Diastereoselective Synthesis of Polyfunctional-Pyrrolidines via Vinyl Epoxide Aminolysis/Ring-Closing Metathesis: Synthesis of Chiral 2,5-Dihydropyrroles and (1*R*,2*S*,7*R*,7a*R*)-1,2,7-Trihydroxypyrrolizidine

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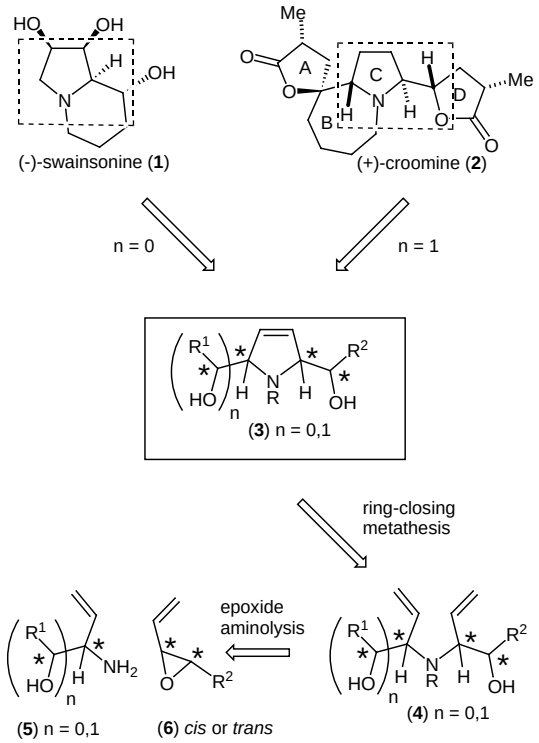
Abstract: This paper describes an efficient and diastereoselective method for preparing 2-substituted-2,5-dihydropyrroles in racemic and optically active form via acid catalysed or microwave assisted aminolysis of vinyl epoxides with allyl amine followed by ring-closing metathesis. Using this method, (1*R*,2*S*,7*R*,7a*R*)-1,2,7-trihydroxypyrrolizidine could be prepared by elaboration of a chiral 2-substitited-2,5-dihydropyrrole.

Key words: 2,5-dihydropyrroles, vinyl epoxide, aminolysis, ring-closing metathesis

Polyhydroxylated pyrrolizidine and indolizidine alkaloids [e.g swainsonine (**1**)] are well known potent glycosidase enzyme inhibitors.[1,2] Some of these alkaloids exhibit anti-viral and anti-HIV activity by effectively inhibiting the enzymatic processing of glycoproteins.[3] While many of these alkaloids and their derivatives have been prepared for structure-activity studies there is still a need for new synthetic methods to prepare a variety of analogues to allow a better understanding of the structural requirements for glycosidase inhibition and to develop more potent, selective and less toxic drugs.[4] Structurally related molecules are found in the stemona family of alkaloids. These compounds have been isolated from the roots of the *Stemona* and *Croomine* species that have been used as traditional medicines by the Chinese and Japanese to treat respiratory diseases such as bronchitis, pertussis, and tuberculosis and have also found use as anthelmintic agents.[5] These alkaloids have novel polycyclic structures, as is illustrated by the representative member croomine (**2**). Their unique structural features coupled with their interesting biological properties have stimulated the development of new synthetic methodology and synthetic strategies for the synthesis of these alkaloids.[6] The structural similarity between **1** and **2** is highlighted in Scheme 1. A central structural feature of these alkaloids is a poly-functionalised pyrrolidine ring with one (at C-2, in the case of **1**) or two (at C-2 and C-5, in the case of **2**) appended hydroxy-alkyl substituents.

Our general retro-synthetic analysis, illustrated for swainsonine (**1**) and croomine (**2**) is shown in Scheme 1. The key poly-functionalised pyrrolidines of the type **3** should readily be obtained from regioselective ring-opening of vinyl epoxides **6** with allylic amines **5** to give the dienes **4**, which upon *N*-protection and ring-closing metathesis should furnish the desired pyrrolidines **3**. The regioselective ring opening of vinyl epoxides with ammonia and benzyl and cyclohexyl amine has been reported[7] while the ring-closing metatheses (RCM) reaction is well documented as a versatile and efficient process for making heterocyclic rings.[8–10] We report here an efficient method for preparing poly-functionalised pyrrolidines of the type **3** using the above strategy and the synthesis of the trihydroxypyrrolizidine (**16**), the ring-contracted analogue of 1,2-di-*epi*-swainsonine, and the C,D-ring analogue **19** of croomine (**2**).



