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# Short syntheses of (*S*)-pipecolic acid, (*R*)-coniine, and (*S*)-δ-coniceine using biocatalytically-generated chiral building blocks †,‡,§

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**Abstract**

The kinetic resolutions of both (±)-N-(benzyloxycarbonyl-2-(hydroxymethyl)piperidine [(±)-**5**] and (±)-N-(*tert*-butoxycarbonyl)-2-(hydroxymethyl)piperidine [(±)-**6**] catalyzed by the enzyme acylase I from *Aspergillus* species (AA-I) afforded the chiral building blocks (*S*)-**5** and (*S*)-**6**, respectively; which were used for the syntheses of the title natural products and derivatives of (*S*)-pipecolic acid. The syntheses were short (2–4 steps) and proceeded with satisfactory overall yield. 

## 1. Introduction

The piperidine ring is an ubiquitous structural feature in numerous secondary metabolites and biologically active compounds. Some examples of natural products include alkaloids with the structure of 2-alkyl-piperidine[2] [e.g.; (*R*)-coniine **1**, Fig. 1], indolizidine alkaloids[3] [e.g.; (*S*)-δ-coniceine **2**], and non-proteinogenic amino acids[4] [e.g.; (*S*)-pipecolic acid **3**]. This last compound, besides being a natural product itself,[5] it is a component of many natural peptides[6] and immunosuppressor agents[7] [e.g.; FK-506 and rapamycin], as well as an intermediate for their syntheses. Additionally, the piperidine nucleus is a frequent structural moiety in many synthetic pharmaceuticals[8] [e.g.; anesthetic (*S*)-bupivacaine **4**].[9] Due to the known dependence between the biological activity of a molecule and its absolute configuration,[10] it is convenient to have ready access to non-racemic functionalized piperidines.[11]

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‡ Taken from the projected Ph.D. thesis of F. S.-S.

§ Dedicated to Professor Dieter Seebach on the occasion of his 60th birthday, and in recognition of his outstanding contribution to Organic Chemistry.

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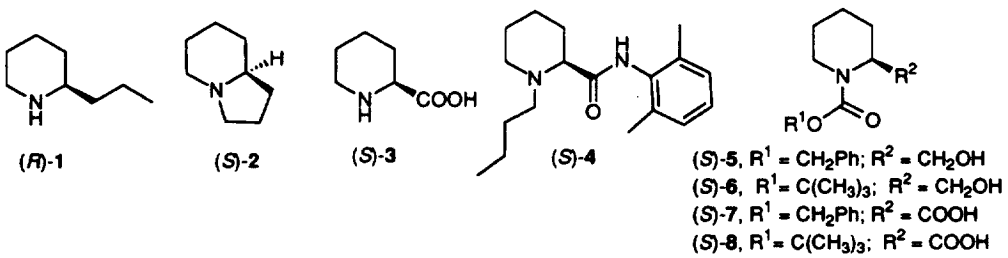



Fig. 1.

In connection with our ongoing project on synthetic applications of biocatalytically-generated chiral building blocks,[12] we have achieved efficient EPC-syntheses[13] of derivatives of both enantiomers of 2-(hydroxymethyl)piperidine [namely, (*S*)-**5** and (*S*)-**6**, Fig. 1] through transesterifications catalyzed by the enzyme acylase I from *Aspergillus* species (AA-I hereafter).[14] The functionality existing in these N-protected amino alcohols should make them useful intermediates for the syntheses of the above indicated natural products and related compounds.[15–17]

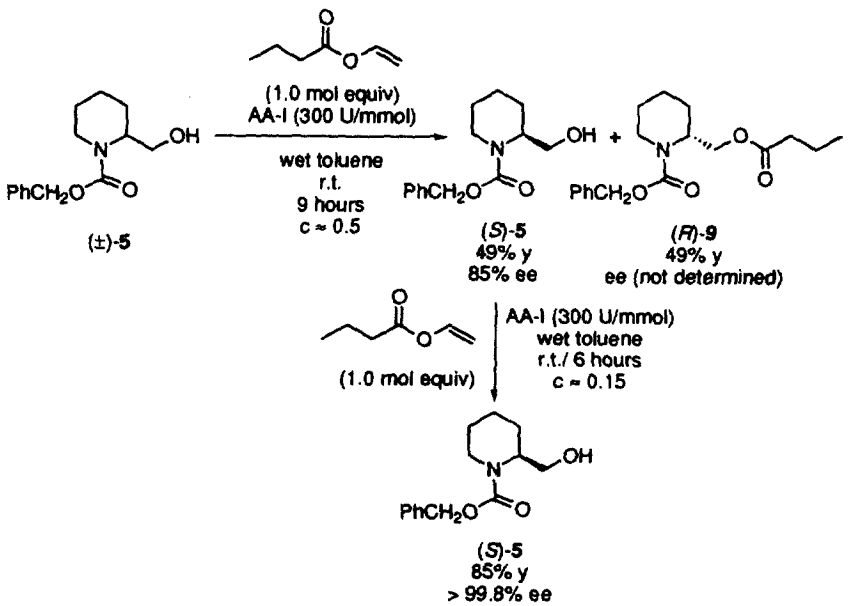
In this paper we report full details on the kinetic resolutions of (±)-N-(benzyloxycarbonyl)-2-(hydroxymethyl)piperidine (±)-**5** and (±)-N-(*tert*-butoxycarbonyl)-2-(hydroxymethyl)piperidine (±)-**6** catalyzed by AA-I, as well as the syntheses of (*R*)-coniine **1**, (*S*)-δ-coniceine **2**, and (*S*)-pipecolic acid **3**, and its derivatives (*S*)-**7** and (*S*)-**8**, from the chiral building blocks (*S*)-**5** and (*S*)-**6** (Fig. 1). Albeit the structures of the target molecules are quite simple, they have attracted a great interest, especially to test synthetic methodologies. Although many syntheses of these compounds have been reported,[18–20] most of them are not efficient; they are lengthy with low overall yield, and use non-readily available starting materials.

## 2. Results and discussion

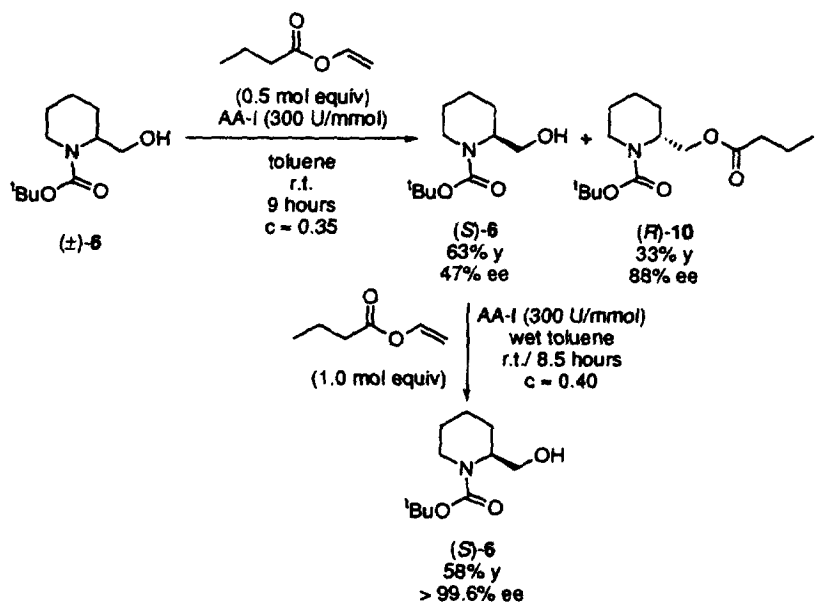
In our first experiments on transesterifications catalyzed by AA-I, we briefly studied the acetylation of (±)-**6** using vinyl acetate as the reagent.[14] Although this kinetic resolution went with moderate enantioselectivity[21] (E=16), we were able to obtain enantiomerically pure (*S*)-**6**, albeit in modest chemical yield. Recently we found that, in general, the butyrylations (using vinyl butyrate as the acylating agent) are faster and more enantioselective than the cognate acetylations.[1] We have also observed the same effect in the kinetic resolution of both (±)-**5** and (±)-**6**;[22] thus, the butyrylations catalyzed by AA-I of these substrates were more enantioselective than the acetylations, reaching values of E=25. With this level of enantioselectivity, it was possible to get the N-protected amino alcohols (*S*)-**5** and (*S*)-**6** in high enantiomeric purities (>98% ee) if the kinetic resolutions were carried out at relatively high conversions.[23] A more convenient tactic is to run two consecutive reactions,[25] that would allow us to obtain the target molecules in enantiomerically pure form and in satisfactory overall yield.

