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Organocatalytic enantioselective synthesis of quinolizidine alkaloids (+)-myrtine, (−)-lupinine, and (+)-*epi*epiquinamide

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ABSTRACT

The organocatalytic synthesis of quinolizidine alkaloids (+)-myrtine, (−)-lupinine, and (+)-*epi*-epiquinamide is described. It involved, as the key step, an enantioselective intramolecular aza-Michael reaction (IMAMR) catalyzed by Jørgensen catalyst **I**, affording the common precursor with high enantioselectivity. This compound was subsequently transformed into the three alkaloids in a highly diastereoselective manner.

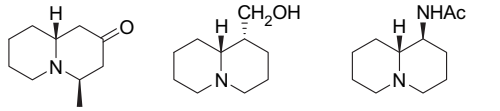
1. Introduction

The azabicyclic skeleton of quinolizidine is a relevant structural subunit present in numerous alkaloids. The wide range of biological activities found in this family of natural products make them ideal targets for total synthesis.[1]

In the past decade organocatalysis has become a thriving area of widely applicable asymmetric reactions,[2] thereby accelerating the development of new methods to assemble useful molecules with high enantiomeric purity. On the other hand, the aza-Michael reaction constitutes one of the best methods for the formation of C–N bonds and has emerged as a very powerful tool for the synthesis of nitrogen-containing heterocycles in its intramolecular version.

Despite the synthetic utility of this transformation, the catalytic enantioselective aza-Michael reaction remained undeveloped until very recently.[3] Furthermore, most of the examples reported in this field are intermolecular reactions, while the intramolecular version has remained almost unexplored.[4] In this context, we have recently developed a catalytic enantioselective intramolecular aza-Michael reaction (IMAMR). Thus, when carbamates bearing a remote α,β-unsaturated aldehyde moiety were treated with chiral diarylprolinol ethers, the IMAMR took place with high levels of enantioselection, giving rise to the corresponding enantiomerically enriched nitrogen heterocycles.[4c,e]

The synthetic utility of our approach is now illustrated with the total synthesis of three quinolizidine alkaloids, namely (+)-myrtine **1**, (−)-lupinine **2**, and (+)-*epi*epiquinamide **3** (Fig. 1).



1 [(+)-myrtine] **2** [(−)-lupinine] **3** [(+)-*epi*epiquinamide]

Fig. 1. Quinolizidine alkaloids.

2. Results and discussion

A common carbamate precursor, *N*-Boc 2-[(*R*)-piperidin-2-yl] acetaldehyde (**5**), was assembled by means of an organocatalytic IMAMR. Accordingly, conjugated aldehyde **4** was treated with Jørgensen diarylprolinol **I** in $CHCl_3$ at −50 °C in the presence of benzoic acid as an additive, thus affording the piperidine aldehyde **5** in 63% yield and 94% ee (Scheme 1).[4e] The synthesis of compound

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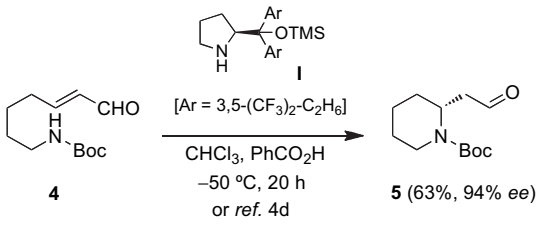
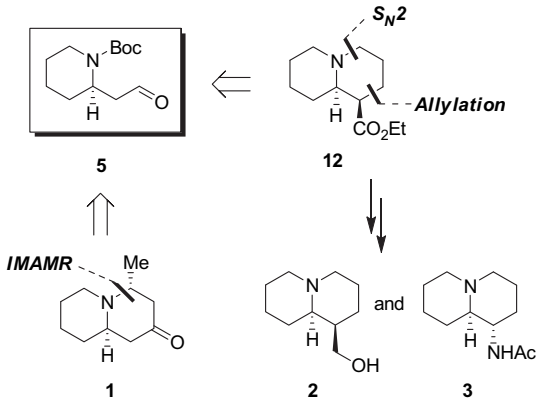
5 was also described by Carter et al. starting from **4** in a MeOH–DCE mixture at −25 °C by using the same catalyst.[4d] This aldehyde was used as the starting substrate for the synthesis of alkaloids **1**–**3**. The retrosynthetic analysis is depicted in Scheme 1.



Scheme 1. Synthesis of the common precursor **5**.

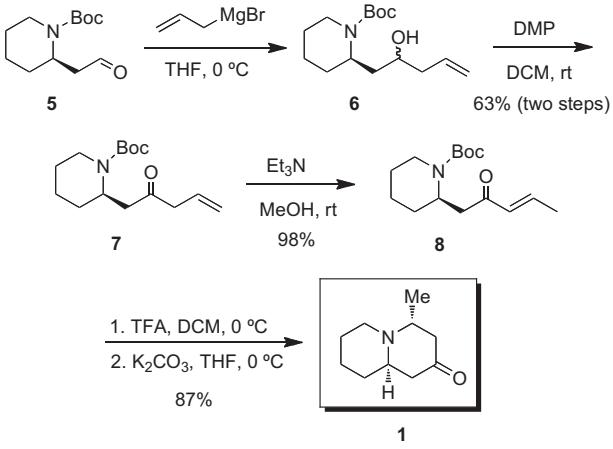
In our approach, the key step in the synthesis of **1** involved a highly diastereoselective IMAMR on the appropriate precursor that was in turn prepared from piperidine **5**. On the other hand, the key intermediate for the synthesis of **2** and **3** was the bicyclic β-amino ester **12**. In these cases, the second chiral center was installed by means of a highly diastereoselective allylation reaction followed by further cyclization onto the nitrogen atom through an S_N2-type displacement (Scheme 2).