Scheme 1

Enantiomerically enriched *trans*- or racemic *cis*-vinyl epoxides **7** were readily prepared using literature procedures.[7a,11] Using the conditions described by Somfai,[7] the vinyl epoxides **7** were heated at 110 °C in a sealed tube in an excess of allyl amine (20 equiv) in the presence of

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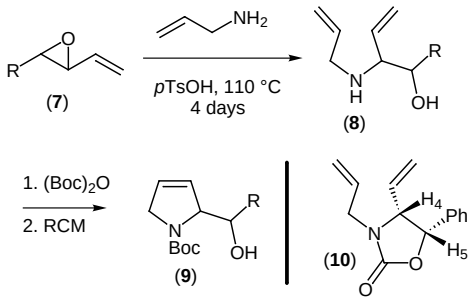
p-TsOH (0.1–0.2 equiv) for 4 days (Scheme 2, Table). Despite the seemingly harsh reaction conditions these reactions cleanly provided the required amino alcohols **8** in excellent yields (Table).[12] In the case of **7a** two regioisomeric products were obtained that were readily separated by column chromatography as single diastereomers, while the reactions of **7b**–**d** were essentially regioselective (< 5% of the other regioisomer could be detected on a large scale synthesis) and diastereomerically pure **8b**–**d** were obtained in excellent yields.



Scheme 2

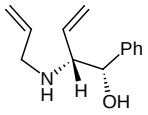
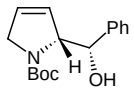
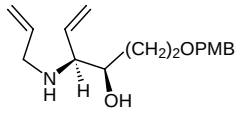
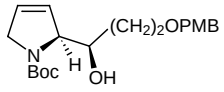
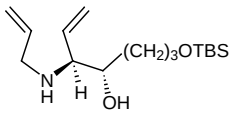
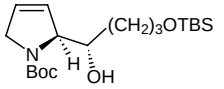
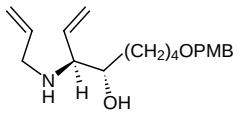
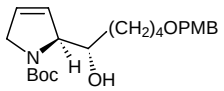
The relative stereochemistry of **8a** was established by conversion (triphosgene, Et_3N) to its corresponding 4,5-*cis*-oxazolidinone derivative **10**. ^1H NMR analysis of this compound showed a typical *cis*-coupling constant for $J_{4,5}$ of 8.5 Hz[7] thus establishing that product **8a** arises from **7a** via an inversion reaction at the allylic stereogenic centre.

Protection of the amino group of **8a**–**d** as its *N*-Boc derivative followed by a ring-closing metathesis reaction at high dilution in refluxing dichloromethane, using commercially available benzylidene bis(tricyclohexylphosphine)-dichlororuthenium (Grubbs' catalyst), provided the 2,5-dihydropyrroles **9a**–**c** in high overall yields (Table).[13]

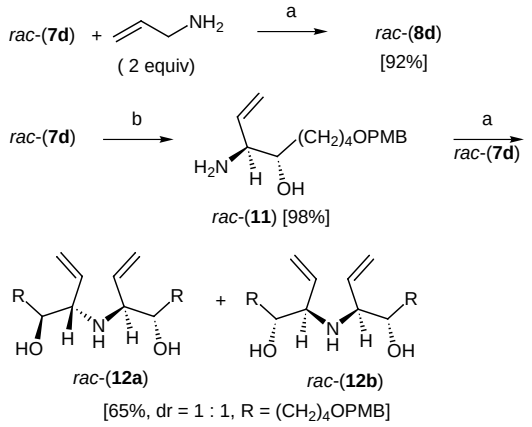
In some initial studies we have studied some aminolysis reactions of *rac*-**7d** using microwave heating.[7b] We have found that by using 1 mole equivalent of lithium triflate in acetonitrile[14] that good to excellent yields of aminolysis products can be obtained using 1–2 mole equivalents of allyl amines under microwave heating conditions (Scheme 3).[15] Thus treatment of *rac*-**7d** under these conditions at 120 °C for 1 h gave **8d** in 92% yield using only 2 mole equivalents of allyl amine. The microwave–lithium triflate assisted reaction of a 1:1 mixture of the more complex allyl amine *rac*-**11** and *rac*-**7d**, a model study for the key reaction in our proposed croomine (**7**) synthesis, gave a 1:1 mixture of the diastereomeric amino-diols **12a** and **12b** in 65% yield.

