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Novel stereocontrolled syntheses of tashiromine and epitashiromine

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Full Research Paper

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Abstract

A novel stereocontrolled approach has been developed for the syntheses of tashiromine and epitashiromine alkaloids from cyclooctene β-amino acids. The synthetic concept is based on the azetidinone opening of a bicyclic β-lactam, followed by oxidative ring opening through ring C–C double bond and reductive ring-closure reactions of the *cis*- or *trans*-cyclooctene β-amino acids.

Introduction

Indolizidine alkaloids are an important class of naturally occurring compounds which have received considerable attention as a result of their valuable physiological properties. A number of representatives of this class exhibit glycosidase inhibitory activity or antimetastatic, anticancer, antitumour or anti-HIV properties [1-3]. A large number of natural products contain an indolizidine framework, among them (−)-δ-coniceine, (−)-swainsonine, indolizidine 167B [4-10], (+)-lentiginosine [11-15], (+)-slaframine [16], (−)-elaeokanine C [17], (+)-cyclizidine [18], lepadiformine [19], the highly oxygenated (+)-castanospermine [20,21], or pumiliotoxin [22]. Figure 1 illustrates the structures of several such compounds.

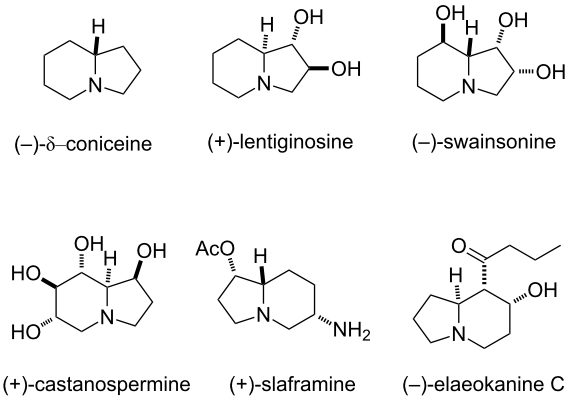


Figure 1: Some indolizidine alkaloids.

Tashiromine is a natural indolizidine alkaloid isolated from *Maackia tashiroi* (1990). Strategies for the synthesis of

indolizidine derivatives have received considerable interest from synthetic and medicinal chemists (Figure 2). A number of synthetic approaches have been described earlier for construction of the indolizidine framework; access to tashiromine in racemic form can be achieved through the alkylation of succinimide, followed by ring closure via acyliminium intermediates [23,24], the reduction of cyclized pyridinium salts [25], iminium cascade cyclization [26], alkyne-mediated hydroformylation–cyclization [27], or electrophilic pyrolidinone alkylation followed by ring closure [28,29]. Pyrrolidine alkylation and nucleophilic ring closure followed by C–C double bond hydroboration [30] leads to racemic epitashiromine, as does the *N*-alkylated succinimide transformation through the corresponding indolizidinone [31].

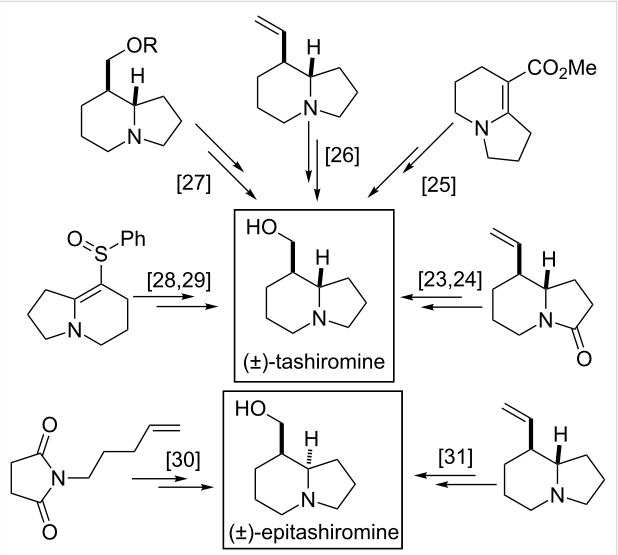


Figure 2: Approaches to racemic tashiromine and epitashiromine.

