

## Total synthesis of dendrobate alkaloid (+)-241D, isosolenopsin and isosolenopsin A: application of a gold-catalyzed cyclization†

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A new approach to total syntheses of piperidine alkaloids (+)-241D, isosolenopsin and isosolenopsin A has been developed from D-alanine. The key step to access the chiral pyridinone intermediate was achieved *via* a gold mediated cyclization. Finally, various reduction conditions afforded the natural products in few steps and good overall yields.

## Introduction

In the past decades gold catalysis has emerged as an important tool in all fields of synthetic organic chemistry.<sup>1</sup> After initial theoretical and methodological investigations, many applications in the natural products synthesis field have been reported in the literature.<sup>2</sup> We recently described a new synthetic way to obtain pyridinones *via* a gold-catalyzed methodology<sup>3</sup> involving a favoured 6-endo-dig cyclization.<sup>4</sup> In order to illustrate the efficiency of our method, we have undertaken the total synthesis of three natural *cis*-2,6-dialkylpiperidine-containing alkaloids: dendrobate alkaloid (+)-241D (**1**), (2*R*,6*S*)-isosolenopsin (**2**) and (2*R*,6*S*)-isosolenopsin A (**3**) (Fig. 1). Due to the wide diversity of potent biological activities,<sup>5</sup> this class of compounds still attracts considerable attention. Alkaloid (+)-241D (**1**) has been isolated from the methanolic skin extracts of the Panamanian poison frog *Dendrobates speciosus*<sup>6</sup> and has shown to be a non-competitive blocker of acetylcholine to ganglionic nicotinic receptor channels.<sup>7</sup> Both piperidines **2** and **3**, which are constituents of the venom of fire ant *Solenopsis*,<sup>8</sup> demonstrate powerful hemolytic, necrotic, antibiotic and antifungal activities<sup>5b,9</sup> as well as anti-HIV properties.<sup>9</sup> Moreover isosolenopsin A **3** was found to be a blocker of the neuromuscular transmission<sup>10</sup> and is also a potent and selective inhibitor of the neuronal nitric oxide synthase.<sup>11</sup>

Since they have been isolated, numerous total syntheses of these alkaloids in racemic and optically pure forms have been published.<sup>12</sup> The key step in these methodologies generally involved intramolecular Mannich type cyclizations,<sup>12a-d</sup> Comins's 2,3-dihydro-4-pyridone intermediates from acyl

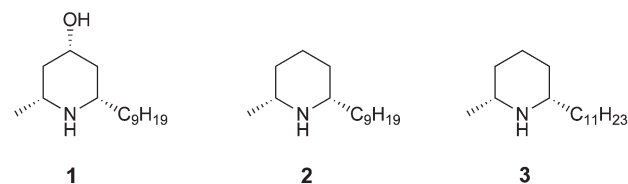
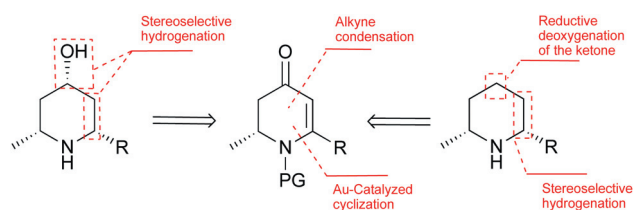


Fig. 1 Structure of dendrobate alkaloid (+)-241D, isosolenopsin and isosolenopsin A.



Scheme 1 Retrosynthetic analysis of piperidine alkaloids.

pyridinium<sup>12e</sup> or Chenevert's enzymatic route.<sup>12f</sup> Nevertheless there is still a need to develop more efficient methods.

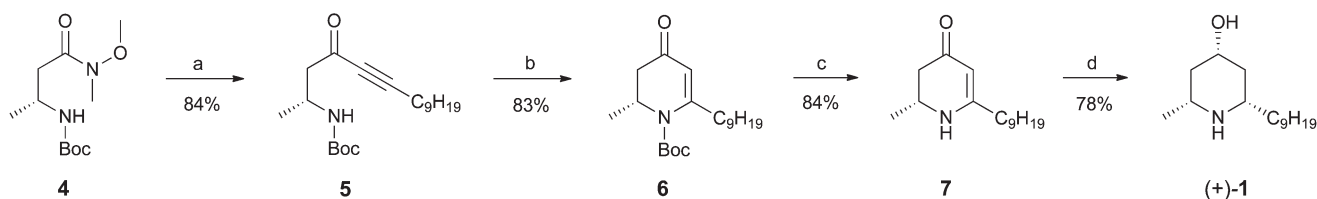
Following a methodology which had previously been developed in our laboratory on gold-catalyzed cyclization of  $\beta$ -amino-ynones to 2,6-disubstituted pyridinones,<sup>3</sup> we describe in this report a new approach towards these natural products. The strategy is based on two key features (Scheme 1): (1) a gold-catalyzed approach to a chiral pyridinone from D-alanine and (2) stereoselective reductions to afford the desired piperidine alkaloids.

## Results and discussion

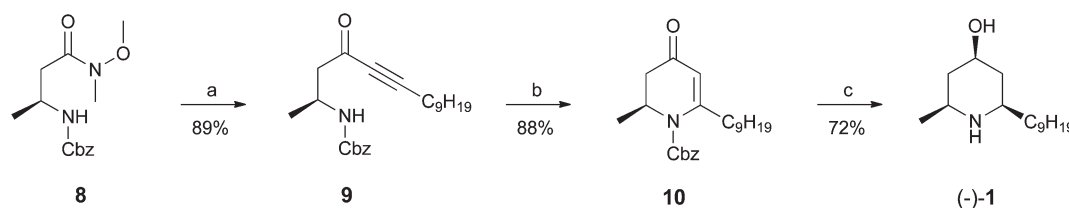
Our studies began with the synthesis of alkaloid (+)-241D (**1**). The synthetic strategy started with the preparation of the chiral synthon **6** (Scheme 2) which was obtained from the  $\beta$ -amino ynone derivative **5** according to our previously reported

