Strategy for the Assembly of Chiral Bicyclic Lactams: A Concise Synthetic Route to (–)-Coniceine

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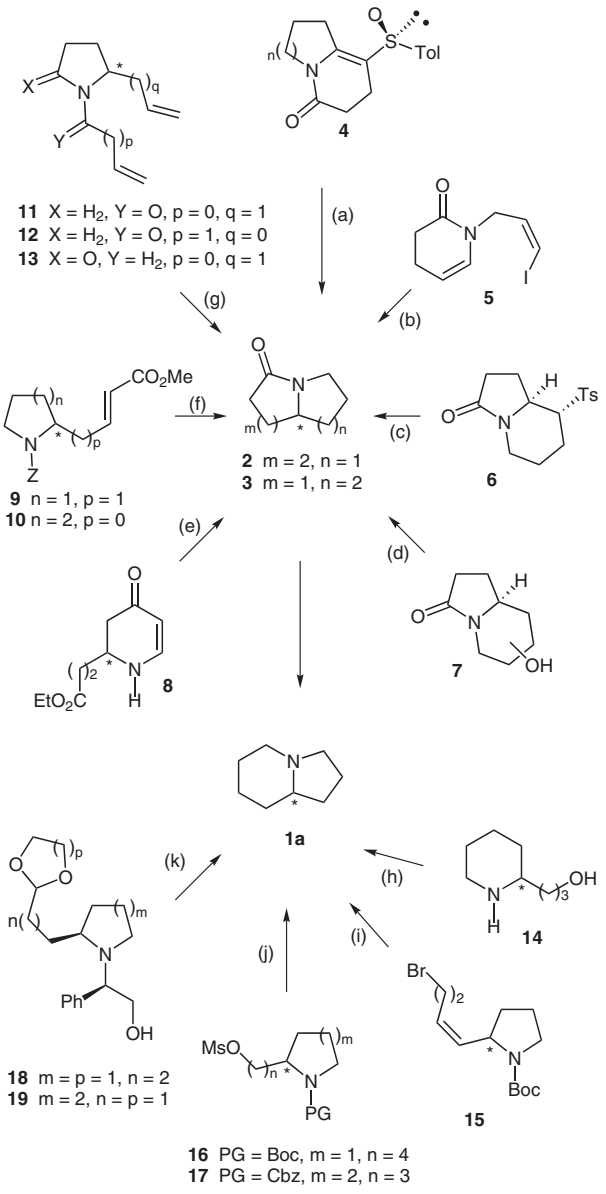
Abstract: A concise asymmetric synthesis of chiral bicyclic lactams combining a highly stereoselective 1,2-addition on SAMP hydrazones with a ring closure metathesis has been achieved. The synthetic utility of this approach has been emphasized by the total synthesis of (–)-coniceine in high enantiomeric excess.

Key words: alkaloids, lactams, metathesis, ring closure, stereoselectivity

In the past decade, a whole range of biologically active indolizidine and quinolizidine alkaloids have been isolated from the skin secretions of neotropical amphibians[1] and these lipophilic skin alkaloids have caught the attention of the medical world due to their potential biological activities.[2] δ-Coniceine (**1a**) is a very representative member of this class of bicyclic compounds having a nitrogen-atom ring juncture.[3] However, it is not considered as a true alkaloid (i.e., not naturally occurring), but has been shown to derive from the poison hemlock alkaloid coniine by chemical transformation. Despite the fact that δ-coniceine is the structurally simplest indolizidine alkaloid, it has attracted great attention from the synthetic chemists since its elaboration serves as a testing ground for new synthetic methodology and provides foundation for extension to more complex and functionalized systems. Consequently, this has resulted in several successful approaches to the compound in both racemic[4] and optically active forms.[5,6] The asymmetric syntheses of this indolizidine alkaloid that have appeared in print can be cursorily classified into two main categories. The first one hinges upon the reduction of the carbonyl function of the fused chiral six and five-membered lactams **2** and **3**, and the main synthetic approaches to these lactamic systems are portrayed in Scheme 1. Thus, compound **2** was obtained by reduction of the chiral sulfinylenamide **4**[5a,b] (path a) and by an asymmetric Heck reaction of an iodoalkenyl unsaturated piperidone **5**[5c,d] (path b). The five-membered analogue **3** was obtained by reduction of the tosyl group of diastereopure **6**[5e] (path c), by chemical manipulation of *N*-α or -γ-hydroxyalkylated lactams **7**[5f,g] (path d) and by a double reduction/cyclization sequence applied to the chiral enaminone **8**[5h] (path e). Convergent strategies leading indifferently to the parent compounds **2** and **3** have been also developed, such as the concomitant reduction/cyclization sequence applied to proline and biocatalytically enantioenriched piperidine derived esters **9**[5i] and **10**,[5j] respectively (path f) and the annulation of the polyenic compounds, **11**,[5k] **12**,[5l] and **13**[5m] relying on the ring-closing metathesis (RCM) reaction as the ultimate step (path g).



