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Abstract—This paper describes the establishment of a new synthetic route to the hydrobromide salt of (+)-coniceine **1** with high enantiopurity in five steps and 8% overall yield. The key step is the reductive photocyclization of an acyclic chiral dienamide, for which a convenient one-pot synthesis is described.

1. Introduction

Simple indolizidine alkaloids (1-azabicyclo[4.3.0]nonanes), which include 5-alkyl, 3,5- or 5,8-dialkyl and 5,6,8-trialkyl indolizidines, are present in the skins of Central and South American amphibians.[1] Some of these natural products have been shown to be non-competitive blockers of nicotinic acetylcholine receptor channels in the muscle and ganglia membranes,[1] and are thus potentially useful for studying the mechanisms of neuromuscular transmission. Some examples of these alkylated indolizidine alkaloids are shown in Figure 1 along with the simplest indolizidine, coniceine **1**. While currently not established as a natural product, coniceine has attracted great interest from chemists, usually as an illustrative target demonstrating the viability of synthetic routes to indolizidine derivatives. This has resulted in numerous successful syntheses of racemic[2] and enantiomerically pure[3] coniceine.

Reductive photocyclization was first reported as a synthetic tool in 1981,[4] and has since been used in a number of total syntheses of racemic indole,[5] piperidine[6] and ergoline-type[7] alkaloids. Although a number of possibilities exist for inducing stereoselectivity in photochemical reactions,[8] little attention has been paid to performing asymmetric synthesis using reductive photocyclization. In a few early reports, reductive photocyclization was carried out in the presence of chiral metal hydride complexes, but both the chemical yields and enantioselectivities were low.[9] More recently, we have developed a methodology for the synthesis of 2-substituted piperidines in high enantioselectivity utilizing

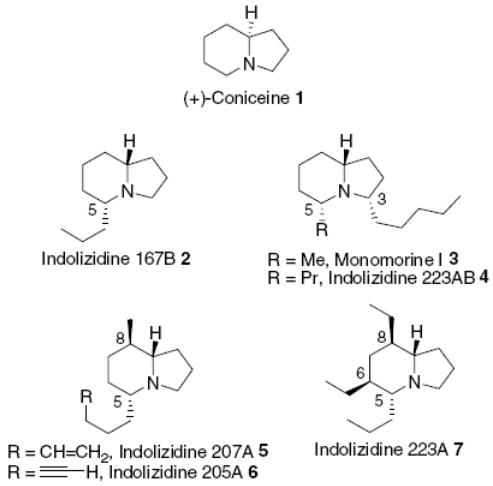

Figure 1. Coniceine **1** and a selection of simple, naturally occurring indolizidines **2**–**7**.

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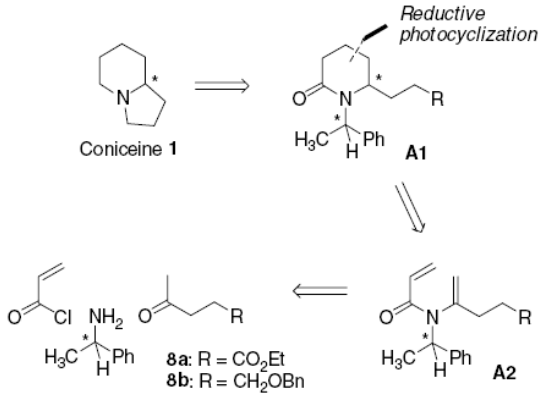
the reductive photocyclization of chiral dienamides.[10] We reasoned that the scope of this methodology could be extended to achieve a short synthesis of (+)-coniceine, thus providing an entry to the indolizidine alkaloids.

The overall retrosynthetic rationale is shown in Scheme 1. Coniceine **1** should be accessible from piperidinone **A1** in which R is either CO_2Et or CH_2OBn. Piperidinone **A1**, in turn, could be obtained by a stereoselective reductive photocyclization of chiral dienamide **A2**. The stereoselectivity of this reaction should originate from the selected enantiomer of α-methylbenzylamine, used as a starting material along with acryloyl chloride and ketone **8a** (commercially available) or **8b** (readily available by benzylation of the commercially available 5-hydroxy-pentan-2-one[11]). Herein we report an original and efficient synthesis of enantiomerically pure (+)-coniceine, based on this strategy.

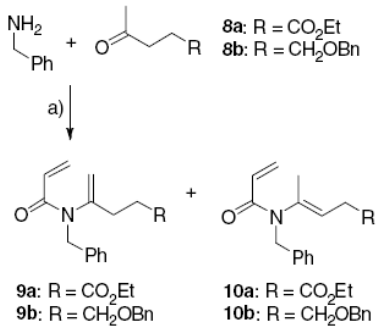


Scheme 1. Retrosynthetic analysis for the indolizidine skeleton (coniceine **1**) based on the reductive photocyclization of chiral dienamides.

2. Results and discussion

2.1. Model study

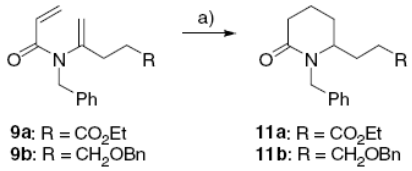
Initially, we carried out a model study using *N*-benzyl derivatives, in order to identify the more convenient dienamide side chain (ester or protected alcohol). For the preparation of the requisite dienamides **9a** and **9b**, a convenient one pot procedure was developed, which avoided the isolation of unstable imine intermediates (Scheme 2). Thus, ketones **8a** and **8b** were reacted with benzylamine in the presence of 4 Å molecular sieves in THF followed by the addition of Et_3N and acryloyl chloride to afford isomeric mixtures **9a**/**10a** and **9b**/**10b** in 85% (**9a**/**10a** = 47:53) and 93% (**9b**/**10b** = 43:57) yield, respectively. The use of CH_2Cl_2 as the solvent, or of $^iPr_2NEt$ as the base, or variation of the reaction temperature only decreased the yields and/or selectivities. In each case, however, the structural isomers could easily be separated by column chromatography. Although the effective yields of dienamides **9a** and **9b** are moderate, this one-pot methodology has the advantage of being rapid and convenient. It should be noted that dienamides **9a** and **9b** are unstable in the presence of trace amounts of acids (for example, in $CDCl_3$) or when heated



Scheme 2. One-pot synthesis of dienamides **9a** and **9b**. Key: (a) 4 Å molecular sieves, THF, rt; then $H_2C{=}CHCOCl$, Et_3N, THF, −15 °C to rt. **9a**/**10a**: 85% (**9a**/**10a** = 47:53), **9b**/**10b**: 93% (**9b**/**10b** = 43:57).

extensively: under such conditions, facile isomerization to **10a** and **10b**, respectively, is observed.

