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Strategies for the asymmetric construction of pelletierine and its use in the synthesis of sedridine, myrtine and lasubine

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Abstract:

Three methods for the asymmetric synthesis of both enantiomers of pelletierine **6** are reported. Bella's proline-based Mannich process gave (*R*)- and (*S*)-Cbz-protected **6** in good yields from Δ^1-piperideine **14** and in reasonable enantiomeric excess (74-80% e.e.). An intramolecular aza-Michael, cinchona-based, organocatalytic method is also reported and with commercially available 9-amino quinine (**24a**) and quinidine (**24b**) catalysts Cbz-protected α,β-unstaturated ketone **23** also gave (*R*)- and (*S*)-Cbz-protected **6** in good yields and enantiomeric excess (90-99% e.e.). This material was used to synthesise both optically active forms of deoxyhalofuginone (**26**), an analogue of febrifugine which is of interest as an anti-fibrotic agent. Finally, a resolution of racemic pelletierine using (*R*)- and (*S*)-mandelic acid **27** is reported. This scalable method gave both enantiomers of Cbz- and Boc-protected **6** in excellent enantiomeric excess (≥ 99%). Both highly enantioenriched forms of **6** (obtained from the resolution study) were used to synthesise several alkaloids. Firstly, (–)-(*S*)-Cbz-protected pelletierine **17** was used to prepare naturally occurring sedridine (**32**) and its epimer allosedridine (**8**). Then the preparation of both enantiomers of the quinolizidine myrtine (**33**) by an olefination-intramolecular aza-Michael sequence is reported. Finally, the synthesis of the epimeric quinolizidine alkaloids, lasubine I (**34**) and lasubine II (**35**), from (+)- and (–)-Boc-protected pelletierine (**29**) respectively, is discussed.

Introduction

Heterocycles are the most widespread recurring motif in pharmaceuticals. In turn one of the most common of these heterocyclic units is the piperidine ring[1] which, possessing a range of different substituent patterns, is found as a core structural motif in various pharmaceuticals.[2] One substantial sub-group of these include a substituent in the 2-position of the heterocycle and a selection of representative 2- and 1,2-substitued piperidine-based pharmaceuticals are depicted in Figure 1.[2] These compounds possess a variety of biological actions, for example methylphenidate (**1**), better known as ritalin, is widely prescribed to treat hyperactivity and chronic sleep disorders. Mefloquine (**4**), also known as lariam, is an anti-malarial and racemic perhexiline (**5**) is an antifungal agent.

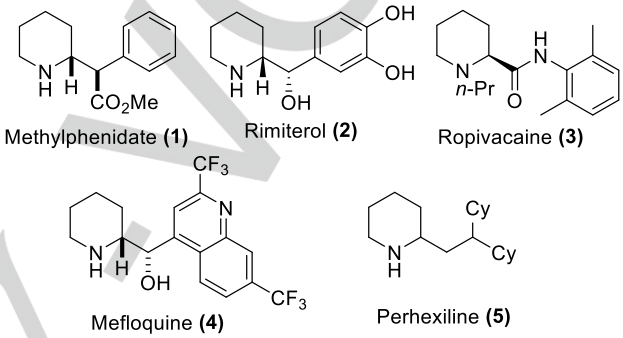

Figure 1. Representative 2-substituted piperidine-containing pharmaceuticals.

Functionalised piperidine derivatives also feature in many natural products.[3] The breadth of structures and biological activities presented by these compounds mean they are attractive to both chemists and biologists. One large group of biologically and structurally interesting piperidine alkaloids are those presenting a 2-substituent, which, with and without additional substituents, have been isolated from various different plants (see Figure 2 for selected examples).[2,4]

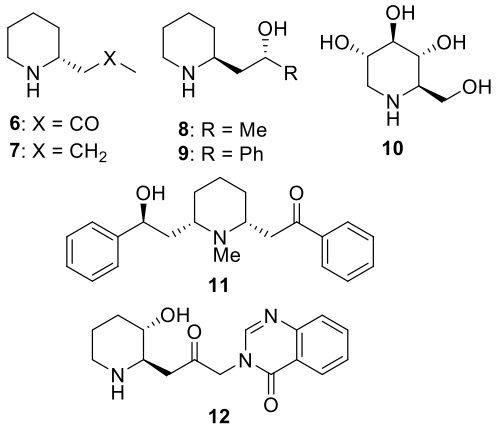

Figure 2. Representative 2-substituted piperidine containing natural products.

Pelletierine (**6**), a 2-acetyl substituted piperidine, was first isolated in 1878 by Tanret from the root bark of the pomegranate tree (*Punica Granafum L.*).[5] Compound **6** has an interesting history: it is isolated in an optically active form, however, it co-occurs with a compound termed isopelletierine, which is simply

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racemic pelletierine (it is now appreciated that β-keto amines, like **6**, undergo isomerisation, see Scheme 3) and its exact structure was not unequivocally confirmed until its first synthesis in 1961.[6] More recently several new methodologies have been developed to obtain this and related molecules in optically active form.[7] Part of this interest stems from the fact that **6** represents a useful, functionalised building block to assemble more complex structures.[8] Coniine (**7**), a toxic substance from several plants famously including poison hemlock (*Conium maculatum*), contains an unfunctionalised *n*-propyl substituent.[9] It is likely that natural products like **6** are assembled biosynthetically from a Mannich-type process, therefore, unsurprisingly the 1,3-amino oxygenation pattern is frequently found in this class of compounds.[10] For example, amino alcohols such as allosedridine **8** and sedamine **9** are representative members of this piperidine family.[11] Deoxynojirimycin **10** is an example of a natural product which has additional oxidation within the piperidine ring. This compound has disease relevant α-glucosidase activity and two *N*-alkylated analogues of **10** (termed miglitol and miglustat) are clinically useful and an epimer (migalastat) has just been given FDA approval for the treatment of Anderson-Fabry disease.[12] Lobeline **11**, isolated from plants of the *Lobelia* family, resembles **9** but has an additional oxidised phenethyl substituent.[13] Finally, febrifugine (**12**) is a di-substituted piperidine-based natural product that has potent biological activities and also includes a 1,3-amino oxygenation pattern.[14]

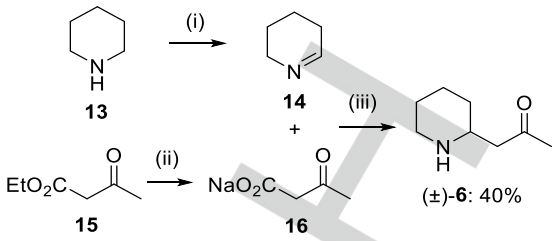
As a consequence of their distribution and important activities methods to prepare the types of compounds included in Figures 1 and 2 are of significance – particularly those able to introduce the substituents in a stereocontrolled manner.

Results and Discussion

The Mannich and *N*-conjugate addition reactions represent two of the most direct methods to prepare β-amino ketones. Therefore, in our efforts to develop syntheses of 2-substituted piperidines bearing a keto-side-chain, we focused on each of these processes.

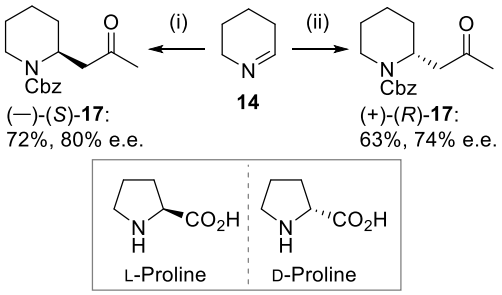
2.1 The Mannich reaction for the synthesis of pelletierine

Based on a reported procedure the synthesis of racemic pelletierine **6** was achieved as shown in Scheme 1.[7c] Piperidine **13** was initially *N*-halogenated and the intermediate *N*-chloro compound was then immediately dehydrohalogenated. As reported, the product from this process is a mixture of compounds which represent surrogates for imine **14**. This mixture was taken up in EtOH-Et_2O and was directly reacted with the sodium salt of acetoacetic acid **16** (prepared by base hydrolysis of ethyl acetoacetate **15**) in a decarboxylative Mannich reaction. Following this procedure (±)-pelletierine **6** was reproducibly produced in approximately 40% overall yield (Scheme 1).



Scheme 1. Δ^1-Piperideine **14**-based synthesis of (±)-pelletierine **6**. Reagents and conditions: (i) NCS, ether, rt; then KOH, EtOH, 0 °C to rt; (ii) $NaOH_{(aq)}$, reflux, 4 h, then rt, 18 h; (iii) reflux, 4 h, 40%.

An asymmetric organocatalytic version of the intermolecular Mannich reaction detailed in Scheme 1 has been reported by Bella.[7n] We have used this method to prepare both optically active versions of pelletierine and in turn used this material to prepare analogues of febrifugine (**12**).[15] As summarised in Scheme 2, use of L- or D-proline facilitated the enantioselective intermolecular Mannich reaction of **14** with an excess of acetone in a DMSO-water (9:1) solvent mixture. This led to a rapid and reproducible reaction generating unnatural and natural pelletierine respectively. In order to purify and characterise the secondary amine adducts they were directly converted into their Cbz-protected forms. Use of L-proline in this manner gave (–)-**17** in 72% yield from **14**, whereas D-proline generated (+)-**17** in 63% yield. Analysis by chiral HPLC demonstrated that (–)-**17** was produced in 80% e.e., whereas the value for (+)-**17** was 74%. It has been established that laevorotatory Cbz-pelletierine, (–)-**17**, possesses a 2*S* configuration, whereas dextrotatory (+)-**17** possesses *R*-stereochemistry (Scheme 2).[7n]



Scheme 2. Proline-based asymmetric synthesis of Cbz-protected pelletierine **17**. Reagents and conditions: (i) L-Pro (20 mol%), acetone, DMSO-H_2O (9:1), rt, 1 h then CbzCl, Na_2CO_3, DCM-H_2O (3:2), 0 °C to rt, 72%, 80% e.e.; (ii) D-Pro (20 mol%), acetone, DMSO-H_2O (9:1), rt, 1 h then CbzCl, Na_2CO_3, DCM-H_2O (3:2), 0 °C to rt, 63%, 74% e.e.

Although the yields for the two-step process were good and the enantiomeric excesses obtained were reasonably high they did prove to be slightly lower than those reported.[7n] The reason for this, we believe, is not solely due to the inherent selectivity of the proline-mediated Mannich reaction. It is known[16] that β-keto amines, like **6**, can undergo isomerisation and we believe, that in this free-base form, isomerisation occurs during the course of

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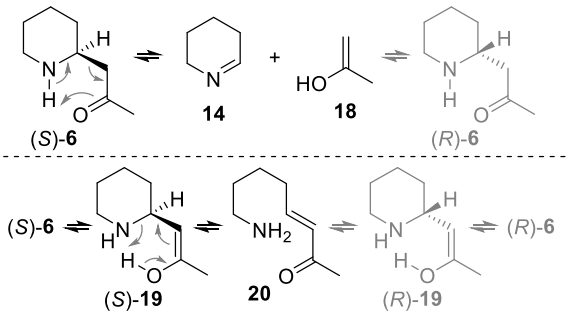
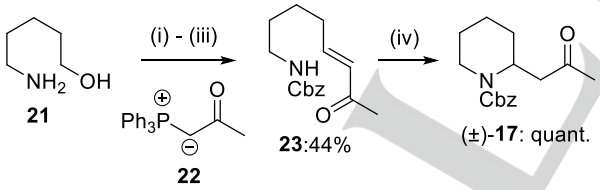
the organocatalysed Mannich reaction and/or the work-up procedure. As shown in Scheme 3 this isomerisation can occur either *via* a *retro*-Mannich process, or *via* a *retro*-Michael process and these reversible reactions lead to gradual erosion of the optical purity of **6**. In contrast, prolonged storage of solutions of optically active **17** in organic solvents (chlorinated solvents and alcohols) demonstrated no loss of enantiopurity.



Scheme 3. *Retro*-Mannich and *N*-conjugate addition mechanisms for the racemisation of **6**.

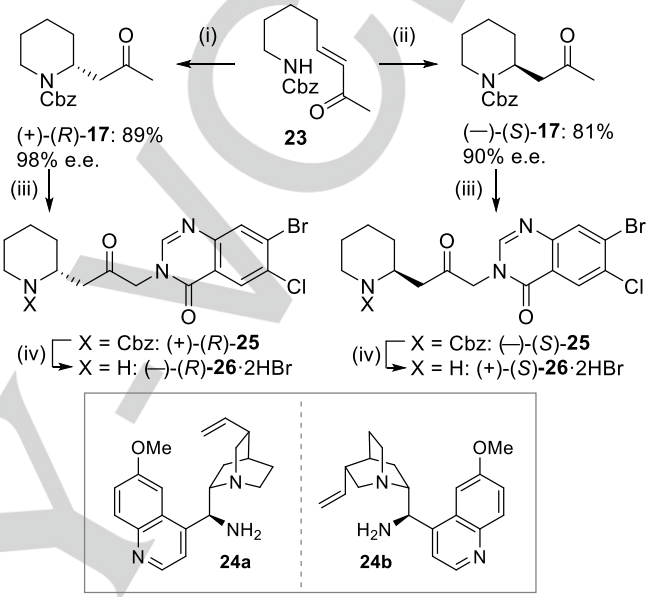
2.2. Intramolecular aza-Michael-type reaction for the synthesis of pelletierine

An alternative method to prepare pelletierine by an intramolecular aza-Michael-type reaction (IMAMR)[17] was also considered. Racemic Cbz-protected pelletierine **17** was prepared by a straight-forward four-step process from 5-amino pentanol **21**. This was first converted into its Cbz-protected form before Swern oxidation generated 2-hydroxy Cbz-protected piperidine (Scheme 4). The masked aldehyde was then reacted with stabilised ylide **22** in order to form *trans*-enone **23**, which, upon treatment with a Lewis acid, underwent an intramolecular aza-Michael reaction (IMAMR) to produce racemic **17**.



Scheme 4. IMAMR for the synthesis of (±)-Cbz-protected pelletierine **17**. Reagents and conditions: (i) CbzCl, $NaHCO_3$, THF-H_2O (1:1); (ii) $(COCl)_2$, DMSO, TEA, DCM, -78 °C; (iii) **22**, PhMe, 110 °C, 44%; (iv) $BF_3{\cdot}OEt_2$, MeCN, rt, quant.