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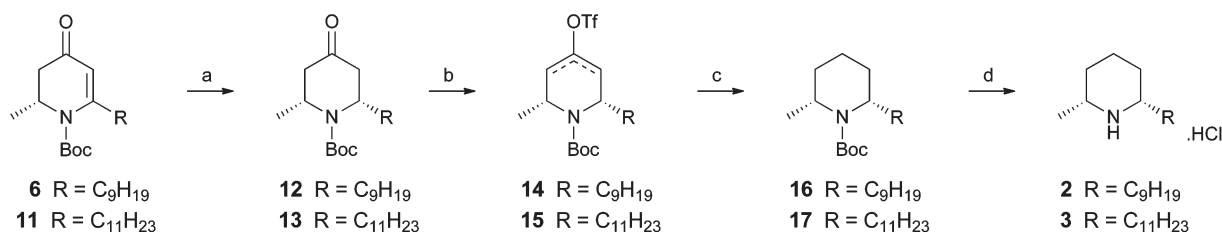
† Electronic supplementary information (ESI) available: Copies of <sup>1</sup>H and <sup>13</sup>C NMR of all new compounds. See DOI: 10.1039/c2ob25685a



**Scheme 2** Synthesis of alkaloid (+)-241D. *Reagents and conditions:* (a) Undecyne, BuLi, THF,  $-78\text{ }^{\circ}\text{C}$  to  $-5\text{ }^{\circ}\text{C}$ , 4 h; (b)  $\text{PPh}_3\text{AuCl}$  (5 mol%),  $\text{AgSbF}_6$  (5 mol%), DCE, rt, 1 h; (c) HCl (3 N), MeOH, rt, 18 h; (d) 10% Pd/C,  $\text{H}_2$ , MeOH, rt, 72 h.



**Scheme 3** Synthesis of alkaloid (-)-241D. *Reagents and conditions:* (a) Undecyne, BuLi, THF,  $-78\text{ }^{\circ}\text{C}$  to  $-5\text{ }^{\circ}\text{C}$ , 4 h; (b)  $\text{PPh}_3\text{AuCl}$  (5 mol%),  $\text{AgSbF}_6$  (5 mol%), DCE, rt, 1 h; (c) 10% Pd/C,  $\text{H}_2$ , MeOH, rt, 6 days.



**Scheme 4** Synthesis of isosolenopsin and isosolenopsin A. *Reagents and conditions:* (a) 10% Pd/C,  $\text{H}_2$ , MeOH, rt, 4 h; (b) KHMDS,  $\text{PhNTf}_2$ , THF,  $-78\text{ }^{\circ}\text{C}$  to rt, 20 h; (c) 10% Pd/C,  $\text{H}_2$ ,  $\text{Li}_2\text{CO}_3$ , EtOAc, rt, 18 h; (d) HCl (2.2 N), EtOAc, rt, 18 h.

procedure.<sup>3</sup> Thus the amino ynone **5** could be produced in two steps with excellent overall yield (84%) from readily available *N*-Boc-*D*-alanine *via* Arndt–Eistert homologation, Weinreb amide formation<sup>13</sup> leading to **4** then subsequent addition of undecyne lithium acetylide.

It should be mentioned that the Weinreb amide **4** could also be obtained quantitatively from the corresponding commercially available *N*-protected  $\beta$ -amino acid using usual peptides coupling reagents (TBTU...). Then the gold-catalyzed intramolecular cyclisation of this intermediate **5** using  $\text{PPh}_3\text{AuCl}$  in the presence of a silver salt in 1,2-dichloroethane at room temperature gave in 1 hour the expected enantiopure pyridinone **6** in good yield (Scheme 2). With this chiral synthon **6** in hand, the synthesis of dendrobate alkaloid (+)-241 D (**1**) was studied. To reduce both C–C and C–O double bonds the first tests were carried out by hydrogenation of **6** over Pd/C followed by reduction with  $\text{NaBH}_4$  but these attempts were unsuccessful since they led to a mixture of diastereoisomers.<sup>14</sup> Thus acid-catalyzed removal of the Boc-protecting group was achieved before the catalytic hydrogenation of the generated 2,3-dihydropyridone **7** to give a unique *cis*-diastereoisomer. The best result, 78% isolated yield of target molecule (+)-**1** was obtained with 10% Pd/C as catalyst at room temperature for 72 hours under a hydrogen pressure of 8 bars to reduce both the alkene and ketone functions. The spectroscopic data and the optical rotation for (+)-(**1**)

$[\alpha]_{\text{D}}^{25} = +7.0$  ( $c$  0.92,  $\text{CHCl}_3$ ) are consistent with the literature values.<sup>12</sup>

Next, replacement of the Boc protecting group by a Cbz one aimed at providing the target compound in a one step less sequence. For this alternative route, we chose to synthesize the levorotatory natural product<sup>15</sup> (–)-(**1**) starting from *N*-Cbz-*L*-alanine (Scheme 3). The synthesis was straightforward with concomitant deprotection, reductions of the C–C and C–O double bonds by hydrogenation in similar conditions and after 6 days afforded the enantiomer (–)-(**1**) in 72% yield. This approach revealed to be slightly more efficient (46% overall yield over 4 steps in the first case and 56% over 3 steps in the second case).

The existence of a single enantiomer in both cases was confirmed by  $^{13}\text{C}$  NMR experiment using (*S*)-(–)-*tert*-butylphenylphosphinothioic acid which was shown to be very useful in the determination of the enantiomeric excess of various classes of non racemic compounds.<sup>16</sup> The full details of this enantiomer analysis are provided in the ESI†, and from examination of these spectra, it can be assumed that our products are enantiomerically pure (in the limit of detection of the NMR method).

