Total synthesis of (±)-Vertine with *Z*-selective RCM as a key step†

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A concise total synthesis of the strained pentacyclic alkaloid (±)-Vertine has been achieved in eleven steps with the key steps being pelletierine condensation, Suzuki–Miyaura coupling, and ring-closing metathesis.

Vertine (also called Cryogenine) was first isolated in 1962 by Ferris from *Decodon verticillatus* (*L.*) *Ell* and classified as a member of the *Lythraceae* alkaloids.[1] Vertine displays a wide range of biological activities, including anti-inflammatory, sedative, and antispasmodic properties. It also plays a role in glucose level regulation in blood and lowers blood pressure.[2]

The strained 12-membered macrolactone structure incorporating three stereogenic centers, two of which are part of the macrocycle, and an induced chiral biaryl axis, is synthetically challenging and attracted our interest. Moreover, we had previously synthesized Lasubine I[3] and thus were interested in the more challenging **1** (Fig. 1). To the best of our knowledge, the syntheses of neither Vertine (**1**) nor structural analogues possessing the *Z*-configured α,β-unsaturated macrolactone (*e.g.* Verticillatine, Lythrine)[4] have been reported previously. Here we detail the first total synthesis of (±)-Vertine.

Our first approach built on our synthesis of Lasubine I[3] with macrolactonisation[5] as ring-closing strategy. While we succeeded in synthesizing an advanced intermediate (Fig. 2), the route was not efficient and, worse, all attempts to macrolactonise without isomerisation of the alkene failed.[6]

The strategy using a Suzuki–Miyaura aryl–aryl coupling[7] for the macrolactone also ran into difficulties.[8]

This publication details our third, and finally successful, approach to (±)-Vertine using ring closing metathesis (RCM).

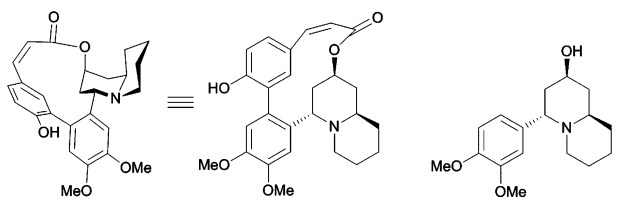

Fig. 1 Two *Lythraceae* alkaloids.

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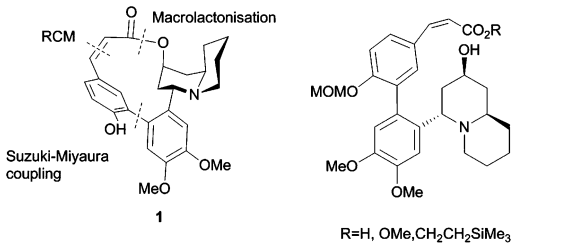
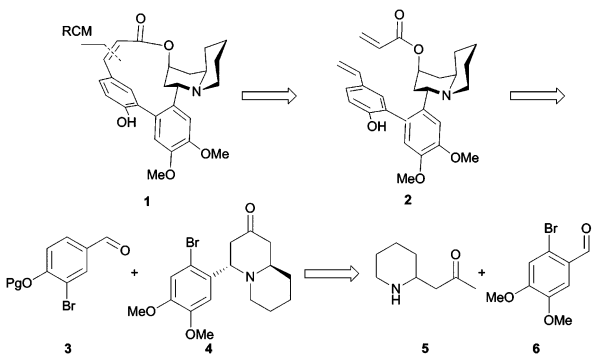


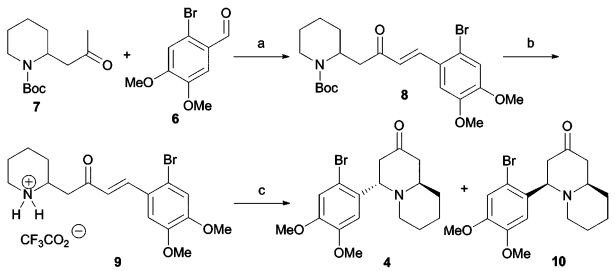
Fig. 2 Left: ring closing strategies. Vertine is shown in the conformation adopted in the solid state.[9] Right: late stage intermediate in an attempted synthesis *via* macrolactonisation.

While representing a strategy which has been used extensively in the synthesis of natural products,[10] the route *via* RCM was not our first choice because of the lack of precedent for the formation of a *Z*-alkene α to a carbonyl function. The synthesis would include key intermediate **2**, obtained from diastereoselective ketone reduction and acylation of the biaryl product resulting from a Suzuki–Miyaura cross coupling between quinolizidinone **4** and a boronate generated from the bromo-arene **3**. In contrast to the $Cr(CO)_3$-mediated synthesis of an analogue of **4** used in the Lasubine I synthesis,[3] we saw an opportunity to use a pelletierine condensation between pelletierine (**5**) and aldehyde **6** to access **4** (Scheme 1).