Following a two recent reports, the enantioselective version of this type of IMAMR was also studied as a means to produce enantioenriched **17**.[7o,p] Thus, under Sánchez-Roselló's and Fan's conditions, treatment of **23** with quinine-based amine **24a** gave (+)-**17** in good yield (Scheme 5). Importantly the *pseudo*-enantiomer of **24a** is commercially available, therefore, the enantiomeric form of **17** was similarly accessed from quinidine-based amine **24b** in similar yield. Both (*R*)- and (*S*)-**17** accessed from this study were used to prepare (–)- and (+)-deoxyhalofuginone **26**, a compound of interest as an analogue of the natural product febrifugine (**12**, Figure 2).[15] The enantioexcess recorded for Cbz-protected (*R*)- and (*S*)-deoxyhalofuginone (**25**), derived from these sequences were 98% and 90% respectively and this high level of optical purity enabled an X-ray crystal structure of (*R*)-**25** to be obtained, which confirmed the sense of selectivity for the stereoselective IMAMR (Figure 3).



Scheme 5. Cinchona-based asymmetric synthesis of (+)- and (–)-Cbz-protected pelletierine **17** and their use in the synthesis of (–)- and (+)-deoxyhalofuginone **26**. Reagents and conditions: (i) **24a** (20 mol%), TFA (40 mol%), THF, rt, 18 h, 91%, 98% e.e.; (ii) **24b** (20 mol%), TFA (40 mol%), THF, rt, 18 h, 90%, 90% e.e.; (iii) see ref. 15; (iv) HBr, AcOH, see ref. 15.

The comparatively better enantiomeric excess observed for the formation of **17** with the cinchona catalysts must be factored with their increased price in comparison to, particularly L- but also D-proline.[18] Therefore, a less costly alternative was considered for the larger scale preparation of optically active (protected) pelletierine.

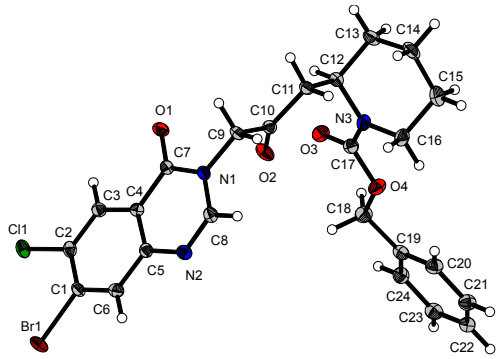


Figure 3. Single X-ray crystal structure of (*R*)-Cbz-deoxyhalofuginone **25** (thermal ellipsoids drawn on the 50% probability level).[19]

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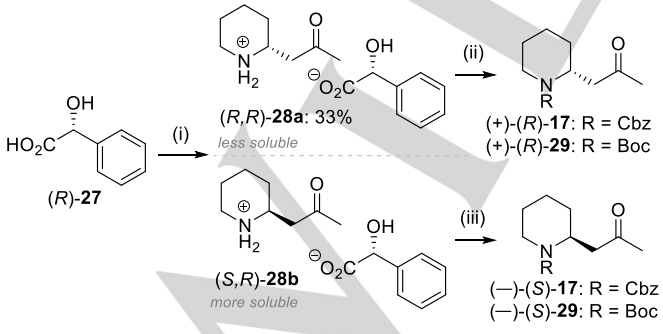
2.3. Resolution of racemic pelletierine 6

Although direct enantioselective syntheses of **6** are elegant the preparation of a racemic mixture followed by its resolution could still be a straightforward, scalable alternative, and this is particularly true in situations where both enantiomers might be of value.[20] A cheap and potentially very effective method for obtaining enantioenriched amines is the use of a chiral acid and the resolution of the resultant diastereomeric salt based on solubility differences. The resolution of racemic pelletierine **6** was reported by Galinovsky, Bianchetti, and Vogl,[21] and then modified and extended by Beyerman and Maat.[22] This was achieved using non-commercially available, enantiomerically pure 6,6'-dinitrobiphenyl-2,2'-dicarboxylic acid. It should be noted that it was reported that the free base, obtained by treating the ammonium salt with hydrochloric acid and then with sodium carbonate, was observed to racemise in aqueous and in ethanolic solution, and, in particular, in alkaline medium (see Scheme 3).[16] Beyerman's development was to repeat the resolution but to add picric acid directly to the reaction mixtures. This produced a precipitate of crystalline *R*-(–)-pelletierine picrate and thus avoided the racemisation of free-base pelletierine. In relation to the resolution of 2-substituted piperidines, in 1999 an efficient procedure for the resolution of 2-methylpiperidine was described by Sage *et al.* which used both enantiomers of mandelic acid as the resolving agent.[23] A similar strategy was applied by Nanayakkara *et al.* in 2008 for the resolution of racemic 2-undecylpiperidine. This enabled access to enantiomers of the fire ant venom alkaloids solenopsin and isosolenopsin A, B, and C.[24]

Therefore, subsequent to the multi-gram preparation of racemic **6** (Scheme 1) the use of both enantiomers of mandelic acid **27** were considered as potential resolving agents. An equimolar amount of (*R*)-mandelic acid **27** was added to a stirred solution of (±)-**6** in MeOH. Then Et_2O was added (MeOH-Et_2O; 1:2.5) and gratifyingly it was found that (*R,R*)-pelletierine mandelate **28a** readily crystallised from this mixture leaving the more soluble diastereomeric (*S,R*)-pelletierine mandelate **28b** in solution (Scheme 6).



Scheme 6. Resolution of pelletierine **6** using mandelic acid **27**: Synthesis of enantioenriched protected pelletierine **17** and **29**. Reagents and conditions: (i) (±)-**6**, MeOH-Et_2O, 0 °C, 22 h; (ii) recrystallise (MeOH-Et_2O); then CbzCl, *i*-Pr_2NEt, DCM, 0 °C to rt, 18 h, 33%, >99% e.e.; or Boc_2O, Et_3N, DCM, 0 °C to rt, 18 h, quant.; (iii) $KOH_{(aq)}$, then (*S*)-**6**, MeOH-Et_2O, 0 °C, 22 h, recrystallise (MeOH-Et_2O); then CbzCl, *i*-Pr_2NEt, DCM, 0 °C to rt, 18 h, 41%, >99% e.e.; or Boc_2O, Et_3N, DCM, 0 °C to rt, 18 h, 90%.

The mixture was stored in the fridge (approx. 5 °C) for 22 h. It was then filtered, to give the insoluble salt, which was further recrystallised using a mixture of MeOH and Et_2O. The recrystallised salt was converted into both Cbz-pelletierine **17**, or Boc pelletierine **29**, for characterisation and storage. In this manner (+)-**17** was ultimately isolated from (±)-**6** in 33% overall yield and > 99% e.e. The mother liquors, containing mainly the more soluble (*S,R*)-pelletierine mandelate salt **28b**, were collected, combined and in this way enantioenriched (*S*)-pelletierine **6** was recovered by base treatment. Treatment of this material with (*S*)-mandelic acid **27**, in an otherwise identical procedure to that described above for the production of (*R*)-**17**, led to the isolation of (*S*)-**17**, which was produced in a 41% overall yield and > 99% e.e. (Scheme 6).

The optical purity of protected pelletierine accessed by this route was determined by the HPLC analysis of both enantiomeric forms of Cbz-pelletierine **17**. However, it also proved possible to use ^{1}H-NMR spectroscopy of the insoluble, **28a** and soluble salts, **28b**, to determine their diastereomeric ratio. This method was used to determine how many recrystallisations were required in order to ultimately obtain high optical purity of **17** (see ESI section). In terms of absolute stereochemistry, material obtained from either salt **28a** and **28b** was compared to the literature data[15] and was also consistent with the previous work discussed above in Schemes 2 and 5. In addition the absolute stereochemistry of the insoluble salt **28a** was further confirmed by single crystal X-ray crystallography (Figure 4).[25]

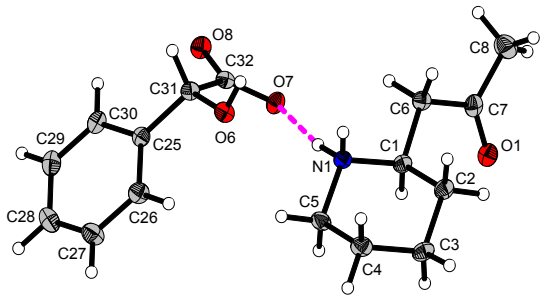


Figure 4. Single X-ray crystal structure of (*R,R*)-pelletierine mandelate **28a** (thermal ellipsoids drawn on the 50% probability level).[25]

With a reliable means to access multi-gram amounts of both enantiomers of Cbz- and Boc-pelletierine, **17** and **29**, in excellent enantiomeric excess >99% e.e., we then sought to investigate their use for the synthesis of other optically active natural products bearing a substituted piperidine motif within their structure.

2.4. Asymmetric synthesis of sedridine 32 and allosedridine 8

The most commonly occurring members of the sedum alkaloid family are 2-substituted saturated nitrogen heterocycles featuring a 1,3-amino alcohol moiety.[11] Representative are sedridine **32** and its diastereomer allosedridine **8** which differ in

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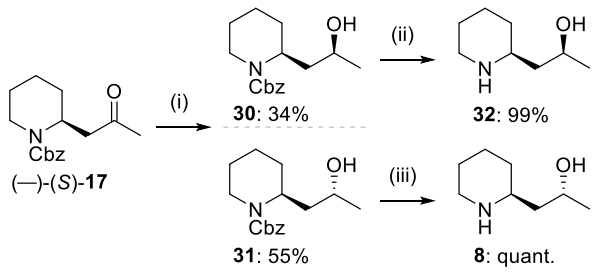
the stereogenic secondary alcohol unit in the side chain. These two sedum alkaloids were prepared from (*S*)-Cbz-pelletierine **17**, prepared from the more soluble mandelate salt **28b** (see Scheme 6), using $NaBH_4$ as the reducing agent.[26] The non-diastereoselective reduction produced both natural sedum alkaloids which differ in polarity. This enabled their separation on silica-gel by flash column chromatography. Both Cbz-sedridine **30** and allosedridine **31** were then deprotected by hydrogenolysis of the carbamate group in the presence of Pearlman's catalyst, which led to (+)-sedridine **32** and (–)-allosedridine **8** in very good yield (Scheme 7). The spectroscopic data and optical behaviour of **32** and **8** prepared *via* this sequence was consistent with the structure and stereochemistry of the naturally occurring amino alcohols.[11]



Scheme 7. Asymmetric synthesis of sedridine **32** and allosedridine **8**. Reagents and conditions: (i) $NaBH_4$ (2 eq.), MeOH, 0 °C, 3 h; (ii) H_2, $Pd(OH)_2$, MeOH, rt, 18 h, 99%; (ii) H_2, $Pd(OH)_2$, MeOH, rt, 18 h, quant.

In addition, both (+)-**32** and (–)-**8** proved crystalline and single crystal X-ray structures for both[27] served to confirm the structure of these alkaloids and were consistent with stereochemical data reported by Beyerman and Fodor[7b] (Figure 5).

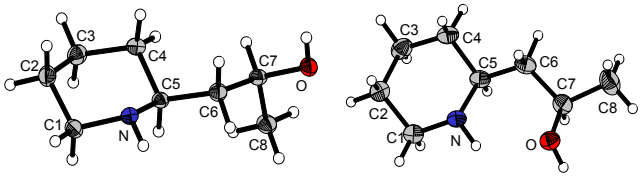


Figure 5. Single crystal X-ray structures of (+)-(*S*,*S*)-sedridine **32** and (–)-(*S*,*R*)-allosedridine **8** (thermal ellipsoids drawn on the 50% probability level).[27]

2.5. Synthesis of the quinolizidine alkaloids (+)- and (–)-myrtine (33) and (–)-lasubine I (34) and II (35)

Indolizidine and quinolizidine containing alkaloids feature a bicyclic 4.3.0 and 4.4.0 ring structure respectively, encompassing the nitrogen atom at a ring fusion point (Figure 6).[28] Numerous examples of natural products containing this core structural motif exist. Myrtine (**33**), from *Vaccinium myrtillus*,[29] and lasubine I and II (**34** and **35**) from *Lagerstroemia subcostata*,[30] are representative examples of quinolizidine alkaloids. Both compounds include a 1,3-amino oxidation pattern and over the years have proved popular synthetic targets.[29,30]

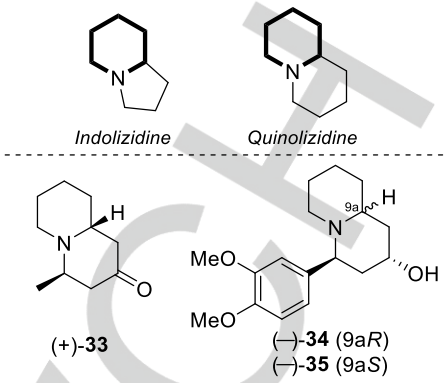
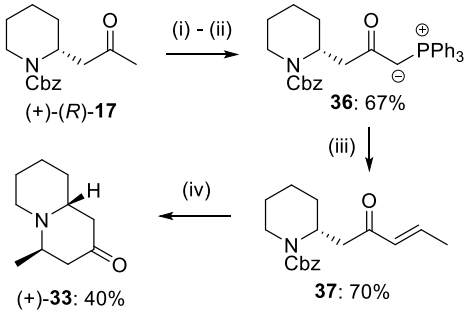


Figure 6. Indolizidine and quinolizidine alkaloids: Structures of (+)-myrtine (**33**) and (–)-lasubine I (**34**) and (–)-lasubine II (**35**).

It was planned to use the resolved pelletierine in order to access the core quinolizidine in compunds **33**, **34** and **35** by an initial olefination of the methyl ketone, followed by an intramolecular aza-Michael-type reaction (IMAMR). In terms of **33**, rather than attempting a direct aldol-type reaction with acetaldehyde we elected to make use of the regioselective bromination process used in our deoxyfebrifugine syntheses.[15] Thus, highly enantioenriched (+)-Cbz-pelletierine **17** was introduced to an α-bromination process, using TMSOTf as a Lewis acid and DIPEA as a base, to produce a silyl enol ether intermediate which was directly brominated with *N*-bromosuccinimide. After work-up the protected α-bromopelletierine was then used, without purification, to produce ylide **36** by the reaction with Ph_3P in toluene, followed by base treatment (Scheme 8). In this manner, **36** was produced in approximately 67% from (+)-Cbz-pelletierine **17**.



Scheme 8. Synthesis of (+)-myrtine **33**. Reagents and conditions: (i) TMSOTf, DIPEA, DCM, rt, 1 h; then NBS, 2 h; (ii) Ph_3P, toluene, rt, 18 h; then K_2CO_3 in MeOH-H_2O, 67%; (iii) MeCHO, THF, rt, 7 h, 70%; (iv) HBr-AcOH, rt, 4 h; then K_2CO_3, MeOH, rt, 4 h, 40%.

