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Concise Chemoenzymatic Three-Step Total Synthesis of Isosolenopsin through Medium Engineering

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A short and efficient total synthesis of the alkaloid isosolenopsin and its enantiomer has been achieved. The key step was a ω-transaminase-catalysed regioselective monoamination of the diketone pentadecane-2,6-dione, which was obtained in a single step through the application of a Grignard reaction. Initial low conversions in the biotransformation could be overcome by optimisation of the reaction conditions employing suitable cosolvents. In the presence of 20 vol.-% *N*,*N*-dimethylformamide (DMF) or *n*-heptane the best results were obtained by employing two enantiocomplementary ω-transaminases originating from *Arthrobacter* at 30–40 °C; under these conditions, conversions of more than 99 % and perfect stereocontrol (*ee* > 99 %) were achieved. Diastereoselective chemical reduction (H_2/Pd/C) of the biocatalytic product gave the target compound. The linear three-step synthesis provided the natural product isosolenopsin in diastereomerically pure form (*ee* > 99 %, *dr* = 99:1) with an overall yield of 64 %.

Introduction

Functionalised chiral piperidines are popular key elements in a vast number of synthetic protocols and are among the most common skeletal fragments found in natural products.[1] Due to the wide range of useful pharmacological properties, extensive efforts have been devoted to the (stereoselective) synthesis of such compounds.[2] In particular, simple 2,6-disubstituted piperidines constitute an important class of natural products due to their biological activity and abundant occurrence in nature. Prominent examples are the secreted fire ant venom alkaloids from *Solenopsis invitica*; selected members of this family were found to display cytotoxic, insecticidal, hemolytic, antibacterial, antifungal and necrotic properties.[3] Furthermore, physiological investigations revealed that for example, isosolenopsin A (**1b**) selectively inhibits designated neuronal nitric oxide synthases (nNOS),[4] whereas solenopsin A (**2b**) inhibits the regulator protein phosphatidylinositol-3-kinase (PI3K); the latter is involved in controlling apoptosis, proliferation and angiogenesis.[5]

These diverse biological activities and the apparent simple structure of piperidines (Figure 1) have made attractive targets to study and showcase new synthetic methods. Several racemic and asymmetric total syntheses have been reported based on chiral pool precursors and catalytic (asymmetric) transformations, in addition to electrochemical and auxiliary controlled methods.[6] Although several routes are very elegant and involve highly sophisticated key steps, the long reaction sequences and the use of an orthogonal protecting-group strategy has hampered their overall efficiency. Hence, more capable and environmental begin methods are still desired.

n = 8: Isosolenopsin (**1a**)
n = 10: Isosolenopsin A (**1b**)
n = 12: Isosolenopsin B (**1c**)
n = 14: Isosolenopsin C (**1d**)

n = 8: Solenopsin (**2a**)
n = 10: Solenopsin A (**2b**)
n = 12: Solenopsin B (**2c**)
n = 14: Solenopsin C (**2d**)

Figure 1. Secreted fire ant venom alkaloids and their structure.

Recently, we demonstrated that 2,6-diketones **3** serve as useful precursors for the synthesis of the optically pure 2,6-disubstituted piperidine scaffold **8** through enzymatic reductive amination (Scheme 1).[7] A ω-transaminase (ω-TA)[8–10] catalysed regio- and stereoselective monoamination of **3** at the sterically less demanding (ω-1)-keto moiety, yielding preferentially amino-ketone **4**, which underwent spontaneous ring-closure to give the corresponding Δ1-piperideines **6** in enantiomerically pure form. Based on this

