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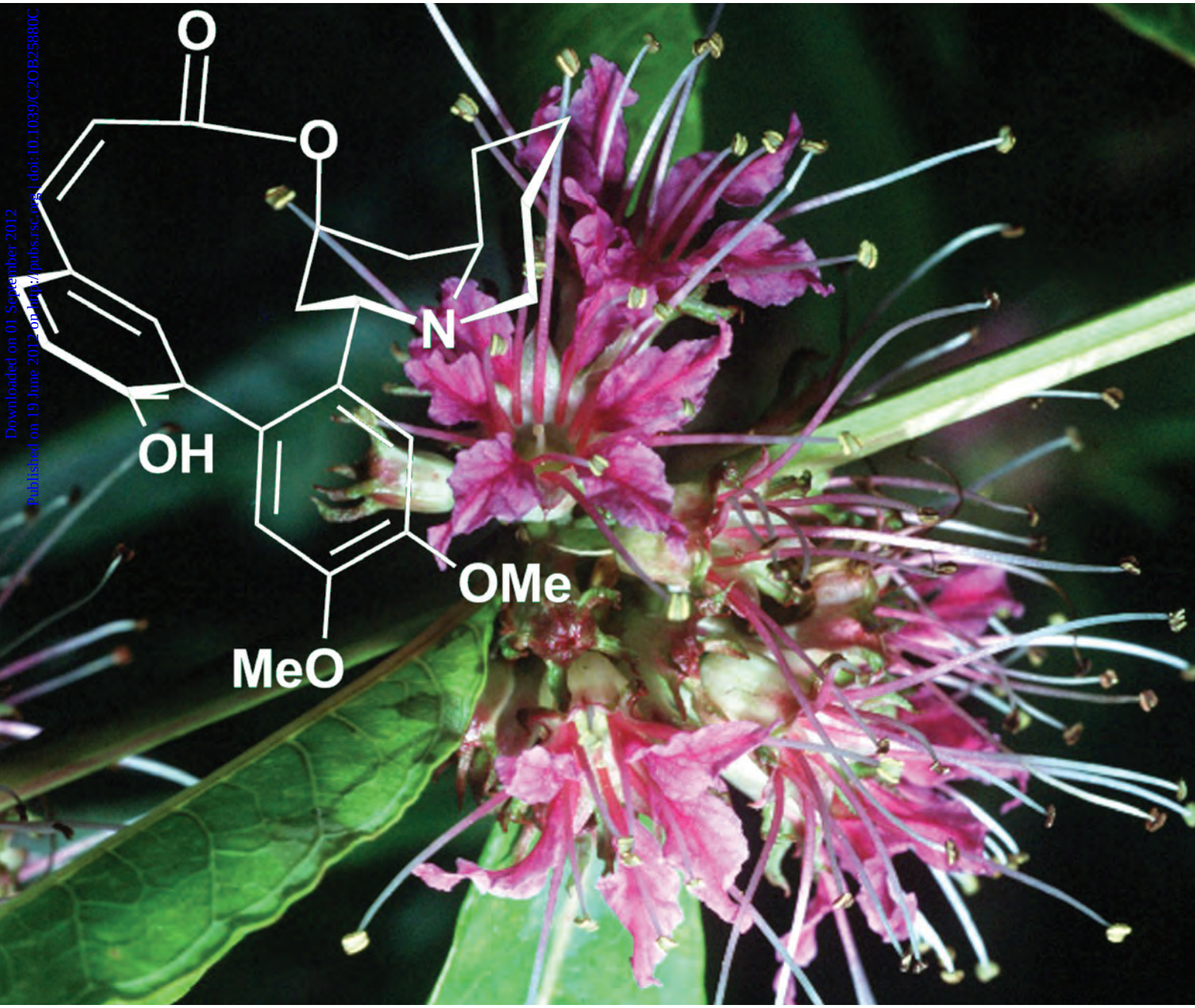

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PAPER

Asymmetric synthesis of (+)-vertine and (+)-lythrine†

Laëtitia Chausset-Boissarie, Roman Àrvai, Graham R. Cumming, Laure Guénée and E. Peter Kündig*

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The total syntheses of the *Lythracea* alkaloids (+)-vertine and (+)-lythrine are described. Enantioenriched pelletierine is used as a chiral building block and engaged into a two step pelletierine condensation leading to two quinolizidin-2-one diastereomers in a 8 : 1 ratio. The major product is used in the synthesis of (+)-vertine *via* aryl–aryl coupling and ring closing metathesis to provide a *Z*-alkene α to the lactone carbonyl function. The same procedure was used for (+)-lythrine after base induced epimerization of the main quinolizidin-2-one diastereomer. Alternative classical ring closure strategies like macrolactonisation or aryl–aryl coupling failed.