Accordingly, **4** was synthesized *via* a condensation between pelletierine[11] (**5**) and aldehyde **6**. The reaction, proposed to proceed by an aldol condensation followed by a Michael addition, afforded a mixture of two diastereomeric quinolizidinone products.[12,13] Using 1 M aq. NaOH in THF at room temperature (rt) **4** and **10** were obtained in a 4 : 1 ratio. The desired diastereomer **4** was isolated in 53% yield. Treatment of the mixture with a base in protic media or longer reaction time resulted in isomerisation of **4** into **10** *via* retro-Michael/Michael addition. In order to increase the diastereomeric ratio and the overall yield of the process, a two-step procedure was developed (Scheme 2). This involved an aldol



Scheme 1 Retrosynthetic analysis.



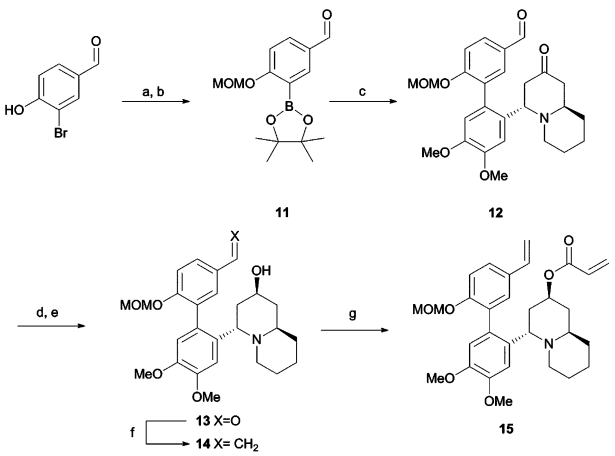
Scheme 2 Synthesis of **4**. *Reagents and conditions*: (a) NaOH [1 M], MeOH/H_2O, reflux, 91%; (b) TFA, CH_2Cl_2, 0 °C, quantitative; (c) NaOH [1 M], THF, rt, 72%, ratio **4**:**10** = 9:1.

condensation between the Boc protected pelletierine **7** and bromoveratraldehyde **6** leading to **8**. Deprotection with trifluoroacetic acid (TFA) and cyclisation under basic conditions yielded **4** and **10** in a 9 : 1 ratio. Diastereomer **4** was isolated in 66% overall yield.

The structures of **4** and **10** were assigned from their NMR and IR spectra. Quinolizidinone **10** shows Bohlmann bands in its IR spectrum.[14] These are absent in **4**. The position of the NMR signal of the benzylic proton (C4) is also diagnostic: the chemical shift is at 4.85 ppm in **4** but at δ 3.82 ppm in **10**.

Boronate **11** was synthesized in 2 steps in 85% yield from commercial 3-bromo-4-hydroxybenzaldehyde (Scheme 3).

Suzuki–Miyaura coupling between **11** and **4** afforded biaryl **12** in 80% yield. The product was isolated as a mixture of two apparent atropisomers in a ratio of 3 : 1 (^{1}H NMR, 500 MHz, 298 K, d_8-toluene). Variable temperature NMR (d_8-toluene, 298 to 388 K) revealed a coalescence temperature of 353 K, showing that we are dealing not with true atropoisomers, but with rotamers, as expected for biaryls having only three substituents in the *ortho*-position.[15] Attempts to selectively methylenate aldehyde **12** were not successful and we therefore proceeded with a reduction of both carbonyl functions. L-Selectride proved to be the best choice affording a single



Scheme 3 Synthesis of **15**. *Reagents and conditions*: (a) MOMCl, DIPEA, CH_2Cl_2, 0 °C to rt, 98%; (b) $Pd(dppf)Cl_2$, $(PinB)_2$, dioxane, 140 °C, MW, 87%; (c) **4**, $Pd(PPh_3)_4$, CsF, DME, 110 °C, 80%; (d) L-Selectride, THF, −78 °C, 62%; (e) MnO_2, Et_2O/acetone, rt, 30 min 98%; (f) *n*BuLi, $[Ph_3PCH_3][Br]$, THF, 0 °C to rt, 65%; (g) acrylic acid, Mukaiyama's salt, Et_3N, CH_2Cl_2, rt, 84%.