Several synthetic procedures have also been developed for the preparation of tashiromine or epitashiromine enantiomers.

(+)-Tashiromine has been synthetized from a pyrrolidinone derivative through chiral Lewis acid-catalysed cyclization to substituted pyrrolidinones [17], by the intramolecular cyclization of a chiral alkenylated pyrrolidinone, followed by hydroxylation [32], or by the intramolecular ring closure of chiral pyrrolidine diesters followed by ester and oxo group reduction [33], while the syntheses of (+)-epitashiromine starts from a chiral morpholine derivative, with nitrone 1,3-dipolar cycloaddition and reduction [34] (Figure 3).

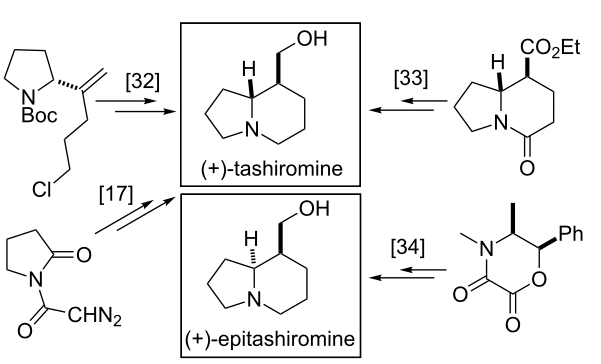


Figure 3: Synthetic routes to (+)-tashiromine and (+)-epitashiromine.

(−)-Tashiromine has been accessed through the ring closure of difunctionalized acyclic chiral sulfonamide-based β-amino acids [35], the cyclization of pyrrole derivatives with a chiral side-chain [36], or the enantioselective arylation of pyrrole, followed by saturation [37]. The transformation of chiral functionalized pyrrole or pyrrolidine derivatives has served as the basis of the construction of (−)-epitashiromine [38,39] (Figure 4).

The oxidative functionalization of cyclic β-amino acid derivatives has been reported to be a convenient route for the preparation of *N*-heterocyclic β-amino acid derivatives [40,41] or for the stereocontrolled synthesis of functionalized cispentacins

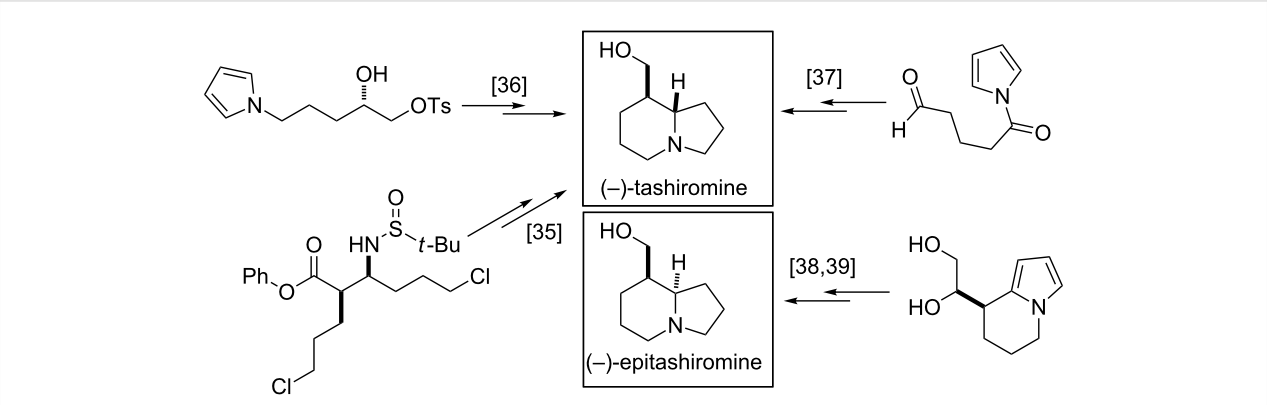


Figure 4: Synthetic routes to (−)-tashiromine and (−)-epitashiromine.