Schemes 1 and 2 show representative resolution procedures to obtain enantiomerically pure (*S*)-**5** and (*S*)-**6**, respectively.[24,26] Racemic (±)-**5** was butyrylated in wet toluene[27] and catalyzed by AA-I (Scheme 1).[28] The reaction was carried out with up to *ca.* 50% conversion ($^1$H-NMR evidence). The butyrate[29] (*R*)-**9** and the alcohol (*S*)-**5** (of 85% ee) were readily separated by flash-chromatography, and the enantiomerically enriched alcohol was submitted to a second kinetic resolution, which was carried out with up to *ca.* 15% conversion,[30] to give enantiomerically pure (*S*)-**5** in *ca.* 42% overall yield for the two steps.[31]

Enantiomerically pure (*S*)-**6** was obtained in an analogous manner (Scheme 2). In this case, the second




Scheme 1.



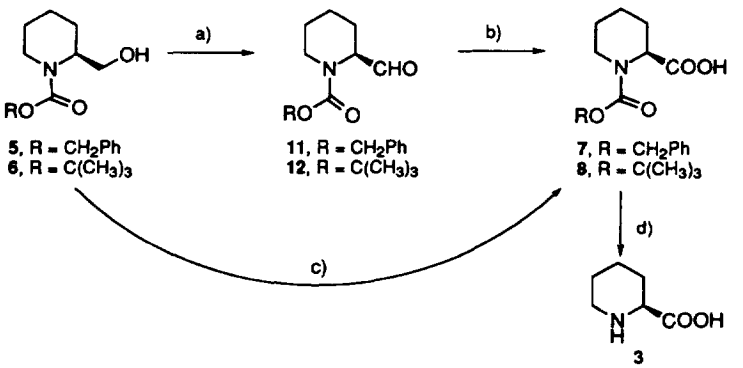

Scheme 2.

acylation was carried out in wet toluene, because we observed that the reaction in this solvent was slighty faster than in toluene.

The transformations indicated in Schemes 1 and 2 were carried out up to an 80 mmol scale, and the results were reproducible. Additionally, the enzyme could be recovered and reused, showing the same enantioselectivity and nearly the same activity.

With a ready supply of the chiral building blocks (*S*)-**5** and (*S*)-**6** in hand, we applied them to the syntheses of (*S*)-pipecolic acid **3**, (*R*)-coniine **1**, and (*S*)-δ-coniceine **2**. The syntheses of (*S*)-pipecolic acid **3** and its derivatives **7** and **8** are shown in Scheme 3. Swern oxidation[32] of both **5** and **6** gave a high

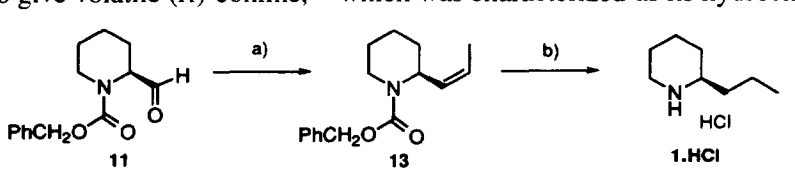
yield, affording the relatively unstable protected amino aldehydes **11** and **12**, respectively;[33,34] which, in turn, were oxidized with potassium permanganate to the N-protected derivatives of (*S*)-pipecolic acid **7** and **8**, respectively. Meanwhile the direct oxidation of **5** to **7** was achieved in satisfactory yield (77%) with Jones reagent.[35] We were unable to oxidize the N-*tert*-butoxycarbonyl derivative **6** to the acid **8**, probably reflecting a poor stability of this protecting group under the conditions of Jones oxidation. (*S*)-Pipecolic acid **3** was obtained in high yield (94%) by the hydrolytic removal of the benzyloxycarbonyl group in **7**. We also tried the deprotection of the N-*tert*-butoxycarbonyl group from **8** (treatment with trifluoroacetic acid); but, although the reaction was clean (t.l.c. evidence), we could not obtain a good yield of (*S*)-pipecolic acid after ion-exchange chromatography. Since the synthesis of (*S*)-pipecolic acid through the N-benzyloxycarbonyl derivative proceeded efficiently, we did not pursue its synthesis further through compound **8**.




a) DMSO/$(COCl)_2$ (2:1, v/v), $CH_2Cl_2$, -70°; $Et_3N$, from -70° to r.t. (92% from **5**; 85% from **6**). b) $KMnO_4$, $MgSO_4$, acetone, r.t. (80% from **9**; 70% from **10**). c) From **5**: $CrO_3$, $H_2SO_4$, $H_2O$, acetone, 0° (77%). d) From **7**: $H_2$, Pd/C, MeOH, r.t. (94%).

Scheme 3.

The synthesis of (*R*)-coniine **1** is indicated in Scheme 4. The aldehyde **11** reacted with the ylide formed from ethyl triphenylphosphonium bromide to give the olefin **13** as a single isomer,[36] which was hydrogenated to give volatile (*R*)-coniine,[37] which was characterized as its hydrochloride.

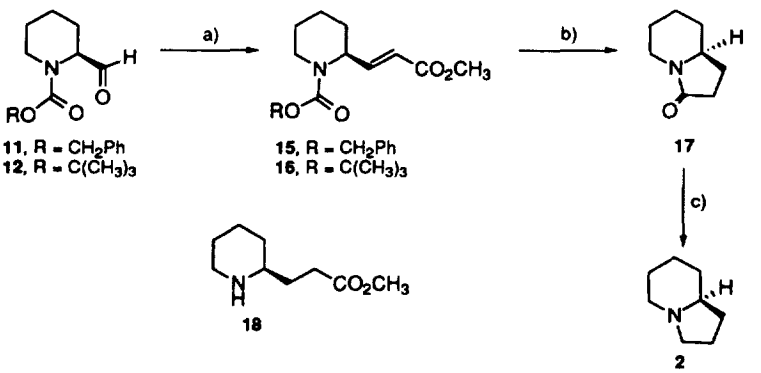



a) $Ph_3P^+CH_2CH_3\ Br^-$, BuLi, THF, from -70° to r.t. (76%). b) $H_2$, Pd/C, MeOH, r.t.; HCl, $H_2O$, $Et_2O$ (75-85%).

Scheme 4.

We carried out two syntheses of (*S*)-δ-coniceine starting from both **11** and **12** (Scheme 5). The Wittig reactions of both aldehydes **11** and **12** and the stabilized phosphorane **14** in methylene chloride were totally stereoselective giving the (*E*)-α,β-unsaturated esters **15** and **16**, respectively, in nearly quantitative yield.[38] The transformation of the N-Boc-derivative **16** to the indolizidinone **17** was performed in a three-stage reaction sequence (saturation of the double bond, hydrolysis of the carbamate, and cyclization),

which was realized without purification of intermediates, in 82% overall yield. On the other hand, the catalytic hydrogenation of **15** proceeded with N-deprotection, saturation of the double bond, and cyclization, affording **17**, along with a small and variable amount of the amino ester **18**; this mixture was heated at reflux in toluene to give **17** in 85% overall yield from **15**. Although the reduction of **17** to volatile δ-coniceine has been disclosed several times,[39] some of these reported procedures were not reproducible in our hands. The best reagent to obtain (*S*)-δ-coniceine was the borane/dimethyl sulfide complex, which gave the target molecule in good yield.[37]




a) $Ph_3P{=}CHCO_2CH_3$ (**14**), $CH_2Cl_2$, r.t. (97% from **11**; 95% from **12**). b) From **15**: $H_2$, Pd/C, MeOH, r.t.; toluene, reflux (85%). From **16**: $H_2$, Pd/C, MeOH, r.t.; 4M HCl, dioxane, AcOEt, r.t.; NaOAc, EtOH, reflux (82%). c) $BH_3/SMe_2$, THF, r. t. (80-85%).