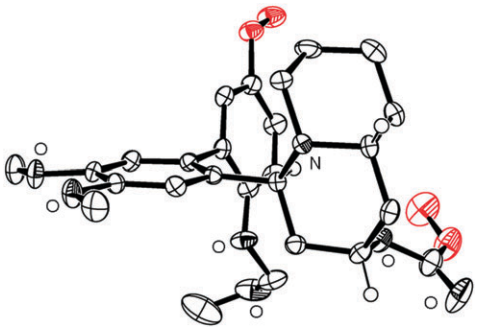
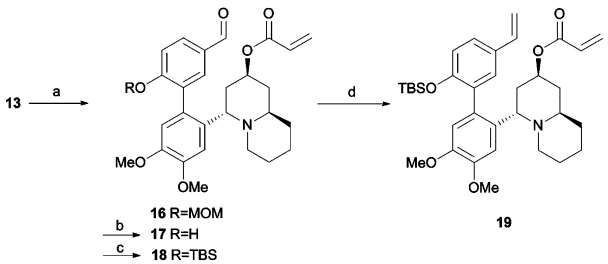


Fig. 3 ORTEP diagram of intermediate **15** (in red: alkenes that are to be involved in RCM to form the 12-membered macrolactone).

diastereomer in 62% yield. The relative configuration of the secondary alcohol was assigned by analogy to Lasubine I.[3] Next, aldehyde **13** was obtained by oxidation with MnO_2 in 98% yield. Wittig reaction followed by acylation under Mukaiyama's conditions then afforded the ester **15**. An X-ray structure determination of **15** confirmed the relative configuration of the molecule (Fig. 3).[16]

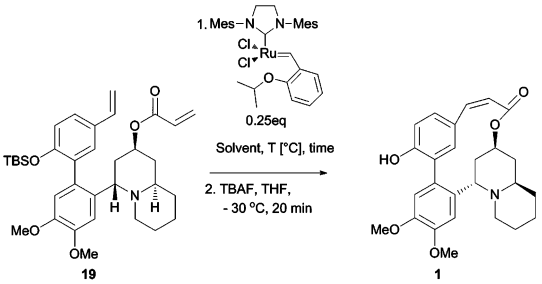
All attempts to cleave the MOM group by using HCl,[17] TFA,[18] TMSBr,[19] *p*-TsOH,[20] $NaHSO_4{\cdot}SiO_2$,[21] I_2/MeOH,[22] or a Lewis acid[23] either gave unidentified byproducts or incomplete deprotection. To circumvent this problem RCM was attempted before the MOM cleavage. This furnished cyclised product in $<10\%$ yield. The presence of unidentified side products prevented its isolation in pure form. The phenol protecting group was therefore changed from MOM to TBS as shown in Scheme 4 with the final step being carried out by the use of Nysted reagent. This avoided problems due to the presence of the acrylate group.[24,25]

RCM of **19** to form the strained macrolactone was not easy. The RCM product was formed in low yield only in CH_2Cl_2 (Table 1, entry 1). The use of hexafluorobenzene was reported to improve the yield in RCM reactions.[26] However, in our case this led to the degradation of **19** (Table 1, entry 2). By switching to toluene we slightly increased the yield (Table 1, entry 3). The use of toluene at 110 °C turned out to be best. This gave the product with a moderate yield of 37%. The addition of one equivalent of $Ti(OiPr)_4$ did not improve the yield of the reaction. The TBS protecting group was removed quantitatively with TBAF (−30 °C, 20 min) affording (±)-Vertine **1** in 37% yield from **19**. The spectral data are in good agreement with the literature data.[9,27]



Scheme 4 Synthesis of **19**. *Reagents and conditions*: (a) Et_3N, acryloyl chloride, 4-DMAP, CH_2Cl_2, 0 °C, 84%; (b) TFA, CH_2Cl_2, 0 °C, 87%; (c) Et_3N, TBSCl, 4-DMAP, CH_2Cl_2, 0 °C, 83%; (d) Nysted reagent, $TiCl_4$, THF, 0 °C, 60%.

Table 1 RCM reaction: screening of conditions



Entry	Solvent	T/°C	Time/h	Yield (%)
1	CH_2Cl_2	45	72	15
2	Hexafluorobenzene	65	72	Decomposition
3	Toluene	70	72	20
4	Toluene	110	16	37
5[a]	Toluene	110	16	35

[a] 1 equivalent of $Ti(OiPr)_4$ was added.

In conclusion we have completed the first total synthesis of (±)-Vertine. The synthetic route proceeds in 11 linear steps with an overall yield of 6%. It includes the first example of the formation of a *Z*-configured α,β-unsaturated macrolactone by RCM. The strategy is sufficiently general to allow the synthesis of not only analogues of (±)-Vertine, but also of other members of the Vertine family.

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27 Initial ^1H and ^{13}C NMR spectra differed from those reported in ref. 9 and we feared that we may have isolated the product containing opposite atropisomerism. Extensive NOE analyses showed this not to be the case. The problem turned out to arise from the presence of small quantities of tetrabutylammonium salts from the desilylation step. Once removed by chromatography on neutral alumina the spectral match was excellent.

