Stereoselective Synthesis of *iso*-Dolaproine *via* Dynamic Kinetic Resolution

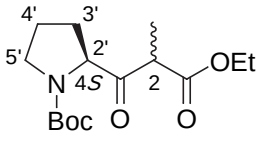
Damien Lavergne, Céline Mordant, Virginie Ratovelomanana-Vidal, and Jean-Pierre Genet*

Supporting Information: Experimental procedures and characterizations for new compounds **3**, **5**-**8**, and for Boc-(2*S*)-iso-Dap **9**.

Tetrahydrofuran (THF) and diethyl ether (Et_2O) were distilled from sodium-benzophenone. Dichloromethane (CH_2Cl_2) was distilled from calcium hydride. Acetone for the catalyst preparation was distilled over potassium carbonate. Other solvents were used without any purification. Triethylamine was distilled from potassium hydroxyde. All air and/or water sensitive reactions were carried out under an argon atmosphere.

The nuclear magnetic resonance spectra were recorded on a Bruker AC 200 or Avance 400 instrument at 200 or 400 MHz respectively for ^1H and 50 or 100 MHz respectively for ^{13}C. The solvent and the instrument are given for each product. The chemical shifts are expressed in parts per million (ppm) referenced to residual chloroform (7.26 ppm for ^1H and 77.1 ppm for ^{13}C), residual dimethyl sulfoxyde (2.50 ppm for ^1H and 39.7 ppm for ^{13}C) residual water (4.64 ppm for ^1H), or residual benzene (128.0 ppm for ^{13}C). Data are reported as follows: chemical shifts (δ), multiplicity (recorded as s, singlet; d, doublet; t, triplet; q, quadruplet; m, multiplet; and br, broad), coupling constants, integration and assignment.

Mass spectra (MS) were recorded by the ENSCP Mass Spectroscopy Service on a Hewlett-Packard HP 5989 A spectrometer. Ionization was obtained either by electronic impact (EI, 70eV) or chemical ionization with ammonia (CI, NH_3) and data are reported as m/z (relative intensity). Elementary analysis were performed by the Regional Microanalyses Service, Pierre et Marie Curie University. Melting points (m.p.) were determined on a Kofler melting point apparatus or on a Büchi apparatus and are uncorrected. Optical rotations were measured on a Perkin-Elmer 241 polarimeter or a Jasco P-1010 polarimeter.



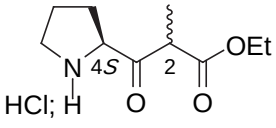
3

Ethyl (4*S*)-3-(*N*-*tert*-butoxycarbonyl-2'-pyrrolidinyl)-3-oxo-2-methylpropanoate, mixture of 2*R* and 2*S* epimers 3

A solution of Boc-(*S*)-proline (21.5 g; 100 mmol) in tetrahydrofuran (125 mL) was cooled to 0°C, and *N*,*N*'-carbonyldiimidazole (17.82 g; 110 mmol; 1.1 eq.) was added in small portions under vigorous stirring. After evolution of gas, the mixture was stirred at room temperature for 4 hours, then recooled to -10°C. In a 2 L three-necked reactor equipped with a mechanical stirrer and argon inlet, a solution of ethyl hydrogen methylmalonate (29.2 g; 200 mmol; 2 eq.) in tetrahydrofuran (125 mL) was cooled to -10°C. A solution of *iso*-propylmagnesium bromide in diethyl ether (195 mL of a 2.05 M solution; 400 mmol; 4 eq.)

was added dropwise, the temperature of the reaction mixture being kept below 5°C. The resulting slurry was stirred at room temperature for 2 hours, then recooled again to -10°C before adding dropwise *via cannula* the solution of imidazolide, the temperature of the reaction mixture being kept below 5°C. The homogeneous reaction mixture was vigorously stirred at room temperature for 110 hours, with gradual apparition of a white suspension. The reaction mixture was quenched at 0°C with 10 % citric acid and acidified to pH 3 (approximately 500 mL). The aqueous phase was decanted and extracted with ethyl acetate-benzene (4:1) (500 mL × 3). The combined organic layers were washed with water (200 mL), saturated aqueous sodium hydrogen carbonate (200 mL × 2), and saturated aqueous sodium chloride (200 mL), dried over sodium sulfate, filtrated and concentrated under reduced pressure to give a yellow oil. The residue was purified by silica gel column chromatography using ethyl acetate-cyclohexane (1:9 to 5:5) as eluent to give the *β*-keto ester **3** (24.56 g; 82 % yield) as a pale yellow oil. ^{1}H NMR analysis showed a mixture of 2*R* and 2*S* diastereoisomers.