Scheme 1 Synthetic approaches to indolizidine

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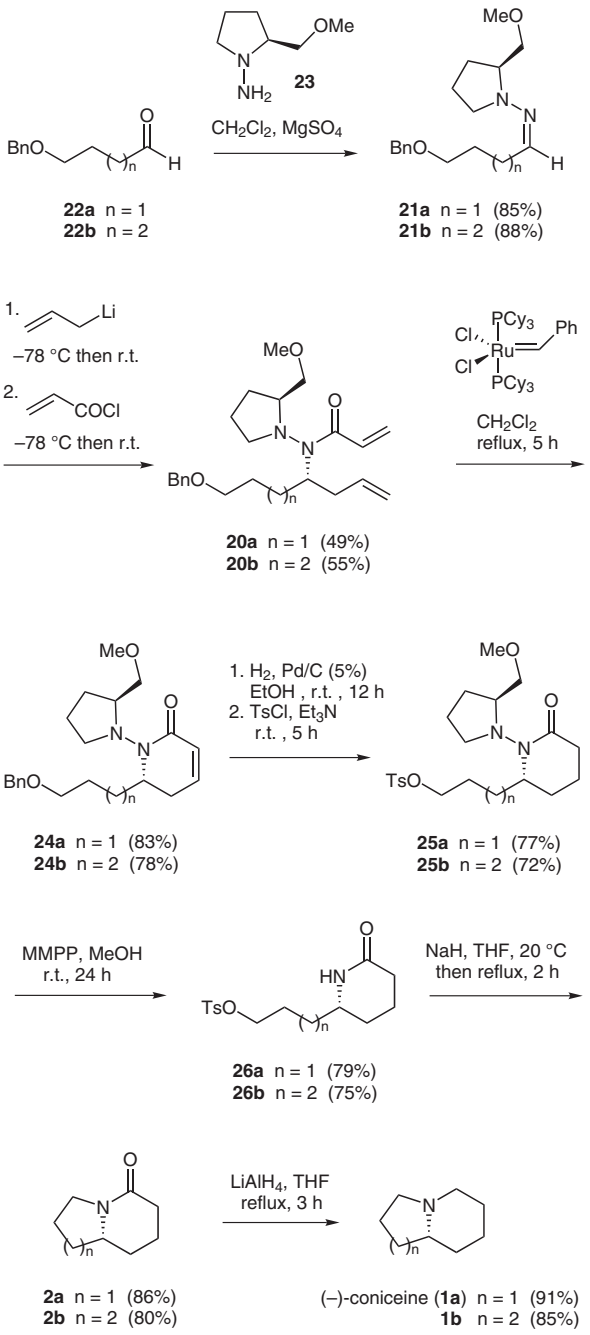
The second conceptual approach to **1a** disclosed in Scheme 1 is based upon the preliminary elaboration of a pyrrolidine or piperidine derivative equipped with an appropriate functionality to secure the subsequent assembly of the bicyclic framework.[6] In this context the final creation of the newly formed heterocycle was usually ensured by an intramolecular N-alkylation reaction involving an halide deriving from the amino alcohol **14**[6a] (path h), an alkenyl halide **15** obtained by asymmetric deprotonation of a protected pyrrolidine[6b] (path i), and finally structurally different mesylates **16**[6c] and **17**[6d] (path j). The fused alkaloid was also accessed by an intramolecular reductive aminocyclization involving deprotected amino acetals **18**[6e] and **19**[6f] (path k).