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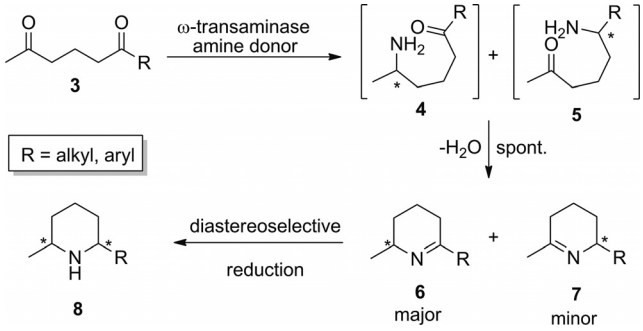
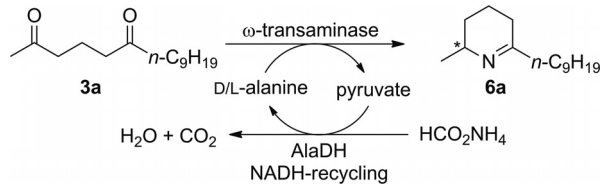
concept, we now report an extension of this method for the total synthesis of isosolenopsin [(2*S*,6*R*)-**1a**] and its enantiomer (2*R*,6*S*)-**1a**.[11]



Scheme 1. Chemoenzymatic asymmetric synthesis of 2,6-disubstituted piperidines involving regio- and stereoselective monoamination.

Results and Discussion

Various enantiocomplementary ω-TAs were tested for the transformation of diketone **3a** into the corresponding Δ1-piperideines **6a** and **7a** under designated reaction conditions by employing alanine as amine donor (Scheme 2). The equilibrium was shifted towards the product side by removal/recycling of the formed pyruvate with an alanine-dehydrogenase (AlaDH).[12] Unfortunately, only low conversions were achieved, probably due to the low solubility of diketone **3a** in pure buffer solution. Subsequently, various water-miscible organic solvents [acetonitrile, tetrahydrofuran (THF), *N*,*N*-dimethylformamide (DMF), 1,2-dimethoxyethane (DME), dimethyl sulfoxide (DMSO)] and immiscible solvents (EtOAc, toluene) were assayed at 10 vol.-%. Although most of the investigated ω-TAs gave insufficient conversions (less than 5%), four showed conversions of around 25%, rendering them targets for a more detailed study. Notably, regioisomer **7a** was not detected for any enzyme investigated (see the Supporting Information).



Scheme 2. Monoamination of diketone **3a** to yield Δ1-piperideine **6a**. *Reagents and conditions:* lyophilised *E. coli* cells containing the overexpressed ω-TA (20 mg), diketone **3a** (12 mg, 50 mM), PLP (1 mM), NAD^+ (1 mM), ammonium formate (150 mM), D- or L-alanine (500 mM), AlaDH (12 U), FDH (11 U), organic cosolvent and KPi buffer (100 mM, pH 7.0), 30 °C, 24 h in an Eppendorf orbital shaker (700 rpm).

Focussing on the four most promising ω-TAs identified, originating from *Arthrobacter citreus*,[13c] *Arthrobacter* sp.[13d] *Pseudomonas fluorescens*,[13a,13b] and *Hyphomonas neptunium*,[9f] the influence of the concentration of water-miscible (DMF, DME, DMSO) and immiscible (toluene) solvents at concentrations in the range 5–40 vol.-% was investigated [for the analytical scale: 25 mM **3a** (6 mg/mL); 1.00 mL total volume]. The first two enzymes are (*S*)-selective, whereas the latter two are (*R*)-selective. The conversion obtained depended on the solvent and on the enzyme employed (Figure 2); whereas the use of enzymes from *P. fluorescens* and *H. neptunium* led to conversions of 25% at maximum, the two enantiocomplementary ω-TAs from *Arthrobacter* turned out to be superior. For example, the (*S*)-selective ω-TA from *A. citreus* gave conversions up to 60% when DMF was applied. Notably, increasing the concentration of DMF led to higher conversions, whereas the reverse trend was observed for toluene or DME as cosolvent. In the case of toluene, this is probably due to the lower availability of the organic substrate in the aqueous phase. An analogous observation was made for the ω-TA from (*R*)-*Arthrobacter* sp. For this enzyme, piperidine **6a** was obtained with 60% conversion by applying 5 vol.-% toluene and 80% conversion in the presence of 40 vol.-% DMF.