In a second part, we describe our four-step route for the total synthesis of enantiopure alkaloidal natural products isosolenopsin (**2**) and isosolenopsin A (**3**) (as hydrochlorides) respectively starting from the chiral synthons **6** and **11** (Scheme 4). A similar sequence of reactions as for **6** was carried out to

prepare **11** (71% overall yield from **4**). Our approach began with hydrogenation of **6** and **11** over 10% Pd/C in MeOH leading to **12** and **13** as single stereoisomers. To avoid the reduction of the ketone, hydrogenation was carried out at atmospheric pressure. The *cis*-stereochemistry was easily confirmed by NOE experiment and is in accordance with the results we previously reported.<sup>3</sup> These piperidones **12** and **13** were converted to the 2,6-disubstituted piperidines **16** and **17** by formation of a mixture of enol triflates (**14**, **15**) followed by a catalytic hydrogenation<sup>17</sup> in 94 and 96% yield respectively over the two-step sequence.<sup>18</sup> In the last step, treatment with HCl afforded the targets isosolenopsin alkaloids as hydrochloride salts in the insoluble part. Purification by recrystallization in EtOH–EtOAc (1 : 3) delivered the pure (2*R*,6*S*) stereoisomer: (+)-isosolenopsin hydrochloride as colorless crystals in 72% yield and (+)-isosolenopsin A hydrochloride as white needles in 90% yield.

The measured optical rotations for **2**·HCl:  $[\alpha]_{\text{D}}^{25} = +11.1$  (*c* 0.92, CHCl<sub>3</sub>) and for **3**·HCl:  $[\alpha]_{\text{D}}^{25} = +10.4$  (*c* 1.17, CHCl<sub>3</sub>) were in fair agreement with the literature values.<sup>19</sup> Compounds **2** and **3** were obtained with an overall yield of 31% and 41% respectively starting from the corresponding Weinreb amide (over 6 steps in each case).

## Conclusion

In conclusion, we have achieved the synthesis of three representative members of the 2,6-disubstituted class of piperidine alkaloids. We have demonstrated in this work that dihydropyridinones, easily accessible from amino acids by a gold-catalyzed approach, are useful chiral synthons for the total synthesis of such alkaloids. The scope and utility of this type of chiral intermediates will be further explored using other natural product targets.

## Experimental section

All reagents of high quality were purchased from commercial suppliers, and used without further purification. All reactions requiring anhydrous conditions were performed under an argon atmosphere using oven dried glassware. DCE and THF were distilled from CaH<sub>2</sub> and Na/benzophenone, respectively. <sup>1</sup>H and <sup>13</sup>C NMR were recorded at 500 or 300 and 125 or 75 MHz respectively, using CDCl<sub>3</sub> (and TMS as internal standard).  $\delta$  values are given in parts per million (ppm), coupling constants (*J* values) are given in Hertz (Hz), and multiplicity of signals are reported as follows: s, singlet; d, doublet; t, triplet; q, quadruplet; m, multiplet; bs, broad singlet. Thin layer chromatography was performed using precoated silica gel plate (0.2 mm thickness). Infrared spectra were recorded using a diffuse reflectance accessory (DRA) for solids and attenuated total reflectance (ATR) for liquids. All melting points are uncorrected. Optical rotations were measured at the sodium D line on a digital polarimeter at ambient temperature. Compounds **4** and **8** were prepared according to literature procedures.

### (*R*)-*tert*-Butyl 4-oxopentadec-5-yn-2-ylcarbamate (**5**)

To a stirred solution of 1-undecyne (1.6 mL, 8.12 mmol, 4.0 eq) in 7 mL of dry THF at –78 °C under argon atmosphere was

added dropwise a solution of BuLi 2.5 M in hexane (3.1 mL, 7.71 mmol, 3.8 eq). The solution was stirred for 1 h at –78 °C. Then, a solution of Weinreb amide obtained from Boc-D-Ala-OH (0.5 g, 2.03 mmol, 1.0 eq) in 7 mL of dry THF was added and stirred for 15 min keeping the temperature at –78 °C then at –50 °C during 1 h. The reaction mixture was allowed to reach to –5 °C and, after 1.5 h, the reaction was quenched by addition of a 1 M NaH<sub>2</sub>PO<sub>4</sub> solution (35 mL). The aqueous phase was extracted with EtOAc (3 × 25 mL). The combined organic layers were washed with brine, then dried over Na<sub>2</sub>SO<sub>4</sub> and evaporated *in vacuo*. Purification of the residue by flash column chromatography on silica gel using CH<sub>2</sub>Cl<sub>2</sub> then CH<sub>2</sub>Cl<sub>2</sub>–EtOAc (95 : 5) as eluents gave **5** as a clear oil in 84% yield:  $[\alpha]_{\text{D}}^{25} = +1.4$  (*c* 1.18, CHCl<sub>3</sub>); IR (ATR): 3349, 2210, 1693, 1670 cm<sup>–1</sup>; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): two conformers in a 92/8 ratio  $\delta$  4.79 (bs, 0.92H) and 4.41 (bs, 0.08H), 4.20–4.01 (m, 1H), 2.76 (dd, *J* = 16.1 Hz, *J* = 5.3 Hz, 1H), 2.66 (dd, *J* = 16.1 Hz, *J* = 6.1 Hz, 1H), 2.36 (t, *J* = 7.1 Hz, 2H), 1.58 (quint., *J* = 7.4 Hz, 2H), 1.44 (s, 9H), 1.41–1.23 (m, 12H), 1.21 (d, *J* = 6.7 Hz, 3H), 0.88 (t, *J* = 6.9 Hz, 3H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>):  $\delta$  186.1, 155.0, 95.3, 81.0, 79.3, 51.3, 43.4, 31.8, 29.4, 29.2, 29.0, 28.9, 28.4, 27.6, 22.6, 20.5, 19.0, 14.1; HRMS (ESI, *m/z*): Calcd for C<sub>20</sub>H<sub>35</sub>NO<sub>3</sub>Na: 360.2515, found [M + Na]<sup>+</sup>: 360.2516.