Scheme 2. Retrosynthetic analysis.

(+)-Myrtine **1** (see Fig. 1) is a naturally occurring quinolizidine alkaloid isolated from *Vaccinium myrtillus*. Although it was discovered more than three decades ago -its structure and absolute configuration were determined in 1978-,[5] only six asymmetric synthesis of this alkaloid have been described to date. Two of them relied on the use of enantiomerically pure starting materials derived from the chiral pool.[6] Two more syntheses employed either sulfoxides or 8-phenylmenthol as chiral auxiliaries.[7] The last one was based on a copper-catalyzed enantioselective conjugated addition reaction.[8] Finally, an organocatalytic enantioselective synthesis of (+)-myrtine appeared in the literature early this year.[9]

In our strategy, aldehyde **5** reacted with allylmagnesium bromide to afford a diastereomeric mixture of alcohols **6**, which were readily oxidized with Dess–Martin periodinane (DMP). The resulting ketone **7** was then treated with Et_3N in MeOH, thus promoting a highly efficient double bond isomerization that gave access to the α,β-unsaturated ketone **8**.[10] Removal of the Boc *N*-protecting group provided the substrate for the IMAMR. Complete selectivity was achieved in this cyclization step when K_2CO_3 was employed as a base in THF at 0 °C. In this manner, the desired alkaloid **1** was obtained in 87% yield (Scheme 3).[11]



Scheme 3. Synthesis of (+)-myrtine **1**.

As a result, we have performed the second organocatalytic synthesis of (+)-myrtine in six steps and 34% overall yield starting from the *N*-Boc protected aldehyde **4**.

(−)-Lupinine **2** (see Fig. 1) is one of the parent members of the quinolizidine group of alkaloids isolated from the yellow lupin seeds (*Lupinus luteus*) and it was first reported over a hundred years ago.[12] Several asymmetric syntheses of this alkaloid have been devised, most of them based on chiral pool-derived starting materials.[13] Only one synthesis reported by Ma and Ni in 2004 took advantage of the Sharpless asymmetric epoxidation in order to generate the corresponding chiral centers of the molecule.[14]

On the other hand, (−)-epiquinamide **3′** (Fig. 2) was isolated in 2003 from the poison frog *Epipedobates tricolor* and it was claimed to act as an agonist of the nicotinic receptors.[15] This alkaloid has attracted considerable attention from the synthetic community, and several asymmetric syntheses have been recently reported. Again, most of them made use of starting materials coming from the chiral pool.[16] Optically active precursors obtained by enzymatic resolution have also been employed in the preparation of **3**.[17] Very recently, two more asymmetric syntheses of (−)-epiquinamide involving an asymmetric hydroxylation reaction as the key step have been reported in the literature.[18] However, only one report deals with the preparation of the epiquinamide C1-epimer **3** (Fig. 2).[17]

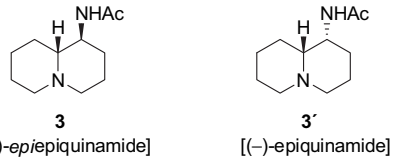
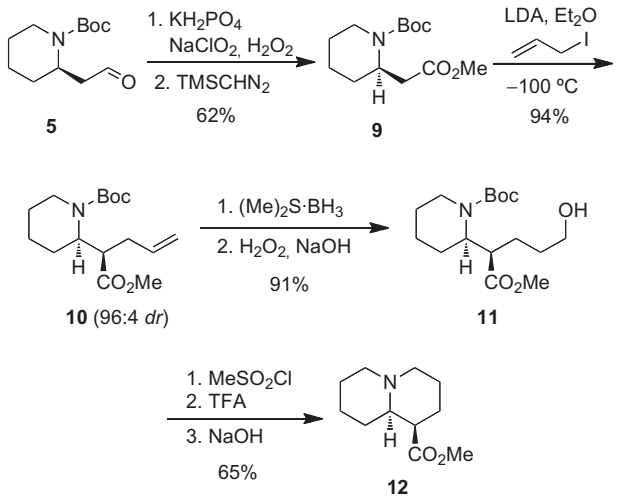


Fig. 2. Epiquinamide epimers.

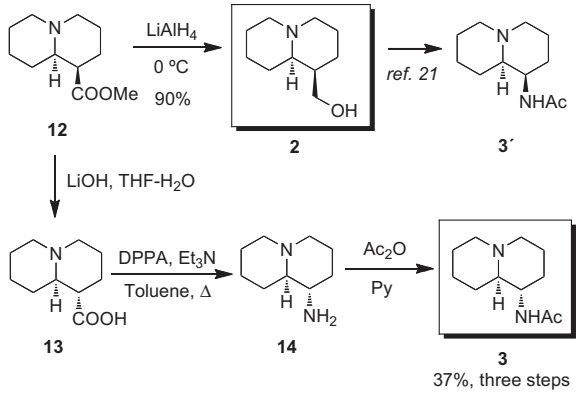
In accordance with the retrosynthetic analysis shown in Scheme 2, we have performed the first organocatalytic synthesis of (−)-lupinine **2** and (+)-*epi*epiquinamide **3** from a common precursor **12**. Thus, aldehyde **5** was transformed into the corresponding methyl ester **9** through oxidation followed by treatment with $TMSCHN_2$. The installation of the second stereocenter of the molecule was achieved by treatment of the lithium enolate of **9** with allyl iodide at −100 °C, thus affording compound **10** in 94% yield and excellent diastereoselectivity (96:4 dr).[19] Next, the double bond was transformed into the corresponding alcohol **11** by means of the sequence hydroboration–oxidation. After mesylation of the hydroxyl functionality and removal of the Boc protecting group, a smooth cyclization through an S_N2-type process took place upon

basification, giving rise to the bicyclic derivative **12** in good yield (Scheme 4).



