclisation 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^oC to give the silyl ether **18** in 97 % yield. Oxidative removal of the *O*-PMB 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 neutralised by ion-exchange chromatography to give (-)-swainsonine **1** in excellent overall yield (93%) and purity.



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

This synthetic compound had identical ^1H 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, MeOH) [lit.[29] $[\alpha]_D^{26}$ -82.6, (c 1.03, MeOH); lit.[8] $[\alpha]_D^{23}$ -86, (c 0.30, MeOH);

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

Conclusion

In conclusion, an alternative synthetic strategy has been developed that allows the synthesis of (-)-swainsonine. The oxazolidinone group has been found to be a useful protecting group in the RCM 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.

Experimental

Full details are available as supplementary data that are available on the web (http://www.publish.csiro.au/journals/ajc).

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[27] The structure of **15**, and hence **13**, was established by its formation, as a by-product, in the benzylation of compound **17** in reference 14.

[28] Kindly provided by Dr. Reg Smith, from Phytex Australia, Sydney.

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GRAPHICAL ABSTRACT

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