Having identified two suitable enzymes with opposite stereopreference [*Arthrobacter citreus* for the (*S*)- and

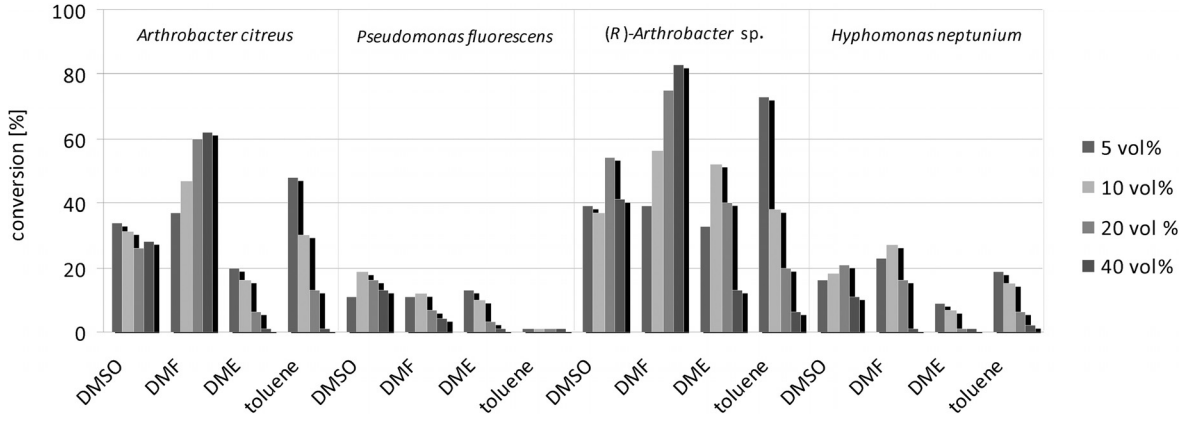


Figure 2. Conversions for the monoamination of diketone **3a** in the presence of various organic cosolvents employing (*R*)- and (*S*)-selective ω-TAs. *Reagents and conditions:* diketone **3a** (6 mg/mL, 25 mM), lyophilised *E. coli* cells containing overexpressed ω-TA (20 mg), PLP (1 mM), NAD^+ (1 mM), ammonium formate (150 mM), D- or L-alanine (500 mM), AlaDH (12 U), FDH (11 U), organic cosolvent, K-phosphate buffer (100 mM, pH 7.0), 30 °C, 24 h in an Eppendorf orbital shaker (700 rpm).

Arthrobacter sp. for the (*R*)-enantiomer] and cosolvents, further optimisation of temperature and pH was conducted. The biocatalytic monoamination of **3a** was tested at different pH values (ranging from 6.5 to 9.9) at varied DMF concentrations (20 and 40 vol.-%) (Figure 3). Subsequently, the conversion was studied as a function of temperature at varied DMF concentrations (20 and 40 vol.-%; Figure 4). Thereby, the highest conversion was obtained for the asymmetric reductive amination of diketone **3a** at 20 vol.-% DMF, pH 6.5, and 30 °C with the ω-TA originating from (*R*)-*Arthrobacter* sp., whereas 20 vol.-% DMF (pH 7.0) and elevated temperatures of 40 °C were best suited for the (*S*)-selective ω-TA of *Arthrobacter citreus*.