[42] and their acyclic counterparts [43,44] (Figure 5). The oxidative ring cleavage of various vicinal diols and the transformation of the resulting dialdehyde intermediates has been efficiently applied in recent years for the synthesis of a series of valuable organic molecules [45-52]. In particular, Davies and co-workers have utilized the oxidative ring opening of cyclic vicinal diols followed by ring closure for access to pyrrolizidine alkaloids [45].

Results and Discussion

We describe here a novel access route for the synthesis of tashiromine and epitashiromine by starting from an unsaturated bicyclic β-lactam. The retrosynthetic concept of the synthesis is represented on Scheme 1 and was based on the lactam ring opening, in continuation followed by oxidative ring opening of the formed β-amino esters and by reductive ring closure as key steps.

Bicyclic β-lactam (±)-**1** [53,54] was first transformed by azetidinone opening to the corresponding amino ester hydrochloride (±)-**2** [53,54], *N*-protection of which with benzyl chloroformate (Z-Cl) afforded protected amino ester (±)-**3** in 78% yield. In agreement with our earlier observations [40-42] C–C double bond functionalization of the cyclooctene β-amino ester via dihydroxylation with *N*-methyl morpholine *N*-oxide (NMO) in the presence of OsO_4 afforded the corresponding *all-cis* dihydroxylated ethyl β-aminocyclooctanecarboxylate (±)-**4** in 90% yield (for dihydroxylation, see also reference [54]) (Scheme 2). Amino ester (±)-**4** was next subjected through its vicinal diol moiety to oxidative ring opening with $NaIO_4$ in