A series of reductive photocyclizations of dienamides **9a** and **9b** were then performed, using benzene/MeOH as the solvent and $NaBH_4$ as a reducing agent,[7,12] to give piperidinones **11a** and **11b**, respectively (Scheme 3). The reactor type and reaction times were varied, and the results are listed in Table 1. The reductive photocyclization of benzyloxy dienamide **9b** using a quartz reactor gave the highest yield in the shortest reaction time (37%/2.5 h; entry 4). Therefore, we retained this side chain and these conditions for the chiral version of this reaction, described below.



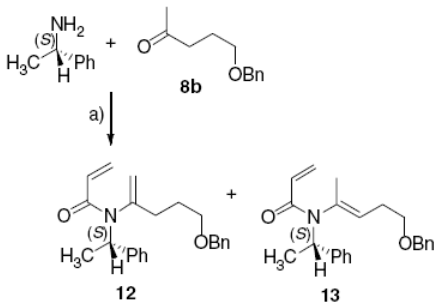
Scheme 3. Reductive photocyclization of **9a** and **9b** giving piperidinones **11a** and **11b**. Key: (a) hν, $NaBH_4$ (8 equiv), benzene/MeOH (9:1), rt. Further conditions in Table 1.

Table 1. Reductive photocyclization of **9a** and **9b** giving piperidinones **11a** and **11b**

Entry	R	Reactor	Time (h)	Yield (%)
1	CO_2Et	Pyrex	6	21
2	CO_2Et	Quartz	2.75	16
3	CH_2OBn	Pyrex	6	27
4	CH_2OBn	Quartz	2.5	37

2.2. Synthesis of (+)-coniceine

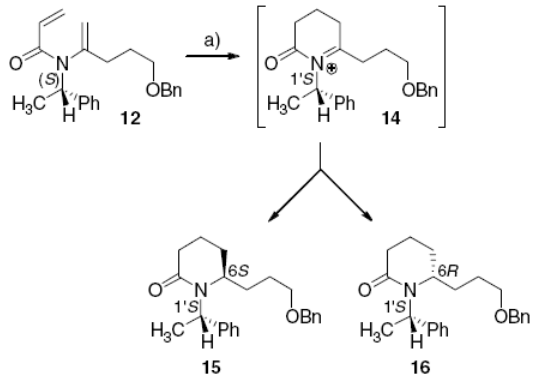
(*S*)-(−)-α-Methylbenzylamine was chosen as the chiral auxiliary. Our previous work on piperidine systems suggested that reductive photocyclization using this antipode should preferentially lead to a (6*S*)-piperidone derivative (**A1**, Scheme 1).[10] As shown in Scheme 4, the one-pot synthesis of dienamides was employed successfully for the preparation of chiral dienamide **12**. On a multigram scale, this reaction affords the isomeric mixture **12**/**13** in 87% yield



Scheme 4. One-pot synthesis of dienamide **12** and isomer **13**. Key: (a) 4 Å molecular sieves, THF, rt; then $H_2C{=}CHCOCl$, THF, −15 °C to rt. **12**/**13**: 87% (**12**/**13** = 53:47).

(**12**/**13** = 53:47). Thus, as was the case in the model study, the effective yield of the desired dienamide **12** is moderate, but this pathway provides chiral dienamide **12** in a straightforward fashion with no isolation of the unstable intermediate imine being necessary; isomers **12** and **13** are easily separated by column chromatography.

Based on the results of the model study, the reductive photocyclisation of dienamide **12** was performed using a quartz reactor; other reaction conditions were varied. Two diastereomeric piperidinones were obtained as an inseparable mixture: the desired (1′*S*,6*S*)-isomer **15** and the undesired (1′*S*,6*R*)-isomer **16** (Scheme 5); the results



Scheme 5. Reductive photocyclization of **12** yielding diastereomeric piperidinones **15** and **16**, via iminium ion **14**. Key: (a) *hν*, $NaBH_4$, quartz reactor. Further conditions in Table 2.

are listed in Table 2. When the reaction was performed in benzene/MeOH (9:1) at rt (entry 1), the piperidinones were obtained in a rather disappointing 39% combined yield and 54% de. We were satisfied to find that when benzene was replaced by (less toxic) toluene, the yield rose to 56%, although the de decreased to 42% (entry 2). This equates to an increase in the effective yield of **15**, from 30% to 40%. Changes in de were insignificant when the reaction was performed at lower temperatures (entries 4–6). The optimum temperature for high de was around −15 °C (entry 5); however, when overall yields are taken into account, the effective yield of **15** remains at 40–44% over the temperature range examined. Satisfyingly, when scaled up, only a slight decrease in overall yield was observed along with a slight increase in de (entry 3).

The reaction presumably proceeds via iminium ion **14** and the anticipated (6*S*)-selectivity can be explained by the nucleophilic addition of hydride on intermediate iminium ion **14** from the less hindered of the two diastereotopic faces.[10,13] The diastereoselectivity was determined from ^{1}H NMR spectra, in which chemical shift differences were observed for the benzylic proton of the (*S*)-α-methylbenzyl group and for the benzylic protons of the benzyloxy group in each diastereoisomer (see Section 4). The unequivocal attribution of the absolute configurations of the two diastereoisomeric products was not possible from NMR data, but this was achieved at a later stage.