Since pyrrolidine and piperidine are salient and ubiquitous structural features of a wide array of natural products, most of the synthetic approaches disclosed in Scheme 1 rely on the development of functionalized precursors deriving from the natural chiral pool (e.g., proline, serine, pyroglutamic acid, pyroglutaminol, and phenylglycinol). Consequently synthetic routes involving tailor-made stereocontroling agents (e.g., oxazolidine, chiral sulfinyl group, biocatalytically generated amino alcohols) are rather scant.

We wish to report in this paper a concise and conceptually different asymmetric synthetic approach to the representative alkaloid δ-coniceine (**1a**), which hinges upon the installation of the mandatory stereogenic centre and the assembly of the piperidine template at the very early stage of the synthesis. This approach combines a ring-closing metathesis with the highly diastereoselective nucleophilic 1,2-addition of an allyllithiated species on a chiral SAMP hydrazone preequipped with a suitably substituted appendage liable to secure the ultimate formation of the fused model.

The first facet of the synthesis depicted in Scheme 2 was the elaboration of the diolefinic hydrazide **20a**. The synthesis started with the preparation of hydrazone **21a**, which was readily accessible by simply mixing the protected hydroxycarboxaldehyde **22a** with the enantiomerically pure hydrazine, (*S*)-(–)-1-amino-2-(methoxymethyl)pyrrolidine (SAMP, **23**). Owing to the efficiency and to the high level of diastereoselection observed upon reaction of SAMP hydrazones with organometallic reagents[7] the assembly of the diolefinic hydrazide **20a** was performed as a single one-pot reaction. Thus chiral hydrazone **21a** was submitted to addition reaction with allyllithium[8] and the lithium hydrazide salt was intercepted with acryloyl chloride to afford the requisite dienehydrazide **20a**. This polyenic compound, candidate for the planned RCM reaction was obtained essentially as a single diastereomer detectable by NMR spectroscopy (de ≥ 95% after chromatographic treatment) then confirming the remarkable stereoselectivity associated with the diastereofacial 1,2-addition process[7] allowing the introduction of the absolute stereochemistry early in the sequence. This bis-olefin **20a** was then subjected to a ring-closure metathesis which ranks high in the hierarchy of synthetic



Scheme 2

tactics for the elaboration of nitrogen containing ring systems.[9] Gratifyingly this technique delivered a very satisfactory yield of the virtually diastereochemically pure cyclic enehydrazide (*S*,*S*)-**24a**.

Interestingly, the double bond of **24a** can be regarded as a chemical handle for alternative functionalizations and henceforth **24a** represents a potentially useful synthetic intermediate for the synthesis of piperidine alkaloids and functionalized related congeners. Catalytic hydrogenation of the olefinic double bond of **24a** was accomplished with the concomitant release of the benzyl protection of the hydroxyalkyl appendage and conversion into the tosylate (*R*,*S*)-**25a** could be efficiently achieved in the sequel (77%

over two steps). Treatment of (*R*,*S*)-**25a** with magnesium monoperoxyphthalate (MMPP)[10] triggered off the formation of the NH-free piperidone (*R*)-**26a** with the release of the chiral appendage. This operation delivered very satisfactory yield of the virtually enantiopure 6-alkylpiperidin-2-one (*R*)-**26a** and set up the system for cyclization. The subsequent deprotonation/annulation sequence proceeded uneventfully to afford the fused lactam **2a** with an excellent yield. The absolute configuration as well as the enantiopurity of (*R*)-**2a** was determined by comparing the sign and optical rotation value with that of an authentic sample assembled by a conceptually different synthetic route.[5k] Interestingly the viability and versatility of the process was emphasized by the synthesis of the homologue of the series, that is, the octahydroquinolizinone (*S*)-**2b**[11] (Scheme 2). This compound was obtained by the same reaction sequence applied to the cyclic enehydrazide (*S*)-**24b** readily assembled from the protected hydroxycarboxaldehyde **22b**, via **21b** and **20b**. Compound (*S*)-**2b** was obtained in high yield and excellent enantioselectivity by this process. Finally reduction of **2a** with lithium aluminum hydride[5e] in diethyl ether at 25 °C for two hours provided 85% yield of (*R*)-**1a**. The absolute configuration was confirmed to be *R* and enantiopurity of our synthetic (*R*)-(–)-coniceine [(*R*)-**1a**] was clearly established from the optical rotation and spectroscopic data that matched with those reported for the natural product.[12] Incidentally reduction of chiral bicyclic lactam **2b** gave access to the optically inactive quinolizidine (**1b**) in high yield.[4e]

In summary a simple procedure has been devised for the assembly of chiral piperidones with a functionalized appendage at C2 in high enantiopurity. Additionally, a route to bicyclic lactams has been achieved and the synthetic utility of these compounds has been further enhanced by the total synthesis of (–)-coniceine (**1a**).