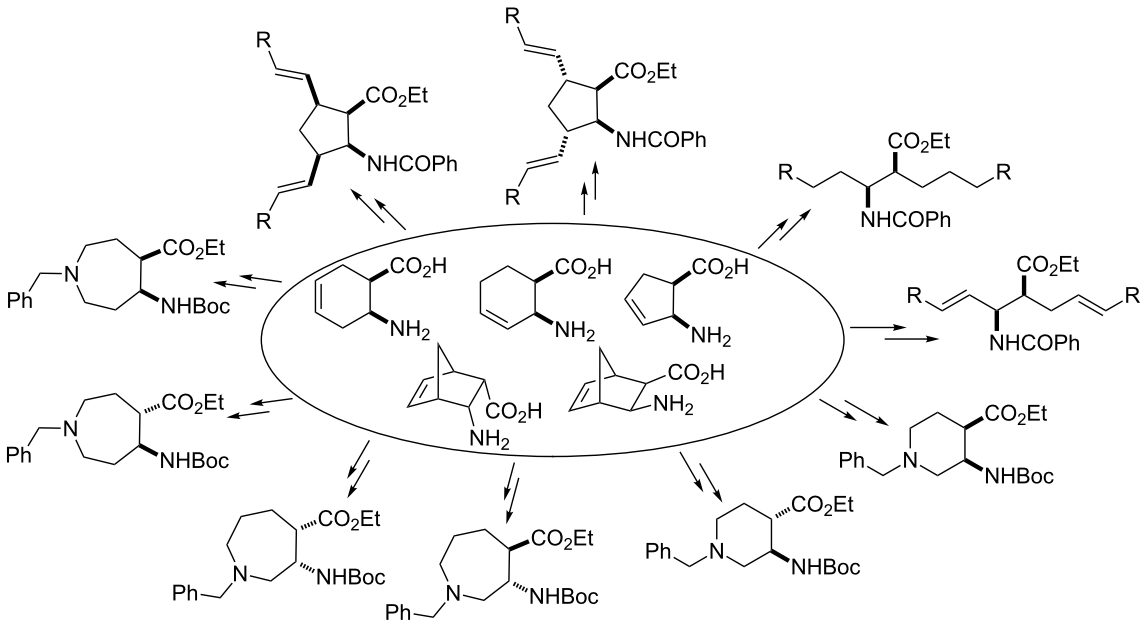
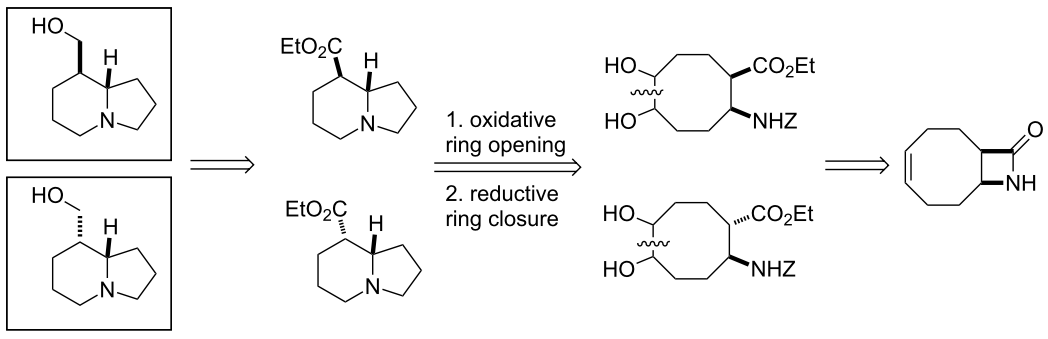
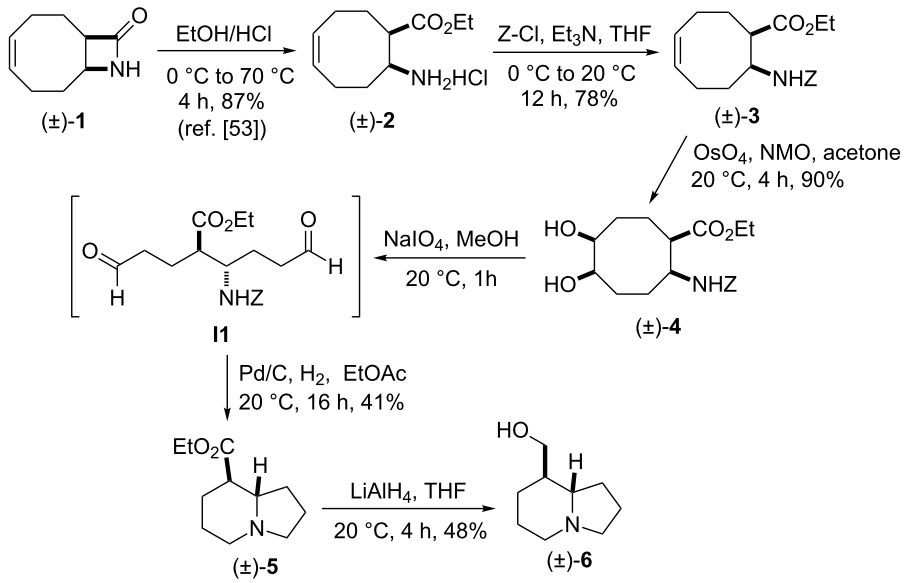


Figure 5: Oxidative functionalizations of cyclic β-amino acids.



Scheme 1: Retrosynthesis of tashiromine and epitashiromine.



Scheme 2: Synthesis of (±)-tashiromine ((±)-**6**).

MeOH at 20 °C, which resulted (monitored by TLC) in the corresponding ring-opened unstable diformyl intermediate (**I1**), which after work-up was immediately used without further purification (for several similar types of acyclic diformyl intermediates, see references [40,41,43,44]). Thus, the crude material was submitted to catalytic hydrogenolysis and after *N*-deprotection underwent double cyclization–reduction to furnish indolizidine ester (±)-**5** in 41% yield after purification by chromatography.