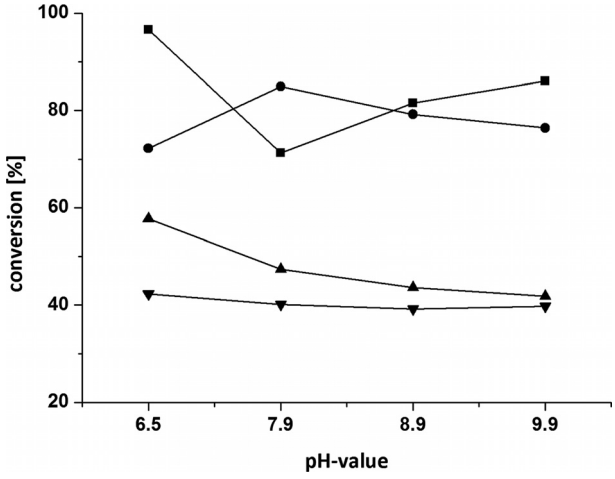


Figure 3. Influence of pH on the conversion of diketone **3a** at varying DMF concentrations: (●) 20 vol.-% DMF, (*R*)-*Arthrobacter* sp., (■) 40 vol.-% DMF, (*R*)-*Arthrobacter* sp., (▲) 20 vol.-% DMF, *A. citreus*, (▼) 40 vol.-% DMF, *A. citreus*. *Reagents and conditions:* diketone **3a** (25 mM), lyophilised *E. coli* cells containing the overexpressed ω-TA (20 mg), PLP (1 mM), NAD^+ (1 mM), ammonium formate (150 mM), D- or L-alanine (500 mM), AlaDH (12 U), FDH (11 U), 20–40 vol.-% DMF, KPi buffer (100 mM), 30 °C, 24 h, 700 rpm.

Although conversions above 95% were achieved by employing the reaction conditions mentioned above, *n*-heptane was also investigated due to the similarity in polarity of the solvent to the starting material **3a** (Figure 5). For solubility reasons, the substrate still needed to be predissolved in DMF (5 vol.-% final conc.). Despite the formation of a biphasic system, the reaction resulted in full conversion (> 99%) at 20 vol.-% *n*-heptane for the ω-TA from (*R*)-*Arthrobacter* sp. and 85% conversion for the (*S*)-ω-TA from *Arthrobacter*.

The synthetic potential was finally demonstrated in the total synthesis of both enantiomers of isosolenopsin [(2*S*,6*R*)-**1a** and (2*R*,6*S*)-**1a**]. Starting with a Grignard reaction, the required diketone **3a** was obtained in a single step from commercially available dihydropyrane-2-one **9** in 65% yield (Scheme 3). The subsequent biotransformation was conducted under the optimised conditions on an increased scale (36 mg, 0.15 mmol, 25 mM); the ω-TA of *Arthrobacter* sp. gave access to the (*R*)-enantiomer, whereas the ω-TA of *Arthrobacter citreus* gave the (*S*)-enantiomer of piperidine

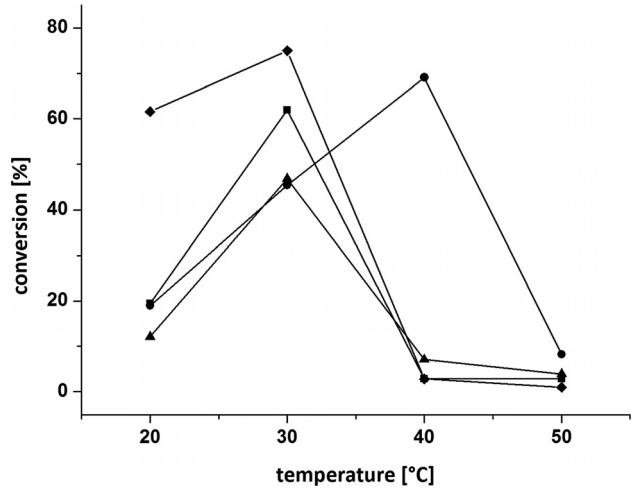


Figure 4. Influence of temperature on the conversion of diketone **3a** at varying DMF concentrations: (♦) 40 vol.-% DMF, (*R*)-*Arthrobacter* sp., (■) 20 vol.-% DMF, (*R*)-*Arthrobacter* sp., (●) 20 vol.-% DMF, *A. citreus*, (▲) 40 vol.-% DMF, *A. citreus*. *Reagents and conditions:* diketone **3a** (25 mM), lyophilised *E. coli* cells containing the overexpressed ω-TA (20 mg), PLP (1 mM), NAD^+ (1 mM), ammonium formate (150 mM), D- or L-alanine (500 mM), AlaDH (12 U), FDH (11 U), 20–40 vol.-% DMF, KPi buffer (100 mM, pH 7.0), 20–50 °C, 24 h, 700 rpm.