Scheme 5.

Summarizing, we have demonstrated that the chiral building blocks **5** and **6** are useful for the syntheses of enantiomerically pure piperidine derivatives. It is worth mentioning that the derivatives of pipecolic acid **7** and **8**, and their enantiomers,[26,40] can be employed in the synthesis of analogues of FK-506, rapamycin and other immunosuppressors,[7] as well as for the preparation of pipecolic acid-containing peptides.[6,41,42] Additionally, the functionality of some of the chiral building blocks (e. g.; **11**, **12**, **13**, **15**, **16**, and **17**) reported in this paper make them suitable for the preparation of more complex molecules.

## 3. Experimental

All the reactions with sensitive materials were carried out using dry solvents under argon atmosphere. All the solvents and chemicals were commercially available and, unless otherwise indicated, were used as received. When necessary, THF and toluene were freshly dried over sodium/benzophenone ketyl. DMSO was distilled from $CaH_2$ under a reduced pressure of argon. $Et_3N$ was distilled from $CaH_2$ or KOH under an argon atmosphere. Commercially available $CH_2Cl_2$ (Fluka puriss quality) kept over molecular sieves was used. The enzyme acylase I from *Aspergillus* species (AA-I) was purchased from Aldrich or Sigma.[28] $^1$H-NMR and $^{13}$C-NMR spectra were measured in a Varian-UNITY-400, Varian-XL-300, Varian-Gemini-200, or a Bruker AM-200; chemical shifts are reported in parts per million (δ), and the coupling constants are indicated in Hz. Unless otherwise indicated, all the NMR spectra were measured at room temperature (298 K). $^1$H-NMR spectra are referenced to the residual proton in the deuterated solvent. $^{13}$C-NMR spectra are referenced to the chemical shift of the deuterated solvent. The multiplicity

of the signals in the $^{13}$C-NMR spectra were determined by APT or DEPT experiments. The IR spectra were performed on a Perkin–Elmer-657 spectrometer, the frequencies in the IR spectra are indicated in $cm^{-1}$. All the mass spectra are low-resolution electron-impact mass spectra (70 eV), and were recorded in a RMU-GMG spectrometer from Hitachi–Perkin–Elmer. Microanalysis were realized by E. Barbero (Instituto de Química Orgánica, C. S. I. C.) on a Carlo Erba EA 1180-Elemental Analyzer. The optical rotations were measured on a Perkin–Elmer 241 MC polarimeter; all the optical rotations were measured at room temperature. All the preparative chromatographies were done with silica gel (40–63 mm) using the technique of flash-chromatography.[43]

### 3.1. Synthesis of (±)-N-(benzyloxycarbonyl)-2-(hydroxymethyl)piperidine (±)-5

A solution of (±)-2-(hydroxymethyl)piperidine (20 g, 174 mmol) in THF (300 ml) was treated with aqueous 1 M $K_2CO_3$ (500 ml, 500 mmol) and benzyl chloroformate (27 ml, 191 mmol). The mixture was stirred at room temperature overnight, and then 5% aqueous HCl was added until pH=2. The organic phase was separated and the aqueous phase was saturated with NaCl and extracted with AcOEt (twice). The combined organic extracts were washed with water and dried over anhydrous $MgSO_4$. After evaporation of the solvent and chromatography using hexane:AcOEt mixtures (in the ratio of between 80:20 and 0:100), pure (±)-**5** was obtained (39.8 g, 90% yield). White solid: m.p. 49–52°C. $^1$H-NMR (200 MHz, $CDCl_3$) δ 7.36–7.25 (m, 5H), 5.13 (s, 2H), 4.36 (m, 1H), 4.03 (br d, *J*=13.1, 1H), 3.83 (ddd, *J*=11.1, 8.7, 6.1, 1H), 3.63 (distorted dt, *J*=11.3, 5.7, 1H), 2.95 (br distorted t, *J*=12.0, 1H), 2.20 (broad s, 1H), 1.86–1.39 (m, 6H). $^{13}$C-NMR (50.3 MHz, $CDCl_3$) δ 156.2 (s), 136.5 (d), 128.2 (d, 2C), 127.7 (d), 127.5 (d, 2C), 66.9 (t), 60.6 (t), 52.5 (d), 39.9 (t), 25.0 (t), 24.8 (t), 19.2 (t). IR (KBr) ν 3450, 2950, 2880, 1680, 1430, 1360, 1270, 1170, 1140, 1050, 700. MS *m/z* 218 (M−31, 7), 174 (23), 140 (2) 128 (3), 91 (100), 84 (5), 83 (6), 65 (7), 57 (16), 55 (7), 45 (7), 41 (8). Anal. calcd for $C_{14}H_{19}NO_3$: C, 67.45%; H, 7.68%; N, 5.62%. Found: C, 67.80%; H, 7.58%; N, 5.82%.

### 3.2. Synthesis of (±)-N-(tert-butoxycarbonyl)-2-(hydroxymethyl)piperidine (±)-6

A solution of (±)-2-(hydroxymethyl)piperidine (20 g, 174 mmol) in THF (300 ml) was treated with aqueous 1 M $K_2CO_3$ (500 ml, 500 mmol) and di-*tert*-butyldicarbonate (44 ml, 191 mmol). The solution was stirred at room temperature overnight, and then 5% aqueous HCl was added until pH=2. The organic phase was separated and the aqueous phase was saturated with NaCl and extracted with AcOEt (twice). The combined organic extracts were washed with water and dried over anhydrous $MgSO_4$. After evaporation of the solvent, a crude product was obtained, which was purified by crystallization from MeOH–$Et_2O$ to give (±)-**6** (35.5 g, 95% yield). White solid: m.p. 81–84°C. $^1$H-NMR (300 MHz, $CDCl_3$) δ 4.30 (m, 1H), 3.94 (br d, *J*=12.5, 1H), 3.83 (ddd, *J*=11.0, 9.3, 5.9, 1H), 3.61 (dt, *J*=11.0, 5.5, 1H), 2.89 (br t, *J*=12.5, 1H), 2.00 (broad s, 1H), 1.61 (m, 6H), 1.47 (s, 9H). $^{13}$C-NMR (50.3 MHz, $CDCl_3$) δ 156.3 (s), 79.8 (s), 61.8 (t), 52.6 (d), 39.9 (t), 28.4 (q, 3C), 25.3 (t), 25.2 (t), 19.6 (t). IR (KBr) ν 3440, 2940, 2890, 1655, 1425, 1370, 1280, 1170, 1150, 1060, 1050, 870. MS *m/z* 184 ($M^+$−31, 23), 128 (100), 84 (90), 57 (89), 56 (21), 55 (23), 41 (30). Anal. calcd for $C_{11}H_{21}NO_3$: C, 61.37%; H, 9.83%; N, 6.51%. Found: C, 61.36%; H, 10.13%; N, 6.64%.