Melting points were determined on a Reichert-Thermopan apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AM 300 spectrometer. Optical rotations were measured on a Perkin-Elmer P 241 polarimeter. Elemental analyses were obtained using a Carlo-Erba CHNS-11110 equipment. The silica gel used for flash column chromatography was Merck Kieselgel of 0.040–0.063 mm particle size. Petroleum ether (PE, boiling range, 40–60 °C), EtOAc, acetone, and MeOH were used as eluents. Dry glassware was obtained by oven-drying and assembled under argon. Argon was used as the inert atmosphere and was passed through a drying tube to remove moisture. The glassware was equipped with rubber septa and reagent transfer was performed by syringe techniques. THF and Et_2O were distilled from sodium benzophenone ketyl immediately before use. MeOH and EtOH were distilled from Mg turnings and CH_2Cl_2 from CaH_2, before storage on 4 Å molecular sieves. The aldehydes **22a**[13] and **22b**[14] were prepared according to reported procedures.

Hydrazones 21a,b; General Procedure

(*S*)-1-Amino-2-methoxymethylpyrrolidine (SAMP, 15.6 g, 0.12 mol) and $MgSO_4$ (500 mg) were added to a solution of the aldehyde **22a** or **22b** (0.1 mol) in CH_2Cl_2 (60 mL) and the mixture was stirred at r.t. for 12 h. $MgSO_4$ was filtered off and the solvent was evaporated under vacuum. The crude residue was purified by flash column chromatography (EtOAc–PE, 30:70) to afford hydrazone **21a** (29.6 g, 85%) or **21b** (32.1 g, 88%) as a colorless oil.

(*S*)-4-Benzyloxybutylidene-2-methoxymethylpyrrolidin-1-ylamine [(*S*)-(21a)]

$[\alpha]_D^{25}$ –84.0 (*c* 3.80, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.79–1.88 (m, 6 H), 2.22–2.29 (m, 2 H), 2.58–2.66 (m, 1 H), 3.26–3.57 (m, 9 H), 4.46 (s, OC*H*$_2$Ph, 2 H), 6.61 (t, *J* = 5.6 Hz, 1 H, CH=N), 7.19–7.32 (m, 5 H_{arom}).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.1, 26.7, 27.8, 29.8, 50.2, 59.1, 63.4, 69.7, 72.8, 74.7, 127.4, 127.5, 128.3, 138.0, 138.6.

Anal. Calcd for $C_{17}H_{26}N_2O_2$: C, 70.31; H, 9.02; N, 9.65. Found: C, 70.06; H, 9.24; N, 9.41.

(*S*)-5-Benzyloxypentylidene-2-methoxymethylpyrrolidin-1-ylamine [(*S*)-(21b)]

$[\alpha]_D^{25}$ –81.3 (*c* 2.10, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.53–1.96 (m, 8 H), 2.19–2.24 (m, 2 H), 2.65–2.73 (m, 1 H), 3.36–3.59 (m, 9 H), 4.49 (s, 2 H, OC*H*$_2$Ph), 6.63 (t, *J* = 5.5 Hz, 1 H, CH=N), 7.21–7.35 (m, 5 H_{arom}).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.1, 24.5, 26.6, 29.3, 32.9, 50.4, 59.2, 63.5, 70.2, 72.8, 74.8, 127.5, 127.6, 128.3, 138.6, 138.8.

Anal. Calcd for $C_{18}H_{28}N_2O_2$: C, 71.02; H, 9.27; N, 9.20. Found: C, 70.83; H, 9.50; N, 8.98.