Optically active **9b** (ee 94% based on that of **7b**) was converted to the known (1*R*,2*S*,7*R*,7a*R*)-1,2,7-trihydroxypyrrolizidine (**16**) according to Scheme 4. Catalytic *cis*-dihydroxylation of **9b** with osmium tetroxide/*N*-methylmorpholine *N*-oxide,[16] gave the expected diol **13** in 79% yield. The stereochemistry of the produced diol being completely controlled by the C2 substituent of the 2,5-dihydropyrrole **9b**. Treatment of **13** with trifluoroacetic acid

Table Synthesis of **8** and **9** According to Scheme 2

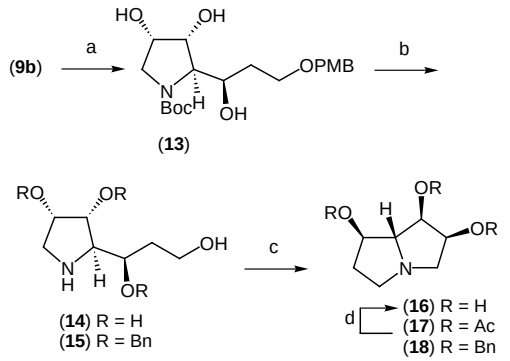
Vinyl Epoxide **7**	Amino alcohol **8**, yield [%]	Pyrrolidine **9**, yield [%][c]
trans-(2*S*,3*S*)-(**7a**) R = Ph	 (**8a**) [65][a]	 (**9a**)[d] [86]
trans-(2*R*,3*R*)-(**7b**) R = -$(CH_2)_2$OPMB	 (**8b**) [90]	 (**9b**) [87]
cis-(2*R**,3*S**)-(**7c**) R = -$(CH_2)_3$OTBS	 (**8c**) [93][b]	 (**9c**) [89][b]
cis-(2*R**,3*S**)-(**7d**) R = -$(CH_2)_4$OPMB	 (**8d**) [88][b]	 (**9d**) [77][b]

[a] A 2:1 mixture of **8a** and its regioisomer were formed in 97% combined yield.
[b] Racemic product formed from racemic **7**.
[c] Overall yield from **8**.
[d] $[\alpha]_D^{22}$ +131 (c 0.14, $CHCl_3$).



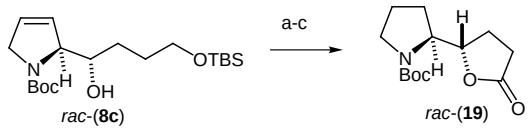
Scheme 3 Microwave heating
Reagents: a) LiOTf (1 equiv), MeCN, 120 °C, 1 h, microwave heating. b) Concd aqueous NH_3, 110 °C, 20 min, microwave heating.

using anisole[17] (10 equiv) as a carbocation scavenger gave the amino alcohol **14** in 90% yield after purification by ion-exchange chromatography. Initially we attempted cyclisation of the tri-*O*-benzyl derivative **15** of **14** in an attempt to produce the pyrrolizidine **18** using either Ph_3P, CBr_4, Et_3N[18] or Mitsunobu conditions,[19] however, none of the desired product was obtained from a complex product mixture. However, the less sterically demanding, unprotected tetrol **14** could be cyclised to **16** under Mitsunobu conditions using pyridine as solvent.[20] The product was difficult to purify and the crude reaction mixture was thus treated with Ac_2O–pyridine to provide the triacetate **17** in poor overall yield (18%). The triacetate **17** could be converted to its triol **16** upon base (K_2CO_3–MeOH) treatment. The ^1H and ^{13}C NMR spectra of **16** and **17** were identical to that of the previously synthesised compound.[21,22]



Scheme 4 *Reagents*: a) OsO_4 (5 mol%), NMO (2 equiv), acetone–water (9:6), r.t., 24 h (79%), b) TFA (120 equiv), anisole (10 equiv), CH_2Cl_2, r.t., 2.5 h; ion- exchange chromatography (90%). c: (i) DEAD (1.2 equiv), Ph_3P (1.2 equiv), pyridine, 0 °C, 18 h; (ii) Ac_2O–pyridine (18% overall for **14**). d) K_2CO_3/MeOH, r.t., 1.5 h (100%).