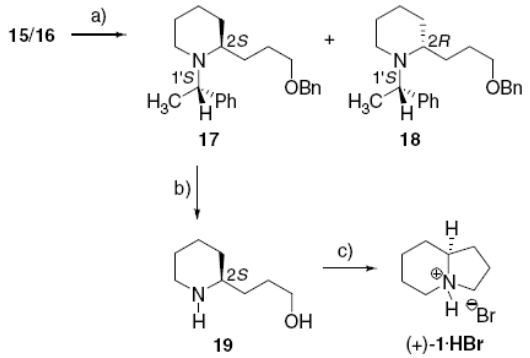
Reduction of the amide function in the **15**/**16** mixtures using $LiAlH_4$ in refluxing THF gave a mixture of amines **17** and **18** (Scheme 6). This mixture was easily separated by column chromatography, thus affording pure **17** in around 61% yield and pure **18** in around 16% yield. Removal of the two benzylic groups in **17** was accomplished by hydrogenation over 10% Pd/C with $HCOONH_4$ as the hydrogen source.[14] The desired amino alcohol **19** was isolated simply by filtration and concentration, which provided an essentially pure product as judged by NMR. Cyclization of crude **19** was achieved using CBr_4 and PPh_3 in MeCN using a minor modification of a lit. procedure.[15] Aqueous workup gave (+)-coniceine hydrobromide **1**·**HBr** in 58% yield for the last two steps.

The isolated (+)-coniceine hydrobromide **1**·**HBr** showed identical NMR spectral data and melting point to those reported in the lit. for the racemic hydrobromide[16] and had

Table 2.

Entry	Solvent	Temperature (°C)	Time (h)	Yield of **15**/**16** (%)	de[e]	Yield of **15** (%)
1[a]	Benzene/MeOH 9:1	rt	2.5	39[c]	54	30
2[a]	Toluene/MeOH 9:1	rt	2.5	56[c]	42	40
3[b]	Toluene/MeOH 9:1	rt	2.5	46[d]	50	35
4[a]	Toluene/MeOH 9:1	5	2.5	54[c]	54	42
5[a]	Toluene/MeOH 9:1	−15	2	50[c]	62	41
6[a]	Toluene/MeOH 9:1	−30	2	58[c]	52	44

[a] Approx. 1 mmol scale.
[b] 4.2 mmol scale.
[c] Corrected yields, after taking some **8b** contained in the starting material into account (calculated from NMR).
[d] Corrected yield, reaction performed on a **12**/**13** 89:11 mixture (NMR).
[e] Estimated from ^{1}H NMR.



Scheme 6. Synthesis of (+)-coniceine hydrobromide **1·HBr** from piperidinone mixture **15/16**. Key: (a) $LiAlH_4$, THF, Δ. **17**: 61%, **18**: 16%. (b) $HCOONH_4$, 10% Pd/C, MeOH, Δ. (c) CBr_4, PPh_3, MeCN, rt, 58% (for two steps).

$[\alpha]_D^{22} = +5.5$ (*c* 0.88, EtOH). To the best of our knowledge, there are no other reports that include the specific rotation of (+)- or (−)-**1·HBr**, hence we liberated the free amine of **1** on a small scale. The sample showed spectral data identical to those in the lit.[3d,i] and a specific rotation of $[\alpha]_D^{22} = +9.5$ (*c* 1.13, EtOH) {lit.[16] $[\alpha]_D^{23} = +9.3 \pm 0.6$ (*c* 1.76, EtOH)} which confirmed the structure to be (+)-coniceine **1**, as expected. Our value for the specific rotation indicated a product of high enantiopurity. Further verification was obtained by adapting a lit. NMR method[17] for the determination of enantiomeric ratios using an authentic sample of (±)-**1·HBr** as reference. Our synthesis provided (+)-coniceine hydrobromide **1·HBr** in which only one enantiomer was detected (>97% ee within detection limits).

3. Conclusion

We have established a convenient new pathway to (+)-coniceine hydrobromide **1·HBr** in highly enantiopure form in only five steps and 8% overall yield. This is the first synthesis that employs reductive photocyclization of a chiral dienamide as the key step. An attractive feature of this methodology is that the opposite enantiomer of the desired indolizidine is equally accessible, in principle, simply by using the opposite enantiomer of the chiral auxiliary. An extension of this methodology for the total synthesis of more complex indolizidine alkaloids can readily be envisaged.

4. Experimental

4.1. General

THF was distilled under N_2 from potassium/benzophenone. CH_2Cl_2 was distilled under N_2 from CaH_2. Benzene and toluene were dried over sodium. EtOAc and cyclohexane for column chromatography were distilled before use. Benzyl amine, benzyl bromide, MeOH and (*S*)-(−)-α-methylbenzylamine were distilled and dried over 4 Å molecular sieves. Et_3N, ethyl levulinate, MeCN and $^iPr_2NEt$ were dried over 4 Å molecular sieves. All other solvents and chemicals obtained from commercial sources were, unless otherwise stated, used without further purification.

Melting points were determined on Reichert microscope apparatus and are uncorrected. Specific rotations were measured on a Jasco DIP-370 polarimeter using a 10 cm cell. IR spectra were recorded on a Perkin–Elmer 881 spectrometer and ν are expressed in cm^{-1}. NMR spectra were recorded on a 400 MHz Bruker AC 400 spectrometer; chemical shifts are referenced to the residual solvent peak. Where applicable, assignments were based on *J*-modulation experiments: (−) designates a (C) or a (CH_2); (+) designates a (CH) or a (CH_3). GC–MS were recorded on Agilent Technologies 6890N GC equipped with an Agilent 5973 Mass Selection Detector operating in EI mode (70 eV); numbers in parentheses in MS spectral data are relative abundances. HRMS were recorded on a Micromass Q-Tof Micro (3000 V) apparatus in ESI mode. Elemental analyses were determined on a Thermofinnigan Flash EA 1112. TLC was performed on Merck TLC aluminum sheets, silicagel 60, F_{254}. Visualisation of spots was effected with UV-light and/or ninhydrin in EtOH/AcOH. Flash chromatography was performed with silica gel 60 (70–230 mesh ASTM). Unless otherwise stated, flash chromatography was performed in the eluent system for which the R_f-values are given. Progressions of the reactions were, when applicable, followed by NMR and/or TLC.