Dienehydrazides 20a,b; General Procedure

PhLi (1.8 M in dibutyl ether, 2.22 mL, 4 mmol) was added dropwise to a solution of allyltriphenyltin (1.56 g, 4 mmol) in Et_2O (15 mL). After stirring at r.t. for 30 min, the suspension was cooled at –78 °C and a solution of hydrazone (*S*)-**21a** or (*S*)-**21b** (4 mmol) in Et_2O (5 mL) was added dropwise by syringe. The mixture was stirred at –78 °C for 30 min, then allowed to warm to r.t., and stirred for an additional 12 h. The mixture was then recooled to –78 °C and acryloyl chloride (6 mmol, 545 mg) was added dropwise. After stirring at this temperature for 30 min, the mixture was allowed to warm to r.t. over 3 h. H_2O (15 mL) was added dropwise, the mixture was filtered, and extracted with CH_2Cl_2 (3 × 30 mL). The combined organic extracts were dried ($MgSO_4$), the solvent was removed under vacuum, and the product purified by flash column chromatography (EtOAc–PE, 30:70) to afford dienehydrazide **20a** (0.38 g, 49%) or **20b** (0.44 g, 55%) as a yellow oil.

(*S*,*S*)-*N*-[1-(3-Benzyloxypropyl)but-3-enyl]-*N*-(2-methoxymethylpyrrolidin-1-yl)acrylamide [(*S*,*S*)-(20a)]

$[\alpha]_D^{25}$ –13.1 (*c* 1.66, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.51–1.89 (m, 7 H), 2.12–2.18 (m, 1 H), 2.63–2.85 (m, 3 H), 3.06–3.31 (m, 8 H), 3.48 (t, *J* = 6.5 Hz, 2 H_{SAMP}), 4.49 (s, 2 H, OC*H*$_2$Ph), 4.96–5.13 (m, 2 H_{vinyl}), 5.55 (dd, *J* = 2.2, 10.4 Hz, 1 H_{vinyl}), 5.68–5.81 (m, 1 H_{vinyl}), 6.28 (dd, *J* = 2.2, 17.2 Hz, 1 H_{vinyl}), 7.06 (dd, *J* = 10.4, 17.2 Hz, 1 H_{vinyl}), 7.25–7.36 (m, 5 H_{arom}).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.2, 26.3, 27.7, 30.3, 37.1, 51.9, 56.6, 58.5, 58.9, 70.3, 72.9, 73.7, 117.1, 126.2, 127.5, 127.6, 128.3, 129.3, 136.0, 137.2, 169.3.

Anal. Calcd for $C_{23}H_{34}N_2O_3$: C, 71.47; H, 8.87; N, 7.25. Found: C, 71.33; H, 9.01; N, 7.09.

(*S*,*S*)-*N*-(1-Allyl-5-benzyloxypentyl)-*N*-(2-methoxymethylpyrrolidin-1-yl)acrylamide [(*S*,*S*)-(20b)]

$[\alpha]_D^{25}$ –18.3 (*c* 1.22, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.33–1.48 (m, 2 H), 1.55–1.94 (m, 7 H), 2.15–2.28 (m, 1 H), 2.58–2.94 (m, 3 H), 3.02–3.33 (m, 8 H), 3.47 (t, *J* = 6.7 Hz, 2 H_{SAMP}), 4.49 (s, 2 H, OC*H*$_2$Ph), 4.94–5.09 (m,

2 H_{vinyl}), 5.56 (dd, J = 2.2, 10.4 Hz, 1 H_{vinyl}), 5.65–5.82 (m, 1 H_{vinyl}), 6.28 (dd, J = 2.3, 17.3 Hz, 1 H_{vinyl}), 7.07 (dd, J = 10.4, 17.3 Hz, 1 H_{vinyl}), 7.25–7.32 (m, 5 H_{arom}).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.3, 24.3, 26.5, 29.7, 33.4, 37.1, 51.9, 56.8, 58.5, 59.0, 70.3, 72.9, 73.7, 117.0, 126.2, 127.5, 127.6, 128.3, 129.3, 136.1, 138.5, 169.2.

Anal. Calcd for $C_{24}H_{36}N_2O_3$: C, 71.96; H, 9.06; N, 6.99. Found: C, 72.22; H, 9.01; N, 6.78.