Introduction

Fifty years ago, Ferris and co-workers isolated phenylquinolizidinine alkaloids from *Decodon verticillatus*, a flowering plant in the *Lythraceae* family, commonly known as waterwillow or swamp loosestrife and endemic to wetlands in the eastern half of the United States.[1] Later Schwarting and co-workers[2] examined *Heimia salicifolia* and other *Heimia* species. Vertine (**1**) and Lythrine (**2**) are two of the most studied alkaloids of this family. They display a wide range of biological activities such as anti-inflammatory, sedative, and antispasmodic actions. They also play a role in glucose level regulation in blood and lower blood pressure.[3] These al/kaloids are *Z*-configured α,β-unsaturated 12-membered lactones which possess a quinolizidine ring substituted at C2 with an axially oriented oxygen group and, with an equatorially oriented aromatic ring at C4. Two of the three stereogenic centers are part of the lactone ring as is the induced chiral aryl–aryl axis. The two alkaloids differ in the configuration at the bridgehead carbon (C10) of the quinolizidine ring. Thus, the quinolizidinine ring is either *cis*-fused, as in vertine or *trans*-fused as in lythrine (Fig. 1).[4] Attracted by the challenging ring structure we undertook studies towards their syntheses. In a preliminary communication we reported the synthesis of (±)-vertine.[5] Here we describe the synthesis of (+)-vertine and the first total synthesis of (+)-lythrine. While our synthetic study was in progress, Khan's group published the isolation and X-ray structure determination of (+)-vertine.[6]

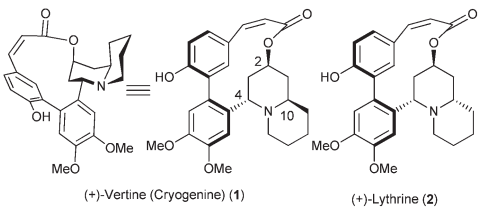


Fig. 1 Structures of (+)-vertine and (+)-lythrine.

This provided for the first time information of the induced axial chirality of **1**.