Scheme 4. Synthesis of the bicyclic β-amino ester **12**.

With intermediate **12** in hand, reduction of the ester moiety with $LiAlH_4$ afforded the desired natural product (−)-lupinine **2** (Scheme 5) in 20% overall yield starting from aldehyde **4**.



Scheme 5. Synthesis of (−)-lupinine **2** and (+)-*epi*epiquinamide **3**.

Additionally, the ester functionality of the bicyclic derivative **12** was hydrolyzed by treatment with lithium hydroxide. During this process, a complete epimerization of the ester-containing stereocenter occurred affording the corresponding carboxylic acid **13**.[20] This compound was subjected to a Curtius-type rearrangement by reaction with diphenylphosphoryl azide (DPPA) and Et_3N under refluxing toluene. The resulting amine **14** was acylated in situ to afford the desired alkaloid **3** in 37% yield (three steps). Therefore, by using this strategy, (+)-*epi*epiquinamide **3** (Scheme 5) was obtained in 8% overall yield starting from aldehyde **4**.

Finally, the transformation of lupinine **2** into epiquinamide **3′** has been recently described following the sequence oxidation of the hydroxyl functionality to the corresponding carboxylic acid-Curtius rearrangement -nitrogen acetylation.[21] Therefore, our synthetic route also constitutes a formal synthesis of **3′**.

3. Conclusion

In conclusion, an organocatalytic asymmetric synthesis of the quinolizidine alkaloids (+)-myrtine **1**, (−)-lupinine **2**, and (+)-*epi*-epiquinamide **3** has been described. The process takes advantage of the organocatalytic enantioselective IMAMR previously developed in our group, which allows the preparation of the common piperidine precursor **5** in high yield and enantioselectivity. The key step in the synthesis of **1** was a highly diastereoselective IMAMR that gave access to the second cycle of the natural product. For the syntheses of **2** and **3**, a highly diastereoselective allylation reaction allowed to install the second stereocenter.

4. Experimental section

4.1. General experimental methods

Reactions were carried out under argon atmosphere unless otherwise indicated. The solvents were purified prior to use: THF, diethyl ether, and toluene were distilled from sodium/benzophenone, dichloromethane, and acetonitrile were distilled from calcium hydride. The reactions were monitored with the aid of thin-layer chromatography (TLC) on 0.25 mm precoated silica gel plates. Visualization was carried out with UV light and aqueous ceric ammonium molybdate solution or potassium permanganate stain. Flash column chromatography was performed with the indicated solvents on silica gel 60 (particle size 0.040–0.063 mm). ^1H and ^{13}C NMR spectra were recorded on a 300 or 400 MHz spectrometers. Chemical shifts are given in ppm (δ), with reference to the residual proton resonances of the solvents. Coupling constants (J) are given in hertz (Hz). The letters m, s, d, t, and q stand for multiplet, singlet, doublet, triplet, and quartet, respectively. The letters br indicate that the signal is broad. Aldehyde **4** was previously reported.[4e]

4.2. Synthesis of (*R*)-*N*-*tert*-butoxycarbonyl-2-[(*R*)-piperidin-2-yl]acetaldehyde (5)

In a flame-dried, 10 mL round bottomed flask, (*E*)-(7-*tert*-butoxycarbonylamino)-2-heptenal (43 mg, 0.20 mmol) was dissolved in dry chloroform (1.6 mL) and the solution was cooled to −50 °C. Over this solution, a mixture of (*S*)-2-[bis(3,5-bis(trifluoromethyl)phenyl)-(trimethylsilyloxy) methyl]pyrrolidine (**I**) (23.8 mg, 0.04 mmol), and benzoic acid (4.9 mg, 0.04 mmol) in chloroform (0.4 mL) was added and the resulting solution was stirred at −50 °C for 22 h. After the mixture was allowed to reach 0 °C, it was quenched with aqueous saturated NH_4Cl and extracted with dichloromethane (3×5 mL). The organic extracts were washed with brine, dried over anhydrous Na_2SO_4, and concentrated to dryness under vacuum. After flash chromatography over silica gel using *n*-hexane/ethyl acetate (10:1) as eluent, 29 mg of aldehyde **5** were obtained as a colorless oil (63% yield, 94% ee). $[\alpha]_D^{25}$ +48.4 (*c* 1.0, $CHCl_3$) [lit.[22] $[\alpha]_D^{25}$ +48.0 (*c* 1.0, $CHCl_3$)]. The spectroscopic data are in agreement with those previously reported in literature.[22] ^1H NMR (300 MHz, $CDCl_3$) δ 1.44 (s, 9H), 1.37–1.73 (m, 6H), 2.48–2.56 (m, 1H), 2.69–2.78 (m, 2H), 3.98 (br d, J=13Hz, 1H), 4.83 (br s, 1H), 9.72 (dd, J_1=3.2 Hz, J_2=2.2 Hz, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 18.9 (CH_2), 25.2 (CH_2), 28.3 ($3CH_3$), 28.9 (CH_2), 39.3 (CH_2), 44.6 (CH_2), 45.9 (CH), 79.9 (C), 154.7 (C), 200.8 (C). HRMS (EI^+) calcd for $C_{12}H_{22}NO_3$ [$M+H^+$] 228.1584, found 228.1594. After reduction of the aldehyde with $NaBH_4$ (3 equiv) in MeOH, the enantiomeric ratio of the corresponding *p*-chlorobenzoate was determined with the aid of HPLC analysis: Chiracel IC (25 cm×0.46 cm column), hexane/isopropanol 90:10, flow=1.0 mL/min, $t_{R\ minor}$=11.5 min, $t_{R\ major}$=14.7 min.