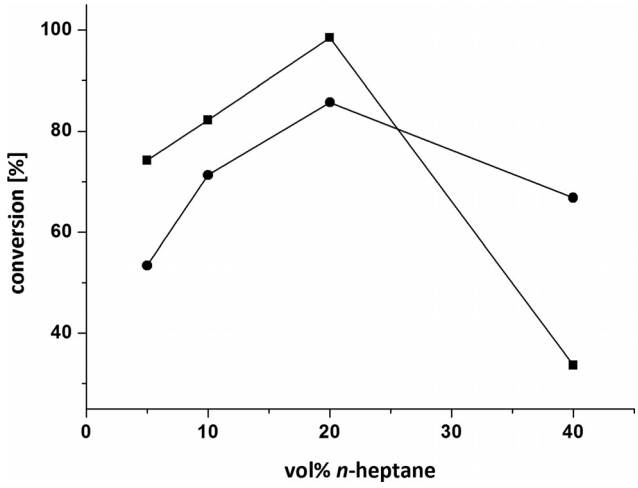
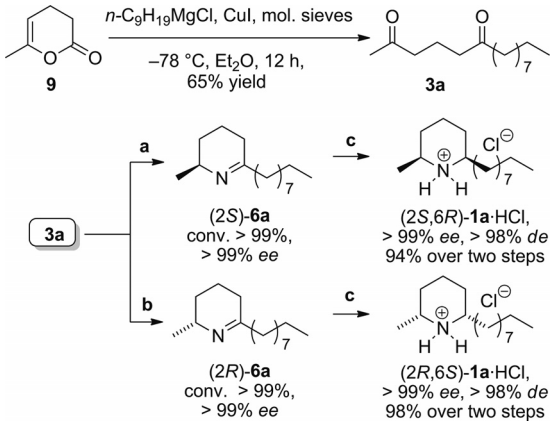


Figure 5. Reductive amination of diketone **3a** in an aqueous two-phase system: (■) (*R*)-*Arthrobacter* sp., (●) *A. citreus*. *Reagents and conditions:* diketone **3a** (25 mM) dissolved in 5 vol.-% DMF, lyophilised *E. coli* cells containing the overexpressed ω-TA (20 mg), PLP (1 mM), NAD^+ (1 mM), ammonium formate (150 mM), D- or L-alanine (500 mM), AlaDH (12 U), FDH (11 U), 5–40 vol.-% *n*-heptane, KPi buffer (100 mM, pH 7.0), 30 °C, 24 h, 700 rpm.

6a. Both reactions yielded the corresponding cyclic imine (*R*)- and (*S*)-**6a**, respectively, in optically pure form (*ee* > 99%) at full conversion (> 99% in both cases). Notably, the reaction times were prolonged (48 h) to ensure full conversion and hence simplify the work up procedures. Due to the instability of imine **6a**, it was directly subjected to diastereoselective reduction using hydrogen with Pd/C as catalyst after extraction. Under these conditions, the second stereocentre was established under perfect substrate control, affording the natural product (2*S*,6*R*)-**1a** and (2*S*,6*R*)-**1a** in

diastereomerically pure form [*dr* (*syn*/*anti*) = 99% as deduced by GC and NMR analysis] in an excellent yield of 94–98% (over two steps). Thus, starting from pyranone **9**, the natural alkaloids (+)-**1a** and (–)-**1a** were obtained in optically pure form in 64% overall yield.



Scheme 3. Chemoenzymatic synthesis of both enantiomers of isosolenopsins (2*S*,6*R*)-**1a** and (2*R*,6*S*)-**1a** under the optimised reaction conditions. *Reagents and conditions:* (a) Diketone **3a** (36 mg, 0.15 mmol, 25 mM) dissolved in DMF (20 vol.-%), ω-TA from *Arthrobacter citreus*, PLP (1 mM), NAD^+ (1 mM), L-alanine (20 equiv.), ammonium formate (150 mM), 11 U FDH, 12 U AlaDH, 48 h, 40 °C, 700 rpm; (b) same as for (a) but with the ω-TA from (*R*)-*Arthrobacter* sp. at 30 °C with D-alanine and 20 vol.-% *n*-heptane, 5 vol.-% DMF; (c) Pd/C, H_2 (1 atm.), 4 h, 22 °C; precipitation with etherial HCl solution (5 equiv.).