### (2*R*)-*tert*-Butyl 2-methyl-6-nonyl-4-oxo-1,2,3,4-tetrahydro-pyridine-1-carboxylate (**6**)

To a degassed solution of amino ynone **5** (0.5 g, 1.48 mmol, 1.0 eq) in 1,2-dichloroethane (7 mL) under argon was added PPh<sub>3</sub>AuCl (37 mg, 0.074 mmol, 5 mol%) and AgSbF<sub>6</sub> (25.5 mg, 0.074 mmol, 5 mol%). After the resulting mixture was stirred at room temperature for 1 h, Et<sub>2</sub>O (7 mL) was added and the resulting mixture was filtered through a Celite plug. After removal of solvents under reduced pressure, the crude product was purified by flash column chromatography (silica gel, cyclohexane–EtOAc 8 : 2) to give **6** as a pale yellow oil in 83% yield:  $[\alpha]_{\text{D}}^{25} = -229$  (*c* 1.10, CHCl<sub>3</sub>); IR (ATR): 1711, 1665, 1589 cm<sup>–1</sup>; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):  $\delta$  5.37 (s, 1H), 4.81–4.76 (m, 1H), 3.09–3.03 (m, 1H), 2.81 (dd, *J* = 16.9 Hz, *J* = 6.2 Hz, 1H), 2.30–2.24 (m, 1H), 2.22 (d, *J* = 16.9 Hz, 1H), 1.54 (s, 9H), 1.48–1.20 (m, 17H), 0.88 (t, *J* = 6.9 Hz, 3H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>):  $\delta$  193.7, 158.7, 152.1, 111.0, 82.8, 52.1, 42.7, 36.0, 31.8, 29.4, 29.4, 29.2, 28.1, 27.9, 22.6, 16.5, 14.1; HRMS (ESI, *m/z*): Calcd for C<sub>20</sub>H<sub>35</sub>NO<sub>3</sub>Na: 360.2515, found [M + Na]<sup>+</sup>: 360.2516.

### (2*R*)-1,2-Dihydro-2-methyl-6-nonylpyridin-4(3*H*)-one (**7**)

Compound **6** (0.4 g, 1.18 mmol, 1 eq) was treated with HCl (3 N)–methanol (6 mL) during 20 h at rt. After confirming the completion of reaction by TLC, methanol was evaporated under reduced pressure and a 20% K<sub>2</sub>CO<sub>3</sub> solution (1.6 mL, 2.36 mmol, 2 eq) was added. The aqueous layer was extracted with ether (3 × 10 mL). The combined organic layers were washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub> and evaporated under reduced pressure. Flash column chromatography (silica gel, CH<sub>2</sub>Cl<sub>2</sub>–MeOH 95 : 5) gave compound **7** as a white solid in 84% yield: mp = 55–56 °C;  $[\alpha]_{\text{D}}^{25} = +260$  (*c* 1.02, CHCl<sub>3</sub>);

IR (DRA): 3271, 1607, 1570, 1522  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  4.97 (s, 1H), 4.80 (bs, 1H), 3.79–3.72 (m, 1H), 2.36 (dd,  $J = 16.1$  Hz,  $J = 4.8$  Hz, 1H), 2.25 (dd,  $J = 16.1$  Hz,  $J = 13.2$  Hz, 1H), 2.20–2.12 (m, 2H), 1.54 (quint.,  $J = 7.4$  Hz, 2H), 1.30 (d,  $J = 6.5$  Hz, 3H), 1.36–1.20 (m, 12H), 0.88 (t,  $J = 6.9$  Hz, 3H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  192.7, 165.9, 98.3, 49.1, 43.2, 35.2, 31.8, 29.4, 29.3, 29.2, 29.1, 27.6, 22.6, 20.4, 14.1; HRMS (ESI,  $m/z$ ): Calcd for  $\text{C}_{15}\text{H}_{27}\text{NONa}$ : 260.1990, found  $[\text{M} + \text{Na}]^+$ : 260.1988.

#### (2R,4S,6S)-2-Methyl-6-nonylpiperidin-4-ol (+)-1

In a 10 mL reactor equipped with a magnetic stirrer and a  $\text{H}_2$  funnel was placed substrate **7** (100 mg, 0.42 mmol, 1.0 eq) in methanol (3 mL). 10% Pd/C (45 mg, 0.042 mmol, 0.1 eq) was added and the suspension was stirred under  $\text{H}_2$  (8 bars) at room temperature for 72 hours. The reaction mixture was filtered through a Celite plug and the filtrate was concentrated under reduced pressure. Column chromatography of the crude product (silica gel, EtOAc–MeOH 1 : 1) afforded compound (+)-**1** as a white solid in 78% yield: mp = 108–109 °C (lit.<sup>12f</sup> mp = 108–109 °C);  $[\alpha]_{\text{D}}^{25} = +7.0$  ( $c = 1.00$ , MeOH) [lit.<sup>12f</sup>  $[\alpha]_{\text{D}}^{25} = +6.5$  ( $c = 2.00$ , MeOH)]; IR (DRA): 3267, 3181, 2958, 2918, 2848  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  3.69–3.62 (m, 1H), 2.73–2.66 (m, 1H), 2.58–2.52 (m, 1H), 2.00–1.94 (m, 2H), 1.63 (bs, 2H), 1.50–1.20 (m, 16H), 1.13 (d,  $J = 6.2$  Hz, 3H), 1.06–0.95 (m, 2H), 0.88 (t,  $J = 6.9$  Hz, 3H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  69.4, 54.8, 50.2, 43.8, 41.7, 36.7, 31.9, 29.7, 29.5, 29.5, 29.3, 26.0, 22.7, 22.4, 14.1; HRMS (ESI,  $m/z$ ): Calcd for  $\text{C}_{15}\text{H}_{32}\text{NO}$ : 242.2484, found  $[\text{M} + \text{H}]^+$ : 242.2485.