4.3. Synthesis of (*R*)-*tert*-butyl 2-(2-oxopent-4-en-1-yl) piperidine-1-carboxylate (7)

Allylmagnesium bromide (2.1 mL of freshly prepared 0.5 M solution in THF, 1.04 mmol) was added dropwise to a solution of

aldehyde **5** (214 mg, 0.94 mmol) in THF (10 mL) at 0 °C. The mixture was allowed to reach room temperature and stirred for 1 h. Then, a saturated aqueous NH_4Cl solution was added, the quenched reaction mixture was extracted with ethyl acetate (3×10 mL) and the combined organic layers were dried over anhydrous Na_2SO_4. Solvents were removed under reduced pressure to afford a diastereomeric mixture of alcohols **6** that were used without further purification. To a solution of **6** in dichloromethane (15 mL) Dess–Martin periodinane (DMP) (477 mg, 1.2 mmol), and $NaHCO_3$ (100.8 mg, 1.2 mmol) were added at 0 °C. The reaction mixture was allowed to warm until room temperature and stirred for 5 h. Saturated aqueous NH_4Cl solution was added, the quenched reaction mixture was extracted with dichloromethane (3×10 mL) and the combined organic layers were dried over anhydrous Na_2SO_4. Solvents were removed under reduced pressure and the crude mixture was purified by flash chromatography on silica gel using *n*-hexane/ethyl acetate (6:1) as eluent to afford 158 mg of ketone **7** (63% yield, two steps) as a light yellow oil. $[\alpha]_D^{25}$ +11.9 (*c* 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.43 (s, 9H), 1.50–1.69 (m, 6H), 2.65 (d, *J*=6.0 Hz, 2H), 2.72–2.81 (m, 1H), 3.15–3.27 (m, 2H), 3.93–3.97 (m, 1H), 4.70–4.72 (m, 1H), 5.10–5.19 (m, 2H), 5.82–5.96 (m, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 18.9 (CH_2), 25.2 (CH_2), 28.3 (CH_2), 28.4 ($3CH_3$), 39.4 (CH_2), 42.8 (CH_2), 47.2 (CH_2), 47.7 (CH), 79.6 (C), 118.9 (CH_2), 130.5 (CH), 154.7 (C), 206.8 (C). HRMS (EI$^+$) calcd for $C_{15}H_{26}NO_3$ [M+H$^+$] 268.1907, found 268.1901.

4.4. Synthesis of (*R*,*E*)-*tert*-butyl 2-(2-oxopent-3-en-1-yl) piperidine-1-carboxylate (8)

To a solution of ketone **7** (158 mg, 0.59 mmol) in methanol (15 mL), Et_3N (3 mL) was added and the mixture was stirred for 10 h. Solvents were removed under reduced pressure and the crude mixture was purified by flash chromatography on silica gel using *n*-hexane/ethyl acetate (6:1) as eluent to afford 154 mg of **8** (98% yield) as a colorless oil. $[\alpha]_D^{25}$ +7.0 (*c* 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.42 (s, 9H), 1.53–1.63 (m, 5H), 1.88 (dd, J_1=6.8 Hz, J_2=1.5 Hz, 3H), 2.71–2.75 (m, 3H), 3.95–3.99 (m, 1H), 4.66 (m, 1H), 6.12 (dd, J_1=15.8 Hz, J_2=1.5 Hz, 1H), 6.87 (dq, J_1=15.8 Hz, J_2=6.9 Hz, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 18.3 (CH_3), 18.8 (CH_2), 25.2 (CH_2), 28.0 (CH_2), 28.3 ($3CH_3$), 39.2 (CH_2), 40.5 (CH_2), 47.8 (CH), 79.5 (C), 131.9 (CH), 143.2 (CH), 154.7 (C), 198.5 (C). HRMS (EI$^+$) calcd for $C_{15}H_{25}NO_3$ [M$^+$] 267.1834, found 267.1832.

4.5. Synthesis of (4*R*,9a*R*)-hexahydro-4-methyl-1*H*-quinolizin-2(6*H*)-one [(+)-myrtine, 1]

A solution of TFA (0.6 mL) in dichloromethane (4 mL) was added at 0 °C to a solution of **8** (68 mg, 0.25 mmol) in dichloromethane (2 mL). After 1 h, TLC showed total consumption of the starting material and the crude reaction mixture was concentrated to dryness. The residue was dissolved in methanol (4 mL) and K_2CO_3 (105 mg, 0.76 mmol) was added at 0 °C. The reaction mixture was stirred for 1 h and then concentrated to dryness. A saturated aqueous NH_4Cl solution was added, the quenched reaction mixture was extracted with dichloromethane (3×5 mL) and the combined organic layers were dried over anhydrous Na_2SO_4. Solvents were removed under reduced pressure and the crude was purified by flash chromatography on silica gel (*n*-hexane/ethyl acetate/E_3N, 2:1:0.1) to afford 37 mg (87% yield) of (+)-myrtine (**1**) as a light yellow oil. $[\alpha]_D^{25}$ +10.1 (*c* 1.5, $CHCl_3$) [lit.[8] $[\alpha]_D^{25}$ +10.2 (*c* 1.8, $CHCl_3$)]. The spectroscopic data are in agreement with those previously reported in literature.[8] ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.96 (d, *J*=6.8 Hz, 3H), 1.18–1.37 (m, 2H), 1.67–1.72 (m, 5H), 2.21–2.26 (m, 2H), 2.47 (dt, J_1=11.5 Hz, J_2=2.8 Hz, 1H), 2.60–2.69 (m, 1H), 2.75–2.87 (m, 2H), 3.41–3.36 (m, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 11.0 (CH_3), 23.4 (CH_2), 25.8 (CH_2), 34.2 (CH_2), 48.0 (CH_2), 48.7 (CH_2), 51.4 (CH_2), 53.4 (CH), 57.1 (CH), 209.7 (C). HRMS (EI$^+$) calcd for $C_{10}H_{17}NO$ [M$^+$] 167.1310, found 167.1314.