The Wittig reaction of **36** with acetaldehyde in dry THF smoothly afforded *trans*-enone (–)-**37** in 70% yield. The Cbz group in enone **37** was removed with HBr-AcOH and the intermediate ammonium salt was converted to the secondary amine with K_2CO_3. In turn this underwent an IMAMR process to give the desired alkaloid, **33**. Although the yield (40%) was moderate complete diastereoselectivity was observed in the cyclisation step, when K_2CO_3 was employed as a base in MeOH. Data,

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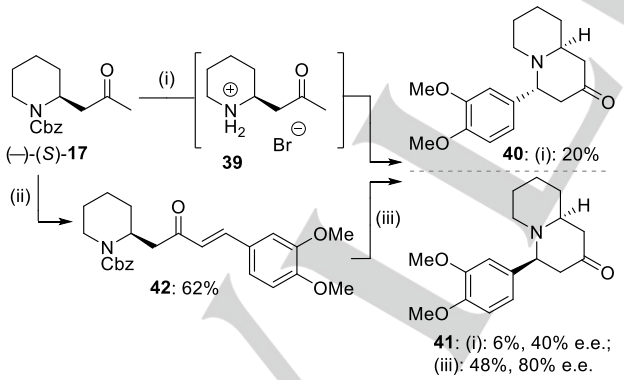
including specific rotation, were in agreement with that reported in the literature.[29] In an identical manner to that described above (–)-(*S*)-Cbz-pelletierine **17** gave enantiomeric (–)-myrtine **33** which was obtained in a 17% overall yield for the four-step sequence (not shown).

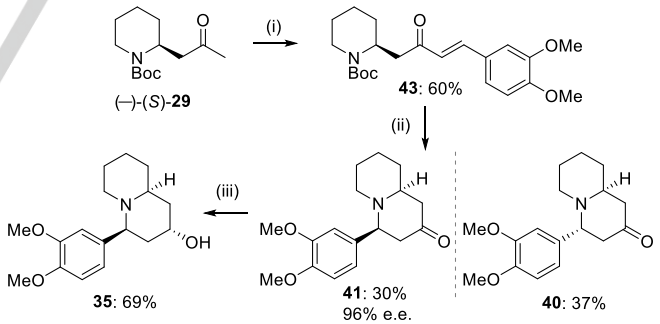
(–)-Lasubine I (**34**) and II (**35**) are examples of additional quinolizidine alkaloids of interest.[30] These natural products, featuring a 2-substituted piperidine and a 3,4-dimethoxyphenyl unit, attached to carbon-4 of the fused-bicyclic ring, differ in terms of their stereochemistry at position 9a. In the case of lasubine I (**34**) there is a *cis*-relationship between the 9a-hydrogen atom and the aryl unit (akin to myrtine (**33**), Scheme 8), whereas its diastereomer, lasubine II (**35**), has a *trans*-relationship between the aryl group and the 9a-hydrogen. Stereochemically, (–)-lasubine I (**34**) can be traced back to (*R*)-pelletierine (**6**), whereas, synthetically, lasubine II (**35**) would originate from (*S*)-pelletierine (**6**). These compounds have been prepared from protected pelletierine previously[28] and since we had access to both enantiomeric forms of **17** in very high optical purity, their synthesis was considered.

We initially decided to study a directed, cross-aldol condensation-IMAMR cascade sequence[31] between pelletierine (**6**) and veratraldehyde (**38**). Deprotection of (–)-(*S*)-Cbz-pelletierine (**17**) to ammonium salt **39** was achieved using HBr-AcOH. Then, following a procedure adapted from the literature,[32] **39** was directly treated with **38** and three equivalents of NaOH in a mixture of H_2O-EtOH (1:6) for 3 h at room temperature. Unlike the myrtine synthesis (Scheme 8) this process is not diastereoselective and gave a mixture of the *cis*-fused isomer **40** and the *trans*-fused isomer **41**. These were formed in a ratio of 1:4 (**40**:**41**).[33] Pleasingly, the diastereomers proved chromatographically separable, and this gave samples of **40** and **41** in 3% and 20% isolated yields respectively (Scheme 9).



Scheme 9. Synthesis of *cis*- and *trans*-arylquinolizidines **40** and **41**. Reagents and conditions: (i) HBr-AcOH, 0 °C to rt, 4 h, then 3,4-$(MeO)_2C_6H_3CHO$ **38**, NaOH, EtOH-H_2O (2:3), 0 °C to rt, 3 h, **40**: 20%, **41**: 3%, 40% e.e.; (ii) 3,4-$(MeO)_2C_6H_3CHO$ **38**, pyrrolidine (20 mol%), DCM, rt, 24 h, 62%; (iii) HBr-AcOH, 0 °C to rt, 4 h, then $NaOH_{(aq)}$, MeOH, rt, 2 days, **41**: 48%, 80% e.e.

Based on our experience with the racemisation of unprotected pelletierine **6** (Scheme 3), we were keen to prove whether, or not, the excellent optical purity of the starting material, **17**, was retained during the course of the reaction sequence. There is a reported HPLC method[34] for **41** and using these conditions it was clear that, unfortunately, competitive racemisation had occurred during this sequence (enantiomeric ratio 70:30). Thus, based on the low isolated yields of **40** and **41**, and more importantly the marked erosion of optical purity observed with the direct aldol-IMAMR sequence, we next considered a stepwise approach using protected **17** since this material does not racemise (*vide supra*). A pyrrolidine catalysed Mannich-type reaction converted (–)-(*S*)-Cbz-pelletierine **17** to *trans*-(*S*)-α,β-unsaturated ketone **42**. This process successfully occurred in 62% yield. Subsequent cleavage of the Cbz group in **42** and treatment of the product with base over a prolonged reaction period afforded a mixture of the desired aryl quinolizidines, **40** and **41** (Scheme 9). The crude ratio for this mixture was approximately 90:10 in favour of the *trans*-diastereomer **41**, which could be isolated in 48% yield from **42**. More significantly, and in contrast to the aldol-IMAMR method, only a moderate loss of optical purity was detected by HPLC (80% e.e.). Although this represented an advance, based on the moderate yields encountered for the Cbz-removal-cyclisation sequence, and the loss in overall optical purity, we felt that we might be able to improve the overall efficiency of this sequence. Since the Cbz group is not likely to be compatible with basic reaction conditions, we felt that a change of the protecting group to a Boc group might be a good way to produce the required enone by a direct aldol reaction. This then might enable production of the precursors **40**, and **41** with better yields and with reduced loss of enantiopurity (observed when the free-base was used, Scheme 9). Thus, (*S*)-Boc-pelletierine **29** was introduced to a cross aldol condensation, promoted by NaOH in MeOH at 60 °C for 18 h. This afforded (+)-(*S*)-enone-**43** in 60% (Scheme 10).



Scheme 10. Synthesis of *cis*- and *trans*-arylquinolizidines **40** and **41** by a cross-aldol-IMAMR sequence from (–)-(*S*)-Boc-pelletierine **29** and conversion of **41** to (–)-lasubine II (**35**). Reagents and conditions: (i) 3,4-$(MeO)_2C_6H_3CHO$ **38**, NaOH, MeOH, 65 °C, 18 h, 60%; (ii) TFA, DCM, 0 °C to rt, 2 h, then NaOH, H_2O-MeOH (1:1), rt, 2 days, **40**: 37%, **41**: 30%, 96% e.e.; (iii) L-selectride, THF, -78 °C, 2 h, 69%.

The penultimate part in the synthesis of the natural product (–)-lasubine II (**35**) is a two-step process involving the removal of Boc group followed immediately by cyclisation. This generates arylquinolizidinone **40** and **41** and significantly the relative ratio of these diastereomers can be adjusted depending on the reaction time and conditions. For instance, on prolonged

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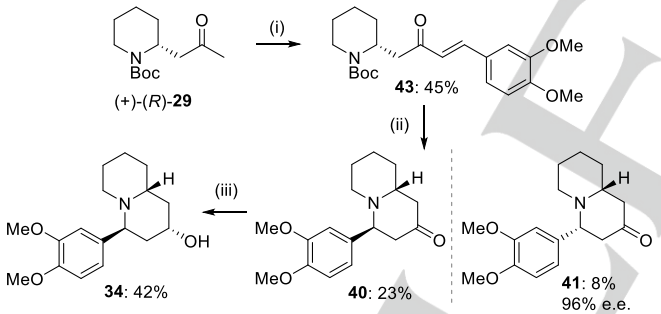
reaction *trans*-arylquinolizidinone, **41**, the direct precursor of naturally occurring (–)-lasubine II (**35**), can be formed in comparatively larger amounts.[34] After Boc removal with TFA IMAMR was achieved by treating a mixture of the intermediate ammonium salt in methanol with NaOH at rt for 48 h. This afforded **41** and its *cis*-diastereomer **40** in a ratio of 1:1.2 (determined by proton NMR spectroscopy performed on the crude reaction mixture). This outcome is consistent with the longer reaction time, which allows the reaction to come under thermodynamic control, thereby forming comparatively more of the *trans*-diastereomer. These isomers were separated and pleasingly HPLC demonstrated that only minor epimerisation had occurred during this sequence. The enantiopurity of the resolution derived Boc-pelletierine **29** (>99% e.e.) was only eroded slightly to 96% for compound **41** obtained in this manner. The final step in this synthesis was the well-reported[7f] diastereoselective reduction of (–)-**41** by L-selectride. Only (–)-lasubine II **35** was isolated following this process in 69% yield.

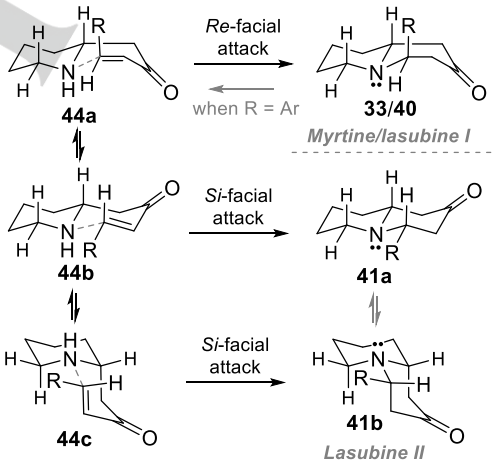
As shown in Scheme 11, under identical conditions to those described above, (+)-(*R*)-**29** gave enone (*R*)-**43**. The Boc group in **43** was then removed and a modified IMAMR step was performed. In this reaction the time for the cyclisation was reduced to 30 min and the base used was ammonium hydroxide.[34] This gave a separable mixture of **40** and **41** in a 3:1 ratio. Enantiopurity for compound **41** was checked by the chiral HPLC method and the main diastereomer, **40**, isolated in 23% yield, was converted to (–)-lasubine I (**34**) by a diastereoselective L-selectride reduction.



Scheme 11. Synthesis of *cis*- and *trans*-arylquinolizidines **40** and **41** by a cross-aldol-IMAMR sequence from (+)-(*R*)-pelletierine **29** and conversion of **40** to (–)-lasubine I (**34**). Reagents and conditions: (i) 3,4-$(MeO)_2C_6H_3CHO$ **38**, NaOH, MeOH, 65 °C, 18 h, 45%; (ii) TFA, DCM, 0 °C to rt, 2 h, then $NH_{3(aq)}$, MeOH, rt, 0.5 h (**40**:**41**; 3:1, crude mixture), **40**: 23%, **41**: 8%, 96% e.e.; (iii) L-selectride, THF, -78 °C, 2 h, 42%.

2.6. Stereoselectivity in the quinolizidine IMAMR

The stereoselectivity of the intramolecular aza-Michael addition in the syntheses of myrtine (**33**) and lasubine I (**34**) and II (**35**) is of interest. Natural (+)-myrtine is formed from the *Re*-facial attack of the nucleophilic piperidine nitrogen atom at the electrophilic β-carbon. As shown in Scheme 12 consideration of the possible transition state indicates that the chair-chair fused *trans*-bicyclic quinolizidine will lead to preferential *Si*-facial attack, even after flipping the ring to the *cis*-decalin form. Based on this we propose that the more favoured process, in this case, must involve a chair-boat transition state. This enables the nucleophilic addition to occur at the *Re*-face of the alkene generating **33** (R = Me). It would appear that when R = Me this process is either effectively irreversible - under the conditions employed - or that this diastereomer is strongly favoured over its counterpart. None of the diastereomer, termed epi-myritine was detected during the synthesis of **33** (see Scheme 8). Moving to lasubine, as discussed above, depending on the conditions employed for the quinolizidine forming step the relative amounts of the 2-ketoquinolizidines **40** and **41** alter. The lasubine I precursor **40** can be produced in approximately a 3:1 ratio, relative to **41**, using ammonium hydroxide over a short (30 min) reaction period. Whereas, **41** can be produced in larger relative amounts (**40**:**41**; approx. 1:3) if the IMAMR is performed over a longer period using sodium hydroxide as the base. In the latter case it should be noted that the preferentially formed isomer (**41**) has different relative stereochemistry to that observed in the synthesis of myrtine. This finding suggests that **40** may be the kinetic product and that, where R = aryl, epimerisation may proceed selectively at the benzylic position (C-4) through a *retro*-aza-Michael/aza-Michael sequence (or possibly Mannich, see Scheme 3), in order to ultimately afford the thermodynamically more favourable product **41**. Further work aimed at explaining these different outcomes is underway.



Scheme 12. Proposed chair-chair and chair-boat conformations for the IMAMR with α,β-unsaturated ketone **44** (Ar = aromatic ring).

Conclusions

In summary, we have reported three methods for the synthesis of both enantiomers of the β-amino ketone natural product pelletierine (**6**). Two organocatalytic methods, using a proline-mediated Mannich reaction and a cinchona-mediated intramolecular *N*-conjugate addition reaction of α,β-unsaturated ketone **23**, are detailed. The latter gives high enantiomeric excess (90-98% e.e.), a fact at least partly attributed to the lack of racemisation that can occur with unprotected **6**. The third

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method relied on the differential solubilities of the diastereomeric pelletierine-mandelate salts (**28a** and **28b**) and by repeated recrystallisation highly enantioenriched protected-pelletierine can be readily obtained. To exemplify this resolution-based method (*S*)-Cbz-protected pelletierine **17** was used to prepare the sedum alkaloids sedridine **32**, and allosedridine **8**. (*R*)-Cbz-Protected pelletierine **17** was used to prepare (+)-myrtine (**33**), a naturally occurring quinolizidine, in an efficient sequence featuring a novel Wittig olefination. Finally, (*R*)-Boc-protected pelletierine **29** was used to prepare lasubine I (**34**) and its enantiomer, (*S*)-**29**, was used to access lasubine II (**35**).

