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Enzymatic desymmetrization of *meso cis*-2,6- and *cis*,*cis*-2,4,6-substituted piperidines. Chemoenzymatic synthesis of (5*S*,9*S*)-(+)-indolizidine 209D

Robert Chênevert,* Ghodsi Mohammadi Ziarani, Marie Pascale Morin and Mohammed Dasser

Département de chimie, Faculté des sciences et de génie, Université Laval, Québec (QC), Canada, G1K 7P4

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Abstract

The stereoselective acylation of *meso* piperidines **3a**,**b** by vinyl acetate (solvent and acyl donor) in the presence of *Candida antarctica* lipase gave the corresponding (2*S*,6*R*) and (2*S*,4*R*,6*R*) monoesters **2a**,**b** in high enantiomeric purity. (5*S*,9*S*)-(+)-Indolizidine 209D was prepared in eight steps from (2*S*,6*R*)-**2a**.

The piperidine ring is a widespread structural fragment of biologically active natural products. In particular, the 2,6-disubstituted piperidine ring has been found in the skin secretion of neotropical frogs of the family *Dendrobatidae*, and in some species of pines and fire ants. Also, the piperidine ring is a common structural feature of synthetic pharmaceutical compounds. The interest in piperidine derivatives is well displayed by the wealth of published material detailing their sources, synthesis, and biological activities.[1–8]

Recently, we reported the desymmetrization of *meso cis*-2,6- and *cis*,*cis*-2,4,6-substituted piperidines via enzymatic hydrolysis of diacetates **1a**,**b** in phosphate buffer in the presence of *Aspergillus niger* lipase[9,10] (Scheme 1). These hydrolyses gave good to excellent results in terms of both chemical yield and enantioselectivity but the reactions were very slow (several days). Furthermore, the addition of 7% acetonitrile to the reaction medium was necessary to suppress the growth of bacillus (probably a spore contaminant in the commercial enzyme). We report here a novel, more convenient enzymatic desymmetrization of these piperidine systems.

Known diols **3a**,**b** were subjected to enzyme-catalyzed transesterification by treatment with *Candida antarctica* lipase in vinyl acetate (solvent and acyl donor) to give optically active esters **2a**,**b** (Table 1). In general, the transesterification of *meso* diols and the hydrolysis of the corresponding *meso* diesters are complementary and give the opposite enantiomers. As expected, monoesters (2*S*,6*R*)-**2a** and (2*S*,4*R*,6*R*)-**2b** were obtained in good yields and high enantioselectivity.

* Corresponding author. E-mail: robert.chenevert@chm.ulaval.ca

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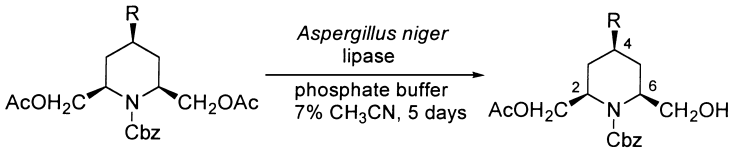
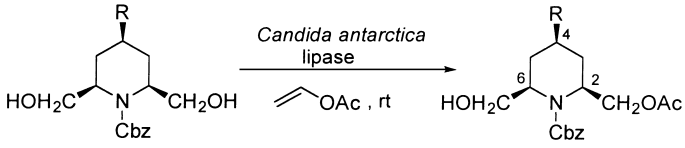


1a) R = H (2*R*,6*S*) – **2a** (R = H): yield = 82%, ee ≥ 98%

1b) R = OMOM (2*R*,4*S*,6*S*) – **2b** (R = OMOM): yield = 76%, ee ³ 98%

Scheme 1.

Table 1
Enzymatic acylation of diols by *Candida antarctica* lipase at rt



3a) R = H (2*S*,6*R*) – **2a** (R = H)

3b) R = OMOM (2*S*,4*R*,6*R*) – **2b** (R = OMOM)