^{1}H NMR ($CDCl_3$, 400 MHz, 24°C) δ **one diastereoisomer** 4.53 and 4.48 (dd, *J* = 8.8 Hz, 4.1 Hz, 1H, H2' two conformers), 4.15 (q, *J* = 7.1 Hz, 2H, $OC\underline{H}_2CH_3$), 3.84 and 3.67 (q, *J* = 7.1 Hz, 1H, $C\underline{H}CH_3$ two conformers), 3.55-3.25 (m, 2H, H5'), 2.25-1.9 (m, 2H, H4'), 1.9-1.6 (m, 2H, H3'), 1.4 (m, 9H, $C(C\underline{H}_3)_3$), 1.34 (d, *J* = 7.2 Hz, 3H, $CHC\underline{H}_3$), 1.28 (m, 3H, $OCH_2C\underline{H}_3$); **the other diastereoisomer** δ identical except 4.40 (m, 1H, H2'), 3.80 and 3.73 (q, *J* = 7.1 Hz, 1H, $C\underline{H}CH_3$ two conformers). ^{13}C NMR ($CDCl_3$, 50 MHz, 24°C) **one diastereoisomer** 206.3 and 205.8 (CO keto conformers), 170.4 ($\underline{C}O_2CH_2CH_3$), 155.0 and 154.3 ($\underline{C}O_2C(CH_3)_3$), 80.3 ($\underline{C}(CH_3)_3$), 65.1 (C2'), 61.3 ($O\underline{C}H_2CH_3$), 48.8 ($\underline{C}HCH_3$), 46.8 (C5'), 29.8 (C4'), 28.3 ($C(\underline{C}H_3)_3$), 24.3 (C3'), 14.0 ($OCH_2\underline{C}H_3$), 13.1 ($CH\underline{C}H_3$); **the other diastereoisomer** δ 205.4 and 204.6 ($\underline{C}O$ keto conformers), 169.9 ($\underline{C}O_2CH_2CH_3$), 154.0 and 153.6 ($\underline{C}O_2C(CH_3)_3$), 80.0 ($\underline{C}(CH_3)_3$), 64.1 and 63.8 (C2'), 60.2 ($O\underline{C}H_2CH_3$), 51.0 and 50.1 ($\underline{C}HCH_3$), 46.8 (C5'), 29.0 and 28.7 (C4'), 28.3 ($C(\underline{C}H_3)_3$), 23.4 and 23.2 (C3'), 14.0 ($OCH_2\underline{C}H_3$), 12.6 ($CH\underline{C}H_3$). MS (CI, NH_3) m/z 317 (27%, $[M+NH_4]^+$), 300 (100%, $[M+H]^+$), 261 (55%, $[M\text{-Boc}+NH_4]^+$), 244 (45%, $[M\text{-Boc}+H]^+$). Anal. Calcd for $C_{15}H_{25}NO_5$: C, 60.18; H, 8.42; N, 4.68. Found: C, 60.04; H, 8.55; N, 4.57.

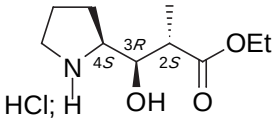


5

Ethyl (4*S*)-3-(2'-pyrrolidinyl)-3-oxo-2-methylpropanoate hydrochloride, mixture of 2*R* and 2*S* epimers 5

Through a solution of ethyl (4*S*)-3-(*N*-*tert*-butoxycarbonyl-2'-pyrrolidinyl)-3-oxo-2-methyl propanoate **3** (3.6 g; 12 mmol) in ethanol (20 mL) at 0°C was bubbled hydrogen chloride for 2 hours. The yellow reaction mixture was then concentrated under reduced pressure and dried under vacuum to give the *β*-keto ester hydrochloride **5** (2.33 g; 83 % yield) as a pink hygroscopic solid. ^{1}H NMR analysis showed an equimolar mixture of 2*R* and 2*S* diastereoisomers.

m.p. 72°C. ^{1}H NMR (D_2O, 400 MHz, 24°C) δ 4.8-4.6 (m, 1H, H2'), 4.15-4.05 (m, 2H, $OC\underline{H}_2CH_3$), 3.31 (t, *J* = 7.1 Hz, 2H, H5'), 2.5-2.4 (m, 1H, H3'), 2.15-1.85 (m, 3H, H3' and H4'), 1.28 and 1.26 (two s, 3H, $CHC\underline{H}_3$ diastereoisomers), 1.2-1.1 (m, 3H, $OCH_2C\underline{H}_3$).