Reduction of the ester group of (±)-**5** with an excess of $LiAlH_4$ in THF at 20 °C gave the corresponding tashiromine (±)-**6** [35-37], which was isolated in 48% yield after purification by column chromatography (Scheme 2). The stereochemistry of (±)-**6** was unequivocally assigned by NMR data, which were consistent with those reported [35-37].

A similar strategy was applied for the synthesis of epitashiromine. On reaction with NaOEt in EtOH at 20 °C, ethyl *cis*-β-aminocyclooctenecarboxylate (±)-**3** underwent epimerization at C-1, leading after 18 h to an equilibrium mixture of *cis* and *trans* amino esters (1:1 ratio determined by ^{1}H NMR on the crude mixture), the required *trans* isomer (±)-**7** being separated from the *cis* counterpart and isolated in a yield of 48% by means of column chromatography. Dihydroxylation of (±)-**7** with NMO/OsO_4 next afforded an oily mixture of *cis* and *trans* dihydroxylated cyclooctane β-amino esters (diastereomeric mixture of (±)-**8**) in 77% overall yield after column chromatography. Our attempts to separate this nearly 1:1 mixture of the two dihydroxylated stereoisomers (determined on the basis of ^{1}H NMR data) failed, but the mixture could be applied in the next ring-opening oxidation step, since it gave only one open-chain diformyl intermediate **I2**.

Similarly to the *cis* isomer, this unstable dialdehyde intermediate was subjected without isolation to catalytic hydrogenolysis, followed by reductive cyclization, to give the corresponding indolizidine ester (±)-**9** in 40% yield. Finally, ester reduction with $LiAlH_4$ in THF resulted in epitashiromine (±)-**10** [32,34,39] in 53% yield after isolation by chromatography (Scheme 3). The stereochemistry of (±)-epitashiromine was assigned by NMR data, which were in agreement with those reported [32,34,39].

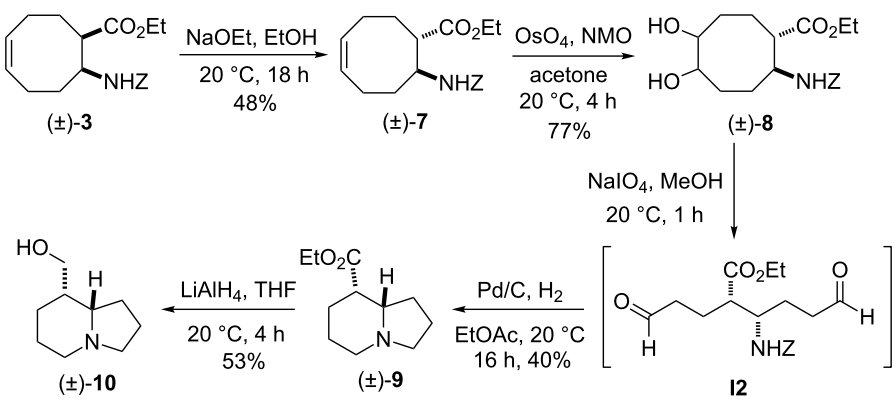
Conclusion

In summary, a novel stereocontrolled efficient method has been presented for the synthesis of tashiromine and epitashiromine alkaloids in six or seven steps, based on the preparation of *cis* or *trans* cyclooctene β-amino esters, followed by their oxidative ring cleavage and double reductive ring-closure reactions.

Experimental

General procedure for the Z-protection of amino esters

To a solution of amino ester hydrochloride ((±)-**2** or (−)-**2**) [29] (17.8 mmol) in THF (40 mL), Et_3N (9 mL) was added at 0 °C, followed by 7.8 mL (1 equivalent) of Z-Cl (a 50% solution in toluene). The mixture was stirred for 14 h at 20 °C, and then was diluted with EtOAc (120 mL). The organic layer was washed with H_2O (3 × 60 mL), dried (Na_2SO_4), and concen-



Scheme 3: Synthesis of (±)-epitashiromine ((±)-**10**).

trated under reduced pressure. The crude material was purified by column chromatography on silica gel (*n*-hexane/EtOAc 4:1), affording the amino ester.