Experimental Section

General experimental: Starting materials were supplied from commercial sources and used without further purification. All commercially available solvents were used as supplied unless otherwise stated. All "dry" solvents were dried and distilled by standard procedures or were processed through a Grubbs type still. Oxygen free nitrogen was obtained from BOC gases and was used without further drying. Infrared spectroscopy was performed on a FT-IR spectrometer. Elemental analyses were carried out by the UCD Microanalytical Laboratory. Routine electrospray mass spectra and high-resolution mass spectra were run on electrospray ionisation (ESI) with a time-of-flight (TOF) analyser. Chiral HPLC was performed on Chiralpak IB, IC, or AS-H columns as stated. The NMR spectra were recorded at 25 °C on 300, 400, 500 MHz spectrometers as indicated. All peak assignments are confirmed by 2D experiments (^{1}H-^{1}H gCOSY, ^{1}H-^{13}C HSQC). TLC (thin layer chromatography) was performed on 60F_{254} aluminium plates with realisation by UV irradiation and/or chemical staining. Flash column chromatography was performed with silica, particle size 0.040-0.063 mm.

Δ^1-Piperideine 14:[7n] Piperidine **13** (5.17 g, 60.72 mmol) was added to a solution of *N*-chlorosuccinimide (15.00 g, 112.33 mmol) in diethyl ether (400 mL). The solution was stirred at room temp. for 1 h. After filtration and rinsing of the precipitate with diethyl ether (40 mL), the diethyl ether solution was washed with water (2 X 400 mL) and brine (200 mL) and then dried with $MgSO_4$. The *N*-chloropiperidine solution was then filtered and carefully concentrated under reduced pressure to roughly 80 mL volume. *CARE: Whilst we never experienced any issues, as a precaution this procedure was conducted behind a blast shield and the solutions were concentrated with the rotary evaporator's bath temperature set to < 40 °C and crude solutions were never evaporated to dryness.* The resultant solution was added dropwise to a solution of KOH (4.00 g, 71.20 mmol) in absolute ethanol (64 mL). During this process the temperature was maintained between 5 and 10 °C. After addition, the mixture was stirred at room temperature for 24 h and filtered. The precipitate was rinsed with absolute ethanol (60 mL), and the combined solution was concentrated to about 25 mL. Ether (200 mL) and water (20 mL) were added and the mixture was extracted. The phases were separated and the aqueous phase was then further extracted with ether (2 X 100 mL). The combined organic phases were washed with brine and dried with anhydrous magnesium sulfate, filtered, and concentrated in *vacuo* to afford **14** (2.5 g, 60%) as yellowish oil, which gradually solidified. This material was subsequently used without further purification and could be stored indefinitely at low temperature.

(±)-1-(Piperidin-2-yl)propan-2-one [(±)-Pelletierine] 6:[7c] Piperidine **13** (8.4 mL, 84 mmol) was added dropwise to a rapidly stirred suspension of NCS (12.76 g, 94 mmol) in ether (422 ml). After stirring for 4 h at room temperature, the mixture was filtered and the filtrate concentrated to approx. 60 mL behind a safety screen. The crude chloroamine solution was then added dropwise into an ice-cold solution of KOH (4.7 g, 84.6 mmol) in absolute ethanol (42 ml). The mixture was allowed to stir overnight. The white precipitate formed was removed by filtration. In parallel, the sodium salt of ethyl acetoacetate was prepared from NaOH (5.0 g, 127 mmol) and ethyl acetoacetate (10.8 ml, 84.6 mmol) in water (170 mL), heating to 50 °C for 4 h and then stirring overnight at room temperature. The crude piperideine **14** and the sodium acetoacetate solutions were combined and refluxed for 4h. The resulting yellow solution was cooled to room temperature, and most of the organic solvent (ether, EtOH) removed under reduced pressure. The aqueous mixture was extracted with CH_2Cl_2 (3 × 65 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The resulting oil was purified by adding ether and filtered; the solvent of filtrate was removed in *vacuo*, affording **6** (4.6 g, 39%) as yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.00-2.93 (m, 2H), 2.64 (td, *J* = 11.7, 2.7 Hz, 1H), 2.48 (d, *J* = 6.3 Hz, 2H), 2.34 (br s, 1H), 2.11 (s, 3H), 1.77-1.70 (m, 1H), 1.60-1.50 (m, 2H), 1.43-1.26 (m, 2H), 1.17-1.06 (m, 1H) ppm.

(–)-(2*S*)-(2-Oxopropyl)piperidine-1-carbamic acid benzyl ester (Cbz-pelletierine) 17:[7n] Δ^1-Piperideine **14** (670 mg, 8.06 mmol, 1 eq.), acetone (27 mL, 367.59 mmol, 46 eq.), DMSO (27 mL), water (3.4 mL), and L-proline (185 mg, 1.61 mmol, 0.2 eq.) were mixed and stirred for one hour at **room** temperature. An aqueous saturated solution of sodium bicarbonate (50 mL) was added to the mixture, which was extracted with CH_2Cl_2 (2 x 50 mL). The organic layer was washed with brine (50 mL), filtered and dried over anhydrous magnesium sulfate. After filtration the solvent was removed under reduced pressure and the crude pelletierine was used immediately without purification. HRMS (ES^+) calcd for $[(C_8H_{15}NO + H)]^+$ 142.1232, found 142.1232 (0.1 ppm). The residue obtained above was diluted in CH_2Cl_2 (25 mL) and a 0.4 M solution of aqueous sodium carbonate (18 mL, 7.20 mmol, 0.9 eq.) was added. The mixture was cooled to 0 °C and benzyl chloroformate (0.9 mL, 6.30 mmol, 0.8 eq.) was added dropwise. The ice bath was removed and the solution was stirred at room temperature overnight. The solution was diluted with CH_2Cl_2 (25 mL), and extracted. The organic layer was washed with water (50 mL), and then with brine (50 mL), dried over anhydrous magnesium sulfate, filtered and concentrated in *vacuo*. This gave the crude product, which was purified by flash column chromatography (CH_2Cl_2/EtOAc; 6:1), which afforded the *title compound* **17** (1.25 g, 72 % yield over two steps) as light yellow oil. R_f = 0.55 (EtOAc/CH_2Cl_2; 1:6);

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$[\alpha]_D^{20}$ = –10.5 (c = 1.00, $CHCl_3$) {lit.,[35] $[\alpha]_D^{28}$ = –10.0 (c = 0.50, $CHCl_3$)}; IR: 3032, 2938, 2862, 1688, 1497, 1353, 1258, 1165, 1049, 735, 697 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.42-7.32 (m, 5H), 5.11 (d, *J* = 12.5 Hz, 1H), 5.08 (d, *J* = 12.5 Hz, 1H), 4.84 (br. s, 1H), 4.07 (br. s, 1H), 2.87 (app. t, *J* = 12.8 Hz, 1H), 2.73-2.61 (m, 2H), 2.15 (s, 3H), 1.78-1.34 (m, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.9 (CO), 155.3 (CO), 136.7 (C), 128.4 (CH), 127.9 (CH), 127.8 (CH), 67.1 (CH_2), 47.5 (CH), 44.3 (CH_2), 39.8 (CH_2), 30.0 (CH_3), 28.3 (CH_2), 25.2 (CH_2), 18.8 (CH_2) ppm; HPLC analysis (Chiralpak IB), heptane/EtOH; 98:2 (1mL/min): (–)-**17** tr = 12.1 min, (+)-**17** tr = 13.6 min; e.r. 91:9.

(+)-(2*R*)-(2-Oxopropyl)piperidine-1-carbamic acid benzyl ester 17: In an identical procedure to that described above, Δ^1-piperideine **14** (670 mg, 8.06 mmol, 1.0 eq.), acetone (27 mL, 367.59 mmol, 46 eq.), DMSO (27 mL), water (3.4 mL) and D-proline (185 mg, 1.61 mmol, 0.2 eq.) gave pelletierine **6** which was converted into its benzyloxycarbamate following the procedure above which afforded the title compound (+)-**17** (1.12 g, 63%) as a light yellow oil, with data as above. $[\alpha]_D^{20}$ = +9.0 (c = 1.00, $CHCl_3$) {lit.,[36] $[\alpha]_D^{25}$ = +10.1 (c = 0.90, $CHCl_3$)}; HPLC analysis (Chiralpak IB) n-heptane/EtOH; 98:2 (1 mL/min): (–)-**17** tr = 12.5 min, (+)-**17** tr = 13.6 min; e.r. 13:87.

***N*-Benzyloxycarbonyl-5-aminopentan-1-ol:**[37] To a solution of 5-aminopentanol **21** (4.10 g, 40.00 mmol) and $NaHCO_3$ (10.00 g, 120.00 mmol) in water (40 mL) was added a solution of benzyloxycarbonyl chloride (9.10 g, 54.00 mmol) in THF (40 mL) at 0 °C. The reaction mixture was warmed to room temperature and stirred vigorously overnight. The mixture was extracted with ethyl acetate (2 x 25 mL). The combined organic layers were washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated in vacuo to afford the crude product. This was triturated with *n*-hexane. The resulting solid was collected by filtration, washed with diethyl ether and dried under reduced pressure to afford the *title compound* (9.00 g, 97%) as a colourless low melting solid. M.p 42-43 °C (Lit.[37] M.p 43-44 °C); R_f = 0.2 (EtOAc/*c*-Hex; 1:1); ^1H NMR (300 MHz, $CDCl_3$): δ 7.40-7.27 (m, 5H), 5.09 (s, 2H), 4.80 (s, 1H), 3.65 (t, *J* = 6.1 Hz, 2H), 3.29-3.12 (m, 2H), 1.70-1.48 (m, 4H), 1.47-1.33 (m, 2H) ppm.

***N*-Benzyloxycarbonyl-2-hydroxypiperidine:**[7p] Under N_2, to a solution of oxalyl chloride (0.61 ml, 6.95 mmol) in CH_2Cl_2 (25 mL) at -78 °C was added anhydrous DMSO (0.90 mL, 12.60 mmol) dropwise over 5 min. The reaction mixture was stirred at -78 °C for 10 min. *N*-Benzyloxycarbonyl-5-aminopentan-1-ol (1.50 g, 6.32 mmol) in CH_2Cl_2 (60 mL) was added dropwise over 5 min and a pale yellow precipitate formed. The reaction mixture was warmed until the precipitate dissolved and then re-cooled to -78 °C and stirred for 10 min. Triethylamine (4.41 mL, 31.60 mmol) was added, the reaction was warmed to room temperature (approx. 0.5 h) before H_2O (15 mL) was added. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (20 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated *in vacuo* to afford the crude product, which was purified by flash column chromatography, (EtOAc/*c*-Hex; 2:3) affording the *title compound* (0.80 g, 53%) as a clear oil which gradually solidified. M.p 51-53 °C; R_f = 0.55 (EtOAc/*c*-Hex; 1:1); ^1H NMR (300 MHz, $CDCl_3$): δ 7.40-7.28 (m, 5H), 5.84-5.78 (m, 1H), 5.17 (s, 2H), 3.91 (br. d, 1H), 3.19 (app. t, *J* = 12.6 Hz, 2H), 1.96-1.39 (m, 6H) ppm.

(7-Oxooct-5-enyl)carbamic acid benzyl ester 23:[7p] To a solution of Cbz-protected 2-hydroxypiperidine (235 mg, 1.0 mmol, 1 eq.) in toluene (10 mL) was added (acetylmethylene) triphenylphosphorane **22**[38] (477 mg, 1.5 mmol, 1.5 eq.) at room temperature. The resulting reaction mixture was stirred at reflux overnight. After removal of the solvent the residue was purified by flash column chromatography (EtOAc/*c*-Hex; 1:2) to give the enone **23** (234 mg, 85%) as light yellow oil. R_f = 0.3 (EtOAc/*c*-Hex; 1:2); ^1H NMR (300 MHz, $CDCl_3$): δ 7.40-7.29 (m, 5H), 6.78 (dt, J = 15.6 and 6.9 Hz, 1H), 6.09 (d, J = 15.6 Hz, 1H), 5.07 (s, 2H), 4.90 (br. s, 1H), 3.22 (m, 2H), 2.31-2.20 (m, 5H), 1.65-1.44 (m, 4H) ppm.

(±)-2-(2-Oxopropyl) piperidine-1-carbamic acid benzyl ester (Cbz-pelletierine) 17: To a solution of enone **23** (137 mg, 0.50 mmol, 1 eq.) in acetonitrile (5 mL) was added borontrifluoride diethyletherate (0.03 mL, 0.25 mmol, 0.5 eq.) at 0 °C. The mixture was stirred at the same temperature for 10-15 min and then 15 min at room temperature. The mixture was poured into saturated aqueous $NaHCO_3$ (25 mL) and extracted with EtOAc (2 x 25 mL). The combined organic layers were dried over anhydrous magnesium sulfate, filtered and the solvent was removed by in vacuo. This afforded the *title compound* **17** (137 mg, 100 %) as light yellow oil. R_f = 0.35 (EtOAc/*c*-Hex; 1:2).

(+)-(2*R*)-(2-Oxopropyl) piperidine-1-carbamic acid benzyl ester [(+)-(*R*)-Cbz-pelletierine] 17: In an identical procedure to that described above, solution of TFA (30 µl, 0.40 mmol) in THF (6 mL) was sequentially added (8*S*,9*S*)-9-amino-9-deoxyepiquinine **24a** (51 mg, 0.20 mmol) and enone carbamate **23** (275 mg, 1.00 mmol) at room temperature. The reaction was stirred for 8 h. After removal of the solvent, the residue was purified by flash column chromatography on silica gel (CH_2Cl_2/EtOAc; 10:1), affording (+)-**17** (245 mg, 89%) as colourless oil. $[\alpha]_D^{20}$ = +8.5 (c = 1.00, $CHCl_3$).

(+)-(2*R*)-2-[2-Oxo-3-(7-bromo-6-chloro-4-oxoquinazolin-4(3*H*)-yl)propyl]piperidine-1-carbamic acid benzyl ester 25: Following the published procedure[15] (+)-**17** was converted into (+)-**25**. HPLC analysis (Chiralpak A-SH), heptane/EtOH; 90:10 (1mL/min): (+)-**25** tr = 18.2 min, (–)-**25** tr = 20.7 min; e.r. 99:1. Recrystallisation of this material (MeOH) led to crystals suitable for X-ray diffraction.