#### (S)-Benzyl 4-oxopentadec-5-yn-2-ylcarbamate (9)

The same procedure described above for compound **5** was followed to prepare **9** starting from 1-undecyne (1.7 mL, 8.56 mmol, 4.0 eq) in THF (8 mL), BuLi 2.5 M in hexane (3.2 mL, 8.13 mmol, 3.8 eq), Weinreb amide obtained from Z-Ala-OH (0.6 g, 2.14 mmol, 1 eq) in THF (7 mL). Yield 0.71 g (89%), clear oil:  $[\alpha]_{\text{D}}^{25} = +1.8$  ( $c = 1.14$ ,  $\text{CHCl}_3$ ); IR (ATR): 3326, 2210, 1697, 1669  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.38–7.29 (m, 5H), 5.16–5.00 (m, 3H), 4.21–4.13 (m, 1H), 2.83 (dd,  $J = 16.3$  Hz,  $J = 4.4$  Hz, 1H), 2.71 (dd,  $J = 16.3$  Hz,  $J = 5.8$  Hz, 1H), 2.34 (t,  $J = 7.1$  Hz, 2H), 1.56 (quint.,  $J = 7.3$  Hz, 2H), 1.42–1.34 (m, 2H), 1.34–1.20 (m, 10H), 1.24 (d,  $J = 6.9$  Hz, 3H), 0.88 (t,  $J = 6.9$  Hz, 3H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  185.8, 155.4, 136.5, 128.5, 128.1, 128.0, 95.6, 80.9, 66.6, 51.1, 43.9, 31.8, 29.3, 29.2, 29.0, 28.8, 27.6, 22.6, 20.4, 18.9, 14.1; HRMS (ESI,  $m/z$ ): Calcd for  $\text{C}_{23}\text{H}_{33}\text{NO}_3\text{Na}$ : 394.2358, found  $[\text{M} + \text{Na}]^+$ : 394.2359.

#### (2S)-Benzyl 2-methyl-6-nonyl-4-oxo-1,2,3,4-tetrahydro-pyridine-1-carboxylate (10)

The same procedure described above for compound **6** was followed to prepare **10** starting from the amino ynone **9** (0.5 g, 1.35 mmol, 1 eq) in 1,2-dichloroethane (6 mL),  $\text{PPh}_3\text{AuCl}$  (33 mg, 0.067 mmol, 5 mol%) and  $\text{AgSbF}_6$  (23 mg, 0.067 mmol, 5 mol%). Yield 0.44 g (88%), pale yellow oil:

$[\alpha]_{\text{D}}^{25} = +222$  ( $c = 1.22$ ,  $\text{CHCl}_3$ ); IR (ATR): 1720, 1665, 1592  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.42–7.34 (m, 5H), 5.41 (s, 1H), 5.26 (AB,  $J_{\text{AB}} = 12.1$  Hz, 1H), 5.22 (AB,  $J_{\text{AB}} = 12.1$  Hz, 1H), 4.92–4.87 (m, 1H), 3.02–2.97 (m, 1H), 2.81 (dd,  $J = 17.1$  Hz,  $J = 6.1$  Hz, 1H), 2.32–2.26 (m, 1H), 2.24 (d,  $J = 17.1$  Hz, 1H), 1.40–1.15 (m, 14H), 1.27 (d,  $J = 6.8$  Hz, 3H), 0.88 (t,  $J = 7.0$  Hz, 3H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  193.5, 158.3, 153.1, 135.2, 128.7, 128.7, 128.4, 111.8, 68.6, 52.2, 42.6, 35.8, 31.8, 29.4, 29.3, 29.2, 29.2, 28.0, 22.6, 16.6, 14.1; HRMS (ESI,  $m/z$ ): Calcd for  $\text{C}_{23}\text{H}_{33}\text{NO}_3\text{Na}$ : 394.2358, found  $[\text{M} + \text{Na}]^+$ : 394.2357.

#### (2S,4R,6R)-2-Methyl-6-nonylpiperidin-4-ol (–)-1

The same hydrogenation procedure described above for (+)-**241D** (+)-**1** was followed to prepare (–)-**1** starting from the compound **10** (0.15 g, 0.40 mmol, 1.0 eq) in MeOH (3 mL), 10% Pd/C (43 mg, 0.040 mmol, 0.1 eq) and  $\text{H}_2$  (8 bars), rt, 6 days. Yield 70 mg (72%), white solid: mp = 108–109 °C (lit.<sup>12a</sup> mp = 107 °C);  $[\alpha]_{\text{D}}^{25} = -6.5$  ( $c = 1.00$ , MeOH) [lit.<sup>12a</sup>  $[\alpha]_{\text{D}}^{25} = -6.5$  ( $c = 1.32$ , MeOH)]; HRMS (ESI,  $m/z$ ): Calcd for  $\text{C}_{15}\text{H}_{32}\text{NO}$ : 242.2484, found  $[\text{M} + \text{H}]^+$ : 242.2484. Spectral data are identical with those reported for (+)-**1** and those reported in the literature.<sup>12f</sup>

