Supporting Information for

Diastereoselective approach to *cis*-4-methyl/thiol-pipecolic esters based on RCM reaction and conjugate Michael addition

Araceli Zárate¹, Laura Orea¹, Jorge R. Juárez¹, Alejandro Castro², Angel Mendoza¹, Dino Gnecco¹ and Joel L. Terán^{*1}

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* Corresponding author

Ethyl 2-((S)-1-phenylethylamino)acetate, 2. To a stirred solution of (S)-phenylethylamine (1 g, 7.8 mmol, 1 eq) in 40 mL of CH₃CN was added the ethyl 2-bromoacetate (0.865 mL, 7.8 mmol, 1 eq) and K₂CO₃ (2.15 g, 15.6 mmol, 2 eq). The reaction mixture was stirred for 2 h at room temperature. Finally, the mixture was filtered and the solvent was evaporated under reduced pressure. The crude

reaction was purified by column chromatography (Silica gel, 80:20 petroleum ether/AcOEt as the eluent) giving the desired compound **2** as a slightly yellow oil (90% yield).

$[\alpha]_D^{20} = -91.3$ (c 1.0, CH_2Cl_2). IR (film) 3329, 2975, 2930, 1738, 1450, 1373, 1196, 1026, 762, 702 cm^{-1} . ^1H NMR (400 MHz, CDCl_3) δ 1.23 (t, $J = 7.1$ Hz, 3H), 1.40 (d, $J = 6.6$ Hz, 3H), 1.95 (s, NH), 3.25 (q, $J = 10.8$ Hz, 2H), 3.79 (q, $J = 6.6$ Hz, 1H), 4.14 (q, $J = 7.1$ Hz, 2H), 7.5 (m, 5H). ^{13}C NMR (100 MHz, CDCl_3) δ 14.04, 24.12, 48.72, 57.57, 60.49, 126.59-128.34, 144.50, 172.42. HRMS (FAB): Calcd for $\text{C}_{12}\text{H}_{17}\text{NO}_2$: 207.1259. Found: 207.1261.

***tert*-butyl (ethoxycarbonyl)methyl(*S*)-1-phenylethyl carbamate, 3.** To a stirred solution of **2** (2.89 g, 13.24 mmol, 1 eq) in 40 mL of H_2O was added the $(\text{Boc})_2\text{O}$ (4.8 mL, 20.9 mmol, 1.5 eq). The reaction mixture was stirred for 5 h at room temperature. Finally, the mixture was extracted with AcOEt, the organic phase was separated and the solvent was evaporated under reduced pressure. The crude was purified by column chromatography (Silica gel, 90:10 petroleum ether/AcOEt as the eluent) giving the desired compound **3** as a white solid (98% yield). The spectroscopic details of NMR were omitted because their spectra present the presence of a complex rotameric mixture.

Diastereomeric mixture of *tert*-butyl 1-(ethoxy carbonyl)but-3-enyl(*S*)-1-phenylethylcarbamate, 4(a+b). A solution of **3** (0.300 g, 0.975 mmol, 1 eq) in anhydrous THF (2.5 mL) was added to a solution of lithium diisopropylamide (0.57 mL of 2 M in THF/heptane/ethylbenzene, 1.15 mmol, 1.2 eq) at -78°C . The resulting mixture was stirred at -78°C for 3 h, and then allyl iodide (0.178 mL, 1.46 mmol, 1.5 eq) was added. The reaction mixture was stirred for 8 h at -20°C ,

quenched with saturated aqueous ammonium chloride, and then extracted with ethyl acetate. The organic layer was dried; concentrate to give the expected diastereomeric mixture as a yellow solid **4(a+b)**. The spectroscopic details of NMR were omitted because their spectra present the presence of a complex rotameric mixture.

Diastereomeric mixture of ethyl 2-((S)-1-phenyl ethylamino)pent-4-enoate, 5(a+b). To a solution of **4(a+b)** (0.295 g, 0.849 mmol, 1 eq) in DCM (12 mL) was added trifluoroacetic acid (0.324 mL, 4.24 mmol, 5 eq). After stirring for 2h at room temperature, the reaction was treated with NaOH and extracted with CH₂Cl₂. The organic layer was dried and concentrated to give the diastereomeric mixture **5(a+b)**. The spectroscopic details of NMR were omitted because their spectra present the presence of a complex rotameric mixture.

Diastereomeric mixture of ethyl 2-(N-((S)-1-phenyl ethyl)acrylamido)pent-4-enoate, 6(a+b). To a stirred solution of diastereomeric mixture **5(a+b)** (1 g, 4.04 mmol, 1.0 eq) in 12 mL of CH₂Cl₂ and 12 mL of H₂O was added K₂CO₃ (1.13 g, 8.08 mmol, 2.0 eq). Then the acryloyl chloride (0.424 mL, 5.25 mmol, 1.3 eq) was added at 0°C. The resulting mixture was stirred for 2 h. After, the reaction was extracted with CH₂Cl₂. The organic layer was dried, concentrated and then chromatographed by using 80:20 petroleum ether/ AcOEt as the eluent to give **6(a+b)** as a yellow oil. The spectroscopic details of NMR were omitted because their spectra present the presence of a complex rotameric mixture.