(–)-(2*S*)-(2-Oxopropyl) piperidine-1-carbamic acid benzyl ester [(–)-(*S*)-Cbz-pelletierine] 17: To a solution of TFA (30 µl, 0.40 mmol) in THF (6 mL) was sequentially added (9*R*)-9-amino-9-deoxyquinidine **24b** (51 mg, 0.20 mmol) and enone carbamate **23** (275 mg, 1.00 mmol) at room temperature. The reaction was stirred for 8 h. After removal of the solvent, the residue was purified by flash column chromatography on silica gel (DCM/EtOAc; 10:1), affording **17** (224 mg, 81%) as colourless oil. $[\alpha]_D^{20}$ = –8.0 (c = 1.00, $CHCl_3$).

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(–)-(2*S*)-2-[2-Oxo-3-(7-bromo-6-chloro-4-oxoquinazolin-4(3*H*)-yl)propyl]piperidine-1-carbamic acid benzyl ester 25: Following the reported procedure[15] (–)-**17** was converted into (**–**)-**25**. HPLC analysis (Chiralpak A-SH), heptane/EtOH; 90:10 (1mL/min): (+)-**25** tr = 18.3 min, (–)-**25** tr = 20.8 min; e.r. 5:95.

(2*R*)-(2-Oxopropyl)piperidin-1-ium·(2*R*)-2-hydroxy-2-phenylacetate salt 28a and (2*S*)-(2-oxopropyl)piperidin-1-ium·(2*R*)-2-hydroxy-2-phenylacetate salt 28b: Isopelletierine **6** (racemic pelletierine) (4.60 g, 32.57 mmol) and (–)-mandelic acid **27** (4.95 g, 32.57 mmol) were mixed with cooling, and methanol (13 mL) was added. The mixture was warmed to affect solution, cooled, and then treated with anhydrous ether (32 mL). After a few minutes crystals began to form. After 22 h at 0 °C, the crystals were collected and dried *in vacuo* (4.40 g). Recrystallisation was performed by dissolving the salt (4.40 g) in methanol (11 mL) and adding ether (22 mL). After 22 h at 0 °C the insoluble pelletierine mandelate **28a** was collected and dried *in vacuo*, (3.37 g). A third recrystallisation was performed by dissolving the salt (3.37 g) in methanol (11 mL) and adding ether (23 mL). After 22 h at 0 °C feathery white needles **28a** (3.15 g, 33% - after three recrystallisations) were collected by filtration; M.p = 138-139 °C; $[\alpha]_D^{20}$ = –59 (c = 1.00, $CHCl_3$); HRMS (ESI) calcd for $[(C_8H_{15}NO + H)]^+$ 142.1232, found 142.1226 (-4.1 ppm); IR 3300-3000 broad, 2958, 1714, 1639, 1582, 1368, 1166, 1063, 732, 683 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.48 (d, *J* = 7.3 Hz, 2H), 7.29 (t, *J* = 7.3 Hz, 2H), 7.21 (t, *J* = 7.3 Hz, 1H), 4.9 (s, 1H), 3.20-3.09 (m, 2H), 2.79 (dd, *J* = 18.5, 6.2 Hz, 1H), 2.51-2.41 (m, 2H), 2.06 (s, 3H), 1.80-1.56 (m, 4H), 1.41-1.31 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 206.4 (C=O), 178.5 (C=O), 142.4 (C), 128.1 (CH), 127.1 (CH), 126.5 (CH), 74.3 (CH), 52.3 (CH), 45.7 (CH_2), 44.3 (CH_2), 30.3 (CH_3), 28.2 (CH_2), 22.4 (CH_2), 22.2 (CH_2) ppm; Anal. Calcd for $C_{16}H_{23}NO_4$: C, 65.51; H, 7.90; N, 4.77%. Found C, 65.58; H, 7.90; N, 4.77%. The soluble salt **28b** from above filtrate was collected and solvent removed under reduced pressure. The resultant viscous yellow oil (4.50 g, 15.3 mmol) in water (40 mL) was cooled with ice-water and basified slowly with solid potassium hydroxide (1.70 g, 30.6 mmol). The liberated, optically active (+)-pelletierine **6** was extracted with DCM (3 x 50 mL) and the combined extracts were dried over $MgSO_4$. The DCM was evaporated *in vacuo* at room temperature. The residual (+)-pelletierine was purified by adding ether (yield 1.80 g, 12.7 mmol, 83% based on salt). In an identical procedure to that described above, a mixture of the resultant enantioenriched (+)-pelletierine **6** (1.80 g, 12.7 mmol), (+)-mandelic acid **27** (1.93 g, 12.7 mmol), MeOH (5.0 mL), and ether (12.6 mL) gave *ent*-**28a** (2.17 g). A second recrystallisation, using MeOH (5.4 mL), and ether (10.8 mL) gave *ent*-**28a** (1.80 g). The final recrystallisation, using MeOH (5.0 mL), and ether (10.0 mL) gave *ent*-**28a** (1.36 g, 37%). $[\alpha]_D^{20}$ = +60.9 (c = 1.00, $CHCl_3$).

(+)-(2*R*)-(2-Oxopropyl) piperidine-1-carbamic acid benzyl ester [(+)-(*R*)-Cbz-pelletierine] 17: *N,N*-Diispropylethyl amine (5.0 mL, 30.0 mmol, 3.0 eq.) was added at 0 °C to a solution of the salt (*R,R*)-pelletierine mandelate **28a** (3.00 g, 10.2 mmol, 1.0 eq.) in CH_2Cl_2 (100 mL), benzylchloroformate (1.4 mL, 10.2 mmol, 1.0 eq.) was then added and the suspension became homogenous. The reaction mixture was stirred at rt overnight. The solvent was removed and the residue was purified by flash column chromatography (CH_2Cl_2/EtOAc, 6:1) to afford (+)-**17** as a transparent oil (2.64 g, 9.6 mmol, 94%). $[\alpha]_D^{20}$ = +10.6 (c = 1.00, $CHCl_3$); HPLC analysis (Chiralpak IB) *n*-heptane/EtOH; 98:2 (1 mL/min): (–)-**17** tr = 11.7 min, (+)-**17** tr = 12.5 min; e.r. 0.1:99.9.

(–)-(2*S*)-(2-Oxopropyl) piperidine-1-carbamic acid benzyl ester [(–)-(*S*)-Cbz-pelletierine] 17: In an identical procedure to that described above, *N,N*-diisporopylethyl amine (2.5 mL, 15.0 mmol, 3.4 eq.) was added at 0 °C to a solution of the salt (*S,S*)-pelletierine mandelate *ent*-**28a** (1.30 g, 4.4 mmol, 1.0 eq.) in CH_2Cl_2 (50.0 ml), benzylchloroformate (0.7 ml, 5.1 mmol, 1.16 eq.) which after work-up and purification afforded (–)-**17** as a transparent oil (1.20 g, 15.0 mmol, 100%). $[\alpha]_D^{20}$ = –11.0 (c = 1.00, $CHCl_3$); HPLC analysis (Chiralpak IB), heptane/EtOH; 98:2 (1 mL/min): (–)-**17** tr = 11.7 min, (+)-**17** tr = 12.5 min; e.r. 99.9:0.1.

(+)-(2*R*)-(2-Oxopropyl) piperidine-1-carbamic acid *tert*-butyl ester [(+)-(*R*)-Boc-pelletierine] 29: Triethylamine (1.35 mL, 9.68 mmol) was added at 0 °C to a solution of the salt (*R,R*)-pelletierine mandelate **28a** (925 mg, 3.15 mmol) in CH_2Cl_2 (7.5 ml), di-*tert*-butyl dicarbonate (760 mg, 3.48 mmol) was then added and the reaction mixture was stirred at rt overnight. The solvent was removed and the residue was purified by flash column chromatography (CH_2Cl_2/EtOAc, 6:1) to afford (*R*)-**29** as a transparent oil (780 mg, 0.57 mmol, 100%). ^1H NMR (400 MHz, $CDCl_3$): δ 4.78-4.66 (m, 1H), 3.96 (d, *J* = 13.2 Hz, 1H), 2.77 (t, *J* = 12.8 Hz, 1H), 2.67-2.60 (m, 2H), 2.18 (s, 3H), 1.71-1.48 (m, 6H), 1.44 (s, 9H) ppm.

(–)-(2*S*)-(2-Oxopropyl) piperidine-1-carbamic acid *tert*-butyl ester [(–)-(*S*)-Boc-pelletierine] 29: In an identical procedure to that described above, triethylamine (0.27 mL, 1.89 mmol, 3.0 eq.) was added at 0 °C to a solution of the salt (*S,S*)-pelletierine mandelate *ent*-**28a** (185 mg, 0.63 mmol, 1.0 eq.) in CH_2Cl_2 (1.5 ml), di-*tert*-butyl dicarbonate (152 mg, 0.63 mmol, 1.0 eq.) was then added and the reaction mixture was stirred at rt overnight. The solvent was removed and the residue was purified by flash column chromatography (CH_2Cl_2/EtOAc, 6:1) to afford (*S*)-**29** as a transparent oil (137 mg, 0.57 mmol, 90%).

(–)-Benzyl (*S*)-2-[(*S*)-2-hydroxypropyl]piperidine-1-carboxylate [(–)-Cbz-sedridine] 30 and (–)-benzyl (*S*)-2-[(*R*)-2-hydroxypropyl]piperidine-1-carboxylate [(–)-Cbz-allosedridine] 31: $NaBH_4$ (76 mg, 2.00 mmol) was added to a stirred solution of ketone **17** (275 mg, 1.00 mmol) in methanol (10 mL) at 0 °C and the reaction was left at room temperature for 4 h. Excess sodium borohydride were quenched with water (15 mL) and extracted with CH_2Cl_2 (2 x 20 mL). The organic layer was dried with anhydrous $MgSO_4$ and the solvent removed under reduced pressure. The diastereomers were purified by flash column chromatography (CH_2Cl_2/EtOAc; 10:1). (–)-**30:** clear oil (103 mg, 37%); R_f = 0.2 (CH_2Cl_2/EtOAc; 10:1 to EtOAc); $[\alpha]_D^{20}$ = –29.2 (c = 1.00, $CHCl_3$) {lit.,[26] $[\alpha]_D^{28}$ = –25.8 (c = 0.1,

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$CHCl_3$)}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.40-7.30 (m, 5H), 5.17 (d, *J* = 12.3 Hz, 1H), 5.12 (d, *J* = 12.3 Hz, 1H), 4.58-4.45 (m, 1H), 4.14-4.04 (m, 1H), 3.60-3.47(m, 1H), 2.76 (td, *J* = 13.2, 2.6 Hz, 1H), 1.99 (t, *J* = 13.3 Hz, 1H), 1.80-1.68 (m, 1H), 1.67-1.37 (m, 5H), 1.37-1.29 (m, 1H), 1.18 (d, *J* = 6.0 Hz, 3H) ppm; ^{13}C NMR (120 MHz, $CDCl_3$): δ 156.9, 136.5, 128.5, 128.1, 127.9, 67.5, 63.3, 47.4, 39.4, 39.3, 29.3, 25.4, 22.5, 19.1 ppm. (–)-**32:** clear oil (152 mg, 55%); R_f = 0.1 (CH_2Cl_2/EtOAc; 10:1); $[\alpha]_D^{20}$ = –52.8 (c = 1.00, $CHCl_3$) {lit.,[26] $[\alpha]_D^{28}$ = –50.6 (c = 0.1, $CHCl_3$)}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38-7.28 (m, 5H), 5.15 (d, *J* = 12.4 Hz, 1H), 5.10 (d, *J* = 12.4 Hz, 1H), 4.45-4.37 (m, 1H), 4.04 (d, *J* = 13.5 Hz, 1H), 3.81 (br s, 1H), 2.90 (t, *J* = 12.8 Hz, 1H), 1.84 (dt, *J* = 14.3, 7.9 Hz, 1H), 1.68-1.36 (m, 7H), 1.18 (d, *J* = 6.0 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.0, 136.8, 128.5, 128.0, 127.9, 67.2, 66.3, 49.0, 40.1, 39.5, 29.5, 25.5, 23.6, 19.0 ppm.

(+)-(*S*)-1-[(*S*)-Piperidin-2-yl]propan-2-ol [(+)-Sedridine] 32: A suspension of Cbz-sedridine **30** (100 mg, 0.36 mmol) and $Pd(OH)_2$ (30 mg) in MeOH (2.5 mL) under a hydrogen atmosphere was stirred overnight. The mixture was filtered through a Celite pad, and the filtrate was evaporated to give **32** (51 mg, 99%) as a solid. M.p 80-82 °C (lit.,[39] M.p 84-85 °C); $[\alpha]_D^{20}$ = +22.0 (c = 1.00, MeOH) {lit.,[26] $[\alpha]_D^{28}$ = +27.5 (c = 0.07, EtOH)}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.10 (dqd, *J* = 9.4, 6.2, 3.5 Hz, 1H), 3.23 (br s, 2H), 3.06 (d, J = 10.6 Hz, 1H), 2.88 (ddt, *J* = 9.7, 6.6, 3.1 Hz, 1H), 2.57 (td, J = 11.8, 2.7 Hz, 1H), 1.84-1.75 (m, 1H), 1.61-1.54 (m, 3H), 1.48-1.34 (m, 4H), 1.17 (d, *J* = 6.3 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 65.1, 54.8, 46.8, 43.6, 31.2, 25.9, 24.6, 23.6 ppm.

(–)-(*R*)-1-[(*S*)-piperidin-2-yl]propan-2-ol [(–)-Allosedridine] 8: A suspension of Cbz-allosedridine **31** (150 mg, 0.54 mmol) and $Pd(OH)_2$ (40 mg) in MeOH (3.5 mL) under a hydrogen atmosphere was stirred overinght. The mixture was filtered through a Celite pad, and the filtrate was evaporated to give **8** (119 mg, 100%) as a solid. M.p 60-62 °C, (lit.,[39] M.p 60-61 °C); $[\alpha]_D^{20}$ = –16.0 (c = 1.00, MeOH) {lit.,[26] $[\alpha]_D^{28}$ = –15.6 (c = 0.05, MeOH)}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.00 (dqd, *J* = 10.4, 6.2, 2.2 Hz, 1H), 3.04 (dp, *J* = 14.1, 1.9 Hz, 1H), 2.72 (tt, *J* = 10.8, 2.5 Hz, 1H), 2.58 (ddd, *J* = 13.6, 12.1, 3.0 Hz, 1H), 1.85-1.77 (m, 1H), 1.66-1.56 (m, 2H), 1.53-1.45 (m, 2H), 1.35-1.20 (m, 2H), 1.13 (d, *J* = 6.2 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 69.2, 58.3, 46.0, 44.2, 34.3, 27.2, 24.4, 23.9 ppm.