6

Ethyl (2*S*,3*R*,4*S*)-3-(2'-pyrrolidinyl)-3-hydroxy-2-methylpropanoate hydrochloride 6

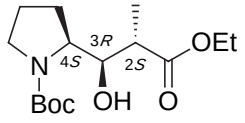
In situ preparation of the catalyst Ru[(*S*)-MeO-BIPHEP]Br_2

(*S*)-MeO-BIPHEP (58.3 mg; 0.100 mmol; 1.1 eq.) and Ru(cyclooctadiene)[η^3-$(CH_2)_2CHCH_3]_2$ (29.1 mg; 0.0912 mmol) were placed in a 50 mL Schlenk tube and the vessel was purged with argon. Anhydrous acetone (10 mL) previously degassed by three vacuum-argon cycles at room temperature was added. To this suspension was added dropwise methanolic HBr (1.10 mL of a 0.182 N solution prepared by adding 48% aqueous HBr in degassed absolute methanol; 0.200 mmol; 2.2 eq.) and the suspension was stirred at room temperature for 30 minutes. The suspension immediately turned yellow, then an orange precipitate appeared, and the solvent was thoroughly evaporated under vacuum to give the catalyst as an orange-brown solid, which was used immediately. The structure of the Ruthenium(II) complex could be tentatively assigned as a binuclear complex[†] [(MeO-BIPHEP)(Br)Ru(μ-$Br)_2$Ru(Br)(MeO-BIPHEP)].

Hydrogenation of **5**

A solution of ethyl (4*S*)-3-(*N*-*tert*-butoxycarbonyl-2'-pyrrolidinyl)-3-oxo-2-methylpropanoate hydrochloride **5** (2.15 g; 9.12 mmol) in degassed absolute ethanol (10 mL) was placed in a Schlenk vessel and degassed by three vacuum-argon cycles at room temperature. This solution was added *via cannula* to the catalyst (0.0912 mmol; 1 mol%) in a glass vessel containing a Teflon-coated magnetic stirrer and placed under argon in a 250 mL stainless steel autoclave. The Argon atmosphere was replaced with Hydrogen by three cycles of pressurizing and the pressure adjusted to 10 bar (145 psi). The autoclave was heated at 50°C and stirring was maintained for 24 hours. After cooling, the reaction mixture was concentrated under reduced pressure to afford the crude *β*-hydroxy ester hydrochloride **6** as a brown oil. ^{1}H NMR analysis revealed a 92.5:7.5 mixture of (2*S*,3*R*) and (2*R*,3*S*) diastereoisomers.

^{1}H NMR (D_2O, 400 MHz, 24°C) δ 4.15-4.05 (m, 2H, OC$\underline{H}_2CH_3$), 3.98 (dd, *J* = 3.2 Hz, 9.3 Hz, 1H, C$\underline{H}$OH), 3.8-3.6 (m, 1H, H2'), 3.2 (m, 2H, H5'), 2.52 (dd, *J* = 7.0 Hz, 9.4 Hz, 1H, C$\underline{H}CH_3$), 2.15-1.65 (m, 4H, H3' and H4'), 1.12 (t, *J* = 7.2 Hz, 3H, $OCH_2C\underline{H}_3$), 1.01 (d, *J* = 7.0 Hz, 3H, $CHC\underline{H}_3$).



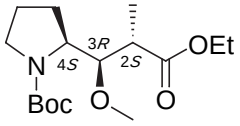
7

Ethyl (2*S*,3*R*,4*S*)-3-(*N*-*tert*-butoxycarbonyl-2'-pyrrolidinyl)-3-hydroxy-2-methylpropanoate 7

Triethylamine (0.90 mL; 6.46 mmol; 1.2 eq.) and di-*tert*-butyl dicarbonate (1.234 g; 5.65 mmol; 1.05 eq.) were added to a stirred solution of crude ethyl (2*S*,3*R*,4*S*)-3-(2'-pyrrolidinyl)-3-hydroxy-2-methylpropanoate hydrochloride **6** (1.280 g; 5.385 mmol) in ethanol (10 mL). After being stirred for 16 hours at room temperature, the mixture was

concentrated under reduced pressure. Tetrahydrofuran (20 mL) was added to the residue and the mixture was stirred for 15 minutes. The resulting precipitate was removed by filtration on a celite pad and washed with tetrahydrofuran. The filtrate was concentrated under reduced pressure and the residue was purified by silica gel column chromatography using ethyl acetate-cyclohexane (3:7 to 5:5) as eluent to give the *N*-Boc *β*-hydroxy ester **7** (1.12 g; 70 % yield) as a pale yellow oil.