4.2. 5-Benzyloxy-pentan-2-one 8b

5-Hydroxy-pentan-2-one (6.00 mL, 59.2 mmol) was added dropwise over 5 min to a mixture of benzyl bromide (15.5 mL, 130 mmol), Bu_4NI (65 mg, 0.18 mmol) and NaI (27 mg, 0.18 mmol) in 50 wt % aq NaOH (16 g, 200 mmol NaOH) at rt. The resulting mixture was then stirred vigorously for 18 h at 35 °C. The mixture was diluted with Et_2O (100 mL) and water (40 mL) and the organic phase isolated. The aqueous phase was extracted with Et_2O (2 × 100 mL) and the combined organic phases were dried over $MgSO_4$, filtered and concentrated under reduced pressure. Residual benzyl bromide was distilled under reduced pressure and flash chromatography of the residue yielded **8b** (6.15 g, 54%) as a colorless oil: R_f (pentane/Et_2O 75:25) = 0.26; bp = 91–93 °C/0.3 mm Hg (lit.[18] bp = 98–100 °C/0.7 mm Hg; lit.[19] bp = 105–110 °C/0.5 mm Hg); ^1H NMR (400 MHz, $CDCl_3$): δ 7.41–7.26 (5H, m), 4.51 (2H, s), 3.51 (2H, t, *J* = 6.4 Hz), 2.58 (2H, t, *J* = 6.4 Hz), 2.16 (3H, s), 1.91 (2H, dt, *J* = 6.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 208.6 (−), 138.4 (−), 128.3 (2C, +), 127.6 (2C, +), 127.5 (+), 72.8 (−), 69.2 (−), 40.3 (−), 29.9 (+), 23.8 (−); IR (neat) 3031 (w), 2932 (m), 2860 (m), 1713 (s), 1453 (m), 1413 (m), 1362 (s), 1166 (m), 1107 (s), 738 (m), 699 (m); GC–MS (EI): *m/z* 164 (10), 107 (28), 101 (14), 92 (13), 91 (100), 85 (18), 65 (11), 58 (10). NMR spectra were in full accordance with those reported in the lit.[18,19]

4.3. General procedure for the synthesis of dienamides

To a suspension of 4 Å molecular sieves (ca. 12.5 g, dried for 24 h at 180 °C/2–4 mm Hg in flask to be used for reaction) in THF (30 mL) at rt under Ar were added the ketone

(5.2 mmol) and the amine (**9a** and **9b**: 5.7 mmol; **12**: 7.8 mmol). The mixture was then stirred vigorously for ca. 40 h at rt under Ar. The mixture was cooled to −15 °C and Et_3N (**9a** and **9b**: 1.09 mL, 7.83 mmol; **12**: 1.50 mL, 10.8 mmol) was added followed by acryloyl chloride (**9a** and **9b**: 0.55 mL, 6.77 mmol; **12**: 0.75 mL, 9.23 mmol) dropwise over 5 min. Stirring was continued for 2.5 h while allowing the mixture to heat slowly to 0 °C. After stirring for 1 h further at rt, the mixture was diluted with THF (20 mL), celite (ca. 20 mL) was added and the resulting mixture filtered, washing the solids with THF (2 × 25 mL). The filtrate was then concentrated and dried in vacuo. Flash chromatography of the residue yielded the dienamide and the isomer.

4.3.1. 4-(Acryloyl-benzyl-amino)-pent-4-enoic acid ethyl ester 9a and 4-(acryloyl-benzyl-amino)-pent-3-enoic acid ethyl ester 10a. Reaction of ethyl levulinate (0.74 mL, 5.19 mmol) with benzyl amine (0.62 mL, 5.68 mmol) following the general procedure yielded **9a** (603 mg, 40%) and **10a** (674 mg, 45%) as colorless oils. **9a**: R_f (cyclohexane/EtOAc 70:30) = 0.43; ^{1}H NMR (400 MHz, benzene-d_6): δ 7.32–7.27 (2H, m), 7.12–7.00 (3H, m), 6.66 (1H, dd, J = 16.8, 2.5 Hz), 6.50 (1H, dd, J = 16.8, 10.1 Hz), 5.35 (1H, dd, J = 10.1, 2.5 Hz), 4.64 (2H, s), 4.58 (1H, s), 4.39 (1H, s), 3.91 (2H, q, J = 7.1 Hz), 2.20 (2H, t, J = 7.2 Hz), 2.03 (2H, t, J = 7.2 Hz), 0.94 (3H, t, J = 7.1 Hz); ^{13}C NMR (100 MHz, benzene-d_6): δ 171.8 (−), 164.9 (−), 146.0 (−), 138.5 (−), 129.3–127.4 (7C, + and −), 114.9 (−), 60.4 (−), 49.0 (−), 31.3 (−), 29.5 (−), 14.2 (+); IR (neat) 3030 (w), 2982 (m), 2935 (w), 1734 (s), 1652 (s), 1618 (m), 1411 (s), 1372 (m), 1161 (m), 1106 (m), 730 (m), 701 (m); GC–MS (EI): m/z 287 (1, M^+), 214 (10), 196 (40), 186 (12), 158 (10), 150 (28), 122 (17), 91 (100), 55 (19). HRMS (TOF MS ES$^+$) calcd for $C_{17}H_{22}NO_3$ $[M+H]^+$ m/z 288.1600. Found: 288.1591. **10a**: R_f (cyclohexane/EtOAc 70:30) = 0.34; ^{1}H NMR (400 MHz, benzene-d_6): δ 7.33–7.28 (2H, m), 7.13–7.00 (3H, m), 6.70 (1H, dd, J = 16.8, 2.6 Hz), 6.57 (1H, dd, J = 16.8, 10.0 Hz), 5.40 (1H, dd, J = 10.0, 2.6 Hz), 5.12 (1H, t, J = 7.5 Hz), 4.64 (2H, s), 3.85 (2H, q, J = 7.1 Hz), 2.54 (2H, d, J = 7.5 Hz), 1.32 (3H, s), 0.89 (3H, t, J = 7.1 Hz); ^{13}C NMR (100 MHz, benzene-d_6): δ 170.0 (−), 164.6 (−), 138.6 (−), 138.5 (−), 129.4–123.4 (8C, + and −), 60.6 (−), 49.5 (−), 33.3 (−), 16.4 (+), 14.2 (+); IR (neat) 3031 (w), 2983 (m), 2935 (w), 1736 (s), 1652 (s), 1616 (m), 1412 (s), 1369 (m), 1257 (m), 1175 (m), 1030 (m), 731 (w), 702 (m); GC–MS (EI): m/z 287 (2, M^+), 214 (18), 200 (58), 160 (13), 91 (100), 55 (12). HRMS (TOF MS ES$^+$) calcd for $C_{17}H_{22}NO_3$ $[M+H]^+$ m/z 288.1600. Found: 288.1612.