4.6. Synthesis of (*R*)-*tert*-butyl 2-[(methoxycarbonyl)methyl] piperidine-1-carboxylate (9)

To a solution of aldehyde **5** (234 mg, 1.03 mmol) in a mixture of methanol (1 mL), acetonitrile (1 mL), and water (1 mL), KH_2PO_4 (387 mg, 2.84 mmol), $NaClO_2$ (1.95 mL, 2.15 mmol), and H_2O_2 30% sol (0.23 mL, 2.05 mmol) were added at 0 °C. The reaction was allowed to reach room temperature and stirred for 2 h. Then, 1 M HCl solution was added until pH 3 and a saturated solution of Na_2SO_3 was added (2 mL). The quenched reaction mixture was extracted with dichloromethane (3×10 mL) and the combined organic layers were dried over anhydrous Na_2SO_4. Solvents were removed under reduced pressure and the crude mixture was dissolved in toluene (5 mL) and methanol (15 mL). Then, a solution of trimethylsilyldiazomethane (2 M in diethyl ether, 1.1 mL, 2.06 mmol) was added dropwise at 0 °C and the reaction was allowed to reach room temperature and stirred for 3 h. Acetic acid (0.5 mL) was added to the reaction mixture and then it was concentrated to dryness. The crude mixture was diluted with diethyl ether (15 mL) and H_2O (15 mL), extracted with diethyl ether (3×15 mL) and the combined organic layers were dried over anhydrous Na_2SO_4. Solvents were removed under reduced pressure and the crude mixture was purified by flash chromatography on silica gel using *n*-hexane/ethyl acetate (5:1) as eluent to afford 165 mg (62% yield) of a colorless oil. $[\alpha]_D^{25}$ +8.6 (*c* 2.0, $CHCl_3$) [lit.[23] $[\alpha]_D^{25}$ +8.1 (*c* 2.0, $CHCl_3$)]. The spectroscopic data are in agreement with those previously reported in literature.[23] ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.37–1.63 (m, 6H), 1.44 (s, 9H), 2.53 (dd, J_1=14.2 Hz, J_2=7.8 Hz, 1H), 2.62 (dd, J_1=14.2 Hz, J_2=7.3 Hz, 1H), 2.74–2.82 (m, 1H), 3.65 (s, 3H), 3.96–4.00 (m, 1H), 4.68–4.69 (m, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 18.9 (CH_2), 25.3 (CH_2), 28.3 (CH_2), 28.4 ($3CH_3$), 35.1 (CH_2), 39.1 (CH_2), 47.9 (CH), 51.7 (CH_3), 79.5 (C), 154.7 (C), 171.9 (C). HRMS (EI$^+$) calcd for $C_{13}H_{24}NO_4$ [M+H$^+$] 258.1704, found 258.1700.

4.7. Synthesis of (*R*)-*tert*-butyl 2-[(*R*)-1-(methoxycarbonyl) but-3-enyl]piperidine-1-carboxylate (10)

A solution of **5** (122 mg, 0.47 mmol) in diethyl ether (2 mL) was cooled to −100 °C and then it was treated with lithium diisopropyl amide (LDA) (0.57 mL, 1 M solution in diethyl ether) and the mixture was stirred for 1 h. Then, a solution of allyl iodide (0.05 mL, 0.5 mmol) in diethyl ether (2 mL) was added and the resulting reaction mixture was stirred for 1 h and warmed until 0 °C. A saturated aqueous NH_4Cl solution was added and the quenched reaction mixture was extracted with diethyl ether (3×25 mL). The combined organic layers were dried over anhydrous Na_2SO_4. Solvents were removed under reduced pressure and the crude mixture was purified by flash chromatography on silica gel (*n*-hexane/ethyl acetate, 8:1) to afford 132 mg (94% yield) of **10** as a colorless oil. $[\alpha]_D^{25}$ +8.2 (*c* 3.0, $CHCl_3$) [lit.[13f] $[\alpha]_D$ −7.5 (*c* 2.84, $CHCl_3$)]. The spectroscopic data are in agreement with those previously reported in literature.[13f] ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.35–1.76 (m, 6H), 1.42 (s, 9H), 2.20–2.39 (m, 2H), 2.86–3.03 (m, 2H), 3.60 (s, 3H), 3.96–3.99 (m, 1H), 4.37–4.40 (br d, *J*=9.6 Hz, 1H), 4.99–5.09 (m, 2H), 5.67–5.80 (m, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 18.9 (CH_2), 25.2 (CH_2), 25.8 (CH_2), 28.3 ($2CH_3$), 28.4 (CH_3), 33.9 (CH_2), 39.4 (CH_2), 45.2 (CH), 51.4 (CH_3), 52.6 (CH), 79.4 (C), 116.9 (CH_2), 134.9 (CH), 154.3 (C), 173.6 (C). HRMS (EI$^+$) calcd for $C_{16}H_{28}NO_4$ [M+H$^+$] 298.2020, found 298.2013.