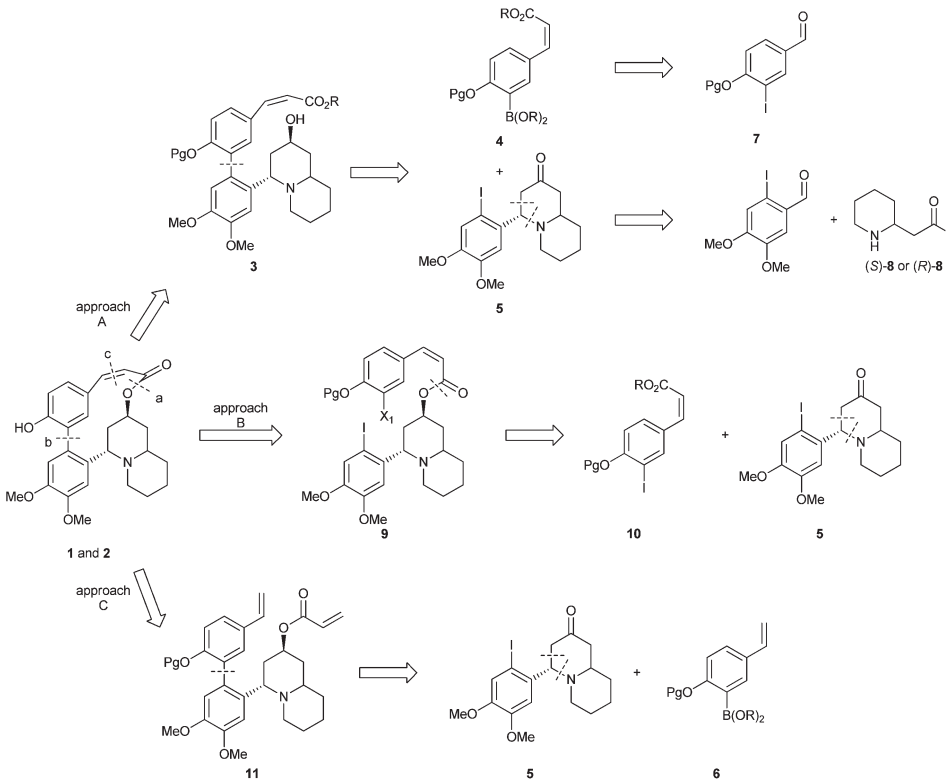
Results and discussion

Our retrosynthetic analysis of **1** and **2** is displayed in Scheme 1. Three scenarios for fragment coupling and final lactone ring closure were envisaged. In a first approach ring closure could be achieved *via* lactonisation[7] (approach A) of key intermediate **3**, obtained from diastereoselective reduction of the biaryl product resulting from a Suzuki–Miyaura cross coupling between quinolizidin-2-one **5** and boronate **4**. The *Z*-unsaturated ester could be accessed *via* a *Z*-selective modified Horner–Wadsworth–Emmons reaction[8] of the corresponding aldehyde **7**. The quinolizidin-2-one **5** is accessible *via* the $Cr(CO)_3$-mediated aza Diels–Alder reaction/radical cyclization method developed for the synthesis of the lythraceae alkaloid (−)-lasubine I.[9] This method provides *cis*-quinolizidin-2-one selectively but it involves an inefficient multi-step synthesis. For this reason and in search of a method that could also be used for *trans*-quinolizidin-2-one we saw an opportunity to develop a diastereoselective pelletierine condensation[10] between the enantioenriched pelletierine and 6-iodoveratraldehyde.

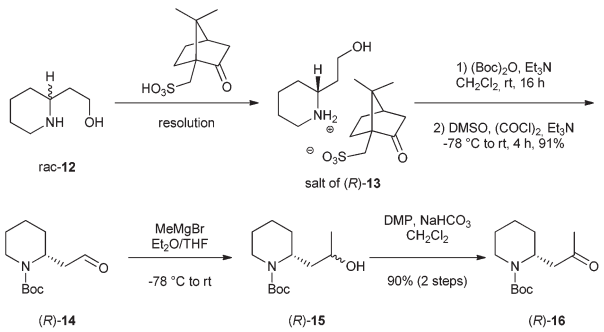
We also considered the possibility of an aryl–aryl cross coupling[11] (approach B) on **9**, formed by esterification between

Department of Organic Chemistry, University of Geneva, 30, quai Ernest Ansermet, CH-1211 Geneva, Switzerland.
E-mail: peter.kundig@unige.ch; Fax: +(41) 223793215;
Tel: +(41) 223796093

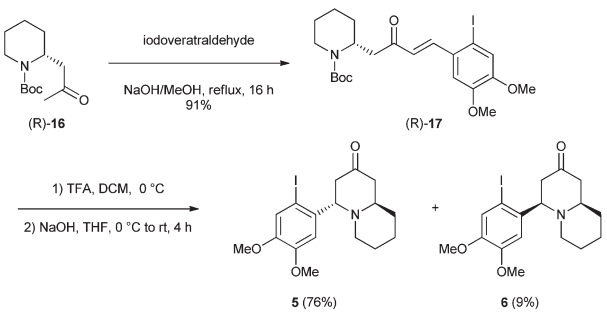
†Electronic supplementary information (ESI) available: Experimental procedures and characterization data for all new compounds along with copies of ^1H and ^{13}C NMR spectra. CCDC 780761, 874077. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c2ob25880c



Scheme 1 Retrosynthetic analysis for the syntheses of (+)-vertine (**1**) and (+)-lythrine (**2**).



Scheme 2 Synthesis of protected pelletierine.

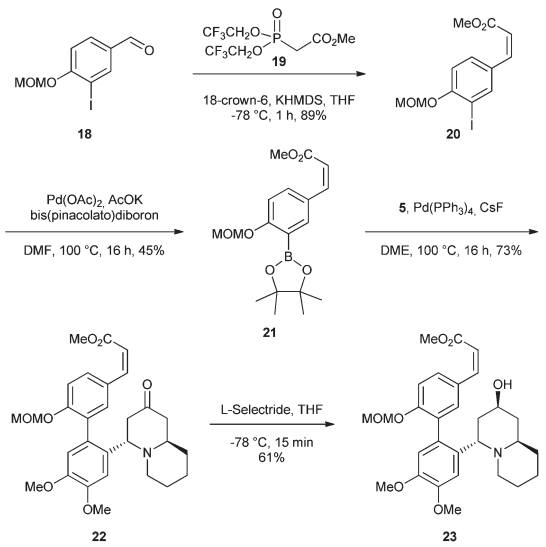


Scheme 3 Synthesis of *cis*-quinolizidinone.