Conclusions

An efficient chemoenzymatic total synthesis of the alkaloid isosolenopsin and its enantiomer has been achieved by using a regioselective monoamination of the corresponding diketone in the key step. Optimisation of the biocatalytic reaction conditions through medium engineering allowed initial low conversions to be overcome. Among various organic solvents tested, *n*-heptane and DMF turned out to be best suited at 30 °C for the (*R*)-selective ω-TA from *Arthrobacter* sp. and at 40 °C for the (*S*)-selective ω-TA from *Arthrobacter citreus*. The final asymmetric reductive monoamination of diketone **3a** proceeded with perfect regio- and stereoselectivity at full conversions. This strategy afforded the natural product in optically pure form with an overall yield of 64–65% over three steps.

Experimental Section

General: All starting materials were obtained from commercial suppliers and used as received unless stated otherwise. Petroleum ether (PE), where used, had a boiling range 63–69 °C. The reactions were carried out with standard Schlenk techniques under an N_2 atmosphere in oven-dried (120 °C) glassware. Preparative chromatographic separations were performed by column chromatography on Merck silica gel 60 (0.063–0.200 mm). TLC was carried out with precoated aluminium sheets (TLC Silica gel 60 F254, Merck) with detection by staining with cerium molybdenum solution or visualisation by UV. Optical rotation was measured at 20 °C with a Perkin–Elmer Polarimeter 341. GC–MS spectra were recorded with an Agilent 7890A GC-system, equipped with an Agilent 5975C mass-selective detector and a HP-5 MS column (30 m × 0.25 mm × 0.25 μm; hydrogen as carrier gas [flow = 0.55 mL/min]). ^1H and ^{13}C NMR spectra were recorded at 20 °C with a 300 Bruker NMR unit spectrometer; chemical shifts are given in ppm relative to Me_4Si (^1H: Me_4Si = 0 ppm) or relative to the resonance of the solvent (^1H: $CDCl_3$ = 7.26 ppm; ^{13}C: $CDCl_3$ = 77.0 ppm). Formate dehydrogenase from *Candida boidinii* (2.2 Umg^{-1}) [one unit will oxidize 1.0 μmol of formate to CO_2 per min at pH 7.6 at 37 °C] was purchased from Codexis (catalogue no. FDH 002). Lyophilised *E. coli* cells containing overexpressed ω-TA were prepared as previously reported.[9a,9b,9g] Purified recombinant L-alanine dehydrogenase was prepared as described in the literature (15 μL of the crude solution are equal to 12 U).[9b]

Pentadecane-2,6-dione (3b): CuI (340 mg, 1.78 mmol) was added to a stirred solution of *n*-$C_9H_{19}MgBr$ (1 M in Et_2O, 8.82 mL, 8.82 mmol)] in Et_2O (30 mL) and MS 3 Å (50 mg) in one portion. The mixture was stirred for 30 min at 21 °C and then cooled to –78 °C. Dihydro-2*H*-pyran-2-one **9** (1.00 g, 8.92 mmol) was added dropwise by using a syringe over a period of 15 min. The reaction mixture was kept at –78 °C, then Grignard reagent (0.5 equiv., 4.46 mL, 4.46 mmol) was added after 4 h and a further portion of Grignard reagent (0.5 equiv., 4.46 mL, 4.46 mmol) was added after 8 h. When TLC monitoring revealed full conversion of the starting material (10 h), the mixture was treated with aqueous HCl solution (1 N, 30 mL) and allowed to warm to room temperature. The reaction mixture was extracted with small portions of EtOAc (4×) and the organic layer was dried with $MgSO_4$. Subsequent filter flash chromatography (PE/EtOAc, 90:10) of the concentrated solution afforded the diketone in 65% yield (1.39 g, 5.79 mmol) as a colourless powder. Spectroscopic data are in agreement with those previously published.[14] M.p 65–66 °C. R_f = 0.49 (PE/EtOAc, 80:20). ^1H NMR (300 MHz, $CDCl_3$): δ = 0.84 (t, $^3J_{15,14}$ = 6.7 Hz, 3 H, 15-H), 1.22 (br. s, 12 H, 9-H, 10-H, 11-H, 12-H, 13-H and 14-H), 1.50 (tt, $^3J_{8,7}$ = 7.3, $^3J_{8,9}$ = 6.6 Hz, 2 H, 8-H), 1.80 (tt, $^3J_{4,3}$ = 7.2, $^3J_{4,5}$ = 7.1 Hz, 2 H, 4-H), 2.09 (s, 3 H, 1-H), 2.30 (t, $^3J_{7,8}$ = 7.5 Hz, 2 H, 7-H), 2.37 (t, $^3J_{3,4}$ = 7.2 Hz, 2 H, 3-H), 2.40 (t, $^3J_{5,4}$ = 7.2 Hz, 2 H, 5-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.2 (C-15), 17.8 (C-4), 22.7 (C-14), 23.9 (C-8), 29.3 (C-11), 29.3 (C-12), 29.5 (C-10), 29.5 (C-9), 30.0 (C-1), 31.9 (C-13), 41.5 (C-3), 42.6 (C-5), 42.9 (C-7), 208.5 (C-2), 210.9 (C-6) ppm. GC–MS (EI, 70 eV): *m*/*z* (%) = 240 (1) [M^+], 155 (15) [$C_{10}H_{19}O^+$], 128 (82) [$C_7H_{12}O_2^+$], 85 (65) [$C_5H_9O^+$], 43 (100) [$C_2H_3O^+$].