4.8. Synthesis of (*R*)-*tert*-butyl 2-[(*R*)-1-(methoxycarbonyl)-4-hydroxybutyl]piperidine-1-carboxylate (11)

To a solution of ester **10** (89 mg, 0.3 mmol) in hexane (2 mL) borane-methyl sulphide complex (9.41 μl, 0.1 mmol) was added dropwise at 0 °C. After 30 min, the cooling bath was removed and stirring was continued for 3 h. Ethanol (0.6 mL), aqueous sodium hydroxide (1% solution; 0.5 mL), and hydrogen peroxide (30% solution; 0.06 mL) were then added to the reaction mixture. The resulting solution was heated under reflux for 1 h, then cooled, diluted with water (5 mL), and extracted with diethyl ether (4×15 mL). The combined extracts were washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered through a pad of Celite® and the filtrate was evaporated to afford the hydroxy ester **11** (86 mg, 91% yield) as a colorless oil. $[\alpha]_D^{25}$ +4.0 (*c* 2.0, $CHCl_3$) [lit.[13f] $[\alpha]_D^{25}$ −4.7 (*c* 2.34, $CHCl_3$)]. The spectroscopic data are in agreement with those previously reported in literature.[13f] ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.39 (s, 9H), 1.42–1.53 (m, 10H), 1.96 (br s, 1H), 2.88–2.95 (m, 2H), 3.59 (m, 5H), 3.92 (br s, 1H), 4.32–4.36 (br d, *J*=9.8 Hz, 1H).

4.9. Synthesis of (1*R*,9a*R*)-methyl octahydro-1*H*-quinolizine-1-carboxylate (12)

Methanesulfonyl chloride (23 μl, 0.30 mmol) was added dropwise to an ice-cold, stirred solution of hydroxy ester **11** (86 mg, 0.27 mmol), and triethylamine (42 μl, 0.30 mmol) in dichloromethane (2 mL). After 2 h, the mixture was diluted with dichloromethane (10 mL), washed with water (2×5 mL), dried over anhydrous Na_2SO_4, and filtered. The filtrate was concentrated to 2 mL and trifluoroacetic acid (0.4 mL) was added. The resulting solution was stirred at room temperature for 1.5 h and then evaporated and the residue finally dried under high vacuum. The dry residue was then treated with ice-cold, aqueous sodium hydroxide (0.78 mL) in dichloromethane (2 mL). After mixing, the layers were separated and the aqueous layer was extracted with dichloromethane (4×5 mL). Solvents were removed under reduced pressure and the crude mixture was purified by flash chromatography on silica gel (dichloromethane/methanol/triethylamine, 20:1:0.1) to afford 35 mg (65% yield) of **12** as a colorless oil. $[\alpha]_{25}^{D}$ −18.4 (*c* 0.5, $CHCl_3$) [lit.[24] $[\alpha]_D^{20}$ −18.0 (*c* 0.42, $CHCl_3$)]. The spectroscopic data are in agreement with those previously reported in the literature.[23] ^{1}H NMR (300 MHz, CDCl3) δ 1.23–1.76 (m, 9H), 1.88–2.13 (m, 4H), 2.52–2.56 (m, 1H), 2.84–2.92 (m, 2H), 3.65 (s, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 22.0 (CH_2), 24.3 (CH_2), 24.8 (CH_2), 26.9 (CH_2), 28.9 (CH_2), 44.4 (CH), 51.1 (CH), 54.9 (CH_2), 57.0 (CH_2), 62.6 (CH_3), 173.8 (C). HRMS (EI^+) calcd for $C_{11}H_{19}NO_2$ [M+H$^+$] 198.1494, found 197.1490.

4.10. Synthesis of (1*S*,9a*R*)-octahydro-1*H*-quinolizine-1-carboxylic acid (13)

LiOH·H_2O (41 mg, 1.0 mmol) was added to a solution of ester **12** (96 mg, 0.33 mmol) in a mixture of THF/H_2O (4:1, 3 mL) at 0 °C. The reaction was allowed to reach room temperature and stirred for 4 h. Then, solvents were removed and the crude was dissolved in methanol and filtered through a short pad of Celite® washing with small portions of methanol. Solvents were again removed under reduced pressure and the crude mixture purified by flash chromatography (CH_2Cl_2/MeOH, 90:10 to 50:50) to give **13** as a white solid (45 mg, 74% yield). Mp 250–252 °C $[\alpha]_D^{25}$ +55.2 (*c* 1.0, EtOH). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.24–1.32 (m, 1H), 1.69–1.81 (m, 7H), 2.02–2.15 (m, 2H), 2.26–2.39 (m, 3H), 2.61 (s, 1H), 3.12–3.24 (m, 2H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 21.1 (CH_2), 23.1 (CH_2), 24.3 (CH_2), 27.3 (CH_2), 29.5 (CH_2), 46.2 (CH), 54.8 (CH_2), 56.0 (CH), 63.7 (CH_2), 173.7 (C). HRMS (EI^+) calcd for $C_{10}H_{17}NO_2$ [M$^+$+H] 184.1338, found 184.1341.