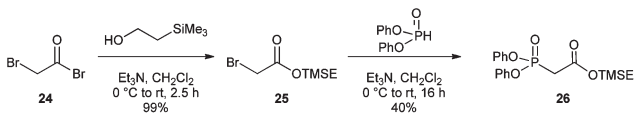
reduced quinolizidinone **5** and *Z*-unsaturated ester **10**. The third approach to **1** or **2** includes ring closing metathesis (RCM) as a key step.[12] We note, however, that to our knowledge there is no precedence of formation of a *Z*-alkene α to a carbonyl group (approach C). In this approach the synthesis of intermediate **11** is required. It should be accessible *via* diastereoselective ketone reduction and acylation of the biaryl product obtained *via* a pathway analogous to that in approach A.

There are several available procedures for the preparation of enantioenriched pelletierine **8** though most require the use of expensive reagents and catalysts or materials difficult of access.[13] We chose to resolve commercially available, racemic 2-piperidineethanol (*rac*-**12**) using (*S*)-10-camphorsulfonic acid according to Hou's procedure[14] to access (*R*)-**8** (Scheme 2) and L-leucine to access (*S*)-**8**. The initially obtained salt of (*R*)-**13** was then protected as a carbamate, and oxidized to the aldehyde (*R*)-**14** by Swern oxidation in 91% yield. Addition of methyl Grignard reagent yielded the secondary alcohol (*R*)-**15** which was directly oxidized with Dess–Martin periodinane (DMP) to give ketone (*R*)-**16** in 90% yield over the two steps (Scheme 2). Using L-Leucine as resolving agent,[15] the same methodology led to (*S*)-**8**.

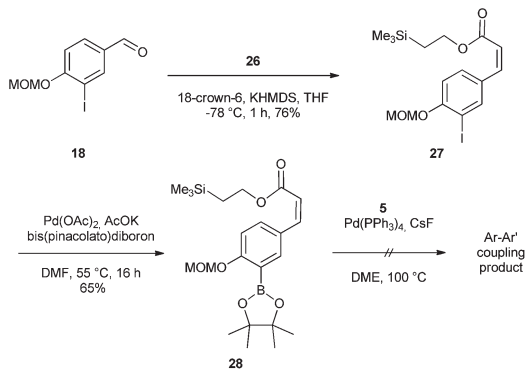
Quinolizidinone **5** was obtained *via* a condensation between pelletierine (*R*)-**8** and 6-iodoveratraldehyde. The reaction, proposed to proceed by an aldol condensation followed by a Michael addition, gives a mixture of *cis*- and *trans*-quinolizidinone products. 1 M aq. NaOH in THF at room temperature (r.t.) afforded *cis* and *trans*-**5** in a 4 : 1 ratio in favor of the *cis*-isomer which was isolated in 52% yield. Unfortunately, partial racemisation was observed likely due to the facile epimerization of the β-amino-ketone.[16] In order to increase the diastereomeric ratio, the overall yield of the process and to suppress racemization, a two step procedure was developed (Scheme 3) wherein, an aldol



Scheme 4 Synthesis of biaryl intermediate **23**.



Scheme 5 Synthesis of phosohonoacetate **26**.



Scheme 6 Attempted synthesis of biaryl by Suzuki–Miyaura coupling.

condensation between Boc protected pelletierine (*R*)-**16** and 6-iodoveratraldehyde led to (*R*)-**17**. Deprotection with trifluoroacetic acid (TFA) and cyclisation under basic conditions yielded a mixture of the diastereoisomers **5** and **6** in a 8 : 1 ratio, favouring **5** with a (4*S*, 9a*R*) relative configuration (Scheme 3). We will describe in a later part of this paper the transformation of **5** to **6**.

We next investigated route A (Scheme 1). First, the unsaturated ester **20** was prepared by a *Z*-selective Still-Gennari modification of the Horner–Wadsworth–Emmons (HWE) procedure.[8a] Under these conditions, aldehyde **18** reacted smoothly with phosphonate **19** providing methyl-acryloyl ester **20** in excellent yield and complete *Z*-stereoselectivity. Boropinacolate derivative **21** was then obtained in modest yield *via* palladium catalyzed coupling.[17] No competition by a Mizoroki–Heck reaction was observed under the conditions used. The coupling of boropinacolate **21** with iodide **5** resulted in the formation of the biphenyl **22** in 73% yield. The *Z*-configuration of the unsaturated ester remained intact in this sequence.