4.3.2. *N*-Benzyl-*N*-(4-benzyloxy-1-methylene-butyl)-acrylamide 9b and *N*-benzyl-*N*-(4-benzyloxy-1-methyl-but-1-enyl)-acrylamide 10b. Reaction of **8b** (1.00 g, 5.20 mmol) with benzyl amine (0.62 mL, 5.68 mmol) following the general procedure yielded **9b** (698 mg, 40%) as a colorless oil and **10b** (930 mg, 53%) as a pale yellowish oil **9b**: R_f (cyclohexane/EtOAc 75:25) = 0.43; ^{1}H NMR (400 MHz, benzene-d_6): δ 7.32–7.00 (10H, m), 6.68 (1H, d, J = 16.8), 6.49 (1H, dd, J = 16.8, 10.1 Hz), 5.33 (1H, d, J = 10.1), 4.68 (2H, s), 4.59 (1H, s), 4.42 (1H, s), 4.26 (2H, s), 3.12 (2H, t, J = 6.5 Hz), 2.04 (2H, t, J = 6.5 Hz), 1.46 (2H, dt, J = 6.5 Hz); ^{13}C NMR (100 MHz, benzene-d_6): δ 164.9 (−), 147.3 (−), 139.2 (−), 138.6 (−), 129.4–127.3 (12C, + and −), 114.2 (−), 73.0 (−), 69.3 (−), 49.1 (−), 31.3 (−), 27.4 (−); IR (neat) 3031 (w), 2935 (m), 2858 (m), 1651 (s), 1617 (m), 1410 (s), 1367 (m), 1258 (w), 1218 (w), 1105 (m), 735 (m), 699 (m); GC–MS (EI): m/z 244 (19), 201 (25), 200 (15), 91 (100). HRMS (TOF MS ES$^+$) calcd for $C_{22}H_{26}NO_2$ $[M+H]^+$ m/z 336.1964. Found: 336.1971; Anal. Calcd for $C_{22}H_{25}NO_2$: C, 78.77; H, 7.51; N, 4.18. Found: C, 78.74; H, 7.57; N, 4.20. **10b**: R_f (cyclohexane/EtOAc 75:25) = 0.34; ^{1}H NMR (400 MHz, benzene-d_6): δ 7.35–7.00 (10H, m), 6.71 (1H, dd, J = 16.8, 2.6 Hz), 6.52 (1H, dd, J = 16.8, 10.1 Hz), 5.34 (1H, dd, J = 10.1, 2.6 Hz), 4.95 (1H, t, J = 7.4 Hz), 4.66 (2H, s), 4.19 (2H, s), 3.02 (2H, t, J = 6.5 Hz), 1.92 (2H, dt, J = 6.5 Hz), 1.42 (3H, s); ^{13}C NMR (100 MHz, benzene-d_6): δ 164.7 (−), 139.0 (−), 138.9 (−), 136.5 (−), 129.6–127.0 (13C, + and −), 73.0 (−), 69.2 (−), 49.4 (−), 28.8 (−), 16.4 (+); IR (neat) 3031 (w), 2922 (w), 2858 (m), 1652 (s), 1615 (m), 1412 (s), 1362 (m), 1258 (m), 1102 (m), 736 (m), 700 (m); GC–MS (EI): m/z 244 (44), 214 (15), 201 (31), 200 (17), 160 (25), 91 (100), 55 (11). HRMS (TOF MS ES$^+$) calcd for $C_{22}H_{26}NO_2$ $[M+H]^+$ m/z 336.1964. Found: 336.1975; Anal. Calcd for $C_{22}H_{25}NO_2$: C, 78.77; H, 7.51; N, 4.18. Found: C, 78.63; H, 7.61; N, 4.24.

4.3.3. *N*-(4-(Benzyloxy-1-methylene-butyl)-*N*-(1-(*S*)-phenyl-ethyl)-acrylamide 12 and *N*-(4-(benzyloxy-1-methyl-but-1-enyl)-*N*-(1-(*S*)-phenyl-ethyl)-acrylamide 13. Reaction of **8b** (2.00 g, 10.4 mmol) with (*S*)-(−)-α-methylbenzylamine (2.00 mL, 15.7 mmol) following the general procedure yielded a **12**/**13** = 89:11 mixture as a pale yellowish oil (1.59 g, 44%) and a **12**/**13** = 17:83 mixture as a pale yellowish oil (1.58 g, 43%). The following characterization of **12** was carried out on the sample containing 11% **13** as judged by NMR: R_f (cyclohexane/EtOAc 75:25) = 0.43; $[\alpha]_D^{22} = -82.8$ (*c* 1.50, MeOH); ^{1}H NMR (400 MHz, benzene-d_6): δ 7.37–6.95 (10H, m), 6.70 (1H, d, J = 16.7 Hz), 6.45 (1H, dd, J = 16.7, 10.2 Hz), 6.25 (1H, q, J = 6.9 Hz), 5.34 (1H, d, J = 10.2 Hz), 4.74 (1H, s), 4.52 (1H, s), 4.20 (2H, s), 3.05–2.93 (2H, m), 1.81–1.64 (2H, m), 1.47–1.34 (2H, m), 1.37 (3H, d, J = 6.9 Hz); ^{13}C NMR (100 MHz, benzene-d_6): δ 164.4 (−), 146.5 (−), 142.0 (−), 139.2 (−), 130.1–127.2 (12C, + and −), 116.0 (−), 72.9 (−), 69.4 (−), 51.9 (+), 33.9 (−), 27.4 (−), 17.2 (+); IR (neat) 3031 (w), 2937 (m), 2859 (m), 1650 (s), 1613 (m), 1407 (s), 1366 (m), 1322 (m), 1264 (m), 1107 (s), 739 (m), 700 (m); GC–MS (EI): m/z 294 (20), 244 (18), 215 (17), 154 (10), 136 (11), 111 (16), 106 (10), 105 (100), 103 (11), 91 (62), 79 (12), 77 (11), 55 (14); HRMS (TOF MS ES$^+$) calcd for $C_{23}H_{27}NO_2Na$ $[M+Na]^+$ m/z 372.1939. Found: 372.1935. The following characterization of **13** was carried out on the sample containing 17% **12** as judged by NMR: R_f (cyclohexane/EtOAc 75:25) = 0.41; $[\alpha]_D^{22} = -60.7$ (*c* 1.45, MeOH); ^{1}H NMR (400 MHz, benzene-d_6): δ 7.37–6.95 (10H, m), 6.72 (1H, dd, J = 16.7, 2.6 Hz), 6.45 (1H, dd, J = 16.7, 10.2 Hz), 6.33 (1H, q, J = 6.9 Hz), 5.34 (1H, dd, J = 10.2, 2.6 Hz), 5.29–4.79 (1H, m), 4.23 (2H, s), 3.19–2.98 (2H, m), 1.90 (2H, m), 1.49–1.05 (3H, m), 1.36 (3H, d, J = 6.9 Hz); ^{13}C NMR (100 MHz, benzene-d_6): δ 164.4 (−), 142.1 (−), 139.0 (−), 134.7 (−), 130.9–127.1 (13C, + and −), 73.1 (−), 69.2 (−), 52.0 (+), 29.0