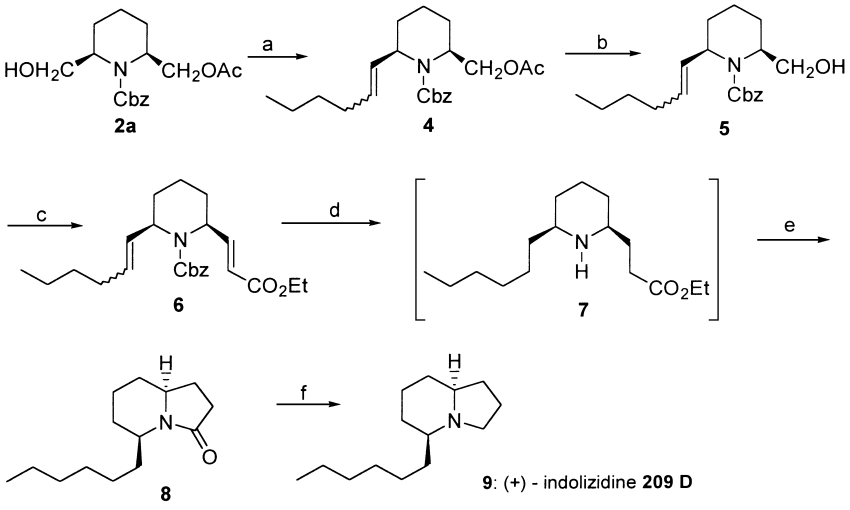
Diol	Time (hours)	Monoacetate	Yield (%)	ee (%)[a]
3a	3	(2*S*,6*R*) – **2a**	80 %	95
3b	5	(2*S*,4*R*,6*R*) – **2b**	83 %	96

[a]Enantiomeric excess was determined by ^{19}F NMR of Mosher's ester

Biocatalytically generated compounds are valuable starting materials for the enantioselective synthesis of natural products[11] or pharmaceuticals.[12] We used monoester **2a** as a building block in the synthesis of (5*S*,9*S*)-(+)-indolizidine 209D. This alkaloid has been isolated in minute quantities from a single population of dendrobatid frogs of Central America and its absolute stereochemistry has been tentatively assigned as (5*R*,9*R*).[13] Enantioselective syntheses of all the four possible stereoisomers of indolizidine 209D have been reported.[14–23] These compounds are potent blockers for nicotinic acetylcholine receptors.[14,24]

(5*S*,9*S*)-(+)-Indolizidine 209D (**9**) was prepared in 8 steps starting with (2*S*,6*R*)-**2a** (Scheme 2). Swern oxidation of **2a** gave the corresponding unstable aldehyde, which, after work up was immediately added to the pentyl Wittig ylide to give the alkene **4** in a mixture of *cis–trans* isomers. The acetate group was hydrolyzed in phosphate buffer in the presence of pig liver esterase to afford alcohol **5**. A second Swern oxidation of **5** gave the corresponding unstable aldehyde which was added to methyl-(triphenylphosphoranylidene) acetate, and diene **6** was obtained as the sole *trans* isomer on the newly formed double bond. The next step was accomplished by hydrogenation of **6** with Pearlman's catalyst. This reaction removed the *N*-Cbz protecting group as well as hydrogenating both carbon–carbon double bonds to afford amino ester **7**. Crude **7** was immediately treated with trimethylaluminum to give lactam

8. The final synthetic step was the reduction of lactam **8** with $LiAlH_4$ to give (5*S*,9*S*)-(+)-indolizidine 209D (**9**); $[\alpha]_D^{25}$ +89.7 (c 0.36, CH_2Cl_2); lit.[14]: $[\alpha]_D^{25}$ +81.8 (c 0.540, CH_2Cl_2).



Scheme 2. Reagents: (a) i; Swern, ii; $Ph_3P(C_5H_{11})Br$, *t*-BuOK, C_6H_6. (b) PLE, phosphate buffer (pH=7). (c) i; Swern, ii; Ph_3PCHCO_2Me, C_6H_6; (d) H_2/Pd, EtOH. (e) Me_3Al, C_6H_6. (f) $LiAlH_4$, THF

1. Experimental

NMR spectra were recorded in $CDCl_3$ solutions at 300 MHz (^1H), 282 MHz (^{19}F), 75 MHz (^{13}C) on a Bruker AC-300 instrument. Infrared spectra were recorded using a Bomem MB-100 (Fourier-transform) spectrometer. Optical rotation values were obtained from a JASCO DIP-300 polarimeter. Column purifications were conducted by flash chromatography on silica gel 60 (230–400 mesh). Pig liver esterase was from Sigma or Amano. *Candida antarctica* lipase was purchased from Boehringer Mannheim.

1.1. General procedure for enzymatic esterification of meso *diol **3a** and **3b***

To a solution of diol **3a** or **3b** (0.19 mmol) in vinyl acetate (3 mL) was added 60 mg of *Candida antarctica* lipase, and the mixture was stirred at rt. The progress of the reaction was monitored by TLC. As the reaction proceeded, the amount of diacetate in the reaction mixture increased before the complete disappearance of the starting material. The reaction was stopped when the trace of diacetate became as visible as the trace of the starting diol. The mixture was filtered and concentrated. The crude product was purified by flash chromatography (20% EtOAc and 80% petroleum ether to pure EtOAc for **3a**, 50% EtOAc and 50% petroleum ether for **3b**) to give monoacetate **2a** and **2b** as colorless oils.