The product was isolated as a mixture of two rotamers in a ratio of 3 : 1 (^{1}H NMR, 500 MHz, 298 K, d^8-toluene). Variable temperature NMR (d^8-toluene, 298 to 363 K) revealed a coalescence temperature of 357 K. Fitting this into Bloch's equation allowed us to determine a $\Delta G^{\neq}$ of 17.3 kcal mol^{-1} for the process. This shows that we are dealing not with true atropoisomers, but with rotamers, as expected for biaryls having only two substituents in the *ortho*-position.[18] Diastereoselective reduction of ketone **22** with L-Selectride was complete within 15 min at −78 °C affording the secondary alcohol **23** in 61% yield (Scheme 4).

In the hope of reducing the number of steps, lactonisation *via* a transesterification was investigated. Lewis acids like Cu(OTf)$_2$, Sc(OTf)$_3$, and TiCl$_4$ have previously been used for accelerating this process.[19] A number of these Lewis acids (ZnCl$_2$, Cu(OTf)$_2$, Sc(OTf)$_3$, TiCl$_4$, Ti(iPrO)$_2$Cl$_2$, BF$_3$·Et$_2$O) were tested, under varying conditions, however either no reaction was observed or decomposition occurred. Following this setback, we sought to carry out a stepwise deprotection and lactonisation, however any attempts to saponify the ester under basic or acidic conditions resulted in no reaction or decomposition. Trimethylsilylether (TMSE) is easier to deprotect *via* treatment with fluoride anion. Commercially available bromoacetylbromide **24** reacted quantitatively with 2-trimethylsilylethanol in the presence of triethylamine. Crude product **25** was used in the subsequent reaction with diphenylphosphite, giving the Ando (diarylphosphono)acetate[20] **26** in unexpectedly low yield of 40% (Scheme 5).

The reaction conditions employed for the preparation *Z*-α,β-unsaturated ester **20** (Scheme 4) were applied to the new (diarylphosphono)acetate **26**. Olefination of aldehyde **18** resulted in the formation of the ester **27** in 76% yield with a *Z*–*E* ratio of >50 : 1. The palladium catalyzed coupling of iodide **27** with bis(pinacolato)diboron afforded the boropinacolate derivative **28** in 65% yield. However, all attempts to perform the Suzuki–Miyaura coupling were unsuccessful (Scheme 6). It is likely that the base preferentially cleaves the TMSE ester rather than activates the boronate.

Performing the cross-coupling reaction before the formation of the *Z*-α,β-unsaturated TMSE ester was next investigated. Biaryl **30** was synthesized and then exposed to the Ando modified HWE reaction conditions,[8b] leading to ester **31** as an inseparable mixture of *Z*–*E* isomers in a 35 : 65 ratio. A diastereoselective reduction provided the axial alcohol. After screening of conditions, cleavage of the ester was achieved with TBAF supported on silica gel,[21] at this stage the *Z*–*E* isomers were separated by column chromatography and **32** was isolated as a single isomer in 59% yield. Attempted formation and cyclisation of an activated ester with either the Mukaiyama[22] or Corey–Nicolaou reagents[23] resulted in decomposition. The use of HBTU[24] led to complex mixtures and any attempts at purification failed (Scheme 7).

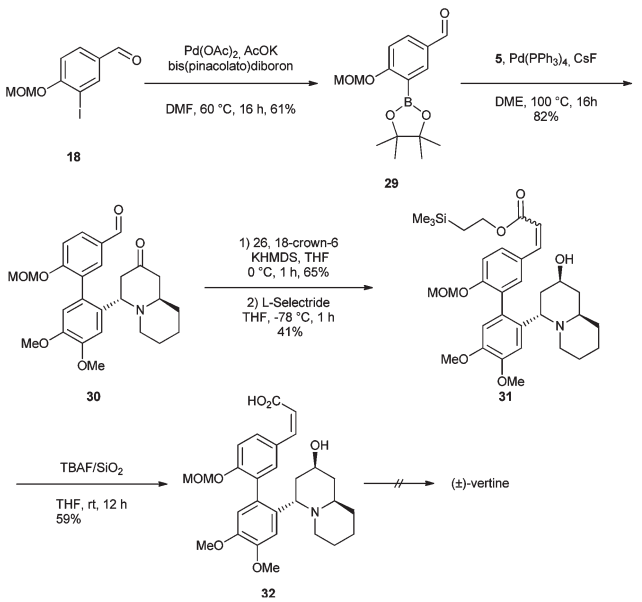
This approach was abandoned, and we briefly investigated aryl–aryl coupling (route B, Scheme 1) as a key step in the lactone formation. A modified Still procedure was applied to aldehyde **18**.[8b] The reaction was completely *Z*-stereoselective;

Z-acrylic acid **34** was obtained in 60% yield after saponification using LiOH. Different conditions for the synthesis of the ester **35** *via trans*-esterification was then tested, the results are summarized in Table 1.