Enehydrazides 24a,b; General Procedure

A solution of the dienehydrazide **20a** or **20b** (1 mmol) and the first-generation Grubbs catalyst (0.05 mmol, 5 mol%) in anhyd CH_2Cl_2 (10 mL) was stirred at r.t. for 24 h under argon. The mixture was concentrated and the resulting residue was purified by column chromatography (EtOAc–PE, 50:50) to give the enehydrazide **24a** (0.30 g, 83%) or **24b** (0.29 g, 78%) as a yellow oil.

(*S*,*S*)-6-(3-Benzyloxypropyl)-1-(2-methoxymethylpyrrolidin-1-yl)-5,6-dihydro-1*H*-pyridin-2-one [(*S*,*S*)-24a]

$[\alpha]_D^{25}$ –24.2 (*c* 0.62, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.42–1.83 (m, 6 H), 1.96–2.05 (m, 2 H), 2.24 (ddd, J = 1.9, 5.8, 17.9 Hz, 1 H, CH_2C=), 2.66 (ddt, J = 2.7, 7.3, 17.9 Hz, 1 H, CH_2C=), 3.10–3.19 (m, 1 H), 3.27–3.34 (m, 5 H), 3.45 (t, J = 6.4 Hz, 2 H_{SAMP}), 3.61–3.69 (m, 2 H), 3.73–3.81 (m, 1 H), 4.46 (s, 2 H, OCH_2Ph), 5.77 (dd, J = 2.6, 9.7 Hz, 1 H, CH=), 6.27–6.34 (m, 1 H, CH=), 7.23–7.35 (m, 5 H_{arom}).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 26.5, 26.8, 27.3, 28.0, 29.0, 52.8, 58.9, 60.5, 61.8, 70.2, 72.9, 76.4, 126.1, 127.5, 127.6, 128.3, 136.8, 138.4, 162.7.

Anal. Calcd for $C_{21}H_{30}N_2O_3$: C, 70.36; H, 8.44; N, 7.81. Found: C, 70.27; H, 8.67; N, 8.06.

(*S*,*S*)-6-(3-Benzyloxybutyl)-1-(2-methoxymethylpyrrolidin-1-yl)-5,6-dihydro-1*H*-pyridin-2-one [(*S*,*S*)-24b]

$[\alpha]_D^{25}$ –29.3 (*c* 0.50, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.34–1.87 (m, 8 H), 1.95–2.04 (m, 2 H), 2.26 (ddd, J = 1.9, 6.0, 18.0 Hz, 1 H, CH_2C=), 2.67 (ddt, J = 2.8, 7.5, 18.0 Hz, 1 H, CH_2C=), 3.11–3.19 (m, 1 H), 3.32–3.38 (m, 5 H), 3.46 (t, J = 6.3 Hz, 2 H_{SAMP}), 3.60–3.69 (m, 2 H), 3.74–3.85 (m, 1 H), 4.49 (s, 2 H, OCH_2Ph), 5.78 (dd, J = 2.6, 9.8 Hz, 1 H, CH=), 6.28–6.35 (m, 1 H, CH=), 7.23–7.34 (m, 5 H_{arom}).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.9, 23.1, 27.2, 27.9, 29.8, 32.0, 52.8, 58.9, 60.6, 61.9, 70.1, 72.9, 76.3, 126.1, 127.5, 127.6, 128.3, 136.8, 138.5, 162.7.

Anal. Calcd for $C_{22}H_{32}N_2O_3$: C, 70.94; H, 8.66; N, 7.52. Found: C, 70.71; H, 8.95; N, 7.40.

Hydrazides (*R*,*S*)-25a and (*S*,*S*)-25b; General Procedure

A solution of enehydrazide **24a** or **24b** (1.5 mmol) in EtOH (20 mL) was stirred with activated Pd/C (10%, 15 mg) at r.t. under an atmosphere of H_2 for 12 h at which time TLC indicated complete consumption of starting material. The mixture was filtered on a pad of Celite that was further eluted with EtOH (40 mL), and then CH_2Cl_2 (40 mL). The filtrate was concentrated under vacuum and the resulting product was dissolved in anhyd CH_2Cl_2 (10 mL). The mixture was cooled to 0 °C and TsCl (1.1 equiv, 1.65 mmol) was added, followed by Et_3N (1.5 equiv, 2.25 mmol). The mixture was warmed to r.t. and stirred for 5 h, at which time H_2O (10 mL) was added. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic fractions were dried ($MgSO_4$), filtered, and evaporated to give a crude product, which was purified by flash column chromatography on silica gel using EtOAc as eluent to afford hydrazides **25a** (0.49 g, 77%) or **25b** (0.47 g, 72%) as a colorless oil.