4.11. Synthesis of [(9*R*,9a*R*)-octahydro-1*H*-quinolizin-9-yl] methanol [(−)-lupinine, 2]

A solution of quinolizidine ester **12** (78 mg, 0.396 mmol) in THF (1 mL) was added dropwise to a suspension of lithium aluminum hydride (21 mg, 0.60 mmol) in Et_2O (7 mL). The resulting mixture was refluxed for 3 h, then cooled and $Na_2SO_4 \cdot 10H_2O$ was added under vigorous stirring until aluminum salts turned white. The suspension was filtered through a short pad of Celite® washing with small portions of diethyl ether. The filtrate was concentrated under vacuum and the residue was purified by flash chromatography (CH_2Cl_2/MeOH/NH_4OH, 97:3:0.1 to 95:5:0.1) to give (−)-lupinine **2** as a white solid (60 mg, 90% yield). Mp 66–68 °C [lit.[14] mp 70–71 °C]. $[\alpha]_D^{25}$ −20.1 (*c* 1.0, EtOH) [lit.[14] $[\alpha]_D^{20}$ −21.0 (*c* 0.25, EtOH)]. The spectroscopic data are in agreement with those previously reported in the literature.[14] ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.15–1.30 (m, 1H), 1.52–1.58 (m, 6H), 1.74–1.80 (m, 4H), 1.99–2.14 (m, 3H), 2.77–2.81 (m, 2H), 3.67 (d, *J*=10.8 Hz, 1H), 4.09–4.14 (m, 1H), 4.75 (br s, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 22.8 (CH_2), 24.5 (CH_2), 25.5 (CH_2), 29.5 (CH_2), 31.2 (CH_2), 38.1 (CH), 57.0 ($2CH_2$), 65.0 (CH), 65.7 (CH_2). HRMS (EI^+) calcd for $C_{10}H_{20}NO$ [M$^+$+H] 170.1545, found 170.1542.

4.12. Synthesis of *N*-[(9*S*,9a*R*)-octahydro-1*H*-quinolizin-9-yl] acetamide [(+)-*epi*epiquinamide, 3]

To a solution of acid **13** (45 mg, 0.25 mmol) in toluene (8 mL) diphenylphosphoryl azide (0.15 mL, 0.70 mmol), and Et_3N (0.11 mL, 0.8 mmol) were successively added. The reaction was heated under reflux and stirred overnight. The solvent was removed in vacuo and 1 N HCl (0.5 mL) was added. The resulting suspension stirred 30 min. The solvent was again removed in vacuo and the residue washed with EtOAc (2×2 mL). The residue was dissolved in pyridine (1.5 mL) and acetic anhydride (1.5 mL) and the mixture stirred overnight. After evaporation of solvents, the residue was twice flash chromatographed on silica gel on a gradient of CH_2Cl_2/MeOH (19:1 to 1:1) to afford **3** as an off-white solid (24 mg, 48% for two steps). Mp 169–171 °C [lit.[21] mp 170–171 °C]. $[\alpha]_D^{25}$ +2.7 (*c* 0.5, $CHCl_3$) [lit.[17] $[\alpha]_D^{25}$ −2.9 (*c* 0.5, CH_2Cl_2)]. The spectroscopic data are in agreement with those previously reported in the literature.[21] ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.20–2.05 (m, 13H), 1.97 (s, 3H), 2.74–2.83 (m, 2H), 3.89 (dd, J_1=10.0 Hz, J_2=4.1 Hz, 1H), 5.31 (br s, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 23.5 (CH_3), 24.0 (CH_2), 24.4 (CH_2), 25.6 (CH_2), 29.0 (CH_2), 32.2 (CH_2), 51.1 (CH_2), 55.8 (CH), 56.5 (CH_2), 67.5 (CH), 169.3 (C). HRMS (EI^+) calcd for $C_{11}H_{21}N_2O$ [M$^+$+H] 197.1648, found 197.1655.

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References and notes

1. (a) Michael, J. P. *Nat. Prod. Rep.* **2008**, *25*, 139; (b) Michael, J. P. *Nat. Prod. Rep.* **2007**, *24*, 191; (c) Michael, J. P. *Nat. Prod. Rep.* **2005**, *22*, 603; (d) Lourenco, A. M.; Maximo, P.; Ferreira, L. M.; Pereira, M. M. A. *Stud. Nat. Prod. Chem.* **2002**, *27*, 233.
2. For recent reviews on organocatalysis, see: (a) Bertelsen, S.; Jørgensen, K. A. *Chem. Soc. Rev.* **2009**, *38*, 2178; (b) Mielgo, A.; Palomo, C. *Chem. Asian J.* **2008**, *3*, 922; (c) MacMillan, D. W. C. *Nature* **2008**, *455*, 304; (d) Dondoni, A.; Massi, A. *Angew. Chem., Int. Ed.* **2008**, *47*, 4638.
3. For recent reviews on asymmetric enantioselective aza-Michael reactions, see: (a) Enders, D.; Wang, C.; Liebich, J. X. *Chem. Eur. J.* **2009**, *15*, 11058; (b) Krishna, P. R.; Sreesailam, A.; Srinivas, R. *Tetrahedron* **2009**, *65*, 9657; (c) Vicario, J. L.;