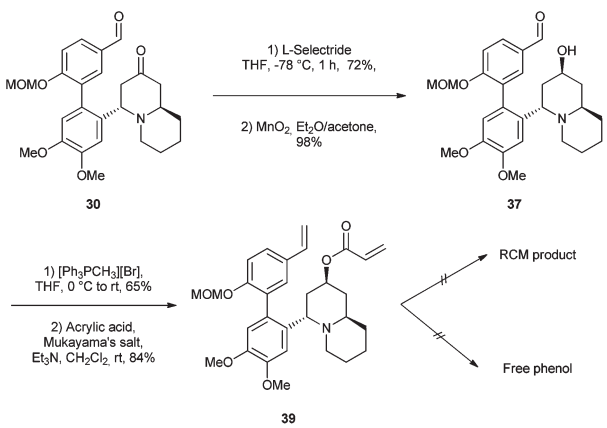
Unfortunately, esterification was problematic due to the propensity of *Z*-**35** to undergo isomerisation to the *E*-isomer (Table 1). Before the coupling with the reduced quinolizinone **33**, *Z*-α,β-unsaturated acid **34** was converted to the acid chloride (Table 1, entries 1; 2; 4). ^{1}H NMR data showed that the *Z*-configuration remained intact at this stage. In the absence of a nucleophilic catalyst (Table 1, entries 1–2), the reaction was slow and the base promoted isomerisation. HBTU, used as activating reagent to promoted coupling (Table 1, entry 3), was also unsuccessful. In the presence of a catalytic amount of DMAP, coupling proceeds in good yield but with complete isomerisation (Table 1, entry 4). The sensitivity of *Z*-α,β-unsaturated esters towards isomerisation under Keck condition (DCC, DMAP) was previously reported in the literature.[25] Attempts of cyclization were then made under classical Stille conditions.[26] These conditions resulted in slow decomposition of the starting material, however, from which no promising compounds could be isolated.

Finally, we embarked on approach C (Scheme 1) to form (+)-vertine with ring closing metathesis (RCM) as a key step. Attempts at selective methylenation of aldehyde **30** were not successful and we therefore proceeded with a reduction of both carbonyl functions. The dicarbonyl compound **30** (Scheme 8) was reduced with L-selectride and the benzylic alcohol was re-oxidized with MnO_2 in 98%. A Wittig reaction followed by an acylation under Mukaiyama's conditions afforded the ester **39**. An X-ray structure determination of the dialkene intermediate **39** confirmed the relative configuration of the molecule (Fig. 2).[27]

All attempts to cleave the MOM group by using HCl,[28] TFA,[29] TMSBr,[30] *p*-TsOH,[31] $NaHSO_4{\cdot}SiO_2$,[32] I_2/MeOH,[33] or a Lewis acid[34] either gave unidentified byproducts or incomplete deprotection. Attempts of RCM on the MOM protected product **39** were therefore investigated, even if the formation of the product of the RCM was detected; no isolation with a decent yield was possible. We hypothesised that Ru coordination to the MOM protecting group could block the catalytic cycle. Another potential problem is readily identified from the structure in Fig. 2. In order to close the distance between the alkene groups (in red) and to carry out an RCM reaction, rotation about the aryl–aryl bond and about the aryl-quinolizidine bond is required. These operations will strongly increase $A^{1,3}$-strain (allylic strain) and this casts doubt on the success of this strategy.

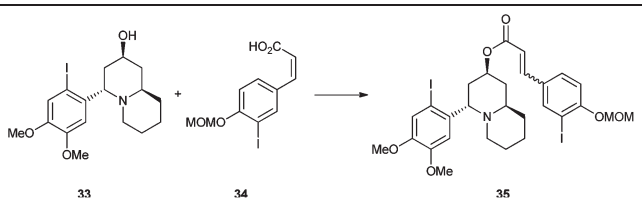


Scheme 7 Attempted synthesis of (±)-vertine by macrolactonisation.