(*R*,*S*)-Toluene-4-sulfonic Acid 3-[1-(2-Methoxymethyl)pyrrolidin-1-yl]-6-oxopiperidin-2-yl]propyl Ester [(*R*,*S*)-25a]

$[\alpha]_D^{25}$ –10.3 (*c* 0.58, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.31–1.69 (m, 7 H), 1.75–2.03 (m, 5 H), 2.27 (t, J = 6.2 Hz, 2 H, CH_2CO), 2.42 (s, 3 H, CH_3), 2.88–2.96 (m, 1 H), 3.17–3.25 (m, 5 H), 3.42–3.50 (m, 2 H), 3.74–3.81 (m, 1 H), 3.92–4.05 (m, 2 H), 7.32 (d, J = 8.1 Hz, 2 H_{arom}), 7.75 (d, J = 8.1 Hz, 2 H_{arom}).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 17.5, 21.6, 23.0, 25.6, 27.2, 27.4, 29.1, 34.0, 53.1, 58.7, 59.7, 62.1, 70.5, 76.7, 127.8, 129.9, 133.0, 144.8, 169.0.

Anal. Calcd for $C_{21}H_{32}N_2O_5S$: C, 59.41; H, 7.60; N, 6.60. Found: C, 59.25; H, 7.88; N, 6.50.

(*S*,*S*)-Toluene-4-sulfonic Acid 4-[1-(2-Methoxymethyl)pyrrolidin-1-yl]-6-oxopiperidin-2-yl]butyl Ester [(*S*,*S*)-25b]

$[\alpha]_D^{25}$ –8.7 (*c* 0.80, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.18–1.42 (m, 5 H), 1.53–2.02 (m, 9 H), 2.25 (t, J = 6.1 Hz, 2 H, CH_2CO), 2.43 (s, 3 H, CH_3), 2.94–3.01 (m, 1 H), 3.20–3.28 (m, 5 H), 3.37–3.49 (m, 2 H), 3.73–3.83 (m, 1 H), 4.00 (t, J = 6.3 Hz, 2 H, CH_2OTs), 7.31 (d, J = 8.0 Hz, 2 H_{arom}), 7.74 (d, J = 8.0 Hz, 2 H_{arom}).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 17.2, 21.9, 23.0, 26.9, 27.4, 28.8, 32.2, 32.4, 34.0, 53.1, 58.7, 59.7, 62.5, 70.4, 76.7, 127.8, 129.8, 133.0, 144.8, 169.0.

Anal. Calcd for $C_{22}H_{34}N_2O_5S$: C, 60.25; H, 7.81; N, 6.39. Found: C, 60.17; H, 8.09; N, 6.62.

Piperidin-2-ones (*R*)-26a and (*S*)-26b; General Procedure

Magnesium monoperoxyphtalate (MMPP·6H_2O 3.75 mmol, 1.86 g) was added to a solution of hydrazide **25a** or **25b** (1.5 mmol) in MeOH (20 mL). The mixture was stirred at r.t. until no starting material remained (TLC monitoring; silica gel Merck GF 254; EtOAc). The mixture was then poured into CH_2Cl_2 (40 mL) and the organic layer was washed with aq sat. $NaHCO_3$ (40 mL). The aqueous layer was separated and extracted with CH_2Cl_2 (3 × 30 mL). The combined organic extracts were washed successively with H_2O (10 mL), brine (10 mL), and dried ($MgSO_4$). Evaporation of the solvent furnished an oily product, which was purified by flash column chromatography using EtOAc as eluent to afford **26a** (0.37 g, 79%) or **26b** (0.36 g, 75%).