### 3.3. Kinetic resolution of N-(benzyloxycarbonyl)-2-(hydroxymethyl)piperidine (±)-5. Synthesis of (S)-(−)-5 and (R)-(+)-9

AA-I (48 g, 300 U/mmol) was added to a solution of (±)-**5** (20 g, 80.3 mmol) in wet toluene (500 ml). The mixture was stirred at room temperature for 5 minutes, and was then treated with vinyl butyrate (10.4 ml, 80.3 mmol). The mixture was stirred at room temperature for 9 hours, and diluted with $CH_2Cl_2$ (*ca.* 200 ml). The enzyme was removed by filtration and washed with $CH_2Cl_2$. After evaporation of the solvent, the crude product was chromatographed (hexane:AcOEt, ratios between 80:20 and 0:100) to give (*R*)-**9** (12.6 g, 49% yield) and (*S*)-**5** (of 85% ee, as determined by g.l.c.; 9.8 g, 49% yield). This enantiomerically enriched material was subjected to a second kinetic resolution using wet toluene (300 ml), AA-I (23.5 g, 300 U/mmol), and vinyl butyrate (5.1 ml, 39.3 mmol). The mixture was stirred at room temperature for 6 hours. The same work-up and purification procedure as in the first kinetic resolution gave a small amount of the butyrate **9** and the enantiomerically pure alcohol (*S*)-**5** (>99.8% ee, as determined by g.l.c.; 8.3 g, 85% yield). The spectroscopic and analytical data of (*S*)-**5** are identical to that reported for (±)-**5**, having a specific rotation of: $[\alpha]_D$ −30.2 ($CHCl_3$, c=1.1).

The analytical and spectroscopic data of (*R*)-(+)-N-(benzyloxycarbonyl)-2-(butyryloxymethyl)piperidine [(*R*)-**9**] are as follows: thick oil; $[\alpha]_D$ +20.7 ($CHCl_3$, c=1.0; for a sample of *ca.* 70% ee).[44] $^1$H-NMR (200 MHz, $CDCl_3$, 313 K) δ 7.33 (m, 5H), 5.12 (s, 2H), 4.54 (m, 1H), 4.30 (dd, *J*=11.1, 8.3, 1H), 4.10 (dd, *J*=11.1, 6.4, 1H), 4.08 (m, 1H), 2.89 (m, 1H), 2.17 (t, *J*=7.5, 2H), 1.69–1.48 (m, 8H), 0.89 (t, *J*=7.4, 3H). $^{13}$C-NMR (50.3 MHz, $CDCl_3$, 313 K) δ 172.4 (s), 155.0 (s), 136.5 (s), 127.9 (d, 2C), 127.3 (d), 127.2 (d, 2C), 66.4 (t), 60.9 (t), 48.9 (d), 38.2 (t), 35.4 (t), 25.8 (t), 24.7 (t), 19.8 (t), 17.7 (t), 13.0 (q). IR (neat) ν 3040, 2940, 1740, 1700, 1500, 1260, 750, 700. MS *m/z* 292 (M−28, 31), 174 (57), 91 (100), 65 (9), 43 (10). Anal. calcd for $C_{18}H_{25}NO_4$: C, 67.69%; H, 7.89%; N, 4.39%. Found: C, 67.95%; H, 8.02%; N, 4.63%.

### 3.4. Kinetic resolution of N-(tert-butoxycarbonyl)-2-(hydroxymethyl)piperidine (±)-6. Synthesis of (S)-(−)-6 and (R)-(+)-10

AA-I (36 g, 300 U/mmol) was added to a solution of (±)-**6** (13 g, 60.5 mmol) in toluene (400 ml). The mixture was stirred at room temperature for 5 minutes, and then was treated with vinyl butyrate (7.8 ml, 60.5 mmol). The heterogeneous suspension was stirred at room temperature for 9 hours, and diluted with $CH_2Cl_2$ (*ca.* 200 ml). The enzyme was removed by filtration and washed with $CH_2Cl_2$. After evaporation of the solvent, the crude product was chromatographed (hexane:AcOEt, ratios between 80:20 and 0:100) to give (*R*)-**10** (88% ee, as determined by g.l.c.; 5.7 g, 33% yield) and (*S*)-**6** (47% ee, as determined by g.l.c.; 8.2 g, 63% yield). This enantiomerically enriched material was submitted to a second kinetic resolution using wet toluene (200 ml), AA-I (23.0 g, 300 U/mmol), and vinyl butyrate (5.0 ml, 38.5 mmol). This mixture was stirred at room temperature for 8.5 hours. The same work-up and purification procedure as in the first kinetic resolution gave the butyrate (*R*)-**10** (ee not determined; 3.8 g, 35% yield) and the enantiomerically pure alcohol (*S*)-**6** (>99.6% ee, as determined by g.l.c.; 4.7 g, 58% yield). The spectroscopic and analytical data of (*S*)-**6** are identical to those reported for (±)-**6**. The specific rotation is $[\alpha]_D$ −40.5 ($CHCl_3$, c=1.0).

The analytical and spectroscopic data of (*R*)-(+)-N-(*tert*-butoxycarbonyl)-2-(butyryloxymethyl)piperidine [(*R*)-**10**] are as follows: thick oil; $[\alpha]_D$ +31.1 ($CHCl_3$, c=0.3; for a sample of >98% ee). $^1$H-NMR (200 MHz, $CDCl_3$) δ 4.49 (broad m, 1H), 4.25 (dd, *J*=11.0, 8.1, 1H), 4.10 (dd, *J*=11.0, 6.8, 1H), 4.00 (broad d, *J*=13.0, 1H), 2.80 (m, 1H), 2.28 (t, *J*=7.4, 2H), 1.70–1.52 (m, 8H), 1.45 (s, 9H), 0.94 (t, *J*=7.4, 3H). $^{13}$C-NMR (50.3 MHz, $CDCl_3$) δ 173.4 (s), 154.9 (s), 79.4 (s), 61.5 (t), 48.7 (d), 39.3 (t), 36.0 (t),

28.3 (q, 3C), 25.3 (t), 25.2 (t), 19.2 (t), 18.3 (t), 13.6 (q). IR (neat) ν 2980, 1750, 1700, 1360, 1250. MS *m/z* 285 ($M^+$, <1), 184 (4), 128 (29), 111 (6), 98 (11), 97 (21), 84 (46), 83 (38), 71 (34), 69 (41), 57 (100), 55 (26), 43 (49), 41 (22).

### *3.5. General procedure for the Swern oxidation of* **5** *and* **6**. *Syntheses of (S)-(−)-N-(benzyloxycarbonyl)-2-(formyl)piperidine* **11** *and (S)-(−)-N-(*tert*-butoxycarbonyl)-2-(formyl)piperidine* **12**

Commercially available 2 M oxalyl chloride solution in $CH_2Cl_2$ (4.3 ml, 8.6 mmol) was diluted with $CH_2Cl_2$ (15 ml) at −70°C under an argon atmosphere. A solution of dry DMSO (1.2 ml, 17.3 mmol) in $CH_2Cl_2$ (5 ml) was slowly added dropwise at −70°C. After stirring for 30 minutes at this temperature, a solution of the corresponding alcohol (7.2 mmol) in $CH_2Cl_2$ (10 ml) was added *via* cannula. The mixture was stirred at −70°C for 90 minutes, and then dry $Et_3N$ (5 ml, 36.1 mmol) was added. Stirring was maintained at −70°C while the formation of the aldehyde was monitored by t.l.c. When the reaction was completed (*ca.* 0.5 hours), water was added at −70°C, the mixture was then allowed to warm slowly to room temperature. The organic layer was then separated and the aqueous phase was extracted with $CH_2Cl_2$ (three times). The combined organic extracts were washed with aqueous 5% HCl (twice), water (twice), 1 M aqueous $Na_2CO_3$ (twice) and finally water (twice). After drying and solvent evaporation, a chromatographically homogeneous product (either **11** or **12**) was obtained. Analytically pure samples of either **11** or **12** were obtained after flash-chromatography (hexane:AcOEt, 85:15). The spectroscopic and analytical data of **11** and **12** are shown below.