Badía, D.; Carrillo, L. *Synthesis* **2007**, 2065; (d) Xu, L.-W.; Xia, C.-G. *Eur. J. Org. Chem.* **2005**, 633; (e) Vicario, J. L.; Badía, D.; Carrillo, L.; Etxebarría, J.; Reyes, E.; Ruiz, N. *Org. Prep. Proced. Int.* **2005**, *37*, 513.
4. (a) Cai, Q.; Zheng, C.; You, S.-L. *Angew. Chem., Int. Ed.* **2010**, *49*, 8666; (b) Bandini, M.; Eichholzer, A.; Tragni, M.; Umani-Ronchi, A. *Angew. Chem., Int. Ed.* **2008**, *47*, 3238; (c) Fustero, S.; Moscardó, J.; Jiménez, D.; Pérez-Carrión, M. D.; Sánchez-Roselló, M.; del Pozo, C. *Chem. Eur. J.* **2008**, *14*, 9868; (d) Carlson, E. C.; Rathbone, L. K.; Yang, H.; Collet, H. D.; Carter, R. G. *J. Org. Chem.* **2008**, *73*, 5155; (e) Fustero, S.; Jiménez, D.; Moscardó, J.; Catalán, S.; del Pozo, C. *Org. Lett.* **2007**, *9*, 5283; (f) Takasu, K.; Maiti, S.; Ihara, M. *Heterocycles* **2003**, *59*, 51.
5. Slosse, P.; Hootele, C. *Tetrahedron Lett.* **1978**, *4*, 397.
6. (a) Remuson, R. *Beilstein J. Org. Chem.* **2007**, *3*, 32; (b) Gardette, D.; Gelas-Mialhe, J.-C.; Gramain, B.; Perrin, B.; Remuson, R. *Tetrahedron: Asymmetry* **1998**, *9*, 1823.
7. (a) Davis, F. A.; Xu, H.; Zhang, J. *J. Org. Chem.* **2007**, *72*, 2046; (b) Comins, D. L.; LaMunyon, D. H. *J. Org. Chem.* **1992**, *57*, 5807.
8. Pizzuti, M. G.; Minnaard, A. J.; Feringa, B. L. *Org. Biomol. Chem.* **2008**, *8*, 3464.
9. Ying, Y.; Kim, H.; Hong, J. *Org. Lett.* **2011**, *13*, 796.
10. A different way to access compound **8** involved the addition of (*E*)–CH_3–CH=CH–MgBr to aldehyde **5** and subsequent oxidation. However, following this sequence, conjugated ketone **8** was obtained in lower yield (when compared to the three step procedure showed in Scheme 3) and as a 2:1 mixture of cis and trans diastereoisomers.
11. The IMAMR also proceeded with high levels of diastereoselection with other bases, such as C_sCO_3, TBAF or *t*-BuOK, although with some erosion of the final yield.
12. (a) Baumert, G. *Chem. Ber.* **1882**, *14*, 634; (b) Baumert, G. *Chem. Ber.* **1881**, *14*, 1321.
13. (a) Santos, L. S.; Mirabal-Gallardo, Y.; Shankaraiah, M.; Simirgiotis, M. J. *Synthesis* **2011**, 51; (b) Airiau, E.; Spangenberg, E.; Girad, N.; Breit, B.; Mann, A. *Org. Lett.* **2010**, *12*, 528; (c) Nöel, R.; Fargeau-Bellassoued, M.-C.; Vanucci-Bacqué, C.; Lhommet, G. *Synthesis* **2008**, 1948; (d) Meng-Yang, C.; Huo-Mu, T.; Ching-An, H.; Nein-Cheng, C. *Heterocycles* **2005**, *65*, 395; (e) Ledoux, S.; Marchalant, E.; Célérier, J.-P.; Lhommet, G. *Tetrahedron Lett.* **2001**, *42*, 5397; (f) Morley, C.; Knight, D. W.; Share, A. C. *J. Chem. Soc., Perkin Trans. 1* **1994**, 2903; (g) Hua, D. H.; Miao, S. W.; Bravo, A. A.; Takemoto, D. J. *Synthesis* **1991**, 970.
14. Ma, S.; Ni, B. *Chem. Eur. J.* **2004**, *10*, 3286.
15. Fitch, R. W.; Garrafo, H. M.; Spande, T. F.; Yeh, H. J. C.; Daly, J. W. *J. Nat. Prod.* **2003**, *66*, 1345.
16. (a) Ref. 12a,b. (b) Srivastava, A. K.; Das, S. K.; Panda, G. *Tetrahedron* **2009**, *65*, 5322; (c) Gosh, S.; Shashidhar, J. *Tetrahedron Lett.* **2009**, *50*, 1177; (d) Voituriez, A.; Ferreira, F.; Pérez-Luna, A.; Chemla, F. *Org. Lett.* **2007**, *9*, 4705; (e) Suyama, T. L.; Gerwick, W. H. *Org. Lett.* **2006**, *8*, 4541; (f) Huang, P.-Q.; Guo, Z.-Q.; Ruan, Y.-P. *Org. Lett.* **2006**, *8*, 1435; (g) Tong, S. T. A.; Barker, D. *Tetrahedron Lett.* **2006**, *47*, 5017; (h) Wijdeven, M. A.; Botman, P. N. M.; Wijtmans, R.; Schoemaker, H. E.; Rutjes, F. P. J. T.; Blaauw, R. H. *Org. Lett.* **2005**, *7*, 4005.
17. Wijdeven, M. A.; Wijtmans, R.; van den Berg, R. J. F.; Noorduim, W.; Schoemaker, H. E.; Sonke, T.; van Delft, F. L.; Blaauw, R. H.; Fitch, R. W.; Spande, T. F.; Daly, J. W.; Rutjes, F. P. J. T. *Org. Lett.* **2008**, *10*, 4001.
18. (a) Tuan, L. A.; Pyeon, H.; Kim, G. *Tetrahedron Lett.* **2010**, *51*, 157; (b) Chandrasekhar, S.; Parida, B. B.; Rambabu, C. *Tetrahedron Lett.* **2009**, *50*, 3294.
19. The diastereoselectivity of the allylation reaction was determined by GC–MS. Compound **10** was previously described by using a different allylation methodology (see Ref. 13f) although with poor selectivity.
20. An analogous epimerization was previously observed: Kanakubo, A.; Gray, D.; Innocent, N.; Wonnacott, S.; Gallagher, T. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 4648.
21. Fitch, R. W.; Sturgeon, G. D.; Patel, S. R.; Spande, T. F.; Garraffo, H. M.; Daly, J. W.; Blaauw, R. H. *J. Nat. Prod.* **2009**, *72*, 243.
22. Angoli, M.; Barilli, A.; Lesma, L.; Passarella, D.; Riva, S.; Silvani, A.; Danielli, B. *J. Org. Chem.* **2003**, *68*, 9525.
23. Davies, S. G.; Fletcher, A. M.; Roberts, P. M.; Smith, A. D. *Tetrahedron* **2009**, *65*, 10192.
24. Agami, C.; Dechoux, L.; Hebbe, S.; Menard, C. *Tetrahedron* **2004**, *60*, 5433.