1.2. N-*Benzyloxycarbonyl*-cis-*2(*S*)-(acetoxymethyl)-6(*R*)-(hydroxymethyl)piperidine **2a***

Yield: 80%; $[\alpha]_D^{25}$ −5.0 (c 2.08, $CHCl_3$); IR (neat) 3450, 2930, 1745, 1690 cm^{-1}; ^1H NMR ($CDCl_3$) 7.35–7.25 (m, 5H), 5.12 (AB system, J=12.4 Hz, 2H), 4.48 (m, 1H), 4.31 (m, 1H), 4.13 (dd, J_1=8.0 Hz, J_2=10.9 Hz, 1H), 3.95 (dd, J_1=6.9 Hz, J_2=10.9 Hz, 1H), 3.56 (d, J=7.6 Hz, 2H), 2.85 (br s, 1H), 1.92

(s, 3H), 1.81–1.45 (m, 6H); ^{13}C NMR ($CDCl_3$) 170.60, 156.79, 136.43, 128.36, 127.89, 127.72, 67.28, 64.38, 64.02, 51.71, 48.45, 24.84, 24.32, 20.50, 14.47.

1.3. N-*Benzyloxycarbonyl*-cis,cis-*2(*S*)-(acetoxymethyl)-4(*R*)-[(methyloxy)methoxy]-6(*R*)-(hydroxymethyl)piperidine* ***2b***

Yield: 83%; $[\alpha]_D^{25}$ +3.6 (c 1.08, $CHCl_3$); IR (neat) 3450, 3035, 2920, 1740, 1690, 1410 cm^{-1}; ^{1}H NMR ($CDCl_3$) 7.26–7.19 (m, 5H), 5.05 (AB system, J=12.5 Hz, 2H), 4.52 (m, 3H), 4.30 (m, 1H), 4.18 (AB system, J=11.9 Hz, 2H), 3.82 (m, 1H), 3.71 (m, 2H), 3.24 (s, 3H), 3.06 (br s, 1H), 1.80 (m, 4H), 1.81 (s, 3H); ^{13}C NMR ($CDCl_3$) 170.6, 156.5, 136.3, 128.3, 127.8, 127.7, 94.6, 68.3, 67.2, 66.4, 65.1, 55.2, 51.1, 47.8, 29.3, 28.3, 20.5.

1.4. N-*Benzyloxycarbonyl*-cis-*2(*R*)-(1-hexenyl)-6(*S*)-(acetoxymethyl)piperidine* ***4***

To a stirred solution of oxalyl chloride (0.13 mL, 1.57 mmol) in 2.5 mL of anhydrous CH_2Cl_2 at −78°C under N_2, was added DMSO (0.167 mL, 2.36 mmol) in 0.78 mL of anhydrous CH_2Cl_2 dropwise and the mixture allowed to react for 5 min at −78°C. Alcohol **2a** (253.5 mg, 0.79 mmol) in 0.78 mL of anhydrous CH_2Cl_2 was added, and the reaction mixture was stirred for 1 h at −78°C. On addition of anhydrous Et_3N (0.44 mL, 3.15 mmol), the dry ice/acetone bath was removed, and the reaction temperature was left to go to rt. The reaction was diluted with 4 mL of CH_2Cl_2 and then poured into 10 mL of CH_2Cl_2 and 5 mL of 10% NH_4OH solution. The aqueous phase was extracted twice with CH_2Cl_2 and the combined CH_2Cl_2 fractions were dried and evaporated. The residue was dissolved in ether and filtered through a $MgSO_4$ pad and the ether evaporated. The crude aldehyde was used immediately in the next step (Wittig reaction) of the synthesis.