General procedure for the dihydroxylation of amino esters

To a solution of *cis* or *trans* Z-protected amino ester ((±)-**3**, (−)-**3** or (±)-**7**) (2.9 mmol) in acetone (30 mL) and H_2O (1 mL), NMO (1.5 equivalents) and 2% OsO_4 in *t*-BuOH (0.7 mL) were added and the mixture was stirred at 20 °C for 4 h. A saturated aqueous solution of Na_2SO_3 (40 mL) was then added, the mixture was extracted with CH_2Cl_2 (3 × 30 mL), and the organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (*n*-hexane/EtOAc 1:4) to give the dihydroxylated amino ester.

General procedure for epimerization of the *cis*-amino ester

To a solution of *cis N*-protected amino ester ((±)-**3** or (−)-**3**) (3.3 mmol) in EtOH (30 mL), EtONa (1.5 equivalents) was added at 0 °C and the mixture was stirred at 20 °C for 18 h. H_2O (70 mL) was then added, the mixture was extracted with CH_2Cl_2 (3 × 30 mL), and the organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The crude material was purified by column chromatography on silica gel (*n*-hexane/EtOAc 9:1) to give the *trans* isomer as a colourless oil.

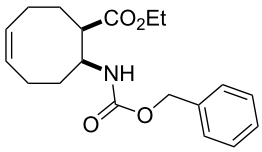
General procedure for the oxidative ring opening/reductive ring closure of dihydroxylated amino esters

To a solution of dihydroxylated amino ester ((±)-**4**, (±)-**8** or (−)-**8**) (2.46 mmol) in MeOH (25 mL), $NaIO_4$ (2 equivalents) was added and the mixture was stirred at 20 °C for 45 min. It was then diluted with H_2O (50 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. The crude mixture was dissolved in EtOAc (30 mL), Pd/C (150 mg) was added and the mixture was stirred at 20 °C for 16 h. The catalyst was next filtered off through Celite. The crude mixture was then purified by column chromatography on silica gel (CH_2Cl_2/MeOH 95:5 or CH_2Cl_2/MeOH 9:1) to give the indolizidine derivative.

General procedure for reduction of the ester

To a solution of indolizidine carboxylate ((±)-**5**, (±)-**9** or (−)-**9**) (1 mmol) in dry THF (15 mL), $LiAlH_4$ (5 equivalents) was added at 0 °C and the mixture was stirred at 20 °C for 4 h. It was then cooled to 0 °C, H_2O (2 mL) was added dropwise and the solid formed was filtered off through Celite. The filtrate was extracted with CH_2Cl_2 (3 × 15 mL), and the combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. The crude oil was purified by column chromatography on silica gel (CH_2Cl_2/MeOH/NH_4OH 90:8:2 or CH_2Cl_2/MeOH/NH_4OH 90:5:5) to give the alkaloid.

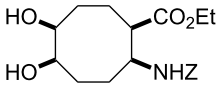
Ethyl (1*R,2*S**)-2-(benzyloxycarbonylamino)cyclooct-5-enecarboxylate ((±)-3)**



A colourless oil (R_f 0.6, *n*-hexane/EtOAc 4:1); yield: 78%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.28 (t, *J* = 7.1 Hz, 3H, CH_3), 1.76–1.87 (m, 2H, CH_2), 1.88–1.97 (m, 1H, CH_2), 1.98–2.07 (m, 1H, CH_2), 2.09–2.18 (m, 2H, CH_2), 2.22–2.31 (m, 1H, CH_2), 2.43–2.52 (m, 1H, CH_2), 2.82–2.89 (m, 1H, H-1), 4.12–4.21 (m, 2H, OCH_2), 4.22–4.30 (m, 1H, H-2), 5.08 (s, 2H, OCH_2), 5.30 (brs, 1H, N-H), 5.60–5.74 (m, 2H, H-5 and H-6), 7.33–7.48 (m, 5H, Ar-H); ^{13}C NMR (100 MHz, DMSO) δ 14.9,