Benzyl (*S*)-2-(2-oxo-3-(triphenyl-λ^5-phosphaneylidene) propyl)piperidine-1-carboxylate 36: A mixture of (–)-Cbz-pelleteirine **17** (550 mg, 2.0 mmol, 1.00 eq.) in dry CH_2Cl_2 (15 mL) was cooled to 0 °C and left for 30 min, DIPEA (0.56 mL, 3.2 mmol, 1.48 eq.) and TMSOTf (0.54 mL, 3.0 mmol, 1.37 eq.) were added, and the mixture was stirred at room temperature for 1 h. NBS (496 mg, 2.8 mmol, 1.28 eq.) was then added in one portion. The mixture was stirred at room temperature for 2 h, then poured into water (40 mL) and extracted with EtOAc (2 x 60 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (60 mL) and brine (60 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated. To a solution of crude Cbz-α-bromopelletierine in toluene (20 mL), Ph_3P (534 mg, 2.0 mmol) was added and stirred at rt for 16 h. Ether (40 mL) was added, and the yellow precipitate was collected by filtration, dissolved in MeOH-CH_3CN (10:10 mL), the solvents was removed by vacuum. Solid was triturated with ether, dried and kept in desiccator. The phosphonium salt then was dissolved in MeOH (20 mL), aqueous Na_2CO_3 (230 mg, 2.0 mmol) in water (6 mL) was added; white suspension was diluted with water (20 mL) and stirred for 2 h. The solution was extracted with EtOAc (2 x 30 mL) and the organic layer washed with water (20 mL), and brine (20 mL), then dried over $MgSO_4$. The solvent was removed in *vacuo* to afford ylide **36** (480 mg, 0.89 mmol, 45%). R_f = 0.15 (EtOAc); HRMS (ESI) calcd for $[(C_{34}H_{35}NO_3P + H)]^+$ 536.2355, found 536.2353 (-0.3 ppm); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.66-7.58 (m, 6H), 7.56-7.50 (m, 3H), 7.47-7.39 (m, 6H), 7.34-7.19 (m, 5H), 5.14-4.97 (m, 2H), 4.86-4.77 (m, 1H), 4.10 (app. d, *J* = 13.0 Hz, 1H), 3.83-3.60 (m, 1H), 2.96 (app. t, *J* = 13.0 Hz, 1H), 2.60 (d, *J* = 6.5 Hz, 2H), 1.86-1.53 (m, 5H), 1.49-1.32 (m, 1H) ppm; ^{13}C NMR* (100 MHz, $CDCl_3$): δ 190.6 (CO), 155.5 (CO), 137.3 (C), 133.0 (d, $^3J_{C-P}$ = 10.0 Hz, CH), 131.9 (d, $^4J_{C-P}$ = 2.7 Hz, CH), 128.7 (d, $^2J_{C-P}$ = 12.2 Hz, CH), 128.3 (CH), 127.5 (CH), 127.4 (CH), 127.2 (s, $^1J_{C-P}$ = 90.7 Hz, C), 66.6 (CH_2), 50.4 (CH), 42.1 (d, $^3J_{C-P}$ = 15.0 Hz, CH_2), 39.7 (CH_2), 27.9 (CH_2), 25.6 (CH_2), 19.0 (CH_2) ppm; ^{31}P NMR (160 MHz, $CDCl_3$): δ 14.87 ppm. *Signal for ylide CHP was not observed.

Benzyl (*R*)-2-(2-oxo-3-(triphenyl-λ^5-phosphaneylidene) propyl)piperidine-1-carboxylate 36: In an identical procedure to that described above, (+)-Cbz-pelleteirine **17** (550 mg, 2.0 mmol, 1.00 eq.) in dry CH_2Cl_2 (15 mL) was cooled to 0 °C and left for 30 min, DIPEA (0.56 mL, 3.2 mmol, 1.48 eq.) and TMSOTf (0.54 mL, 3.0 mmol, 1.37 eq.) were added, and the mixture was stirred at room temperature for 1 h. NBS (496 mg, 2.8 mmol, 1.28 eq.) was then added in one portion. The mixture was stirred at room temperature for 2 h, then poured into water (40 mL) and extracted with EtOAc (2 x 60 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (60 mL) and brine (60 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated. To a solution of crude Cbz-α-bromopelletierine in toluene (20 mL), Ph_3P (534 mg, 2.0 mmol) was added and stirred at rt for 16 h, ether (40 mL) was added, and the yellow precipitate was collected by filtration, dissolved in MeOH-CH_3CN (10:10 mL), the solvents was removed in *vacuo*. Solid was triturated with ether, dried and kept in desiccator. The phosphonium salt than was dissolved in MeOH (20 mL), aqueous Na_2CO_3 (230 mg, 2.0 mmol) in water (6 mL) was added; white suspension was diluted with water (20 mL) and stirred for 2 h. The solution was extracted with EtOAc (2 x 30 mL) and the resultant organic layer washed with water (20 mL), and brine (20 mL), and dried over $MgSO_4$. After filtration the solvent was removed under reduced pressure to afford ylide **36** (720 mg, 1.34 mmol, 67%) with data as above.

(*S,E*)-Benzyl-2-(2-oxopent-3-en-1-yl)piperidine-1-carboxylate 37: To a solution of ylide **36** (107 mg, 0.20 mmol, 1.0 eq.) in anhydrous THF (2 mL) was added acetaldehyde (0.11 mL, 2.00 mmol, 10.0 eq.). The reaction was stirred at rt for 7 h, the solvent was removed in *vacuo*. This gave the crude product,

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which was purified by flash column chromatography (*c*-Hex/EtOAc; 3:1), which afforded the enone **37** (43 mg, 0.143 mmol, 71%) as light yellow oil. R_f = 0.3 (*c*-Hex/EtOAc; 3:1); $[\alpha]_D^{20}$ = +15.5 (c = 1.00, $CHCl_3$); HRMS (ESI) calcd for $[(C_{18}H_{23}NO_3 + H)]^+$ 302.1756, found 302.1751 (-1.7 ppm); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41-7.25 (m, 5H), 6.84 (br s, 1H), 6.08 (d, *J* = 17.1 Hz, 1H), 4.82-4.70 (m, 1H), 5.12 (d, *J* = 12.2 Hz, 1H), 5.09 (d, *J* = 12.2 Hz, 1H), 2.96-2.67 (m, 3H), 1.83 (d, *J* = 5.4 Hz, 3H), 1.71-1.35 (m, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 198.2 (CO), 155.3 (CO), 143.51 (CH), 136.8 (C), 131.8 (CH), 128.5 (CH), 127.9 (CH), 127.8 (CH), 67.1 (CH_2), 48.1 (CH), 40.6 (CH_2), 39.8 (CH_2), 27.8 (CH_2), 25.2 (CH_2), 18.7 (CH_2), 18.3 (CH_3) ppm.

(*R,E*)-Benzyl-2-(2-oxopent-3-en-1-yl) piperidine-1-carboxylate 37: In an identical to that described above, to ylide *ent*-**36** (214 mg, 0.40 mmol, 1.0 eq.) in anhydrous THF (4 mL) was added acetaldehyde (0.22 mL, 4.00 mmol, 10.0 eq.). The reaction was stirred at rt for 7 h, the solvent was removed in *vacuo*. This gave the crude product, which was purified by flash column chromatography (*c*-Hex/EtOAc; 3:1), which afforded the *title compound* **37** (84 mg, 0.28 mmol, 70%) as light yellow oil; $[\alpha]_D^{20}$ = –16.3 (c = 1.00, $CHCl_3$).

(–)-(4*S*,9a*R*)-4-Methyloctahydro-2*H*-quinolizin-2-one [(–)-myrtine] 33: To a solution of **37** (115 mg, 0.38 mmol) in CH_2Cl_2 (3 mL) was added HBr-AcOH (33%, 0.32 mL, 1.8 mmol) at 0 °C, the mixture was stirred at rt for 4 h. The solvent and excess of acid was removed in *vacuo*, and the residue was dissolved in MeOH (5 mL), and K_2CO_3 (415 mg, 3.00 mmol) was added at 0 °C. The reaction mixture was stirred for 3 h and then concentrated to dryness. A saturated aqueous ammonium chloride solution (5 mL) was added, the quenched reaction mixture was extracted with CH_2Cl_2 (3 x 7 ml), and the combined organic layers were dried over anhydrous $MgSO_4$. Solvents were removed under reduced pressure and the crude myrtine was purified by flash column chromatography (CH_2Cl_2/MeOH, 95:5) to afford **33** (34 mg, 53%) as a yellow viscous oil. R_f = 0.25 (CH_2Cl_2/MeOH; 95:5); $[\alpha]_D^{20}$ = – 13.6 (c = 1.0, $CHCl_3$) {lit.,[40] $[\alpha]_D^{25}$ = +10.1 (c = 1.5, $CHCl_3$) for (4*R*,10*R*)-enantiomer} ; HRMS calcd for $[(C_{10}H_{17}NO + H)]^+$ 168.1311, found 168.1307; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.44-3.32 (m, 1H), 2.90-2.74 (m, 2H), 2.71-2.58 (m, 1H), 2.47 (td, *J* = 11.4, 2.9 Hz, 1H), 2.30-2.13 (m, 3H), 1.76- 1.53 (m, 4H), 1.38-1.10 (m, 2H), 0.96 (d, *J* = 6.8 Hz, 3H) ppm.

(+)-(4*R*,9a*R*)-4-Methyloctahydro-2*H*-quinolizin-2-one [(+)-myrtine] 33: In an identical to that described above, enone **37** (90 mg, 0.30 mmol, 1.0 eq.) in CH_2Cl_2 (2.5 mL) was treated with HBr-AcOH (33%, 0.25 mL, 1.41 mmol) at 0 °C, the mixture was stirred at rt for 4 h. The solvent and excess of acid was removed in *vacuo*, and the residue was dissolved in MeOH (4 mL), and K_2CO_3 (325 mg, 2.35 mmol) was added at 0 °C. The reaction mixture was stirred for 3 h and then concentrated to dryness. A saturated aqueous ammonium chloride solution (4 mL) was added, the quenched reaction mixture was extracted with CH_2Cl_2 (3 x 6 mL), the combined organic layers were dried over anhydrous $MgSO_4$. Solvents were removed under reduced pressure and the crude was purified by flash column chromatography on silica to afford **33** (20 mg, 40%) as a yellow viscous oil $[\alpha]_D^{20}$ = + 11.0 (c = 0.2, $CHCl_3$) {lit.,[40] $[\alpha]_D^{25}$ = +10.1 (c = 1.5, $CHCl_3$)}.

(*S,E*)-Benzyl-2-(4-(3,4-dimethoxyphenyl)-2-oxobut-3-enyl)piperidine-1-carboxylate 42: To a solution of (–)-Cbz-pelletierine **17** (138 mg, 0.50 mmol, 1.0 eq.) in dry CH_2Cl_2 (3 mL) was added 3,4-dimethoxybenzaldehyde **38** (83 mg, 0.5 mmol, 1.0 eq.) and pyrrolidine (8 µL, 0.1 mmol, 0.2 eq.). The reaction was stirred at room temperature until the starting material was consumed as evidenced by TLC (24 h). The reaction mixture was concentrated and the residue diluted in ethyl acetate (2 mL) and washed with water (3 x 3 mL). The aqueous extracts were combined and back extracted with ethyl acetate (5 mL). The organic extracts were combined, dried over $MgSO_4$, filtered and evaporated. The product was purified by flash column chromatography (*c*-Hex/EtOAc, 2:1) to give compound **42** (129 mg, 0.31 mmol, 62%) as yellow oil. R_f = 0.25 (*c*-Hex/EtOAc; 2:1); LRMS (ESI) calcd for $[(C_{25}H_{29}NO_5 + Na)]^+$ 446.5, found 446.7; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.52 (d, J = 16.0 Hz, 1H), 7.36-7.22 (m, 5H), 7.14-6.99 (m, 2H), 6.87 (d, *J* = 8.2 Hz, 1H), 6.61 (d, *J* = 16.0 Hz, 1H), 5.11 (d, *J* = 12.5 Hz, 1H), 5.07 (d, *J* = 12.5 Hz, 1H), 4.92-4.84 (m, 1H), 4.16-4.03 (m, 3H), 3.89 (s, 3H), 3.87 (s, 3H), 2.99-2.84 (m, 3H), 1.72-1.54 (m, 5H), 1.51-1.37 (m, 1H) ppm.

(*R,E*)-Benzyl-2-(4-(3,4-dimethoxyphenyl)-2-oxobut-3-enyl)piperidine-1-carboxylate 42: In an identical procedure that described above (+)-Cbz-pelletierine **17** (138 mg, 0.50 mmol, 1.0 eq.) in dry CH_2Cl_2 (3 mL) was added 3,4-dimethoxybenzaldehyde **38** (83 mg, 0.50 mmol, 1.0 eq.) and pyrrolidine (8 µL, 0.1 mmol, 0.2 eq.), affording compound **42** (125 mg, 0.30 mmol, 60%) with data as above.

(4*S*,9a*R*)-4-(3,4-Dimethoxyphenyl)octahydro-2*H*-quinolizin-2-one 40 and (4*R*,9a*R*)-4-(3,4-dimethoxyphenyl)octahydro-2*H*-quinolizin-2-one 41 *via* a direct aldol-IMAMR: A solution of HBr-HOAc (33%, 1.1 mL, 6.00 mmol) was added to (+)-**17** (275 mg, 1.00 mmol) under ice cooling and the solution was stirred at room temperature for 4 h. The reaction mixture was evaporated under reduced pressure and the crude pelletierine hydrobromide **39** was mixed with an equimolar quantity of the veratraldehyde **38** (166 mg, 1.00 mmol) in water (1 mL) and EtOH (0.6 mL). The mixture was cooled at ice-bath temp. granular NaOH (120 mg, 3.00 mmol) was added. After dissolution of the base the reaction mixture was allowed to stir at rt for 3 h and at 65 °C for 3 h. The solution was diluted with ice water (5 mL) and extracted with chloroform (3 x 5 mL). The combined organic fractions were washed with water (5 mL) and dried over $MgSO_4$. The solvent was removed *in vacuo* to provide orange oil, which was purified by flash column chromatography to afford *trans*-fused isomer **41** (84 mg, 0.29 mmol, 29%) and *cis*-fused isomer **40** (45 mg, 0.16 mmol, 16 %). HPLC analysis (Chiralpak IC), *n*-heptane/EtOH; 80:20 (1 mL/min): (–)-**41** tr = 15 min, (+)-**41** tr = 17 min; e.r. 45:55.