#### *3.5.1. (S)-(−)-N-(Benzyloxycarbonyl)-2-(formyl)piperidine* **11**

Compound **11** was obtained from alcohol (*S*)-**5** in 92% yield: thick oil; $[\alpha]_D$ −30.5 ($CHCl_3$, c=1.4). $^1$H-NMR (300 MHz, $CDCl_3$, 313 K) δ 9.61 (s, 1H), 7.35 (m, 5H), 5.17 (s, 2H), 4.70 (broad m, 1H), 4.12 (broad m, 1H), 3.00 (broad m, 1H), 2.22 (m, 1H), 1.75–1.23 (m, 5H). $^{13}$C-NMR (50.3 MHz, $CDCl_3$) δ 200.5 (s), 172.5 (s), 136.2 (s), 128.2 (d, 2C), 127.8 (d), 127.6 (d, 2C), 67.1 (t), 60.8 (t), 42.4 (d), 24.3 (t), 23.2 (t), 20.4 (t). IR (neat) ν 3450, 3040, 2940, 2845, 1700, 1730, 1580, 1500, 1420, 1350, 1250, 1170, 1050, 700. MS *m/z* 247 ($M^+$, <1), 218 (23), 174 (31), 91 (100). Anal. calcd for $C_{14}H_{17}NO_3$: C, 67.98%; H, 6.93%; N, 5.67%. Found: C, 67.82%; H, 7.12%; N, 5.78%.

#### *3.5.2. (S)-(−)-N-(*tert*-Butoxycarbonyl)-2-(formyl)piperidine* **12**

Compound **12** was obtained from alcohol (*S*)-**6** in 85% yield: thick oil; $[\alpha]_D$ −77.4 ($CHCl_3$, c=1.4). $^1$H-NMR (300 MHz, $CDCl_3$) δ 9.59 (s, 1H), 4.55 (m, 1H), 3.95 (m, 1H), 2.90 (m, 1H), 2.15 (m, 1H), 1.70–1.20 (m, 5H), 1.47 (s, 9H). $^{13}$C-NMR (50.3 MHz, $CDCl_3$) δ 201.1 (s), 156.3 (br s), 80.2 (s), 60.7 (very br d), 42.8 (very br, t), 28.1 (q, 3C), 24.5 (t), 23.4 (t), 20.7 (t). IR (neat) ν 2980, 2940, 2870, 1740, 1700, 1480, 1410, 1370, 1280, 1250, 1160, 1050, 1000, 1060, 870, 770. MS *m/z* 213 ($M^+$, <1), 184 (4), 140 (3), 128 (53), 100 (3), 84 (41), 57 (100). Anal. calcd for $C_{11}H_{19}NO_3$: C, 61.95%; H, 8.98%; N, 6.57%. Found: C, 61.72%; H, 9.10%; N, 6.65%.

### *3.6. Synthesis of (S)-(−)-N-(benzyloxycarbonyl)pipecolic acid* **7**

#### *3.6.1. Method A*

Jones reagent was added dropwise to a cooled (0°C) solution of the alcohol **5** (300 mg, 1.20 mmol) in acetone (5 ml) until a brown–orange colour persisted. The mixture was stirred at this temperature for an additional 15 minutes (the reaction was complete as shown by t.l.c.) and then excess isopropanol was added, the solution turning to a dark-green colour. The solvent was evaporated and the residue partitioned

between AcOEt and water. The aqueous phase was extracted with AcOEt (twice). The organic layer was washed with aqueous saturated $NaHCO_3$. The combined aqueous phases were acidified with 10% aqueous $H_2SO_4$ and extracted with AcOEt (twice). The combined organic extracts were dried ($MgSO_4$) and the solvent evaporated to give crude acid (*S*)-(−)-**7**, which was purified by crystallization from $Et_2O$/hexane (250 mg, 77% yield).

*3.6.2. Method B*

$KMnO_4$ (125 mg, 0.79 mmol) was added in small portions, over 1 h, to a stirred suspension of aldehyde **11** (160 mg, 0.65 mmol) and $MgSO_4$ (94 mg, 0.78 mmol) in acetone (5 ml) at room temperature. The mixture was stirred at room temperature for another 30 minutes and then the solvent was removed in vacuo. The residue was filtered using hot water as eluent. The solution was cooled to room temperature and extracted with $CHCl_3$ (twice), acidified with concentrated HCl, and extracted with $CHCl_3$ (twice). The combined organic extracts were washed with brine and dried ($MgSO_4$). The solvent was evaporated to give the target molecule (*S*)-(−)-**7** (137 mg, 76% yield). An analytically pure sample was obtained by crystallization from $Et_2O$/hexane. M.p. 106–109°C (lit.:[45] m.p. 111–113°C). $[\alpha]_D$ −53.0 ($CH_2Cl_2$, c=1.0), $[\alpha]_D$ −57.1 (AcOH, c=1.3) [lit.:[45] $[\alpha]_D$ +56.5, (AcOH, c=0.55) for the enantiomer]. $^1$H-NMR (300 MHz, $CDCl_3$) δ 10.00 (broad s, 1H), 7.33 (m, 5H), 5.16 (s, 2H), 4.95 (m, 1H), 4.10 (m, 1H), 3.05 (m, 1H), 2.25 (m, 1H), 1.80–1.22 (m, 5H). $^{13}$C-NMR (50.3 MHz, $CDCl_3$) δ 176.6 (s), 156.6 (s), 136.3 (s), 128.3 (d, 2C), 127.8 (d), 127.6 (d, 2C), 67.4 (t), 54.1 (d), 41.7 (d), 26.5 (d), 24.5 (d), 20.5 (d). IR (KBr) ν 3700–3000, 2970, 2860, 1730, 1650, 1470, 1430, 1350, 1320, 1280, 1260, 1200, 1160, 1120, 1080, 1070, 1040, 1000, 930, 860, 760, 700. MS *m/z* 263 ($M^+$; <1), 218 (13), 174 (31), 128 (20), 91 (100), 65 (15), 55 (11). Anal. calcd for $C_{14}H_{17}NO_4$: C, 63.87%; H, 6.51%; N, 5.32%. Found: C, 63.89%; H, 6.54%; N, 5.35%.

*3.7. Synthesis of (S)-(−)-N-(tert-butoxycarbonyl)pipecolic acid 8*

$KMnO_4$ (80 mg, 0.51 mmol) was added in small portions, over 1 h, to a stirred suspension of the aldehyde **12** (90 mg, 0.42 mmol) and $MgSO_4$ (60 mg, 0.50 mmol) in acetone (5 ml) at room temperature. The mixture was stirred at room temperature for another 30 minutes and then the solvent was removed in vacuo. The residue was filtered using hot water as eluent. The solution was cooled to room temperature and extracted with $CHCl_3$ (twice), acidified with concentrated HCl, and extracted with $CHCl_3$ (twice). The combined organic extracts were washed with brine and dried ($MgSO_4$). The solvent was evaporated to give the N-protected amino acid (*S*)-(−)-**8** (67 mg, 70% yield). An analytically pure sample was obtained by crystallization from MeOH/$Et_2O$. M.p. 120–123°C (lit.:[46] m.p. 121–122°C). $[\alpha]_D$ −52.4 ($CHCl_3$, c=0.35), $[\alpha]_D$ −55.7 (AcOH, c=0.6) [lit.:[47] $[\alpha]_D$ −56.0 (AcOH, c=1.0)]. $^1$H-NMR (300 MHz, $CDCl_3$, 313 K) δ 9.80 (broad s, 1H), 4.83 (broad m, 1H), 3.95 (broad s, 1H), 2.94 (broad s, 1H), 2.21 (m, 1H), 1.75–1.20 (m, 5H), 1.44 (s, 9C). $^{13}$C-NMR (50.3 MHz, $CDCl_3$, 313 K) δ 177.6, 156.0 (broad), 80.3, 54.1 (very broad), 41.1 (very broad), 28.3 (3C), 26.6, 24.6, 20.7. IR (KBr) ν 3700–3000, 2980, 2945, 1755, 1630, 1480, 1440, 1400, 1370, 1320, 1280, 1260, 1200, 1160, 1140, 1100, 1040, 930, 860, 770, 740. MS *m/z* 229 ($M^+$; <1), 184 (7), 156 (3), 128 (89), 84 (85), 57 (100), 41 (46). Anal. calcd for $C_{11}H_{19}NO_4$: C, 57.63%; H, 8.35%; N, 6.12%. Found: C, 57.48%; H, 8.46%; N, 6.12%.