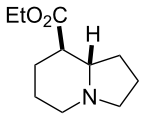
24.4, 25.1, 26.6, 32.3, 46.4, 52.1, 60.6, 66.1, 128.5, 128.6, 129.2, 129.5, 130.7, 138.0, 156.3, 174.5; anal. calcd for $C_{19}H_{25}NO_4$: C, 68.86; H, 7.60; N, 4.23; found: C, 68.59; H, 7.31; N, 3.93.

Ethyl (1*R,2*S**,5*R**,6*S**)-2-(benzyloxycarbonylamino)-5,6-dihydroxycyclooctanecarboxylate ((±)-4)**



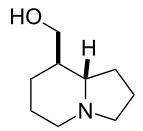
A colourless oil (R_f 0.4, *n*-hexane/EtOAc 1:4); yield: 90%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.26 (t, *J* = 7.15 Hz, 3H, CH_3), 1.62–1.94 (m, 4H, CH_2), 1.97–2.28 (m, 4H, CH_2), 2.77–2.82 (m, 1H, H-1), 3.83–3.89 (m, 2H, H-5 and H-6), 4.02–4.10 (m, 1H, H-2), 4.11–4.19 (m, 2H, OCH_2), 5.09 (m, 2H, OCH_2), 5.49 (brs, 1H, N-H), 7.36–7.48 (m, 5H, Ar-H); ^{13}C NMR (100 MHz, DMSO) δ 14.8, 21.2, 26.9, 28.5, 29.0, 45.4, 51.6, 60.7, 65.9, 72.3, 72.4, 128.4, 128.5, 129.1, 138.1, 156.3, 174.6; anal. calcd for $C_{19}H_{27}NO_6$: C, 62.45; H, 7.45; N, 3.83; found: C, 62.19; H, 7.10; N, 4.13.

Ethyl (8*R,8a*S**)-octahydroindolizine-8-carboxylate ((±)-5)**



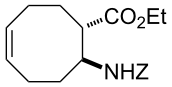
A yellow oil (R_f 0.55, CH_2Cl_2/MeOH 95:5); yield: 41%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.27 (t, *J* = 7.15 Hz, 3H, CH_3), 1.46–1.53 (m, 2H, CH_2), 1.57–1.92 (m, 5H, CH_2), 1.99–2.10 (m, 3H, CH_2), 2.13–2.20 (m, 1H, CH_2), 2.25–2.31 (m, 1H, H-8), 3.03–3.10 (m, 2H, CH_2 and H-8a); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.6, 20.9, 25.1, 29.5, 30.1, 48.4, 52.6, 54.4, 60.6, 65.6, 174.6; MS (ESI) *m*/*z*: 198.5 [M + 1]; anal. calcd for $C_{11}H_{19}NO_2$: C, 66.97; H, 9.71; N, 7.10; found: C, 66.60; H, 10.02; N, 7.39.

((8*R,8a*S**)-Octahydroindolizin-8-yl)methanol; ((±)-tashiromine (±)-6)** [35-37]



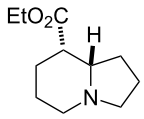
A yellow oil (R_f 0.45, CH_2Cl_2/MeOH/NH_4OH 90:8:2); yield: 48%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.00–1.11 (m, 1H, CH_2), 1.42–1.53 (m, 2H, CH_2), 1.58–1.83 (m, 5H, CH_2), 1.84–1.99 (m, 3H, CH_2), 2.04–2.11 (m, 1H, CH_2), 3.03–3.10 (m, 2H, N-CH), 3.41–3.46 (m, 1H, OCH_2), 3.59–3.64 (m, 1H, OCH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.1, 25.5, 28.0, 29.4, 44.9, 53.1, 54.5, 66.0, 66.9; MS (ESI) *m*/*z*: 156.6 [M + 1]; anal. calcd for $C_9H_{17}NO$: C, 69.63; H, 11.04; N, 9.02; found: C, 69.28; H, 10.70; N, 8.76.