(4*R*,9a*S*)-4-(3,4-Dimethoxyphenyl)octahydro-2*H*-quinolizin-2-one 40 and (4*S*,9a*S*)-4-(3,4-dimethoxyphenyl)octahydro-2*H*-

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quinolizin-2-one 41 *via* a direct aldol-IMAMR: The reaction was repeated with an identical procedure above using (–)-**17** at rt for 3 h afford *trans*-fused isomer **41** (3%) and *cis*-fused isomer **40** (20%). HPLC analysis (Chiralpak IC), *n*-heptane/EtOH; 80:20 (1 mL/min): (–)-**41** tr = 15 min, (+)-**41** tr = 17 min; e.r. 70:30.

(4*R*,9a*S*)-4-(3,4-Dimethoxyphenyl)octahydro-2*H*-quinolizin-2-one 40 and (4*S*,9a*S*)-4-(3,4-dimethoxyphenyl)octahydro-2*H*-quinolizin-2-one 41 *via* (*S*)-Cbz-42: A solution of HBr-HOAc (33%, 0.15 mL, 0.84 mmol) was added to (*S*)-**42** (65 mg, 0.14 mmol) under ice cooling and the solution was stirred at room temperature for 4 h. The reaction mixture was evaporated under reduced pressure and the residue was treated with saturated $NaHCO_3$ solution (6 mL) for 28 h at rt. The products were extracted with CH_2Cl_2 (2 x 7 mL). The combined organic layers were dried and concentrated after filtration to afford a crude mixture (**40**/**41**), which was dissolved in MeOH (0.8 mL) and treated with 2 M NaOH (0.8 mL) for 48 h at rt. The reaction mixture was diluted with H_2O, and products were extracted with CH_2Cl_2 (2 x 5 mL). After concentration, the crude diastereomeric compounds were isolated by flash column chromatography (EtOAc) to afford **41** (19 mg, 48% yield) as a yellow viscous oil. R_f = 0.5 (EtOAc)). Then the column was eluted with (CH_2Cl_2/MeOH; 15:1) affording **40** (2 mg, 5%). R_f = 0.3 (EtOAc)) and HPLC analysis (Chiralpak IC), *n*-heptane/EtOH; 80:20 (1 mL/min): (–)-**41** tr = 14.38 min, (+)-**41** tr = 16.48 min; e.r. 90:10; Data for **41**: IR: 3079, 2955, 2850, 2808, 2750, 1711, 1594, 1509, 1383, 1258, 1148, 1023, 877, 764 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 6.90 (d, *J* = 1.5 Hz, 1H), 6.75 (m, 2H), 3.89 (s, 3H), 3.87 (s, 3H), 3.20 (dd, *J* = 12.1, 3.2 Hz, 1H), 2.78 (d, *J* = 11.4 Hz, 1H), 2.67 (t, *J* = 12.8 Hz, 1H), 2.54–2.22 (m, 4H), 1.78–1.42 (m, 6H), 1.42-1.23 (m, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 207.9, 149.3, 148.3, 135.1, 119.5, 111.0, 109.8, 70.0, 62.5, 56.0, 55.9, 52.8, 50.9, 48.7, 34.3, 25.8, 24.2 ppm. Data for **40**: IR: 3070, 2929, 2853, 1712, 1591, 1512, 1320, 1256, 1142, 1025, 914, 808, 730 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 6.80 (d, *J* = 8.7 Hz, 1H), 6.70-6.64 (m, 2H), 4.23 (dd, *J* = 6.1, 4.0 Hz, 1H), 3.87 (s, 3H), 3.85 (s, 3H), 2.83-2.96 (m, 3H), 2.51–2.66 (m, 2H), 2.37 (dd, J = 14.8, 8.9 Hz, 1H), 2.19 (td, *J* = 11.7, 3.2 Hz, 1H), 1.35–1.74 (m, 6H), 1.14-1.28 (m, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 209.6, 148.5, 148.2, 131.3, 120.7, 111.5, 110.4, 63.7, 55.7, 55.6, 54.0, 51.2, 47.4, 46.7, 31.7, 23.9, 23.2 ppm.

(*S*,*E*)-*tert*-Butyl-2-[4-(3,4-dimethoxyphenyl)-2-oxobut-3-enyl]piperidine-1-carboxylate 43: A solution of compound (*S*)-Boc-**29** (130 mg, 0.54 mmol), veratraldehyde **38** (104 mg, 0.62 mmol) and 6 M NaOH (0.14 mL, 0.81 mmol) in MeOH (9 mL) was heated at 55 °C for 16 h. The reaction mixture was cooled down and evaporated in *vacuo*. Water was added (3 mL) then the aq. layer was extracted with CH_2Cl_2 (3 x 5 mL). The combined organic layers were dried over $MgSO_4$ and evaporated *in vacuo*. The residue was then purified by flash chromatography (CH_2Cl_2:EtOAc; 10:1) to yield colourless oil (126 mg, 0.32 mmol, 60%). $[\alpha]_D^{20}$ = +45.3 (c = 1.0, $CHCl_3$); LRMS (ESI) calcd for $[(C_{22}H_{31}NO_5 + Na)]^+$ 412.5, found 412.7; ^1H NMR (400 MHz, $CDCl_3$): δ 7.55 (d, J = 16.0 Hz, 1H), 7.13 (dd, *J* = 8.3 and 1.7 Hz, 1H), 7.09 (d, *J* = 1.7 Hz, 1H), 6.86 (d, *J* = 8.3 Hz, 1H), 6.65 (d, *J* = 16.0 Hz, 1H), 4.80-4.71 (m, 1H), 4.00-3.94 (m, 1H), 3.92 (s, 6H), 2.90-2.80 (m, 3H), 1.70-1.55 (m, 6H), 1.42 (s, 10H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 198.3, 154.8, 151.3, 149.2, 143.1, 127.4, 124.1, 123.2, 111.0, 109.8, 79.6, 56.0, 55.9, 44.0, 41.5, 39.3, 28.4, 28.1, 25.3, 18.9 ppm.

(*R*,*E*)-*tert*-Butyl-2-[4-(3,4-dimethoxyphenyl)-2-oxobut-3-enyl]piperidine-1-carboxylate 43: In an identical procedure that described above a solution of compound (*R*)-Boc-**29** (780 mg, 3.25 mmol), veratraldehyde **38** (620 mg, 3.75 mmol) and 6 M NaOH (0.7 mL, 4.9 mmol) in MeOH (5 mL) was heated at 55 °C for 16 h which afforded (*R*)-**43** (560 mg, 1.44 mmol, 45%) as a yellow oil. $[\alpha]_D^{20}$ = –42.0 (c = 1.0, $CHCl_3$).

(*R*,*E*)-*tert*-Butyl-2-[4-(3,4-dimethoxyphenyl)-2-oxobut-3-enyl]piperidine-1-carboxylate 43: In an identical procedure that described above a solution of compound (*R*)-Boc-**29** (780 mg, 3.25 mmol), veratraldehyde **38** (620 mg, 3.75 mmol) and 6 M NaOH (0.7 mL, 4.9 mmol) in MeOH (5 mL) was heated at 55 °C for 16 h which afforded (*R*)-**43** (560 mg, 1.44 mmol, 45%) as a yellow oil. $[\alpha]_D^{20}$ = –42.0 (c = 1.0, $CHCl_3$).

(4*R*,9a*S*)-4-(3,4-Dimethoxyphenyl)octahydro-2*H*-quinolizin-2-one 40 and (4*S*,9a*S*)-4-(3,4-dimethoxyphenyl)octahydro-2*H*-quinolizin-2-one 41 *via* (*S*)-Boc-43:[34] TFA (1.3 mL, 17.3 mmol, 54 eq.) was added dropwise to a solution of (*S*)-**43** (100 mg, 0.25 mmol, 1.0 eq.) in dry CH_2Cl_2 (1.0 mL) under N_2 at 0 °C. The resulting mixture was stirred at 0 °C for 2 h and then the reaction was quenched by adding saturated $NaHCO_3$ solution (15 mL) and the products were extracted with CH_2Cl_2 (2 x 4 mL). The combined organic layers were concentrated *in vacuo* giving a yellowish oil. The resulting yellowish oil was dissolved in MeOH (1.3 mL) and treated with 2 M NaOH (1.3 mL) for 48 h at rt. The reaction mixture was diluted with H_2O (10 mL), and products were extracted with CH_2Cl_2 (2 x 4 mL). After concentration, the diastereomeric ratio was determined by ^1H NMR spectroscopy at this stage (**40**:**41**; 1.2:1). The crude mixture was then isolated by flash column chromatography (EtOAc) to afford **41** as (22 mg, 30%) as a yellow viscous oil. R_f = 0.5 (EtOAc)). Then the column was further eluted with (CH_2Cl_2/MeOH; 150:10) affording **40** (27 mg, 37%) as a yellow oil. R_f = 0.3 (EtOAc)); $[\alpha]_D^{20}$ of **41** = –60.0 (c = 1.0, $CHCl_3$) {lit.,[34] $[\alpha]_D^{24}$ = –78.2 (c = 1.5, $CHCl_3$)}, $[\alpha]_D^{20}$ of **40** = –11.6 (c = 1.0, $CHCl_3$) {lit.,[34] $[\alpha]_D^{24}$ = –10.8 (c =0.26, $CHCl_3$)}; HPLC analysis (Chiralpak IC), heptane/EtOH; 80:20 (1 mL/min): (–)-**41** tr = 14.0 min, (+)-**41** tr = 16.0 min; e.r. 98:2.

(2*S*,4*S*,9a*S*)-4-(3,4-Dimethoxyphenyl)octahydro-2*H*-quinolizin-2-ol [(–)-lasubine II] 35: To a flame-dried 5 mL vial was added **41** (15 mg, 0.05 mmol, 1.0 eq.) and THF (0.3 mL). The solution was cooled to -78 °C before dropwise addition of L-selectride (1.0 M in THF, 0.1 mL, 0.10 mmol, 2.0 eq.). The reaction was allowed to stir at -78 °C for 2 h before warming up to 0 °C and quenching with saturated aq. $NaHCO_3$ (0.3 mL). The resulting mixture was warmed to rt and stirred for 30 min before extracting with EtOAc (5 x 2 mL). The combined organic phases were dried over $MgSO_4$, filtered, and concentrated *in vacuo* to yield a yellow residue. The crude product was purified by flash column chromatography (CH_2Cl_2/MeOH; 80:20) affording **35** (10

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mg, 69%) as a colourless oil. R_f = 0.2 (CH_2Cl_2/MeOH; 80:20). $[\alpha]_D^{20}$ = –60.7 (c = 0.32, $CHCl_3$) {lit.,[41] $[\alpha]_D^{25}$ = –56 (c = 0.32, MeOH)}; HRMS (ESI) calcd for $[(C_{17}H_{25}NO_3 + H)]^+$ 292.1913, found 292.1903 (-3.3 ppm); ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.96-6.78 (m, 3H), 4.14 (s, 1H), 3.88 (s, 3H), 3.86 (s, 3H), 3.31 (dd, *J* = 11.3, 2.9 Hz, 1H), 2.68 (d, *J* = 11.3 Hz, 1H), 2.44-2.32 (m, 1H), 1.93–1.21 (m, 12H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 149.0, 147.8, 137.3, 119.6, 110.9, 110.5, 65.0, 63.4, 56.4, 55.9, 55.8, 53.2, 42.8, 40.4, 33.7, 26.2, 24.9 ppm.

(4*S*,9a*R*)-4-(3,4-Dimethoxyphenyl)octahydro-2*H*-quinolizin-2-one 40 *via* (*R*)-Boc-43:[34] TFA (4.0 mL, 52.00 mmol, 67 eq.) was added dropwise to a solution of (*R*)-Boc-**43** (300 mg, 0.77 mmol, 1 eq.) in dry CH_2Cl_2 (4 mL) at 0 °C. The mixture was stirred at 0 °C for 2 h and the reaction was quenched by adding saturated $NaHCO_3$ solution (15 mL). The mixture was basified to pH 6.5 and the combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo* to give a yellowish oil. The oil was dissolved in MeOH (1.5 mL) and treated with NH_4OH (1.5 mL) for 30 min at room temperature. The reaction mixture was extracted with CH_2Cl_2 (4 x 5 mL). The combined organic layers were dried over $MgSO_4$, filtered and evaporated in vacuo. The diastereomeric ratio was determined by ^{1}H NMR spectroscopy at this stage (**40**:**41**; 3:1). The crude product was purified by column chromatography (EtOAc to CH_2Cl_2:MeOH; 80:20) affording **40** (50.4 mg, 23%) as a colourless oil. R_f = 0.2 (EtOAc); $[\alpha]_D^{20}$ = +14.4 (c = 1, $CHCl_3$).

(2*S*,4*S*,9a*R*)-4-(3,4-Dimethoxyphenyl)octahydro-2*H*-quinolizin-2-ol [(–)-lasubine I] 34: L-Selectride (1 M in THF, 0.32 mL, 0.32 mmol) was added to a solution of (+)-**40** (50.4 mg, 0.17 mmol) in THF (0.6 mL) at –78 °C. The mixture was stirred for 2 h, then warmed to 0 °C and quenched with saturated $NaHCO_3$ (1.00 mL). The mixture was warmed to room temperature and stirred for 30 min. The product was extracted with EtOAc (5 x 4 mL) and purified by column chromatography (CH_2Cl_2:MeOH 90:10 to 70:30) affording (–)-**34** (20.5 mg, 42%) as a yellow oil. R_f = 0.35 (CH_2Cl_2:MeOH; 70:30) $[\alpha]_D^{20}$ = –8.4 (c = 1.0, $CHCl_3$) {lit.,[42] $[\alpha]_D^{20}$ = -7.9 (c 0.2, $CHCl_3$); HRMS (EI) calcd for $[C_{17}H_{25}NO_3]^+$ 291.1834, found 291.1843 (+3.1 ppm); ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.87 (d, *J* = 8.1 Hz, 2H), 6.80 (d, *J* = 8.3 Hz, 1H), 4.18 (septet, 1H), 4.12 (s, 1H), 3.87 (d, *J* = 5.7 Hz, 6H), 3.00 (s, 1H), 2.72 (d, *J* = 12.1 Hz, 1H), 2.29 (s, 1H), 1.18–2.12 (series of m, 11H) ppm; ^{13}C NMR (100 MHz; $CDCl_3$) δ 24.1, 24.5, 32.4, 40.2, 40.3, 51.2, 54.0, 55.8, 55.9, 61.9, 65.0, 110.7, 111.9, 120.6, 135.3, 147.8, 148.7 ppm.