#### (2R)-tert-Butyl 2-methyl-4-oxo-1,2,3,4-tetrahydro-6-undecyl-pyridine-1-carboxylate (11)

The same procedure described above for compound **5** was followed to prepare the amino-ynone precursor of **11** starting from 1-tridecyne (1.9 mL, 8.12 mmol, 4 eq) in THF (12 mL), BuLi 2.5 M in hexane (3.1 mL, 7.71 mmol, 3.8 eq) and Weinreb amide obtained from Boc-D-Ala-OH (0.5 g, 2.03 mmol, 1.0 eq) in THF (7 mL). The deprotonation step for **11** was performed from –78 °C to –20 °C over 1 h. Yield 0.65 g (87%), clear oil:  $[\alpha]_{\text{D}}^{25} = +1.5$  ( $c = 1.03$ ,  $\text{CHCl}_3$ ); IR (ATR): 3349, 2211, 1694, 1670  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ): two conformers in a 90/10 ratio  $\delta$  4.78 (bs, 0.9H) and 4.40 (bs, 0.1H), 4.20–4.01 (m, 1H), 2.81 (dd,  $J = 16.2$  Hz,  $J = 5.3$  Hz, 1H), 2.66 (dd,  $J = 16.1$  Hz,  $J = 6.0$  Hz, 1H), 2.36 (t,  $J = 7.2$  Hz, 2H), 1.58 (quint.,  $J = 7.3$  Hz, 2H), 1.44 (s, 9H), 1.41–1.23 (m, 16H), 1.21 (d,  $J = 6.7$  Hz, 3H), 0.88 (t,  $J = 6.9$  Hz, 3H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  186.0, 155.0, 95.3, 81.0, 79.3, 51.4, 43.5, 31.9, 29.6, 29.4, 29.3, 29.0, 28.9, 28.4, 27.7, 22.7, 20.5, 19.0, 14.1; HRMS (ESI,  $m/z$ ): Calcd for  $\text{C}_{22}\text{H}_{39}\text{NO}_3\text{Na}$ : 388.2828, found  $[\text{M} + \text{Na}]^+$ : 388.2829.

The same procedure described above for compound **6** was followed to prepare **11** starting from the corresponding amino ynone (0.5 g, 1.37 mmol, 1 eq) in 1,2-dichloroethane (6 mL),  $\text{PPh}_3\text{AuCl}$  (34 mg, 0.068 mmol, 5 mol%) and  $\text{AgSbF}_6$  (23.5 mg, 0.068 mmol, 5 mol%). Yield 0.44 g (82%), pale yellow oil:  $[\alpha]_{\text{D}}^{25} = -229$  ( $c = 0.97$ ,  $\text{CHCl}_3$ ); IR (ATR): 1711, 1665, 1589  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  5.37 (s, 1H), 4.81–4.76 (m, 1H), 3.09–3.03 (m, 1H), 2.81 (dd,  $J = 16.9$  Hz,  $J = 6.2$  Hz, 1H), 2.30–2.24 (m, 1H), 2.22 (d,  $J = 16.9$  Hz, 1H), 1.54 (s, 9H), 1.48–1.20 (m, 21H), 0.88 (t,  $J = 6.9$  Hz, 3H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  193.7, 158.7, 152.2, 111.0, 82.7, 52.1, 42.7, 36.0, 31.9, 29.6, 29.5, 29.4, 29.3, 29.2, 28.1, 27.9, 22.6,

16.5, 14.1; HRMS (ESI,  $m/z$ ): Calcd for  $C_{22}H_{39}NO_3Na$ : 388.2828, found  $[M + Na]^+$ : 388.2826.

**(2*R*,6*S*)-tert-Butyl 2-methyl-6-nonyl-4-oxopiperidine-1-carboxylate (12)**

In a 10 mL reactor equipped with a magnetic stirrer and a  $H_2$  funnel was placed the substrate **6** (0.3 g, 0.89 mmol, 1.0 eq) in methanol (6 mL). 10% Pd/C (95 mg, 0.089 mmol, 0.1 eq) was added and the suspension was stirred under  $H_2$  (4 bars) at room temperature for 4 hours. The reaction mixture was filtered through a Celite plug and the filtrate was concentrated under reduced pressure. Column chromatography of the crude product (silica gel, cyclohexane–EtOAc 75 : 25) afforded 0.248 g of the compound **12** as a clear oil in 82% yield:  $[\alpha]_D^{25} = -21.5$  ( $c$  1.05,  $CHCl_3$ ); IR (ATR): 1721, 1689  $cm^{-1}$ ;  $^1H$  NMR (500 MHz,  $CDCl_3$ ):  $\delta$  4.77–4.65 (m, 1H), 4.62–4.52 (m, 1H), 2.74–2.64 (m, 2H), 2.34–2.26 (m, 2H), 1.65–1.56 (m, 1H), 1.53–1.43 (m, 1H), 1.49 (s, 9H), 1.38–1.20 (m, 17H), 0.88 (t,  $J = 6.9$  Hz, 3H);  $^{13}C$  NMR (125 MHz,  $CDCl_3$ ):  $\delta$  208.8, 154.8, 80.1, 52.7, 48.3, 45.5, 43.8, 37.0, 31.8, 29.5, 29.5, 29.3, 29.3, 28.4, 27.0, 22.6, 14.1; HRMS (ESI,  $m/z$ ): Calcd for  $C_{20}H_{37}NO_3Na$ : 362.2671, found  $[M + Na]^+$ : 360.2672.

**(2*R*,6*S*)-tert-Butyl 2-methyl-4-oxo-6-undecylpiperidine-1-carboxylate (13)**

Following the reduction procedure described above for compound **12**, the pyridinone **11** (0.3 g, 0.82 mmol) afforded the piperidone **13** as a clear oil (0.24 g, 80%):  $[\alpha]_D^{25} = -19.7$  ( $c$  1.04,  $CHCl_3$ ); IR (ATR): 1722, 1690  $cm^{-1}$ ;  $^1H$  NMR (500 MHz,  $CDCl_3$ ):  $\delta$  4.77–4.65 (m, 1H), 4.63–4.52 (m, 1H), 2.73–2.64 (m, 2H), 2.34–2.26 (m, 2H), 1.65–1.55 (m, 1H), 1.53–1.43 (m, 1H), 1.49 (s, 9H), 1.40–1.17 (m, 21H), 0.88 (t,  $J = 6.8$  Hz, 3H);  $^{13}C$  NMR (125 MHz,  $CDCl_3$ ):  $\delta$  208.8, 154.8, 80.1, 52.7, 48.4, 45.5, 43.8, 37.0, 31.9, 29.6, 29.6, 29.5, 29.4, 29.3, 28.4, 27.0, 22.7, 14.1; HRMS (ESI,  $m/z$ ): Calcd for  $C_{22}H_{41}NO_3Na$ : 390.2984, found  $[M + Na]^+$ : 390.2986.