Ethyl (1*S,2*S**)-2-(benzyloxycarbonylamino)cyclooct-5-enecarboxylate ((±)-7)**



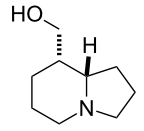
A colourless oil (R_f 0.55, *n*-hexane/EtOAc 4:1); yield: 48%; ^{1}H NMR (400 MHz, DMSO) δ 1.18 (t, *J* = 7.10 Hz, 3H, CH_3), 1.55–1.64 (m, 2H, CH_2), 1.73–1.97 (m, 2H, CH_2), 2.04–2.19 (m, 2H, CH_2), 2.33–2.47 (m, 2H, CH_2), 2.68–2.75 (m, 1H, H-1), 3.88–4.02 (m, 3H, OCH_2 and H-2), 4.96–5.02 (m, 2H, OCH_2), 5.53–5.60 (m, 2H, H-5 and H-6), 7.30–7.44 (m, 5H, Ar-H); ^{13}C NMR (100 MHz, DMSO) δ 14.8, 24.5, 25.1, 29.2, 33.8, 49.2, 52.1, 60.4, 65.9, 128.0, 128.4, 129.0, 129.1, 130.7, 138.2, 156.9, 174.5; anal. calcd for $C_{19}H_{25}NO4$: C, 68.86; H, 7.60; N, 4.23; found: C, 68.57; H, 7.28; N, 3.97.

Ethyl (8*S,8a*S**)-octahydroindolizine-8-carboxylate ((±)-9)**



A yellow oil (R_f 0.45, CH_2Cl_2/MeOH 4:1); yield: 40%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.28 (t, *J* = 7.15 Hz, 3H, CH_3), 1.28–1.33 (m, 1H, CH_2), 1.42–1.55 (m, 2H, CH_2), 1.58–1.64 (m, 1H, CH_2), 1.68–1.86 (m, 3H, CH_2), 2.02–2.18 (m, 3H, CH_2), 2.23–2.27 (m, 1H, CH_2), 2.78–2.81 (m, 1H, H-8), 3.04–3.10 (m, 2H, CH_2 and H-8a), 4.09–4.17 (m, 2H, OCH_2); ^{13}C NMR (100 MHz, DMSO) δ 15.1, 21.2, 22.6, 26.8, 27.3, 42.0, 53.4, 55.0, 60.5, 64.9, 170.4; MS (ESI) *m*/*z*: 198.7 [M + 1]; anal. calcd for $C_{11}H_{19}NO_2$: C, 66.97; H, 9.71; N, 7.10; found: C, 67.28; H, 9.40; N, 6.78.

((8*S,8a*S**)-Octahydroindolizin-8-yl)methanol; ((±)-epitashiromine, (±)-10)** [32,34,39]



A yellow oil (R_f 0.45, CH_2Cl_2/MeOH/NH_4OH 88:8:4); yield: 53%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.56–1.62 (m, 2H, CH_2),

1.65–1.74 (m, 4H, CH_2), 1.97–2.12 (m, 5H, CH_2), 2.20–2.28 (m, 1H, H-8), 2.94–3.00 (m, 1H, CH_2), 3.08–3.14 (m, 1H, N-CH), 3.70–3.75 (m, 1H, OCH_2), 4.13–4.19 (m, 1H, OCH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.2, 23.7, 26.3, 30.1, 35.7, 54.0, 54.9, 66.0, 66.8; MS (ESI) *m*/*z*: 156.4 [M + 1]; anal. calcd for $C_9H_{17}NO$: C, 69.63; H, 11.04; N 9.02; found: C, 69.30; H, 10.71; N, 8.79.

Acknowledgements

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