*3.8. Synthesis of (S)-(−)-pipecolic acid 3*

A mixture of the benzyl carbamate **7** (80 mg, 0.30 mmol) and 10% Pd/C (16 mg) in MeOH (5 ml) was hydrogenated at room temperature under a pressure of *ca.* 45 psi of $H_2$ in a Parr shaker for 6 hours.

The solid was then filtered off and washed. Evaporation of the solvent gave pure (*S*)-pipecolic acid (37 mg, 94% yield). An analytically pure sample was obtained by crystallization from MeOH/$Et_2O$. M.p. 260–262°C (lit.:[18c] 256–261°C). $[\alpha]_D$ −26.8 ($H_2O$, c=0.5) [lit.:[18c] $[\alpha]_D$ −25.9 ($H_2O$, c=1.0)]. $^1$H-NMR (200 MHz, $D_2O$) δ 3.65 (m, 1H), 3.34 (m, 1H), 3.06–2.86 (m, 1H), 2.15 (m, 1H), 1.81–1.42 (m, 5H). $^{13}$C-NMR (50.3 MHz, $D_2O$) δ 174.6 (s), 59.5 (d), 45.3 (t), 27.6 (t), 23.0 (2C, t). IR (KBr) ν 3430, 2970, 1675, 1625, 1400, 1060, 925. MS *m/z* 129 ($M^+$; <1), 84 (100), 56 (37).

### *3.9. Synthesis of (S,Z)-(+)-N-(benzyloxycarbonyl)-2-(1-propenyl)piperidine* **13**

1.4 M BuLi in hexane (1.7 ml, 2.40 mmol) was slowly added to a stirred suspension of ethyl triphenylphosphonium bromide (890 mg, 2.40 mmol) in dry THF (10 ml) at −70°C under argon. The mixture was warmed at 0°C for 30 minutes. The solution was then cooled to −70°C and a solution of the aldehyde **11** (377 mg, 1.53 mmol) in dry THF (5 ml) was added dropwise via cannula. The mixture was left to reach room temperature overnight. The reaction was quenched by the addition of water and extracted with $Et_2O$ (twice). The combined organic extracts were washed with brine, dried ($MgSO_4$), evaporated and chromatographed (hexane:AcOEt, 80:20) to give **13** as a single peak in g.l.c. (301 mg, 76% yield): thick oil; $[\alpha]_D$ +14.6 ($CHCl_3$, c=1.9). $^1$H-NMR (300 MHz, $CDCl_3$) δ 7.34 (m, 5H), 5.72 (m, 1H), 5.58 (m, 1H), 5.16 (d, *J*=12.4, 1H), 5.10 (d, *J*=12.4, 1H), 4.02 (m, 1H), 2.96 (m, 1H), 1.72–1.42 (m, 10H). $^{13}$C-NMR (75 MHz, $CDCl_3$) δ 155.0 (s), 136.8 (s), 128.2 (2C, d), 127.62 (d), 127.58 (2C, d), 127.3 (d), 126.3 (d), 66.7 (t), 47.8 (d), 39.8 (t), 30.1 (t), 25.3 (t), 19.2 (t), 13.0 (q). IR (neat) ν 3030, 2940, 2860, 2320, 1700, 1425, 1350, 1315, 1270, 1260, 1175, 1145, 1070, 1030, 765, 730, 700. MS *m/z* 259 ($M^+$, 2), 174 (6), 168 (48), 158 (2), 128 (5), 124 (28), 91 (100), 82 (10), 65 (14).

### *3.10. Synthesis of (R)-(−)-coniine hydrochloride (1·HCl)*

A mixture of the olefin **13** (100 mg, 0.39 mmol) and 10% Pd/C (20 mg) in MeOH (5 ml) was hydrogenated at room temperature under a hydrogen pressure of *ca.* 45 psi in a Parr shaker for 6 hours. The solid was then filtered off and washed. Evaporation of the solvent gave a residue which was dissolved in $Et_2O$ and treated with concentrated HCl at room temperature. After solvent evaporation and crystallization from MeOH/$Et_2O$, pure (*R*)-coniine hydrochloride (53 mg, 85% yield) was obtained. M.p. 213–215°C (lit.:[19a] m.p. 217–218°C). $[\alpha]_D$ −6.2 (EtOH, c=0.48) [lit.:[19a] $[\alpha]_D$=−6.3 (EtOH, c=0.62)]. $^1$H-NMR (200 MHz, $CD_3OD$) δ 3.89–3.74 (m, 1H), 3.57 (m, 1H), 3.20 (m, 2H), 2.25–2.04 (m, 3H), 1.90–1.49 (m, 8H), 1.17 (t, *J*=7.0, 3H). $^{13}$C-NMR (50.3 MHz, $CD_3OD$) δ 58.0 (d), 46.0 (t), 37.0 (t), 29.7 (t), 23.6 (t), 23.1 (t), 19.3 (t), 14.0 (q). IR (KBr) ν 3450, 2980, 1640, 1585, 1470, 1460, 1014, 1010. MS *m/z* 163 ($M^+$, <1) 127 (2), 112 (1), 98 (3), 85 (8), 84 (100), 70 (7), 56 (23), 43 (11), 41 (9).

### *3.11. Synthesis of (S,E)-(−)-methyl 3-[N-(benzyloxycarbonyl)-2-piperidyl]acrylate* **15** *by tandem Swern–Wittig reaction*

Commercially available 2 M oxalyl chloride solution in $CH_2Cl_2$ (4.8 ml, 9.6 mmol) was diluted with $CH_2Cl_2$ (40 ml) at −70°C under an argon atmosphere. A solution of dry DMSO (1.35 ml, 19.3 mmol) in $CH_2Cl_2$ (30 ml) was added slowly, dropwise, at −70°C. After stirring for 30 minutes at this temperature, a solution of alcohol (*S*)-**5** (2 g, 8.0 mmol) in $CH_2Cl_2$ (30 ml) was added via cannula. The mixture was stirred at −70°C for 90 minutes, and then dry $Et_3N$ (5.5 ml, 40.2 mmol) was added. Stirring was maintained at −70°C while the formation of the aldehyde was monitored by t.l.c. When the reaction was completed (*ca.* 0.5 hours), solid $Ph_3P{=}CHCO_2Me$ (7.6 g, 22.8 mmol). The temperature was allowed

to warm slowly to ambient temperature (overnight). The solvent was removed under vacuum and the residue was dissolved in the minimum amount of $CH_2Cl_2$, added to the top of a column of silica gel and chromatographed (hexane:AcOEt, 80:20) to give diastereoisomerically pure α,β-unsaturated ester **15** (2.21 g, 91% yield): thick oil; $[\alpha]_D$ −71.1 ($CHCl_3$, c=1.1). $^1$H-NMR (300 MHz, $CDCl_3$) δ 7.32 (m, 5H), 6.89 (dd, *J*=16.0, 4.1, 1H), 5.84 (dd, *J*=16.0, 2.1, 1H), 5.14 (s, 2H), 5.04 (m, 1H), 4.09 (m, 1H), 3.74 (s, 3H), 2.89 (m, 1H), 1.85–1.40 (m, 6H). $^{13}$C-NMR (50.3 MHz, $CDCl_3$) δ 165.6 (s), 154.8 (s), 146.5 (d), 136.1 (s), 127.8 (d, 2C), 127.3 (d), 127.1 (d, 2C), 121.4 (d), 66.5 (t), 51.3 (d), 50.8 (q), 39.7 (t), 28.2 (t), 24.5 (t), 19.1 (t). IR (neat) ν 2940, 2860, 1730, 1700, 1660, 1590, 1500, 1420, 1310, 1260, 1170, 1140, 1100, 1050, 700. MS *m/z* 303 ($M^+$; 1), 212 (10), 168 (63), 136 (17), 108 (11), 91 (100), 65 (13). Anal. calcd for $C_{17}H_{21}NO_4$: C, 67.31%; H, 6.98%; N, 4.62%. Found: C, 67.60%; H, 7.02%; N, 4.69%.