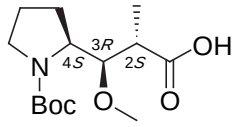
$[\alpha]^{21}_{D}$ -59 (c 1.6, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz, 24°C) δ 4.2-4.1 (m, 2H, OC$\underline{H}_2$CH$_3$), 4.1-3.8 (m, 2H, H2' and C$\underline{H}$OH), 3.6-3.1 (br m, 2H, H5'), 2.6-2.4 (m, 1H, C$\underline{H}$CH$_3$), 2.1-1.6 (m, 4H, H4' and H3'), 1.46 (s, 9H, C(C$\underline{H}_3$)$_3$), 1.27 (t, *J* = 7.1 Hz, 3H, OCH$_2$C$\underline{H}_3$), 1.3-1.15 (br m, 3H, CHC$\underline{H}_3$). ^{13}C NMR (C_6D_6, 100 MHz, 24°C) δ broad peaks (conformers) 176 ($\underline{C}$O$_2$CH$_2$CH$_3$), 155 ($\underline{C}$O$_2$C(CH$_3$)$_3$), 79 ($\underline{C}$(CH$_3$)$_3$), 74 (C5'), 60 ($\underline{C}$HOH and O$\underline{C}$H$_2$CH$_3$), 47 (C2'), 43 and 42 ($\underline{C}$HCH$_3$ conformers), 28 (C($\underline{C}$H$_3$)$_3$), 26, 25 and 24 (C4' and C3' conformers), 15 and 14 (CH$\underline{C}$H$_3$ conformers), 14 (OCH$_2\underline{C}$H$_3$). MS (CI, NH_3) m/z 302 (100%, $[M+H]^+$), 263 (5%, $[M+NH_4\text{-}C_4H_8]^+$), 246 (15%, $[M+H\text{-}C_4H_8]^+$). Anal. Calcd for $C_{15}H_{27}NO_5$: C, 59.78; H, 9.03; N, 4.65. Found: C, 59.87; H, 9.17; N, 4.46.



Ethyl (2*S*,3*R*,4*S*)-3-(*N-tert*-butoxycarbonyl-2'-pyrrolidinyl)-3-methoxy-2-methylpropanoate 8

To a solution of ethyl (2*S*,3*R*,4*S*)-3-(*N-tert*-butoxycarbonyl-2'-pyrrolidinyl)-3-hydroxy-2-methylpropanoate **7** (301 mg; 1.0 mmol) in dichloroethane (15 mL) at room temperature was added 4 Å molecular sieve (300 mg), followed by proton sponge (536 mg; 2.5 mmol; 2.5 eq.) and trimethyloxonium tetrafluoroborate (395 mg; 1.67 mmol; 1.67 eq.). The mixture was stirred at room temperature for 22 hours and then filtered. The filtrate was concentrated under reduced pressure and the residue was purified by silica gel column chromatography using ethyl acetate-cyclohexane (3:7 to 5:5) as eluent to give the *N*-Boc *β*-methoxy ester **8** (200 mg; 63 % yield) as a brown syrup which partially solidified.

$[\alpha]^{21}_{D}$ -79 (c 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400MHz, 24°C) δ 4.15-4.1 (m, 2H, OC$\underline{H}_2$CH$_3$), 4.1-3.8 (m, 2H, H2' and C$\underline{H}$OCH$_3$), 3.6-3.4 (m, 1H, H5'), 3.35 (s, 3H, OC$\underline{H}_3$), 3.3-3.2 (m, 1H, H5'), 2. 5-2.35 (m, 1H, C$\underline{H}$CH$_3$), 2.1-1.6 (m, 4H, H4' and H3'), 1.5 (m, 9H, C(C$\underline{H}_3$)$_3$), 1.3-1.2 (m, 3H, OCH$_2$C$\underline{H}_3$), 1.15 and 1.10 (d, *J* = 7.0 Hz, 3H, CHC$\underline{H}_3$ conformers). ^{13}C NMR ($CDCl_3$, 100 MHz, 24°C) δ 175.1 and 175.0 ($\underline{C}$O$_2$CH$_2$CH$_3$ conformers), 154.5 and 154.2 ($\underline{C}$O$_2$C(CH$_3$)$_3$), 83.5 and 82.1 ($\underline{C}$HOCH$_3$), 79.7 and 79.2 ($\underline{C}$(CH$_3$)$_3$), 61.0, 60.8 and 60.4 (O$\underline{C}$H$_3$ and O$\underline{C}$H$_2$CH$_3$), 58.3 and 58.1 (C2'), 47.2 and 46.7 (C5'), 44.2 and 43.9 ($\underline{C}$HCH$_3$), 28.6 (C($\underline{C}$H$_3$)$_3$), 25.3, 24.9, 24.5, and 24.3 (C4' and C3'), 14.5 and 14.3 (CH$\underline{C}$H$_3$ and OCH$_2\underline{C}$H$_3$). Anal. Calcd for $C_{16}H_{29}NO_5$: C, 60.93; H, 9.27; N, 4.44. Found: C, 61.02; H, 9.38; N, 4.09.