Anhydrous benzene (6 mL) and *t*-BuOK (265 mg, 2.36 mmol) were mixed at rt under N_2, and Ph_3P (C_5H_{11}) (Br) (971 mg, 2.35 mmol) was added to the mixture. After the mixture was stirred for 1.5 h, the crude aldehyde (0.79 mmol, assuming 100% yield from Swern oxidation) was added with 3 mL of anhydrous benzene to the reaction mixture, and it was refluxed for 3 h. The reaction mixture was then partitioned between 20 mL of EtOAc and 10 mL of 10% $Na_2S_2O_3$ solution, and the aqueous phase was extracted 3 times with EtOAc. The organic fractions were dried and evaporated. The crude product was purified by flash chromatography using pure CH_2Cl_2 to 5% EtOAc/95% CH_2Cl_2 to yield compound **4** as a colorless oil (280 mg, 95% yield). Data for *cis*-**4** obtained pure from fractions of the chromatography: $[\alpha]_D^{25}$ −69.6 (c 0.86, $CHCl_3$); IR (neat) 2953, 1745, 1697 cm^{-1}; ^{1}H NMR ($CDCl_3$) 7.34–7.28 (m, 5H), 5.53–5.35 (m, 2H), 5.16–5.06 (m, 3H), 4.50–4.48 (m, 1H), 4.29–4.22 (dd, J_1=8.8 Hz, J_2=10.7 Hz, 1H), 4.00–3.95 (dd, J_1=6.1 Hz, J_2=10.7 Hz, 1H), 2.08–1.95 (m, 2H), 1.97 (s, 3H), 1.75–1.49 (m, 6H), 1.24–1.16 (m, 4H), 0.86–0.82 (t, J=6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$) 170.66, 155.65, 136.66, 132.37, 129.39, 128.26, 127.76, 67.06, 64.28, 48.75, 47.42, 31.62, 30.18, 26.97, 24.92, 22.20, 20.67, 14.58, 13.82; HRMS (CI, NH_3) calcd for $C_{22}H_{32}NO_4$ (MH^+) 374.2331, found 374.2318±0.0011.

1.5. N-*Benzyloxycarbonyl*-cis-*2(*R*)-(1-hexenyl)-6(*S*)-(hydroxymethyl)piperidine* ***5***

The ester **4** (42 mg, 0.12 mmol) was suspended in phosphate buffer (pH 7.0, 3.5 mL), pig liver esterase (40 mg) was added, and the mixture was stirred at rt. The pH of the solution was maintained at its initial value by addition of 0.1 M aqueous NaOH. After the addition of 1 equiv. of base, the aqueous layer was extracted 3 times with ethyl acetate. The combined organic fractions were dried and evaporated. The crude product was purified by flash chromatography (pure CH_2Cl_2 to 20% EtOAc and

80% CH_2Cl_2) to give **5** (35 mg, 88%) as a colorless oil. Data for the *cis*-**5** obtained pure from fractions of the chromatography: $[\alpha]_D^{25}$ −65.3 (c 1.61, $CHCl_3$); IR (neat) 3439, 2932, 1691, 1671 cm^{-1}; ^1H NMR ($CDCl_3$) 7.34–7.28 (m, 5H), 5.54 (dd, J=9.5 Hz, J=10.7 Hz, 1H), 5.43–5.34 (m, 1H), 5.16–5.05 (m, 3H), 4.38–4.34 (m, 1H), 3.61–3.37 (m, 2H), 2.20 (s, 1H), 2.16–1.99 (m, 2H), 1.79–1.46 (m, 6H), 1.24–1.22 (m, 4H), 0.85–0.80 (t, J=6.7 Hz, 3H); ^{13}C NMR ($CDCl_3$) 156.77, 136.53, 132.14. 129.72, 128.31, 127.82, 127.79, 67.25, 64.47, 52.10, 47.64, 31.62, 30.26, 26.92, 24.65, 22.21, 14.84, 13.82; HRMS (CI, NH_3) calcd for $C_{20}H_{30}NO_3$ (MH^+) 332.2226, found 332.2221±0.0010.