Optimisation of Reaction Conditions (Analytical Scale): Lyophilised cells of *E. coli* containing the corresponding overexpressed ω-TA (20 mg) were rehydrated in potassium phosphate buffer (100 mM at varying pH as indicated in Figures 2, 3, 4, and 5) containing PLP (1.0 mM), NAD^+ (1.0 mM), ammonium formate (150 mM), FDH (11 U), Ala-DH (12 U) and D- or L-alanine (500 mM) at room temperature for 30 min. Substrate **3a** (6 mg, 25 mM, dissolved in the corresponding organic solvent as indicated in Figures 2, 3, 4, and 5) was then added and the reductive amination was performed at defined temperature as indicated (Figures 2, 3, 4, and 5) in an Eppendorf orbital shaker (700 rpm, vertical position) for 24 h. After the period of time, the reaction was stopped by addition of saturated Na_2CO_3 (200 μL) and vigorous shaking. The mixture was extracted with EtOAc (3 × 500 μL) and the combined organic layers were dried with $MgSO_4$ and an aliquot was withdrawn for further analysis. Conversions were determined by GC analysis on an achiral phase [column HP-5 (Agilent); carrier gas: hydrogen; temperature program: 100 to 250 °C at 10 °C min^{-1}]: R_t = 8.7 (**6a**), 10.6

(**3a**) min. Determination of enantiomeric excess by GC analysis on a chiral phase [column DEX-CB (Agilent; CP-Chirasil); carrier gas: helium; temperature program: 60 °C (1 min), then 60→90 °C at 5.0 °C min^{-1} then 90→180 °C at 2 °C min^{-1}]: R_t = 37.23 [(2*R*)-**6a**], 37.41 [(2*S*)-**6a**] min.

Biocatalytic Synthesis of Δ^1-Piperideine (*R*)-6a (Preparative Scale): Lyophilised cells of *E. coli* containing overexpressed ω-TA from (*R*)-*Arthrobacter* sp. (125 mg) were rehydrated in K-phosphate buffer (4.8 mL, pH 6.5, 100 mM) containing PLP (1 mM), NAD^+ (1 mM), ammonium formate (150 mM), FDH (11 U), Ala-DH (12 U) and D-alanine (500 mM) at 22 °C for 30 min. Substrate **3a** [36 mg (dissolved in 300 μL DMF), 0.15 mmol, 25 mM], and *n*-heptane (1.2 mL) was added afterwards and the reaction was shaken for 48 h at 30 °C. Saturated aqueous Na_2CO_3 solution was added (1 mL) and the reaction mixture was extracted with EtOAc (4× 5 mL). Combined organic layers were dried with Na_2SO_4, filtered and converted without further purification. The conversion and optical purity was determined as described above. GC–MS (EI+, 70 eV): *m*/*z* (%) = 223 (2) [M^+], 124 (25) [$C_8H_{14}N^+$], 111 (100) [$C_7H_{13}N^+$], 96 (61) [$C_6H_{10}N^+$].