(−), 19.4 (+), 17.3 (+); IR (neat) 3031 (w), 2936 (m), 2859 (m), 1659 (s), 1612 (m), 1409 (s), 1367 (m), 1322 (m), 1267 (m), 1101 (s), 741 (m), 700 (m); GC–MS (EI): *m/z* 258 (10), 244 (16), 215 (11), 154 (22), 138 (10), 124 (26), 111 (23), 106 (10), 105 (100), 103 (10), 91 (53), 84 (11), 79 (12), 77 (11), 70 (12), 55 (14); HRMS (TOF MS ES$^+$) calcd for $C_{23}H_{27}NO_2Na$ $[M+Na]^+$ *m/z* 372.1939. Found 372.1919.

4.4. General procedure for reductive photocyclization of dienamides

To a stirred solution of the dienamide (1.25 mmol) in benzene/MeOH 9:1 or toluene/MeOH 9:1 (250 mL) at rt under Ar was added $NaBH_4$ (380 mg, 10.0 mmol) and Ar was bubbled through the resulting suspension for 15 min. The resulting clear solution was irradiated under Ar in a quartz or a pyrex reactor equipped with a medium pressure mercury lamp (400 W) until TLC showed the reaction to be complete. The solvents were then evaporated and the residue dissolved in CH_2Cl_2 (30 mL) and water (20 mL). The organic phase was isolated and the aqueous phase was extracted with CH_2Cl_2 (2 × 30 mL). The combined organic phases were dried over $MgSO_4$, filtered, concentrated and dried in vacuo. Flash chromatography of the residue yielded the piperidinone(s).

4.4.1. 3-(1-Benzyl-6-oxo-piperidin-2-yl)-propionic acid ethyl ester 11a. Irradiation of **9a** (360 mg, 1.25 mmol) in benzene/MeOH 9:1 at rt for 2.75 h in a quartz reactor following the general procedure yielded **11a** (56 mg, 16%) as a colorless oil: R_f (cyclohexane/EtOAc 25:75) = 0.33; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36–7.23 (5H, m), 5.43 (1H, d, J = 15.1 Hz), 4.14 (2H, q, J = 7.1 Hz), 3.98 (1H, d, J = 15.1 Hz), 3.37–3.29 (1H, m), 2.54–2.47 (2H, m), 2.38–1.68 (8H, m), 1.26 (3H, t, J = 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.6 (−), 170.2 (−), 137.5 (−), 128.4 (2C, +), 127.7 (2C, +), 127.1 (+), 60.6 (−), 47.3 (−), 54.4 (+), 31.8 (−), 30.5 (−), 26.9 (−), 25.9 (−), 17.1 (−), 14.1 (+); IR (neat) 3029 (w), 2949 (m), 1732 (s), 1638 (s), 1452 (m), 1417 (w), 1334 (w), 1260 (m), 1185 (m), 1030 (w), 731 (w), 703 (m); GC–MS (EI): *m/z* 289 (17, M$^+$), 189 (16), 188 (71), 160 (29), 106 (11), 91 (100). HRMS (TOF MS ES$^+$) calcd for $C_{17}H_{23}NO_3Na$ $[M+Na]^+$ *m/z* 312.1576. Found: 312.1562; Anal. Calcd for $C_{17}H_{23}NO_3$: C, 70.56; H, 8.01; N, 4.84. Found: C, 70.59; H, 8.02; N, 4.87.

4.4.2. 1-Benzyl-6-(3-benzyloxy-propyl)-piperidin-2-one 11b. Irradiation of **9b** (420 mg of a mixture of 68.0 mol %/78.8 wt % **9b** and 32.0 mol %/21.2 wt % **8b** as judged by NMR; thus effectively 331 mg, 0.99 mmol **9b**) in benzene/MeOH 9:1 at rt for 2.5 h in a quartz reactor following the general procedure yielded **11b** (127 mg, 37%) as a colorless oil; R_f (EtOAc) = 0.64; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41–7.20 (10H, m), 5.41 (1H, d, J = 15.1 Hz), 4.50 (2H, s), 3.95 (1H, d, J = 15.1 Hz), 3.45 (2H, t, J = 6.5 Hz), 3.37–3.28 (1H, m), 2.55–2.45 (2H, m), 2.30–1.42 (8H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.1 (−), 138.1 (−), 137.5 (−), 128.3–126.9 (10C, +), 72.8 (−), 69.6 (−), 55.0 (+), 47.2 (−), 31.8 (−), 28.6 (−), 26.0 (−), 25.9 (−), 17.1 (−); IR (neat) 3030 (w), 2946 (m), 2865 (m), 1636 (s), 1453 (m), 1415 (w), 1358 (m), 1259 (w), 1100 (m), 738 (m), 701 (m); GC–MS (EI): *m/z* 337 (4, M$^+$), 246 (29), 218 (20), 189 (13), 188 (72), 160 (15), 91 (100). NMR spectra were in full accordance with those reported in the lit.[20]