1.6. N-*Benzyloxycarbonyl*-cis-*2(*S*)-(*trans-*methoxycarbonylethylene)-6(*R*)-(1-hexenyl)piperidine **6**

The Swern oxidation of **5** (262 mg, 0.79 mmol) was performed in the same manner as described above. Methyl(triphenylphosphoranylidene) acetate (792 mg, 2.37 mmol) was added to a solution of the crude aldehyde (0.79 mmol, assuming 100% yield from the Swern oxidation) in anhydrous benzene (8 mL), and the mixture was refluxed for 3 h. After cooling to rt, the mixture was partitioned between 20 mL CH_2Cl_3 and 10 mL of 10% $Na_2S_2O_3$. The aqueous layer was extracted with CH_2Cl_2 and the combined organic fractions were dried and evaporated. The crude product was purified by flash chromatography (pure CH_2Cl_2 to 5% EtOAc and 95% CH_2Cl_2) to give **6** (280 mg, 92%) as a colorless oil. $[\alpha]_D^{25}$ −146.31 (c 0.526, $CHCl_3$); IR (neat) 2953, 1723, 1694, 1645, 1396, 1309 cm^{-1}; ^1H NMR ($CDCl_3$) 7.26–7.23 (m, 5H), 6.98–6.91 (dd, J_1=5.2 Hz, J_2=16.0 Hz, 1H), 5.86–5.80 (dd, J_1=15.9 Hz, J_2=1.7 Hz, 1H), 5.51–5.44 (m, 1H), 5.34–5.25 (m, 1H), 5.10–5.01 (m, 3H), 4.99–4.90 (m, 1H), 3.66 (s, 3H), 2.17–1.84 (m, 2H), 1.70–1.38 (m, 6H), 1.18 (m, 4H), 0.79–0.75 (t, J=6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$) 166.69, 155.43, 149.41, 136.45, 131.78, 129.04, 128.31, 127.92, 127.87, 121.01, 67.29, 51.42, 50.75, 47.89, 31.60, 30.34, 27.53, 26.82, 22.19, 14.94, 13.80; HRMS (CI, NH_3) calcd for $C_{23}H_{32}NO_4$ (MH^+) 386.2331, found 386.2320±0.0011.

*1.7. (5*S*,9*S*)-5-Hexylindolizidin-3-one **8***

Palladium hydroxide (20 mg) was added to a solution of **6** (157 mg, 0.407 mmol) in absolute EtOH (10 mL) and the mixture was stirred under a hydrogen atmosphere (40 psi) for 15 h. The insoluble materials were removed by filtration on Celite, and the filtrate was concentrated under reduced pressure to give the crude amino ester **7**. To a solution of amino ester **7** (87 mg, 0.407 mmol) in CH_2Cl_2 (4 mL) was added dropwise a solution of trimethylaluminum in toluene (2.0 M, 0.245 mL, 0.49 mmol). The solution was stirred for 2 h at rt and then refluxed overnight. The mixture was cooled to rt and then quenched with 1% HCl. The aqueous phase was extracted 3 times with CH_2Cl_2. The combined organic fractions were dried and concentrated under reduced pressure. The crude product was purified by flash chromatography (25% EtOAc and 75% hexane to pure EtOAc) to give lactam **8** as an oil (79 mg, 87%). $[\alpha]_D^{25}$ +20.8 (c 0.678, $CHCl_3$); lit.[17]: $[\alpha]_D$ −19.8 (c 1.15, $CDCl_3$) for the (*R*,*R*) enantiomer; IR (neat) 2928, 2855, 1692, 1422 cm^{-1}; ^1H NMR ($CDCl_3$) 3.40–3.31 (m, 1H), 3.18–3.09 (m, 1H), 2.39–2.21 (m, 3H), 2.12–2.01 (m, 1H), 1.86–1.60 (m, 4H), 1.55–1.18 (m, 12H), 0.84 (t, J=6.5 Hz, 3H); ^{13}C NMR ($CDCl_3$) 174.19, 59.53, 57.47, 32.30, 31.81, 31.70, 29.38, 29.21, 26.78, 24.98, 22.57, 22.51, 13.92.

*1.8. (5*S*,9*S*)-(+)-Indolizidine 209D **9***

To a solution of **8** (80 mg, 0.36 mmol) in ether (4 mL) was added $LiAlH_4$ (27 mg, 0.71 mmol), and the mixture was heated at reflux for 3 h. After cooling to rt, water (0.03 mL), 20% NaOH (0.02 mL) and water (0.1 mL) were added, and the mixture was dried (Na_2SO_4) and filtered on Celite. The organic

phase was evaporated and the crude product was purified by chromatography on neutral alumina (pure hexane to 10% ether and 90% hexane) to give (5*S*,9*S*)-(+)-indolizidine 209D (**9**) as a volatile oil (64 mg, 85%). $[\alpha]_D^{25}$ +89.7 (c 0.36, CH_2Cl_2); lit.[14]: $[\alpha]_D^{25}$ +81.8 (c 0.540, CH_2Cl_2); IR (neat) 2927, 2857, 2780, 1457, 1380 cm^{-1}; ^1H NMR ($CDCl_3$) 3.27 (m, 1H), 2.0–1.2 (m, 23H), 0.84 (t, J=6.5 Hz, 3H); ^{13}C NMR ($CDCl_3$) 65.22, 63.97, 51.29, 34.16, 31.67, 31.10, 30.18, 30.60, 29.50, 25.68, 24.40, 22.47, 20.17, 13.93.

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