### *3.12. Synthesis of (S,E)-(−)-methyl 3-[N-(*tert*-butoxycarbonyl)-2-piperidyl]acrylate* **16**

$Ph_3P{=}CHCO_2Me$ (5.3 g, 15.9 mmol) was added to a solution of the N-protected amino aldehyde **16** (1.13 g, 5.3 mmol) in dry $CH_2Cl_2$ (50 ml). The mixture was stirred at room temperature overnight. The solvent was then evaporated to give a residue which was dissolved in the minimum amount of $CH_2Cl_2$ and added to the top of a column of silica gel and chromatographed (hexane:AcOEt, 80:20) to give **16** as a single isomer (1.35 g, 95% yield): thick oil; $[\alpha]_D$ −90.1 ($CHCl_3$, c=1.0). $^1$H-NMR (300 MHz, $CDCl_3$) δ 6.90 (dd, *J*=15.9, 4.0, 1H), 5.82 (dd, *J*=15.9, 2.2, 1H), 4.95 (m, 1H), 4.00 (m, 1H), 3.74 (s, 3H), 2.81 (m, 1H), 1.80–1.40 (m, 6H), 1.45 (s, 9H). $^{13}$C-NMR (50.3 MHz, $CDCl_3$) δ 166.3 (s), 154.7 (s), 147.5 (d), 121.4 (d), 79.5 (s), 51.4 (d), 51.3 (q), 39.8 (t), 28.7 (t), 28.1 (q, 3C), 25.0 (t), 19.6 (t). IR (neat) ν 2980, 2940, 2860, 1730, 1700, 1660, 1440, 1410, 1370, 1310, 1280, 1270, 1160, 1050, 870, 770. MS *m/z* 269 ($M^+$; 1), 213 (8), 196 (3), 169 (14), 154 (39), 128 (22), 110 (31), 84 (30), 57 (100).

### *3.13. Synthesis of (S)-(+)-indolizidin-3-one* **17**

#### *3.13.1. Method A. From (S,E)-methyl 3-[N-(benzyloxycarbonyl)-2-piperidyl]acrylate* **15**

A mixture of the α,β-unsaturated ester **15** (1.0 g, 3.30 mmol) and 10% Pd/C (200 mg) in MeOH (15 ml) was hydrogenated at room temperature under a pressure of *ca.* 45 psi of $H_2$ in a Parr shaker for 6 hours. The solid was then filtered off and washed. The solvent was removed to give a residue consisting of an inseparable mixture of the target compound **17** and a small amount of the γ-amino ester **18**. The crude product was dissolved in toluene and heated at reflux for 12 hours. After solvent evaporation and filtration through a short pad of silica gel, using acetone as eluent, pure lactam **17** was obtained (390 mg, 85% yield).

#### *3.13.2. Method B. From (S,E)-methyl 3-[N-(*tert*-butoxycarbonyl)-2-piperidyl]acrylate* **16**

A mixture of the α,β-unsaturated ester **16** (700 mg, 2.60 mmol) and 10% Pd/C (70 mg) in MeOH (13 ml) was hydrogenated at atmospheric pressure (using a balloon filled with $H_2$) at room temperature for 30 minutes. The solid was then filtered off and washed. Evaporation of the solvent gave (*S*)-methyl 3-[N-(*tert*-butoxycarbonyl)-2-piperidyl]propionate (650 mg, 92% yield). This compound was dissolved in AcOEt (15 ml) and treated with a 4 M solution of HCl in dioxane (6.5 ml, 26 mmol). The mixture was stirred overnight and then the solvent was removed under vacuum. The residue was triturated with $Et_2O$ to obtain (*S*)-methyl 2-(piperidyl)propionate hydrochloride (496 mg, >98% yield). This hydrochloride was dissolved in EtOH (25 ml), treated with NaOAc (982 mg, 12.0 mmol), and heated at reflux for 6 hours. After solvent evaporation, the residue was filtered through a short pad of silica gel eluting with AcOEt, to give pure **17** (one peak in chiral g.l.c., 302 mg, 91% yield; 84% overall yield from **16**): oil;

$[\alpha]_D$ +35.4 ($CHCl_3$, c=0.2). $^1$H-NMR (300 MHz, $CDCl_3$) δ 4.11 (m, 1H), 3.39 (m, 1H), 2.61 (m, 1H), 2.35 (m, 2H), 2.19 (m, 1H), 1.86 (m, 2H), 1.72–1.51 (m, 2H), 1.45–1.25 (m, 2H), 1.17 (m, 1H). $^{13}$C-NMR (50.3 MHz, $CDCl_3$) δ 172.7 (s), 56.5 (d), 39.4 (t), 32.8 (t), 29.7 (t), 24.6 (t), 23.8 (t), 23.0 (t). IR (neat) ν 3700–3200, 2940, 2860, 1680, 1450, 1425, 1370, 1310, 1270, 1140, 1060, 835. MS *m/z* 139 ($M^+$, 36), 138 (100), 124 (11), 112 (16), 98 (84), 84 (40), 55 (47).

### *3.14. Synthesis of (S)-(+)-δ-coniceine 2*

A $BH_3/SMe_2$ complex (0.43 ml, 4.74 mmol) was added dropwise to a solution of the lactam **17** (220 mg, 1.58 mmol) in dry THF (15 ml) at room temperature under argon. Stirring was maintained at room temperature overnight. The excess of borane was removed by the slow addition of MeOH. The solvent was removed under vacuum to give a δ-coniceine/borane complex [$^{13}$C-NMR (50.3 MHz, $CDCl_3$) δ 65.3 (d), 60.2 (t), 53.5 (t), 26.9 (t), 24.0 (t), 20.9 (t), 19.3 (t), 18.5 (t)], which was stirred with 60% aqueous $CF_3CO_2H$ for 20 minutes at room temperature. After solvent evaporation, the residue was dissolved in EtOH and passed through a Dowex 1X8-200 column ($OH^-$ form) to obtain pure (*S*)-(+)-δ-coniceine (145 mg, 80% yield), identical to that reported in the literature:[20] oil; $[\alpha]_D$ +9.2 (EtOH, c=0.5) [lit.:[20a] $[\alpha]_D$ +9.3±0.6 (EtOH, c=1.77)]. $^{13}$C-NMR (50.3 MHz, $CDCl_3$) δ 62.1 (d), 57.6 (t), 50.0 (t), 26.6 (t), 23.9 (t), 20.4 (t), 19.4 (t), 18.1 (t).

(*S*)-(+)-δ-Coniceine was further characterized as its picrate. The alkaloid was dissolved in EtOH and treated with excess picric acid. The mixture was heated until a clear solution was obtained and then allowed to reach room temperature slowly to obtain yellow needles of (*S*)-(+)-δ-coniceine picrate which were recrystalized from MeOH. M.p. 228–232°C (lit.:[19i] 226–228°C). $^1$H-NMR (200 MHz, $CDCl_3$) δ 10.30 (br s, 1H), 8.90 (s, 2H), 3.90 (m, 2H), 2.84 (m, 3H), 2.28–1.84 (m, 10H). Anal. calcd for $C_{14}H_{18}N_4O_7$: C, 47.46%; H, 5.12%; N, 15.81%. Found: C, 47.30%; H, 5.02%; N, 15.76%.