The racemic 2,5-dihydropyrrole **8c** could be readily converted to the bicyclic butyrolactone **19**, a model for the C,D-ring system of croomine (**2**), as shown in Scheme 5. Catalytic hydrogenation [Pd/C, petroleum ether, H_2 (1 atm), 89%] of the alkene group of **8c**, followed by primary alcohol deprotection (Bu_4NF–THF, 89%) and oxidative cyclization with TPAP–NMO (4 Å mol. sieves, CH_2Cl_2, 94%)[23] gave compound **19** with the correct relative stereochemistry as the C,D-ring system of croomine (**2**).



Scheme 5 *Reagents*: a) Pd/C, H_2 (1 atm), petroleum ether (91%). b) Bu_4NF, THF (89%). c) TPAP, NMO, 4 Å mol. sieves, CH_2Cl_2 (94%).

In conclusion, we have demonstrated that the aminolysis of vinyl epoxides with allyl amine followed by *N*-protection and RCM efficiently gives functionalised 2,5-dihydropyrroles **9**. These compounds are potentially valuable precursors for the synthesis of more complex alkaloids, including chiral polyhydroxylated pyrrolizidine and indolizidine alkaloids and stemona alkaloids.

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(12) *(3S,4R)-3-Allylamino-6-(4-methoxybenzyloxy)-1-hexen-4-ol* (**8b**): (2*R*,3*R*)-3-[2-(4-Methoxybenzyloxy)ethyl]-2-ethenyloxirane (**7b**) (1.647 g, 6.98 mmol) was dissolved in allylamine (11.5 mL, 153.56 mmol), then *p*TsOH.H_2O (355 mg, 1.87 mmol) was added. The mixture was heated at 110 °C under nitrogen in a sealed tube for 4 d. After cooling, all volatiles were removed in vacuo to give a red solid that was purified by column chromatography (gradient elution from 0–12.5% MeOH–CH_2Cl_2) to give the title compound (1.83 g, 90%) as a pale yellow solid. Mp 61.5–62.5 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.24 (d, 2 H, *J* = 9.0 Hz), 6.86 (d, 2 H, *J* = 9.0 Hz), 5.94–5.81 (m,1 H), 5.71 (ddd,1 H, *J* = 8.4, 10.5, 17.4 Hz), 5.22 (dd,1 H, *J* = 1.8, 10.5 Hz), 5.19–5.18 (m,1 H), 5.13–5.12 (m,1 H), 5.08 (dd,1 H, *J* = 1.2, 9.9 Hz), 4.43 (s, 2 H), 3.85 (dt,1 H, *J* = 3.3, 6.6 Hz), 3.79 (s, 3 H), 3.69–3.56 (m, 2 H), 3.28 (apparent dd,1 H, *J* = 6.0, 13.8 Hz), 3.12 (apparent dd,1 H, *J* = 6.3, 14.4 Hz), 3.07 (dd,1 H, *J* = 3.3, 8.4 Hz), 1.80–1.61 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.00 (C), 136.40 (CH), 136.04 (CH), 130.05 (C), 129.18 (CH), 118.28 (CH_2), 116.00 (CH_2), 113.67 (CH), 72.84 (CH_2), 71.38 (CH), 68.27 (CH_2), 65.18 (CH), 55.25 (CH_3), 49.55 (CH_2), 32.76 (CH_2); $[\alpha]_D^{25}$+2.0 (*c* 2.3 $CHCl_3$); MS (CI +ve) *m/z* 292 ($M-1^+$. 100%); HRMS (CI +ve) Calcd for $C_{17}H_{26}NO_3$ (MH^+) 292.191. Found: 292.194.