(*R*)-Toluene-4-sulfonic Acid 3-(6-Oxopiperidin-2-yl)propyl Ester [(*R*)-26a]

White solid; mp 73–74 °C; $[\alpha]_D^{25}$ –13.6 (*c* 0.48, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.33–1.48 (m, 2 H), 1.53–1.65 (m, 4 H), 1.74–1.88 (m, 2 H), 2.12–2.35 (m, 2 H), 2.44 (s, 3 H, CH_3), 3.25–3.31 (m, 1 H), 4.01 (t, J = 6.2 Hz, 2 H, CH_2OTs), 6.88 (br s, 1 H, NH), 7.33 (d, J = 8.2 Hz, 2 H_{arom}), 7.76 (d, J = 8.2 Hz, 2 H_{arom}).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.8, 21.6, 24.7, 27.8, 31.2, 32.6, 52.3, 70.1, 127.9, 129.9, 132.8, 144.9, 172.9.

Anal. Calcd for $C_{15}H_{21}NO_4S$: C, 57.86; H, 6.80; N, 4.50. Found: C, 57.74; H, 6.75; N, 4.43.

(*S*)-Toluene-4-sulfonic Acid 4-(6-Oxopiperidin-2-yl)butyl Ester [(*S*)-26b]

Oil; $[\alpha]_D^{25}$ +8.8 (*c* 0.34, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.22–1.51 (m, 5 H), 1.58–1.69 (m, 3 H), 1.81–1.88 (m, 2 H), 2.19–2.33 (m, 2 H), 2.43 (s, 3 H, CH_3), 3.21–3.32 (m, 1 H), 3.99 (t, J = 6.3 Hz, 2 H, CH_2OTs), 6.63 (br s, 1 H, NH), 7.33 (d, J = 8.1 Hz, 2 H_{arom}), 7.76 (d, J = 8.1 Hz, 2 H_{arom}).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.6, 21.2, 21.6, 28.0, 28.7, 31.3, 36.1, 52.8, 70.2, 127.9, 129.9, 132.5, 144.8, 172.6.

Anal. Calcd for $C_{16}H_{23}NO_4S$: C, 59.05; H, 7.12; N, 4.30. Found: C, 59.22; H, 6.92; N, 4.15.

Bicyclic Lactams (*R*)-2a and (*S*)-2b; General Procedure

Pentane-prewashed NaH (0.88 mmol, 1.1 equiv, 60% dispersion in oil) was suspended in anhyd THF (15 mL) and a solution of the tosylate **26a** or **26b** (0.8 mmol) in anhyd THF (3 mL) was added dropwise by syringe at –20 °C. The mixture was stirred at r.t. for 30 min and then refluxed for 2 h. The mixture was cooled in an ice-water bath and sat. aq NH_4Cl (5 mL) was carefully added. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 20 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated. The crude residue was purified by column chromatography (acetone–PE, 50:50) to give (*R*)-hexahydroindolizin-5-one [(*R*)-**2a**];[5k] yield: 86 mg (86%); $[\alpha]_D^{25}$ –6.3 (*c* 0.30, CH_2Cl_2) {Lit.[5k] $[\alpha]_D^{25}$ –6.6 (*c* 0.4, CH_2Cl_2)} or (*S*)-octahydroquinolizin-4-one [(*S*)-**2b**];[11] yield: 89 mg (80%); $[\alpha]_D^{25}$ +10.2 (*c* 0.91, $CHCl_3$).

Bicyclic Lactams (*R*)-Coniceine (1a) and Quinolizidine (1b); General Procedure

A solution of lactam **2a** or **2b** (0.5 mmol) in THF (2 mL) was added slowly at 0 °C under argon to a suspension of $LiAlH_4$ (0.75 mmol, 1.5 equiv) in anhyd THF (5 mL). The resulting mixture was stirred under reflux for 3 h. After careful hydrolysis with sat. aq NH_4Cl (5 mL), CH_2Cl_2 (15 mL) was added and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 15 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated. The crude residue was purified by column chromatography (EtOAc–MeOH, 50:50) to give (*R*)-coniceine [(*R*)-**1a**];[12] yield: 50 mg (91%); $[\alpha]_D^{25}$ –9.8 (*c* 1.10, EtOH) {Lit.[12] $[\alpha]_D^{23}$ –10.2 (*c* 1.76, EtOH)} or quinolizidine (**1b**);[4e] yield: 53 mg (85%).

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