**(2*R*,6*S*)-tert-Butyl 2-methyl-6-nonyl-4-[(trifluoromethanesulfonyl)oxy]-1,2,5,6-tetrahydropyridine-1-carboxylate (14)**

To a solution of piperidone **12** (0.2 g, 0.59 mmol, 1.0 eq) in 5 mL of dry THF under argon atmosphere at  $-78$  °C was added 1.5 mL (0.76 mmol, 1.3 eq) of a solution of KHMDS (0.5 M in toluene) over a period of 15 min. After the mixture was stirred for 1 h at  $-78$  °C, 0.27 g (0.76 mmol, 1.3 eq) of PhNTf<sub>2</sub> was added. The resulting solution was slowly warmed to ambient temperature overnight (18 h) before being diluted with  $CH_2Cl_2$  and filtered through a plug of neutral alumina. The filtrate was then concentrated under reduced pressure and the residue was purified by column chromatography on silica gel ( $CH_2Cl_2$ –cyclohexane 8 : 2) to furnish 0.26 g (94%) of a mixture of regioisomers of the vinyl triflates, ratio 7 : 3 ( $^1H$  NMR) as a colorless oil. Data of the mixture of regioisomers: IR (ATR): 1694, 1420, 1401, 1208  $cm^{-1}$ ;  $^1H$  NMR (500 MHz,  $CDCl_3$ ):  $\delta$  5.82 (bs, 0.3H), 5.65 (bs, 0.7H), 4.85–4.40 (m, 2H), 2.78–2.68 (m, 1H), 2.17 (d,  $J = 16.9$  Hz, 0.7H), 2.08 (d,  $J = 16.7$  Hz, 0.3H),

1.62–1.20 (m, 16H), 1.48 (s, 9H), 1.30 (d,  $J = 6.9$  Hz, 2.1H), 1.23 (d,  $J = 7.1$  Hz, 0.9H), 0.88 (t,  $J = 6.9$  Hz, 0.9H), 0.88 (t,  $J = 6.9$  Hz, 2.1H);  $^{13}C$  NMR (75 MHz,  $CDCl_3$ ):  $\delta$  154.1, 153.9, 145.0, 119.0, 118.5 ( $^1J_{CF} = 320.4$  Hz), 117.5, 80.3, 80.2, 51.6, 49.1, 47.0, 44.3, 36.1, 34.4, 33.2, 31.9, 31.6, 29.5, 29.5, 29.5, 29.5, 29.3, 29.3, 28.4, 26.8, 26.6, 22.6, 20.9, 20.7, 14.1; HRMS (ESI,  $m/z$ ): Calcd for  $C_{21}H_{36}NO_5F_3NaS$ : 494.2164, found  $[M + Na]^+$ : 494.2162.

**(2*R*,6*S*)-tert-Butyl 2-methyl-4-[(trifluoromethanesulfonyl)oxy]-6-undecyl-1,2,5,6-tetrahydropyridine-1-carboxylate (15)**

The same procedure described above for compound **14** was followed to prepare **15** starting from the piperidone **13** (0.2 g, 0.54 mmol, 1.0 eq) in dry THF (4.5 mL), KHMDS 0.5 M in toluene (1.4 mL, 0.71 mmol, 1.3 eq) and PhNTf<sub>2</sub> (0.25 g, 0.71 mmol, 1.3 eq). Yield 0.26 g (96%), colorless oil, mixture of vinyl triflates, ratio 7 : 3 ( $^1H$  NMR). Data of the mixture of regioisomers: IR (ATR): 1697, 1420, 1401, 1208  $cm^{-1}$ ;  $^1H$  NMR (300 MHz,  $CDCl_3$ ):  $\delta$  5.82 (dd,  $J = 3.2$  Hz,  $J = 3.2$  Hz, 0.3H), 5.65 (dd,  $J = 3.1$  Hz,  $J = 3.1$  Hz, 0.7H), 4.85–4.37 (m, 2H), 2.80–2.66 (m, 1H), 2.17 (d,  $J = 16.8$  Hz, 0.7H), 2.08 (d,  $J = 16.7$  Hz, 0.3H), 1.65–1.20 (m, 20.9H), 1.48 (s, 9H), 1.30 (d,  $J = 7.0$  Hz, 2.1H), 0.88 (t,  $J = 6.7$  Hz, 3H);  $^{13}C$  NMR (75 MHz,  $CDCl_3$ ):  $\delta$  154.1, 154.0, 145.0, 119.0, 118.5 ( $^1J_{CF} = 320.5$  Hz), 117.5, 80.3, 80.2, 51.6, 49.1, 47.1, 44.3, 36.1, 34.4, 33.2, 31.9, 31.7, 29.6, 29.5, 29.5, 29.3, 29.3, 28.4, 26.8, 26.6, 22.7, 20.9, 20.8, 14.1; HRMS (ESI,  $m/z$ ): Calcd for  $C_{23}H_{40}NO_5F_3NaS$ : 522.2477, found  $[M + Na]^+$ : 522.2474.