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Pelletierine • quinolizidine alkaloids • sedum alkaloids • diastereomeric salt resolution • intramolecular aza-Michael reaction (IMAMR)

[1] More than 12,000 piperidine-containing compounds have been included in clinical, or preclinical trials over a 10-year period (1990-2000): P. S. Watson, B. Jiang, B. Scott, *Org. Lett.* **2000**, *2*, 3679-3681.

[2] R. Vardanyan, *Piperidine-based drug discovery*, Elsevier, Netherlands, **2017**. For reviews covering synthetic methods to prepare substituted piperidines, see: (a) M. Buffat, *Tetrahedron*, **2004**, *60*, 1701-1729; (b) A. K. Chattopadhyay, S. Hanessian, *Chem. Commun*. **2015**, *51*, 16450-16467.

[3] S. Funayama, G. A. Cordell, *Alkaloids: A Treasury of Poisons and Medicines*, Academic Press, UK, **2015**. For a discussion of strategies to prepare substituted piperidines, see: (a) I. Bosque, J. C. Gonzalez-Gomez, F. Foubelo, M. Yus, *J. Org. Chem.* **2012**, *77*, 780-789; (b) V. G. Lisnyak, T. Lynch-Colameta, S. A. Snyder, *Angew. Chem. Int. Ed.* **2018**, *57*, 15162-15166 and references therein.

[4] (a) J. C. Craig, S. Y. C. Lee, S. K. Roy, *J. Org. Chem.* **1978**, *43*, 347-349; (b) T. Reynolds, *Phytochemistry* **2005**, *66*, 1399-1406; (c) S. Kobayashi, M. Ueno, R. Suzuki, H. Ishitani, H. S. Kim, Y. Wataya, *J. Org. Chem.* **1999**, *64*, 6833-6841.

[5] C. Tanret, *Compt. Rend. Acad. Sci.* **1878**, *86*, 1270-1272.

[6] R. E. Gilman, L. Marion, *Bull. Soc. Chim. Fr.* **1961**, 1993-1995, and references cited therein.

[7] (a) H. C. Beyerman, L. Maat, *Recl. Trav. Chim. Pays-Bas* **1963**, *82*, 1033-1039; (b) H. C. Beyerman, L. Maat, A. V. Veen, A. Zweistra, *Recl. Trav. Chim. Pays-Bas* **1965**, *84*, 1367-1379, (c) J. Quick, R. Oterson, *Synthesis* **1976**, 745-746; (d) C. Louis, S. Mill, V. Mancuso, C. Hootelé, *Can. J. Chem.* **1994**, *72*, 1347-1350; (e) H. Takahata, M. Kubota, S. Takahashi, T. Momose, *Tetrahedron: Asymmetry* **1996**, *7*, 3047-3054; (f) G. Cheng, X. Wang, D. Su, H. Liu, F. Liu, Y. Hu, *J. Org. Chem.* **2010**, *75*, 1911-1916; (g) T. K. Beng, R. E. Gawley, *J. Am. Chem. Soc.* **2010**, *132*, 12216-12217; (h) I. Coldham, D. Leonori, *J. Org. Chem.* **2010**, *75*, 4069-4077; (i) P. Beak, A. Basu, D. J. Gallagher, Y. S. Park, S. Thayumanavan, *Acc. Chem. Res.* **1996**, *29*, 552-560; (j) D. Hoppe, T. Hense, *Angew. Chem., Int. Ed.* **1997**, *36*, 2282-2316; (k) M. C. Whisler, S. MacNeil, V. Snieckus, P. Beak, *Angew. Chem., Int. Ed.* **2004**, *43*, 2206-2225; (l) M. J. McGrath, J. L. Bilke, P. O'Brien, *Chem. Commun.* **2006**, 2607-2609; (m) R. K. Dieter, C. M. Topping, R. C. Kishan, K. J. Lu, *J. Am. Chem. Soc.* **2001**, *123*, 5132-5133; (n) M. R. Monaco, P. Renzi, D. M. Scarpino Schietroma, M. Bella, *Org. Lett.* **2011**, *13*, 4546-4549; (o) S. Fustero, C. del Pozo, C. Mulet, R. Lazaro, M. Sánchez-Roselló, *Chem. Eur. J.* **2011**, *17*, 14267-14272; (p) J. -D. Liu, Y. -C. Chen, G. -B. Zhang, Z. -Q. Li, P. Chen, J. -Y. Du, Y. -Q. Tu, C. -A. Fan, *Adv. Synth. Catal.* **2011**, *353*, 2721-2730; (q) W. -H. Chiou, G. -T. Chen, C. -L. Kao, Y. -K. Gao, *Org. Biomol. Chem.* **2012**, *10*, 2518-2520.

[8] L. Chausset-Boissaire, R. Àrvai, G. R. Cumming, L. Guénée, E. P. Kündig, *Org. Biomol. Chem.* **2012**, *10*, 6473-6479.

[9] H. Hotti, H. Rischer, *Molecules* **2017**, *22*, 1962-1986.

[10] (a) J. L. Galman, I. Slabu, F. Parmeggiani, N. J. Turner, *Chem. Commun.* **2018**, *54*, 11316-11319; (b) G. W. Morrow, *Bioorganic Synthesis: An Introduction*, Oxford University Press, UK, **2016**.

[11] (a) S. G. Davies, A. M. Fletcher, P. M. Roberts, A. D. Smith, *Tetrahedron* **2009**, *65*, 10192-10213; (b) H. Ren, W. D. Wulff, *Org. Lett.* **2013**, *15*, 242-245.

[12] K. Gao, C. Zheng, T. Wang, H. Zhao, J. Wang, Z. Wang, X. Zhai, Z. Jia, J. Chen, Y. Zhou, W. Wang, *Molecules* **2016**, *21*, 1600-1614.

[13] G. Zheng, P. A. Crooks, *Org. Prep. Proced. Int.* **2015**, *47*, 317-337.

[14] S. Smullen, N. P. McLaughlin, P. Evans, *Bioorg. Med. Chem.* **2018**, *26*, 2199-2220.

[15] R. K. Zaidan, S. Smullen, P. Evans, *Tetrahedron Lett.* **2015**, *56*, 6433-6453.

[16] See for example: (a) F. Galinovsky, R. Hollinger, *Monatsh.* **1954**, *85*, 1012-1014; (b) A. Durant, C. Hootelé, *Can. J. Chem.* **1992**, *70*, 2722-2725; (c) J. R. Harrison, P. O'Brien, D. W. Porter, N. M. Smith, *J. Chem. Soc., Perkin Trans. 1* **1999**, 3623-3631; (d) E.Akiyama, M. Hirama, *Synlett* **1996**, 100-102; (e) L. -H. Yan, F. Dagorn, E. Gravel, B. Séon-Méniel, E. Poupon, *Tetrahedron*, **2012**, *68*, 6276-6283; (f) Z. Amara, G. Bernadat, P. -E. Venot, P. Retailleau, C.

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Troufflard, E. Drège, F. Le Bideau, D. Joseph, *Org. Biomol. Chem.* **2014**, *12*, 9797-9810.

[17] For a review, see: (a) M. Saha, R. G. Carter, *Synlett* **2017**, 2212-2229; (b) M. Sánchez-Roselló, J. L. Acena, A. Simon-Fuentes, C. del Pozo, *Chem. Soc. Rev.* **2014**, *43*, 7430-7453.

[18] Approximate comparative costs of organocatalysts used (Sigma-Aldrich): L-Pro: 100 g = € 112; D-Pro: 5 g = € 114; **24a**: 0.25 g = € 140; **24b**: 0.25 g = € 132.

[19] Compound *R*-**25**, CCDC code: 1898957; Formula: $C_{24}H_{23}BrClN_3O_4$; Unit Cell Parameters: a: 20.02860(14), b: 5.58301(4), c: 20.29450(14); P21.

[20] (a) D. Kozma, *Handbook of optical resolutions via diastereomeric salt formation*, CRC Press, Florida, **2002**; (b) R. A. Scheldon, *Chirotechnology,* Marcel Dekker, US, **1993**.

[21] F. Galinovsky, G. Bianchetti, O. Vogl, *Monatsh.* **1953**, *84*, 1221-1227.

[22] H. C. Beyerman, L. Maat, *Recl. Trav. Chim. Pays-Bas* **1965**, *84*, 385-388.

[23] M. F. A. Adamo, V. K. Aggarwal, M. A. Sage, *Synth. Commun.* **1999**, *29*, 1747-1756.

[24] H. M. T. B. Herath, N. P. D. Nanayakkara, *J. Heterocycl. Chem.* **2008**, *45*, 129-136.

[25] Compound **28a**, CCDC code 1898966; Formula: $[C_8H_{16}NO]^+\cdot[C_8H_7O_3]^-$; Unit Cell Parameters: a: 7.2941(3), b: 8.1026(4), c: 13.2522(5); P1

[26] C. Bhat, S. G. Tilve, *Tetrahedron* **2013**, *69*, 6129-6143.

[27] Compound **32**, CCDC code 1898968; Formula: $C_8H_{17}NO$; Unit Cell Parameters: a: 5.1920(1), b: 9.1464(2), c: 9.0122(2); P21. Compound **8**, CCDC code 1898967; Formula: $C_8H_{17}NO$; Unit Cell Parameters: a: 9.069(1), b: 5.1647(7), c: 9.539(2); P21.

[28] For a detailed recent review, see: J. P. Michael, *The Alkaloids: Chemistry and Biology*, **2016**, *75*, 1-498.

[29] P. Slosse, C. Hootelé, *Tetrahedron* **1981**, *37*, 4287-4294. For a recent synthesis of myrtine, see: J. D. Bell, A. H. Harkiss, C. R. Wellaway, A. Sutherland, *Org. Biomol. Chem.* **2018**, *16*, 6410-6422.

[30] K. Fuji, T. Yamada, E. Fujita, H. Murata, *Chem. Pharm. Bull*. **1978**, *26*, 2515-2521. For representative syntheses of lasubine I and II, see: (a) J. D. Brown, M. A. Foley, D. L. Comins, *J. Am. Chem. Soc.* **1988**, *110*, 7445-7447; (b) D. L. Comins, D. H. LaMunyon, *J. Org. Chem*. **1992**, *57*, 5807-5809; (c) B. M. Trost, C. -I. Jung, *J. Am. Chem. Soc*. **2015**, *137*, 15940-15946; (d) N. V. G. Moorthy, R. Dyapa, S. V. Pansare, *Org. Lett*. **2015**, *17*, 5312-5315; (e) M. J. James, N. D. Grant, P. O'Brien, R. J. K. Taylor, W. P. Unsworth, *Org. Lett.* **2016**, *18*, 6256-6529; (f) N. F. bte Mohamed Aslam, O. Simon, R. W. Bates, *Tetrahedron* **2018**, *74*, 5032-5039.

[31] Note: this reaction could theoretically proceed *via* iminium ion formation followed by an intramolecular Mannich reaction. Under the basic reaction conditions we feel that the chalcone formation-IMAMR sequence alluded to is more likely.

[32] H. Iida, M. Tanaka, C. Kibayashi, *J. Org. Chem.* **1984**, *49*, 1909-1912.

[33] This ratio was readily determined by ^{1}H NMR spectroscopy. The characteristic doublet of doublets for **40** at δ = 4.23 ppm was compared with corresponding doublet of doublets at δ = 3.20 ppm for **41**.

[34] S. -L. Shi, X. -F. Wei, Y. Shimizu, M. Kanai, *J. Am. Chem. Soc.* **2012**, *134*, 17019-17022.

[35] A. – E. Al-Sarabi, A. Bariau, M. Gabant, J. -C. Wypych, P. Chalard, Y. Troin, *Arkivoc* **2007**, (i), 119-133.

[36] E. C. Carlson, L. K. Rathbone, H. Yang, N. D. Collett, R. G. Carter, *J. Org. Chem.* **2008**, *73*, 5155-5158.

[37] M. N. Chatterjee, E. R. Kay, D. A. Leigh, *J. Am. Chem. Soc.* **2006**, *128*, 4058-4073.

[38] F. Ramirez, S. Dershowitz, *J. Org. Chem.* **1957**, *22*, 41-45.

[39] H. Takahata, M. Kubota, N. Ikota, *J. Org. Chem.* **1999**, *64*, 8594-8601.

[40] S. Fustero, J. Moscardo, M. S. Rosello, S. Flores, M. Guerola, C. Pozo, *Tetrahedron* **2011**, *67*, 7412-7414.

[41] J. M. M. Verkade, F. van der Pijl, M. M. J. H. P. Willems, P. J. L. M. Quaedflieg, F. L. van Delft, F. P. J. T. Rutjes, *J. Org. Chem.* **2009**, *74*, 3207-3210.

[42] F. A. Davis, A. Rao, P. J. Carroll, *Org. Lett.* **2003**, *5*, 3855-3857.

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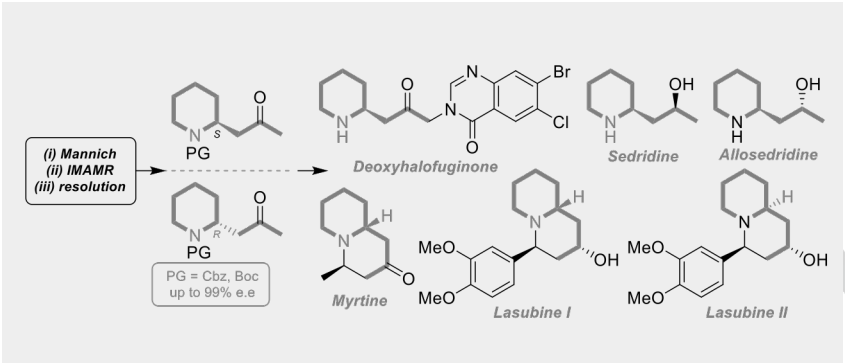

Key Topic* Stereocontrolled synthesis of saturated *N*-heterocycles

*Raed K. Zaidan and Paul Evans**

Page No. – Page No.

Strategies for the asymmetric construction of pelletierine and its use in the synthesis of sedridine, myrtine and lasubine

Three methods are described for the synthesis of both enantiomers of optically active pelletierine. The usefulness of these compounds as building blocks is demonstrated in the asymmetric syntheses of several piperidine-based compounds of interest.

*Asymmetric synthesis of piperidines

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