Biocatalytic Synthesis of Δ^1-Piperideine (*S*)-6a (Preparative Scale): Lyophilised cells of *E. coli* containing overexpressed ω-TA from *Arthrobacter citreus* (125 mg) were rehydrated in KPi buffer (5.7 mL, pH 6.5, 100 mM) containing PLP (1 mM), NAD^+ (1 mM), ammonium formate (150 mM), FDH (11 U), Ala-DH (12 U) and L-alanine (500 mM) at 22 °C for 30 min. Substrate **3a** [36 mg (dissolved in 1.2 mL of DMF), 0.15 mmol, 25 mM] was added and the reaction was shaken for 48 h at 40 °C. Saturated Na_2CO_3 solution was added (0.50 mL) and the reaction mixture was extracted with EtOAc (4× 5 mL). The combined organic layers were dried with Na_2SO_4, filtered and converted without further purification. The conversion and optical purity was determined as described above.

Diastereoselective Reduction; Typical Synthesis of (–)-Isosolenopsin [(2*S*,6*R*)-1a]: A crude solution of the biotransformation containing the corresponding cyclic imine (*S*)-**6a** was treated with palladium on activated charcoal (10 wt.-%). The mixture was stirred vigorously and a stream of hydrogen was bubbled through the solution for 4 h. After full conversion of the starting material (monitored by GC and GC–MS analyses), the solution was filtered through a small plug of Celite 545 and cooled to 0 °C. Etherial HCl solution was added dropwise (ca. 5 equiv.), the solvent removed, and the precipitate was collected. If necessary, the product was recrystallised from pure $CHCl_3$ or purified by filter flash chromatography (Et_2O + 1 vol.-% 2-$PrNH_2$). (+)-Isosolenopsin [(2*S*,6*R*)-**1a**] was obtained as a colourless solid in 98% yield (38.5 mg, 0.15 mmol) over two steps. Analytical data are in full agreement with those previously published.[6a] M.p. 172 °C. R_F = 0.35 (Et_2O + 1 vol.-% 2-$PrNH_2$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.85 (t, $^3J_{14,13}$ = 6.9 Hz, 3 H, 14-H), 1.15–1.50 (m, 15 H), 1.55 (d, $^3J_{Me,1}$ = 6.3 Hz, 3 H, Me), 1.55–2.05 (m, 6 H), 2.06–2.20 (m, 1 H), 2.88 (m_c, 1 H, 1-H), 3.06 (m_c, 1 H, 6-H), 9.01 (br. s, 1 H, NH_2^+), 9.39 (br. s, 1 H, NH_2^+) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.2 (C-14), 19.6 (Me at C-1), 22.8, 23.0, 25.8, 27.6, 29.4, 29.5, 29.6, 29.7, 30.9, 32.0, 33.4, 54.7 (C-5), 58.8 (C-1) ppm. GC–MS (EI+, 70 eV): *m*/*z* (%) = 224 (1) [M^+], 98 (100) [$C_6H_{12}N^+$]. $[\alpha]_D^{20}$ = –9.0 (*c* = 1.0, $CHCl_3$, *ee* > 99%, *de* > 98%); Lit.:[6a] $[\alpha]_D^{25}$ = +11.1 (*c* = 1.02, $CHCl_3$) for the opposite enantiomer.

Synthesis of (+)-Isosolenopsin [(2*R*,6*S*)-1a]: The product was prepared as described for its enantiomer, starting with the crude solution obtained from the biotransformation with (*R*)-*Arthrobacter* sp. (see above). $[\alpha]_D^{20}$ = +8.7 (*c* = 0.96, $CHCl_3$, *ee* > 99%, *de* > 98%).

Supporting Information (see footnote on the first page of this article): Initial experiments (enzyme testings), and GC-MS plus NMR data of all products and intermediates.

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