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13. For a definition and discussion, see: Seebach, D.; Hungerbühler, E. In *Modern Synthetic Methods*; Scheffold, R., Ed.; Salle and Sauerländer: Berlin; 1980; Vol. 2, pp 91–171.
14. The acetylation of (±)-**6** catalyzed by AA-I was briefly mentioned in our first paper on transesterifications catalyzed by AA-I, see: Herradón, B.; Valverde, S. *Synlett* **1995**, 599–602.
15. (a) Derivatives of chiral 2-(hydroxymethyl)piperidine have been prepared by reduction of derivatives of chiral pipecolic acid; although both enantiomers of pipecolic acid are commercially available, they are very expensive; sometimes this inconvenience has hampered planned syntheses of natural products, see: Wong, P. L.; Moeller, K. D. *J. Am. Chem. Soc.* **1993**, *115*, 11434–11445 (especially footnote #16 in that paper!). (b) Racemic pipecolic acid was originally resolved by crystallization of the tartrate salt, see: Yamada, S.; Hohgo, C.; Chibata, I. *Agric. Biol. Chem.* **1977**, *41*, 2413–2416. (c) For recent EPC-syntheses of pipecolic acid, see Ref. 18 cited below. (d) Recently (*S*)-2-(hydroxymethyl)piperidine has been synthesized, in several steps with moderate diastereoselectivity, using (*R*)-phenylglycine as an auto-immolative chiral auxiliary, see: Lingibé, O.; Graffe, B.; Sacquet, M.-C.; Lhommet, G. *Heterocycles* **1995**, *41*, 1931–1934. (e) Previous attempts to obtain chiral derivatives of 2-(hydroxymethyl)piperidine by lipase-catalyzed transformations were

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21. The efficiency of a kinetic resolution is indicated by the value of the enantioselectivity E, as defined in: Chen, C.-S.; Fujimoto, Y.; Girdaukas, G.; Sih, C. J. *J. Am. Chem. Soc.* **1982**, *104*, 7294–7299.
22. Compounds (±)-**5** and (±)-**6** were prepared, in a nearly quantitative yield, from commercially available (±)-2-(hydroxymethyl)piperidine using standard procedures (see Experimental part).
23. Some typical results of kinetic resolutions at high conversion are the following: (a) (±)-**5**/vinyl butyrate (1.0 mol equiv.)/AA-I (300 U/mmol)/toluene/r.t./16 hours/c=60% (as determined by $^1$H-NMR) gave the butyrate (*R*)-**9** (59% yield, ee not determined) and the alcohol (*S*)-**5** (35% yield, 98% ee). (b) (±)-**6**/vinyl butyrate (0.6 mol equiv.)/AA-I (300 U/mmol)/toluene/r.t./24 hours/c=58% gave the butyrate (*R*)-**10** (55% yield, 72% ee) and the alcohol (*S*)-**6** (37% yield, 98% ee).[24]
24. Unless otherwise indicated, all the enantiomeric excesses were determined by capillary gas-liquid chromatography using cyclodextrin-based chiral stationary phases, which were prepared by Mrs. Mª Isabel Jiménez-Vacas (Centro de Química Orgánica, C. S. I. C.), to whom we thank for her assistance.
25. For a discussion of this strategy, see: Sih, C. J.; Wu, S. H. *Topics Stereochem.* **1989**, *19*, 63–125.
26. (a) In principle, it is possible to access to the enantiomers [i.e.; (*R*)-**5** and (*R*)-**6**] by hydrolysis of the butyrate. We were unable to achieve this goal by chemical methods: neither basic nor acidic hydrolysis of **9** or **10** gave the expected alcohols, but the corresponding bicyclic 2-oxazolidinone, which was formed by nucleophilic attack of the hydroxy group (or alcoxide) to the carbamoyl carbonyl group. Acyl-migration is quite common in this kind of amino alcohols; for a discussion, see: Morcuende, A.; Ors, M.; Valverde, S.; Herradón, B. *J. Org. Chem.* **1996**, *61*, 5264–5270. (b) On the other hand, we have carried out some preliminary experiments on the hydrolysis of the esters (*R*)-**9** and (*R*)-**10** catalyzed by AA-

I, both in buffer solution (pH 7) and in an acetone-containing buffer. The reactions are chemoselective, giving the alcohols of (*R*)-configuration [i.e.; (*R*)-**5** and (*R*)-**6**, depending on the structure of the substrate]. Although the enantioselectivity of the hydrolysis was lower than the acylation, it allowed an entry to the enantiomers of the compounds reported in this paper (Faraldos, J.; Herradón, B. unpublished observations).

27. Wet toluene is water-saturated toluene, whose water-content is *ca.* 0.03%, as determined by the modified Karl Fischer method.
28. The enzyme acylase I from *Aspergillus* species (AA-I) was purchased from Aldrich or Sigma. Its specific activity is *ca.* 0.5 U/mg (as defined in the Sigma catalog: one unit can hydrolyze 1.0 mmol of N-acetyl-L-methionine per hour at pH 7.0 and 25°C). For the sake of uniformity, the amount of AA-I used in any experiment is indicated in units per mmol of substrate.
29. The enantiomeric excess of the butyrate (*R*)-**9** could not be determined by capillary g.l.c.
30. We observed that when this conversion degree was achieved [that is, all the (*R*)-enantiomer had reacted], the reaction practically stopped.
31. (a) It must be remembered that the theoretical yield of a kinetic resolution is 50%. (b) When the slow reacting enantiomer racemizes rapidly (Dynamic Kinetic Resolution), it is possible to get a higher yield than the theoretical one; for a recent overview, see: Caddick, S.; Jenkins, K. *Chem. Soc. Rev.* **1996**, *25*, 447–456.
32. Mancuso, A. J.; Huang, S. L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480–2482.
33. Other attempts at oxidation include (a) PCC oxidation [Corey, E. J.; Suggs, J. W. *Tetrahedron Lett.* **1975**, 2647–2650] of (*S*)-**6** gave a complex mixture. (b) The oxidations of (*S*)-**5** and (*S*)-**6** with tetra(n-propyl)ammonium perruthenate (TPAP)/N-methylmorpholine N-oxide (NMO) in $CH_2Cl_2$ gave **11** and **12** in 61% and 86% yield, respectively, but with considerable racemization. (c) Oxidation of (*S*)-**6** with PDC/DMF [Corey, E. J.; Schmidt, G. *Tetrahedron Lett.* **1980**, *21*, 731–734] gave a low yield of **8**.
34. (a) Although analytically pure samples of both **11** and **12** could be obtained by flash-chromatography on silica gel, we observed racemization during this procedure; it was more convenient to use the crude aldehydes in the next steps. The enantiomeric excesses of samples of **11** and **12** were roughly determined by optical rotation and ascertained by conversion to the indolizidinone **17**, whose enantiomeric excess could be directly determined by capillary gas-liquid chromatography.[24] (b) For reviews on the synthesis and reactivity of N-protected α-amino aldehydes, see: Jurczak, J.; Golebiowski, A. *Chem. Rev.* **1989**, *89*, 149–164. (c) Reetz, M. T. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1531–1546.
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36. Only one peak was observed on t.l.c. and chiral g.l.c. Although the $^1$H-NMR spectrum of **13** is complex due to nitrogen inversion, we tentatively assigned the *Z* configuration to the double bond based in the coupling constant ($J$=12.4 Hz) of the olefinic protons.
37. We have observed variable isolated yields of coniine (and hence its hydrochloride) and of δ-coniceine due to the high volatility of these alkaloids.
38. Although we carried out a Wittig reaction of isolated aldehydes **11** and **12**, it was more convenient to use the tandem Swern–Wittig reaction, without isolating the aldehydes (see Experimental part) [Ireland, R. E.; Norbeck, D. W. *J. Org. Chem.* **1985**, *50*, 2198–2200].
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40. For a discussion on the biological activity of unnatural alkaloid enantiomers, see: Brossi, A.; Pei, X.-F. In *The Alkaloids. Chemistry and Pharmacology*; Cordell, G. A., Ed.; Academic Press: San Diego; 1998, Vol. 50, pp 109–139.
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44. The enantiomeric excess of (*R*)-(+)-**9** could not be determined directly by g.l.c., but it may be approximately deduced from the the degree of conversion and the enantiomeric excess of the remaining alcohol (*S*)-**5**.
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