Scheme 8

Table 1 Attempted synthesis of *Z*-**35**



Entry	Equivalent of acid/activation	Coupling conditions	*Z*–*E*-**35**	*Z*-**35** [%]
1	1.25/Oxalyl chloride, *cat* DMF	iPr_2NEt, CH_2Cl_2, rt, 16 h	3 : 1	20
2	2/Oxalyl chloride, *cat* DMF	Et_3N, CH_2Cl_2, rt, 16 h	—:1	—
3	1.5/—	HBTU, iPr_2NEt, MeCN, rt, 16 h	No reaction	
4	1.25/Oxalyl chloride, *cat* DMF	*cat* DMAP, iPr_2NEt, CH_2Cl_2, rt, 16 h	—:1	—

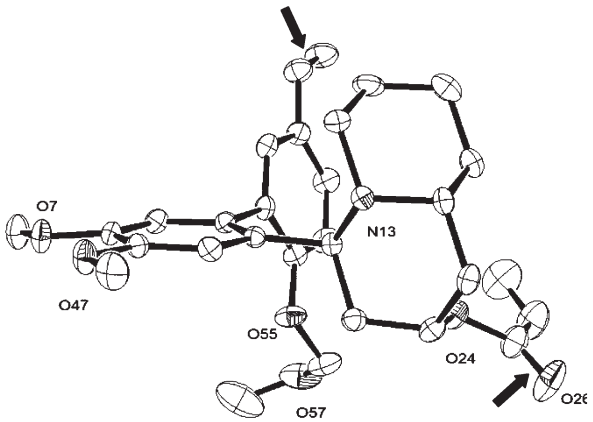
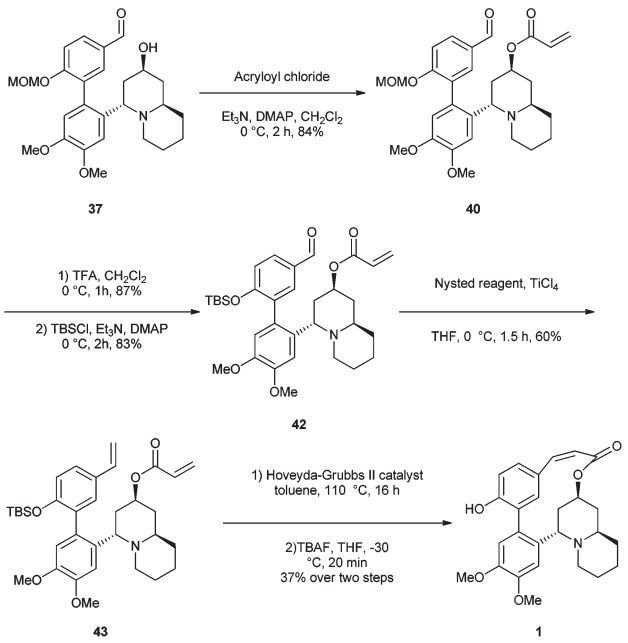
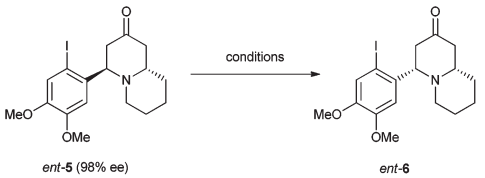


Fig. 2 ORTEP view of the dialkene intermediate **39**. Arrows indicate the alkenes that are to be coupled *via* a RCM reaction.[5]

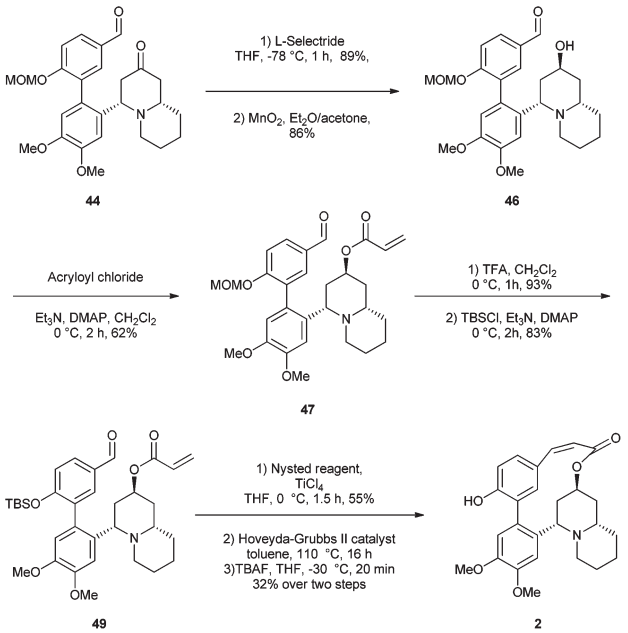


Scheme 9 Synthesis of (+)-vertine.