4.4.3. (*S*)-6-(3-Benzyloxy-propyl)-1-(1′-(*S*)-phenyl-ethyl)-piperidin-2-one 15 and (*R*)-6-(3-benzyloxy-propyl)-1-(1′-(*S*)-phenyl-ethyl)-piperidin-2-one 16. Irradiation of **12** (1.74 g of a **12**/**13** = 89:11 mixture; thus effectively 1.31 g, 3.74 mmol **12**) in toluene/MeOH 9:1 (1 L) at rt for 2.5 h in a quartz reactor following the general procedure yielded **15**/**16** as an inseparable 75:25 mixture (611 mg, 46%) as a colorless oil. The following characterization of **15**/**16** was carried out on a 79:21 mixture, as judged by NMR: R_f (cyclohexane/EtOAc 25:75) = 0.48; $[\alpha]_D^{22} = -90.4$ (*c* 0.50, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41–7.20 (10H, m), 5.94 (0.21H, q, J = 7.1 Hz, CH_3CHN, **16**), 5.74 (0.79H, q, J = 7.1 Hz, CH_3CHN, **15**), 4.50 (0.42H, s, OCH_2Ph, **16**), 4.40 (1.58H, s, OCH_2Ph, **15**) 3.49–3.41 (1.24H, m, NC*H*, **16** and OCH_2CH_2, **15**), 3.19–3.08 (1.76H, m, NC*H*, **15** and OCH_2CH_2, **16**), 2.54–2.43 (2H, m), 1.94–0.82 (8H, m), 1.59 (3H, d, J = 7.1 Hz, CH_3CHN); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.2 (−, **16**), 169.8 (−,**15**), 141.0 (−), 140.7 (−), 138.3 (−), 128.2–127.0 (10C, +), 72.8 (−, **16**), 72.7 (−, **15**), 69.7 (−, **15**), 69.6 (−, **16**), 53.3 (+, **15**), 52.5 (+, **15**), 52.2 (+, **16**), 51.8 (+,**16**), 31.1 (−, **15**), 30.8 (−, **16**), 30.4 (−, **16**), 29.4 (−, **15**), 26.6 (−, **16**), 26.5 (−, **15**), 25.8 (−, **15**), 25.2 (−, **16**), 15.9 (−, **15**), 15.9 (−, **16**), 17.4 (+, **16**), 16.3 (+, **15**); IR (neat) 3030 (w), 2946 (m), 2866 (m), 1635 (s), 1452 (m), 1362 (w), 1292 (w), 1101 (m), 739 (m), 700 (m); GC–MS (EI): *m/z* 351 (35, M$^+$), 260 (20), 232 (11), 202 (22), 156 (18), 138 (16), 120 (39), 106 (11), 105 (100), 104 (13), 103 (10), 98 (89), 91 (72), 79 (14), 77 (13), 55 (10). HRMS (TOF MS ES$^+$) calcd for $C_{23}H_{30}NO_2$ $[M+H]^+$ *m/z* 352.2277. Found: 352.2281.

4.5. (*S*)-2-(3-Benzyloxy-propyl)-1-(1′-(*S*)-phenyl-ethyl)-piperidine 17 and (*R*)-2-(3-benzyloxy-propyl)-1-(1′-(*S*)-phenyl-ethyl)-piperidine 18

To a stirred suspension of $LiAlH_4$ (104 mg, 2.74 mmol) in THF (35 mL) under Ar at 0 °C was added dropwise a solution of **15**/**16** (383 mg, 1.09 mmol) in THF (5 mL). The resulting mixture was then refluxed for 4 h, until TLC (cyclohexane/EtOAc 25:75) showed the reaction to be complete. The mixture was cooled to 0 °C and the reaction was quenched by the dropwise addition of water (ca. 10 drops). The mixture was then dried over $MgSO_4$ and filtered through celite, washing the solids with THF (ca. 75 mL). The clear filtrate was concentrated and dried in vacuo and flash chromatography of the residue yielded **18** (58 mg, 16%) as an orange oil and **17** (223 mg, 61%) as a yellowish oil. **17**: R_f (cyclohexane/EtOAc 1:1) = 0.25; $[\alpha]_D^{22} = -68.4$ (*c* 1.00, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41–7.20 (10H, m), 4.52 (2H, s), 4.06 (1H, q, J = 6.4 Hz), 3.47 (2H, t, J = 6.3 Hz), 2.81–2.69 (1H, m), 2.51–2.40 (1H, m), 2.36–2.35 (1H, m), 1.82–1.20 (10H, m), 1.38 (3H, d, J = 6.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 143.5 (−), 138.7 (−), 128.2–126.5 (10C, +), 72.7 (−), 70.7 (−), 57.4 (+), 55.4 (+), 44.2 (−), 28.9 (−), 26.1 (−), 25.3 (−), 24.6 (−), 21.5 (−), 20.9 (+); IR (neat) 3028 (w), 2932 (s), 2856 (m), 1453 (m), 1363 (w), 1104 (s), 735 (m), 700

(s); GC–MS (EI): *m/z* 246 (19), 189 (16), 188 (100), 105 (46), 91 (21), 84 (48). HRMS (TOF MS ES$^+$) calcd for $C_{23}H_{32}NO$ $[M+H]^+$ *m/z* 338.2484. Found: 338.2499. **18**: R_f (cyclohexane/EtOAc 1:1) = 0.48; $[\alpha]_D^{21} = -6.4$ (*c* 0.50, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.47–7.20 (10H, m), 4.53 (2H, s), 4.05 (1H, q, $J = 6.6$ Hz), 3.51 (2H, t, $J = 6.0$ Hz), 2.83–2.72 (1H, m), 2.46–2.37 (1H, m), 2.32–2.19 (1H, m), 1.82–1.24 (10H, m), 1.28 (3H, d, $J = 6.6$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 146.1 (−), 138.6 (−), 128.3–126.2 (10C, +), 72.8 (−), 70.8 (−), 56.7 (+), 55.5 (+), 44.9 (−), 29.4 (−), 25.7 (−), 25.6 (−), 25.2 (−), 22.6 (−), 14.5 (+); IR (neat) 3029 (w), 2933 (s), 2856 (m), 1452 (m), 1364 (w), 1104 (s), 734 (m), 699 (s); GC–MS (EI): *m/z* 246 (18), 189 (16), 188 (100), 105 (47), 91 (20), 84 (50). HRMS (TOF MS ES$^+$) calcd for $C_{23}H_{32}NO$ $[M+H]^+$ *m/z* 338.2484. Found: 338.2480.