(13) ***N*-Boc Protection**: To a solution of **8b** (1.17 g, 4.01 mmol) in dry THF (70 mL) were added triethylamine (0.98 mL, 7.00 mmol) and di-*tert*-butyldicarbonate (1.53 g, 7.00 mmol) under nitrogen. The mixture was stirred at r.t. for 24 h. All volatiles were then removed in vacuo to give a yellow oil which was purified by column chromatography (gradient elution from 20–40% EtOAc–petroleum ether) to give the *N*-Boc derivative of **8b** (1.507 g, 96%) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.24 (d, 2 H, *J* = 8.4 Hz), 6.87 (d, 2 H, *J* = 8.4 Hz), 6.08 (ddd,1 H, *J* = 6.9, 9.9, 17.1 Hz), 5.85–5.72 (m,1 H), 5.30–5.21 (m, 2 H), 5.16–5.06 (m, 2 H), 4.44 (s, 2 H), 4.09 (m,1 H), 3.93–3.89 (m,1 H), 3.82 (m, 2 H), 3.80 (s, 3 H), 3.73–3.57 (m, 2 H), 1.76 (br s, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ CO not observed, 159.00 (C), 134.96 (CH), 129.98 (CH), 129.12 (CH), 118.38 (CH_2), 116.27 (CH_2), 113.65 (CH), 80.14 (C), 72.84 (CH_2), 70.06 (CH), 68.32 (CH_2), 65.11 (CH), 55.21 (CH_3), 50.12 (CH_2), 33.93 (CH_2), 28.42 (CMe_3); $[\alpha]_D^{25}$ -19.2 (*c* 2.4 $CHCl_3$); MS (CI +ve) *m/z* 392 ($M + 1^+$); HRMS (CI +ve) Calcd for $C_{22}H_{34}NO_5$ (MH^+) 392.244. Found: 392.244. **RCM:** Grubbs' Catalyst (0.219 g, 0.266 mmol) was added to a solution of the above *N*-Boc derivative (1.039 g, 2.634 mmol) in dry DCM (500 mL) under nitrogen. The mixture was heated to reflux for 24 h. The solution was cooled and the solvent was removed in vacuo to give a brown oil which was purified by column chromatography (gradient elution with 20–55% EtOAc–petroleum ether) to give **9b** as a clear oil (0.877 g, 91%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25 (d, 2 H, *J* = 8.4 Hz), 6.86 (d, 2 H, *J* = 8.4 Hz), 5.80 (apparent dd,1 H, *J* = 1.5, 6.3 Hz), 5.64 (apparent dd,1 H, *J* = 2.1, 6.3 Hz), 4.85 (d,1 H, *J* = 8.4 Hz), 4.83–4.80 (m,1 H), 4.44 (s, 2 H), 4.19 (dd,1 H, *J* = 2.1, 15.6 Hz), 4.04–3.97 (m,1 H), 3.87 (apparent t,1 H, *J* = 9.6 Hz), 3.8 (s, 3 H), 3.71–3.56 (m, 2 H), 1.69–1.53 (m, 2 H), 1.48 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.91(CO), 156.14 (C), 130.39 (C), 129.25 (CH), 127.12 (CH), 126.53 (CH), 113.62 (CH), 80.50 (C), 72.84 (CH_2), 71.33 (CH), 71.51 (CH), 67.87 (CH_2), 55.26 (CH_3), 54.68 (CH_2), 31.79 (CH_2), 28.48 (CH_3); $[\alpha]_D^{23}$ -80.3 (*c* 2.4 $CHCl_3$); MS (CI +ve) *m/z* 364 ($M + 1^+$); HRMS (CI +ve) Calcd for $C_{20}H_{30}NO_5$ (MH^+) 364.212. Found: 364.199.

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(22) **17**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.40 (ddd,1 H, *J* = 2.1, 4.2, 4.5 Hz), 5.12 (m,1 H), 4.99 (dd,1 H, *J* = 4.5, 7.8 Hz), 3.50 (dd,1 H, *J* = 2.1, 7.8 Hz), 3.27 (dd,1 H, *J* = 2.1, 11.7 Hz), 3.21 (ddd,1 H, obscured), 2.87 (dd,1 H, *J* = 4.2, 11.7 Hz), 2.71 (ddd,1 H, *J* =6.0, 9.0, 11.1 Hz), 2.07 (s, 3 H), 2.05 (s, 3 H), 2.02 (s, 3 H), 1.95–1.86 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.34 (CO), 170.11 (CO), 170.07 (CO), 77.13 (CH), 74.09 (CH), 73.16 (CH), 71.58 (CH), 57.12 (CH_2), 52.91 (CH_2), 30.54 (CH_2), 21.11 (CH_3), 20.94 (CH_3), 20.75 (CH_3); $[\alpha]_D^{25}$ +5.0 (*c* 0.8 $CHCl_3$); **16**: ^{1}H NMR (300 MHz, D_2O) δ 4.23–4.15 (m, 2 H), 3.86 (dd,1 H, *J* = 4.2, 6.3 Hz), 3.10 (dd,1 H, *J* = 1.8, 6.3 Hz), 3.04–2.98 (m, 2 H), 2.71 (dd,1 H, *J* = 4.2, 11.7 Hz), 2.61 (apparent quint,1 H), 2.08–1.95 (m,1 H), 1.77–1.67 (m,1 H); ^{13}C NMR (75 MHz, D_2O) δ 77.78 (CH), 77.64 (CH), 77.41 (CH), 74.81 (CH), 60.51 (CH_2), 54.85 (CH_2), 35.13 (CH_2).

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