Table 2 Conditions tested for epimerisation of *ent*-**5**



Entry	Conditions	*ent*-**5** : *ent*-**6**	Yield *ent*-**6** [%]	ee *ent*-**6** [%]
1	MeOH, rt, 3 d	No reaction		
2	MeOH, reflux, 4 h	—:1	80	70
3	1 M aq NaOH, MeOH, rt, 3 d	—:1	98	96
4	1 M aq NaOH, THF, rt, 3 d	2 : 1	30	95
	DBU, THF, rt, 3 d	No reaction		



Scheme 10 Synthesis of (+)-lythrine.

We nevertheless decided to investigate the effect of a change in phenol protecting group. After transesterification of the alcohol intermediate **37**, the MOM protecting group was removed using TFA. All attempts to form the product *via* RCM reaction failed. Coordination of the alcohol to the catalyst could block the reaction and therefore the free phenol was protected as a TBS ether. Methylenation of **42** was carried out by the use of Nysted's reagent avoiding problems due to the presence of the acrylate group. The RCM reaction using Hoveyda-Grubbs II catalyst at 110 °C in toluene followed by deprotection with TBAF turned out to be the best condition affording (+)-vertine with a moderate yield of 37% (Scheme 9). An increase of the reaction time at lower temperature was not successful. Under these conditions the reaction was not complete and we observed degradation of the reaction mixture.

The above approach should also be amenable to the synthesis of (+)-lythrine. This required a selective synthesis of *ent*-**6**, the precursor of (+)-lythrine. Condensation between (*S*)-pelletierine and 6-iodovetraldehyde under the conditions previously reported was firstly tested, unfortunately the *trans*-quinolizidinone was obtained with partial racemization. We then proceeded to investigate epimerizition of the *cis*-quinolizidinon *ent*-**5** to the *trans*-quinolizidinone *ent*-**6** *via* a retro-Michael/Michael addition. The conditions tested are summarized in Table 2.

No epimerization was observed when *ent*-**5** was stirred in methanol at r.t. (Table 2, entry 1). Increasing the temperature afforded the *trans*-isomer albeit with partial racemisation (entry 2). Epimerization occurred in the presence of NaOH (entries 3, 4). The *trans*-quinolizidinone was obtained with excellent yield and enantioselectivity (entry 3). Using the same reaction sequence described previously for (+)-vertine resulted in the synthesis of (+)-lythrine (Scheme 10). Again, *Z*-selective metathesis was best carried out by heating a toluene solution of the dialkene precursor and Grubbs-Hoveyda II to reflux for 16 h. The product

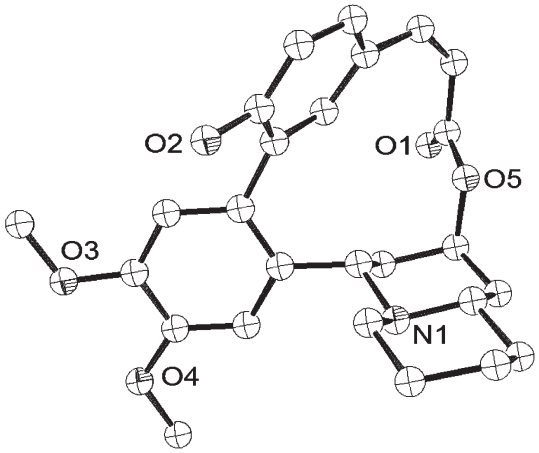


Fig. 3 ORTEP view of (±)-lythrine **2**.

Z-alkene geometry is imposed by ring strain though the reaction is remarkable given the generally exclusive formation of *E*-alkene α to a carbonyl function. The relative configuration of the molecule was confirmed by an X-ray structure determination (Fig. 3).[35] Having access to both X-ray structures of (+)-vertine[6] and (±)-lythrine we can confirm that the only structural difference between this two natural products are the configuration at the bridge carbon (C10) of the quinolizidine ring (Fig. 1). The overall shape of the strained molecules remained the same. An interesting feature clearly visible in Fig. 2 is the torsion angle of 56° between the C═O group and the "conjugated" alkene.

Conclusions

In the course of the work towards the synthesis of (+)-vertine, a number of different approaches were followed. Classical strategies were tested without success and despite the lack of precedent for the formation of *Z*-alkene α to a carbonyl function, RCM proved to be efficient leading to the first example of formation of a *Z*-α,β-configurated unsaturated macrolactone. The facile isomerization of the quinolizidin-2-one gave access to a precursor of (+)-lythrine, whose synthesis was completed using the same reaction sequence as for (+)-vertine.

Acknowledgements

We are grateful to Prof. I. A. Khan for a sample of (+)-vertine. We thank the Swiss National Science Foundation for financial support.

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