4.6. (*S*)-3-Piperidin-2-yl-propan-1-ol (19) and (+)-coniceine hydrobromide 1·HBr

To a solution of **17** (304 mg, 0.901 mmol) in MeOH (40 mL) under Ar at rt was added ammonium formate (568 mg, 9.01 mmol) and 10% Pd/C (205 mg). The resulting mixture was then refluxed for 16.5 h. The mixture was filtered through Celite, washing the filter cake with a little MeOH. The filtrate was concentrated and dried in vacuo. The residual oil, which contained some solids, was then redissolved in CH_2Cl_2 (5 mL) and the suspension filtered though a cellulose plug, washing the plug with a little CH_2Cl_2. The filtrate was concentrated and dried in vacuo, yielding the crude amino alcohol **19** (143 mg) as a pale yellowish oil, which showed NMR spectra in full accordance with those reported in the lit. for the racemate[2a]: ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.61–3.54 (1H, m), 3.53–2.46 (1H, m), 3.08–3.01 (1H, m, $J = 12.5$ Hz), 2.58 (1H, ddd, $J = 12.5$, 12.5, 2.9 Hz), 2.50–2.42 (1H, m), 1.84–1.66 (2H, m), 1.65–1.51 (4H, m), 1.47–1.08 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 62.2 (−), 56.5 (+), 46.1 (−), 35.1 (−), 32.5 (−), 29.9 (−), 25.9 (−), 24.3 (−); GC–MS (EI): *m/z* 143 (1, M^+) 84 (100), 56 (11). The crude amino alcohol was dissolved in MeCN (9 mL) at rt under Ar and PPh_3 (445 mg, 1.697 mmol) and CBr_4 (660 mg, 1.990 mmol) were added. The resulting mixture was stirred at rt for 15 h and was then poured into 5% aq HBr (25 mL) and the mixture was washed with EtOAc (20 mL and 4 × 10 mL). The aqueous phase was basified by addition an excess of Na_2CO_3 and was then extracted with Et_2O (8 × 10 mL). The combined organic phases were extracted with 5% aq HBr (5.0 and 2.5 mL) and the combined aqueous phases were concentrated and dried in vacuo yielding a pale tan paste (ca. 255 mg) containing chloroform-insoluble salts. The residue was suspended in $CHCl_3$ (10 mL) and the supernatant was filtered through a cellulose plug and the filtrate was concentrated and dried in vacuo. The residue (170 mg, pale tan paste) was dissolved in EtOH (0.5 mL) and Et_2O (ca. 15 mL) was added dropwise until precipitation was complete. The supernatant was removed and the residual solids were dried in vacuo, yielding (+)-**1·HBr** (107 mg, 58%) as a pale tan solid: mp = 195.5–198.5 °C (lit.[16] mp = 198–199 °C for (±)-**1·HBr**); $[\alpha]_D^{22} = +5.5$ (*c* 0.88, EtOH); ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.0–10.5 (1H, br s), 3.83–3.72 (1H, m), 3.66 (1H, br d, $J = 10.4$ Hz), 3.00–2.86 (1H, m), 2.77–2.59 (2H, m), 2.38–1.93 (8H, m), 1.87 (1H, br d, $J = 14.7$ Hz), 1.56–1.41 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 67.2 (+), 52.4 (−), 51.9 (−), 28.3 (−), 27.3 (−), 22.6 (−), 22.5 (−), 19.4 (−). NMR spectra were in full accordance with those reported in the lit. for (±)-**1·HBr**.[16]

The free amine **1** was obtained by dissolving (+)-**1·HBr** (ca. 80 mg) in satd aq Na_2CO_3 (0.75 mL). The mixture was extracted with Et_2O (4 × 0.75 mL) and the combined organic phases were distilled over K_2CO_3 in a Kugelrohr apparatus, yielding (+)-**1** (ca. 40 mg) as a colorless oil: bp = 100–105 °C/140 mm Hg (lit.[16] bp = 59–60 °C/19 mm Hg; lit.[21] bp = 75–80 °C/25 mm Hg); $[\alpha]_D^{22} = +9.5$ (*c* 1.13, EtOH) {lit.[16] $[\alpha]_D^{23} = 9.3 \pm 0.6$ (*c* 1.76, EtOH)}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.15–3.02 (2H, m), 2.08 (1H, q, $J = 9.0$ Hz), 1.98 (1H, dt, $J = 11.2$, 3.5 Hz), 1.92–1.52 (8H, m), 1.48–1.36 (1H, m), 1.30–1.16 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 64.5 (+), 54.2 (−), 53.0 (−), 30.9 (−), 30.4 (−), 25.3 (−), 24.4 (−), 20.6 (−); GC–MS (EI): *m/z* 125 (47, M^+), 124 (100), 97 (53), 96 (57), 83 (33), 82 (10), 69 (27), 68 (11), 55 (10). NMR spectra were in full accordance with those reported in the lit.[3d,i]

4.7. Determination of enantiomeric purity using NMR

When adapting the lit. NMR method[17] for determination of enantiomeric ratios of organic ammonium halides, the peak originally at 28.31 ppm in the ^{13}C NMR spectrum for (±)-**1·HBr** split into two separate, equally intense peaks at 28.22 and 28.15 ppm. When an identical experiment was performed on (+)-**1·HBr** only the peak at 28.15 ppm was visible. This latter sample was therefore deduced as having ee >97% (detection limit of the analytical technique).

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