**(2*R*,6*S*)-tert-Butyl 2-methyl-6-nonylpiperidine-1-carboxylate (16)**

To a solution of the vinyl triflates **14** (0.2 g, 0.42 mmol, 1.0 eq) in 21 mL of ethyl acetate was added  $Li_2CO_3$  (62 mg, 0.84 mmol, 2.0 eq) and 10% Pd/C (63 mg, 0.059 mmol, 0.14 eq). The resulting suspension was hydrogenated under 1 atm pressure of hydrogen at rt for 18 h. The reaction mixture was then diluted with  $CH_2Cl_2$  and filtered through a Celite plug, which was washed several times with  $CH_2Cl_2$ . The filtrate was concentrated *in vacuo* and the resulting residue was purified by column chromatography (silica gel,  $CH_2Cl_2$ ) to yield **16** as a colorless oil (109 mg, 79%) and as an inseparable mixture of diastereoisomers, ratio 90 : 10 ( $^1H$  NMR). Data of the mixture of diastereoisomers: IR (ATR): 2925, 2854, 1686, 1362, 1177, 1078  $cm^{-1}$ ; NMR of the spectroscopic data for the unseparated major (2*R*,6*S*) diastereoisomer:  $^1H$  NMR (300 MHz,  $CDCl_3$ ):  $\delta$  4.36–4.21 (m, 1H), 4.10–3.97 (m, 1H), 1.72–1.19 (m, 22H), 1.46 (s, 9H), 1.15 (d,  $J = 7.0$  Hz, 3H), 0.88 (t,  $J = 6.7$  Hz, 3H);  $^{13}C$  NMR (75 MHz,  $CDCl_3$ ):  $\delta$  155.4, 78.8, 50.3, 45.5, 35.1, 31.9, 30.3, 29.7, 29.7, 29.5, 29.3, 28.5, 27.6, 27.5, 22.6, 20.4, 14.1, 14.1; HRMS (ESI,  $m/z$ ): Calcd for  $C_{20}H_{39}NO_2Na$ : 348.2879, found  $[M + Na]^+$ : 348.2880. The product was used in the next step without further purification.

**(2*R*,6*S*)-tert-Butyl 2-methyl-6-undecylpiperidine-1-carboxylate (17)**

Following the reduction procedure described above for compound **16**, the vinyl triflates mixture **15** (200 mg, 0.40 mmol)

afforded **17** (colorless oil, 117 mg, 83%) as an inseparable mixture of diastereoisomers, ratio 97 : 3 ( $^1\text{H}$  NMR). Data of the mixture of diastereoisomers:  $[\alpha]_{\text{D}}^{25} = -8.9$  ( $c$  1.14,  $\text{CHCl}_3$ ); IR (ATR): 2923, 2853, 1686, 1362, 1177, 1079  $\text{cm}^{-1}$ ; spectroscopic data for the unseparated major (2*R*,6*S*) diastereoisomer:  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  4.36–4.21 (m, 1H), 4.10–3.97 (m, 1H), 1.72–1.19 (m, 26H), 1.46 (s, 9H), 1.15 (d,  $J = 7.0$  Hz, 3H), 0.88 (t,  $J = 6.6$  Hz, 3H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  155.4, 78.8, 50.3, 45.5, 35.1, 31.9, 30.3, 29.7, 29.7, 29.6, 29.6, 29.6, 29.3, 28.5, 27.6, 27.5, 22.7, 20.4, 14.1; HRMS (ESI,  $m/z$ ): Calcd for  $\text{C}_{22}\text{H}_{43}\text{NO}_2\text{Na}$ : 376.3192, found  $[\text{M} + \text{Na}]^+$ : 376.3197. The product was used in the next step without further purification.

#### (2*R*,6*S*)-2-Methyl-6-nonylpiperidine hydrochloride (2·HCl)

Compound **16** (0.1 g, 0.31 mmol) was treated with HCl (2.2 N)–EtOAc (3 mL) at rt. After completion of reaction (18 h), the insoluble part was separated and washed with ether. Recrystallisation from absolute EtOH–EtOAc (1 : 3) afforded 2·HCl as white needles in 72% yield: mp = 174–175 °C (lit.<sup>19</sup> mp = 174–175 °C);  $[\alpha]_{\text{D}}^{25} = +11.1$  ( $c = 1.02$ ,  $\text{CHCl}_3$ ) [lit.<sup>19</sup>  $[\alpha]_{\text{D}}^{25} = +11.1$  ( $c$  0.92,  $\text{CHCl}_3$ )]; IR (DRA): 2918, 2851, 2742, 2534, 1584, 1464, 1378  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  9.46 (bs, 1H), 9.08 (bs, 1H), 3.13–3.01 (m, 1H), 2.95–2.83 (m, 1H), 2.22–2.11 (m, 1H), 2.10–1.54 (m, 6H), 1.58 (d,  $J = 6.4$  Hz, 3H), 1.50–1.15 (m, 15H), 0.88 (t,  $J = 6.9$  Hz, 3H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  58.7, 54.6, 33.2, 31.9, 30.8, 29.6, 29.5, 29.4, 29.3, 27.5, 25.7, 22.9, 22.6, 19.5, 14.1; HRMS (ESI,  $m/z$ ): Calcd for  $\text{C}_{15}\text{H}_{32}\text{N}$ : 226.2535, found  $[\text{M} + \text{H}]^+$ : 226.2535.

#### (2*R*,6*S*)-2-Methyl-6-undecylpiperidine hydrochloride (3·HCl)

The same procedure described above for compound 2·HCl was followed for 3·HCl starting from the protected piperidine **17** (110 mg, 0.31 mmol) and HCl (2.2 N)–EtOAc (3 mL). Yield 81 mg (90%), white needles: mp = 150–151 °C (lit.<sup>19</sup> mp = 150–151 °C);  $[\alpha]_{\text{D}}^{25} = +10.4$  ( $c$  1.01,  $\text{CHCl}_3$ ) [lit.<sup>19</sup>  $[\alpha]_{\text{D}}^{25} = +10.0$  ( $c = 1.17$ ,  $\text{CHCl}_3$ )]; IR (DRA): 2919, 2850, 2752, 2540, 1590, 1465, 1384  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  9.45 (bs, 1H), 9.07 (bs, 1H), 3.13–3.01 (m, 1H), 2.95–2.83 (m, 1H), 2.22–2.11 (m, 1H), 2.10–1.54 (m, 6H), 1.58 (d,  $J = 6.1$  Hz, 3H), 1.50–1.15 (m, 19H), 0.88 (t,  $J = 6.9$  Hz, 3H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  58.7, 54.6, 33.2, 31.9, 30.8, 29.6, 29.5, 29.4, 29.3, 27.5, 25.7, 22.9, 22.7, 19.5, 14.1; HRMS (ESI,  $m/z$ ): Calcd for  $\text{C}_{17}\text{H}_{36}\text{N}$ : 254.2848, found  $[\text{M} + \text{H}]^+$ : 254.2846.

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