9

(2*S*,3*R*,4*S*)-3-(*N*-*tert*-butoxycarbonyl-2'-pyrrolidinyl)-3-methoxy-2-methylpropanoic acid Boc-(2*S*)-*iso*-dolaproine 9

To an ice-cooled solution of ethyl (2*S*, 3*R*,4*S*)-3-(*N*-*tert*-butoxycarbonyl-2'-pyrrolidinyl)-3-methoxy-2-methylpropanoate **8** (740 mg; 2.35 mmol) in ethanol (7 mL) was added 1 N aqueous sodium hydroxyde (2.46 mL; 2.46 mmol; 1.05 eq.). The mixture was stirred at 0°C for 30 minutes then at room temperature for 2 hours. After further addition of 1 N aqueous sodium hydroxyde (8.22 mL; 8.22 mmol; 3.5 eq.), the mixture was stirred at room temperature for 12 hours. The resulting solution was acidified to pH 4 by the addition of 1 N aqueous hydrochloric acid, and then extracted with dichloromethane (10 mL × 3). The organic extracts were washed with 1 M aqueous potassium hydrogen sulfate (20 mL), and saturated aqueous sodium chloride (30 mL), dried over sodium sulfate, filtrated and concentrated under reduced pressure to give the desired Boc-(2*S*)-*iso*-Dap **9** (550 mg; 81 % yield) as an off-white solid. Recrystallization from hexane:acetone (1:1) gave off-white rods (440 mg in 3 crops; 80 % yield).

m.p. 154-159°C; $[\alpha]^{21}_{D}$ -97 (c 0.45, $CHCl_3$); ^{1}H NMR (DMSO-d_6, 400 MHz, 80°C) δ 3.88 (dd, *J* = 2.0 Hz, 9.4 Hz, 1 H, C*H*OCH_3), 3.86-3.82 (m, 1 H, H2'), 3.47-3.41 (m, 1H, H5'), 3.31 (s, 3H, OCH_3), 3.21-3.15 (m, 1H, H5'), 2.36 (dd, *J* = 7.0 Hz, 9.4 Hz, 1 H, C*H*CH_3), 1.95-1.65 (m, 4H, H3' and H4'), 1.46 (s, 9H, C(CH_3)$_3$), 1.08 (d, *J* = 7.0 Hz, 3H, CHCH_3). ^{13}C NMR (DMSO-d_6, 100 MHz, 24°C) δ 176.2 and 176.1 (*C*O_2H conformers), 153.5 and 153.3 (*C*O_2C(CH_3)$_3$), 83.2 and 81.4 (*C*HOCH3), 78.7 and 78.5 (*C*(CH_3)$_3$), 60.3 and 60.1 (O*C*H_3), 57.9 and 57.7 (C2'), 46.9 and 46.6 (C5'), 43.4 (*C*HCH_3), 28.4 (C(*C*H_3)$_3$), 25.0, 24.5, 24.2, and 24.0 (C4' and C3'), 14.3 and 14.2 (CH*C*H_3). MS (CI, NH_3) m/z 305 (10%, $[M+NH_4]^+$), 288 (100%, $[M+H]^+$), 249 (12%, $[M+NH_4-C_4H_8]^+$), 232 (15%, $[M+H-C_4H_8]^+$). MS (EI, 70eV) m/z 288 (10%, $[M+H]^{+\bullet}$), 255 (5%), 232 (8%), 170 (20%), 114 (42%), 85 (7%), 70 (100%) 57 (42%). Anal. Calcd for $C_{14}H_{25}NO_5$: C, 58.52; H, 8.77; N, 4.87. Found: C, 58.35; H, 8.77; N, 4.80.

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† For similar ligand (*S*)-BIPHEMP: Mezzetti, A.; Costella, L.; del Zotto, A.; Rigo, P.; Consiglio, G. Gazzetta Chimica Italiana **1993**, *123*, 155. For (*S*)-MeO-BIPHEP: Pfister, X. Ph.D. Dissertation, Université Pierre et Marie Curie, Paris, France, 1995.