General procedure for the ring closing metathesis reaction of **6(a+b)**

To a solution of diastereomeric mixture of **6(a+b)** (0.560 g, 0.165 mmol, 1.0 eq) in 10 mL of CH₂Cl₂ was added Grubbs 2nd generation catalyst (5% mol) at room temperature. The resulting mixture was stirred for 6 h. The resulting mixture was concentrated under reduced pressure. The residue was purified by column chromatography using 70:30 petroleum ether/AcOEt as the eluent to give a mixture of diastereoisomers **7a** and **7b** (**7:3**) as a white solids with a quantitative yield.

Representative procedure for the reduction of and amide function with borane dimethyl sulfide complexes (BMS)

To a stirred solution of **8a** (0.070 g, 0.241 mmol) in 5mL of anhydrous THF at 0°C, under a nitrogen atmosphere, was added BMS (0.12 mL, 1,20 mmol). The reaction mixture was stirred for 8 h at room temperature. After, the reaction was quenched with methanol (3 mL) and stirred for 1 h. Finally, the solvent was evaporated under reduced pressure, and the crude was purified via chromatography column giving the desired compound **9a** as colorless oil (96% yield).

(2*R*,4*S*)-ethyl-4-methyl-1-((*S*)-1-phenylethyl)piperidine-2-carboxylate, 9a. $[\alpha]_D^{20} = +17.7$ (c 1.0, CH₂Cl₂). IR (film) 2922, 2867, 1735, 1452, 1169, 10,26, 738, 696, cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 0.92 (d, *J* =6 Hz, 3H), 1.10 (qd, *J* =3.6, 11.2,12.6, Hz, 1H), 1.30 (m, 6H), 1.46 (m, 3H), 1.86 (dt, *J* =2.4, 2.8, 11.8 Hz, 1H), 2.14 (td, *J* =2.4, 2.8,11.8 Hz, 1H), 2.49 (dt, *J* =3.6, 3.4, 3.6, 11.6 Hz, 1H), 3.38 (dd, *J* =2.8, 10.4 Hz, 1H), 3.96 (q, *J* =6.8, Hz, 1H), 4.22 (m, 2H), 7.32 (m, 5H); ¹³C NMR (100 MHz, CDCl₃) δ 9.00, 14.19, 21.67, 30.54, 33.66, 38.58, 43.46, 57.64, 60.48,

64.00, 126.48-128.17, 143.32, 174.30. HRMS (FAB): Calcd for C₁₇H₂₅NO₂: 275.1885. Found: 275.1888.

(2*S*,4*R*)-ethyl-4-methyl-1-((*S*)-1-phenylethyl)piperidine-2-carboxylate, 9b. [α]_D²⁰ = -99.1 (*c* 1.0, CH₂Cl₂). IR (film) 2983, 2922, 1739, 1453, 1377, 1274, 1169, 1096, 1031, 744, 546, cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 0.85 (d, *J* = 6 Hz, 3H), 1.60 (m, 3H), 1.34 (t, *J* = 7.2 Hz, 3H), 1.51 (d, *J* = 6.8 Hz, 3H), 1.58 (dt, *J* = Hz, 1H), 1.75 (m, 2H), 2.88 (dd, *J* = 2.8, 3.2, 11.4 Hz, 1H), 3.05 (dt, *J* = 2.8, 3.6, 3.4 Hz, 1H), 3.92 (q, *J* = 7.6 Hz, 1H), 4.31 (m, 2H), 7.30 (m, 5H); ¹³C NMR (100 MHz, CDCl₃) δ 14.32, 18.36, 21.63, 30.26, 33.58, 38.71, 44.24, 59.89, 60.62, 64.49, 127.16-128.96, 137.64, 174.37. HRMS (FAB): Calcd for C₁₇H₂₅NO₂: 275.1885. Found: 275.1886.

General procedure for hydrogenolysis in the presence of di-*tert*-butyldicarbonate.

A solution of **9a** (0.030 g, 0.108 mmol, 1.0 eq) and di-*tert*-butyl dicarbonate (0.05 mL, 0.216 mmol, 2.0 eq) in 4 mL of AcOEt containing 30% Pd(OH)₂/C (9 mg) was hydrogenated at room temperature for 18 h. The catalyst was removed by filtration, and the solvent was evaporated. The resulting oil was chromatographed using 9:1 petroleum ether/ AcOEt, as the eluent to give **10a** in 86% yield.

(2*R*,4*S*)-1-*tert*-butyl-2-ethyl 4-methylpiperidine-1,2-di carboxylate, 10a. [α]_D²⁰ = +12 (*c* 0.86, CH₂Cl₂). IR (film) 2970, 2962, 1741, 1699, 1374, 1262, 1170, 1175, 1027, 859 cm⁻¹. ¹H NMR (400 MHz, CDCl₃) δ 0.94 (d, *J* = 6.8 Hz, 3H), 1.27 (t, *J* = 7.1 Hz, 3H), 1.33 (m, 1H), 1.44(s, 9H), 1.78 (m, 3H), 1.96 (m, 1H), 3.36 (b, 1H), 3.59 (b, 1H), 4.18 (m, 2H), 4.35 (t, *J* = 6 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 14.15,

18.89, 25.92, 28.28, 30.76, 32.99, 53.95, 60.84, 79.99, 155.71, 172.93. HRMS (FAB): Calcd for C₁₄H₂₅NO₄: 271.1784. Found: 271.1786.

(2S,4R)-1-*tert*-butyl-2-ethyl 4-methylpiperidine-1,2- dicarboxylate, 10b. $[\alpha]_D^{20} = -14.0$ (c 0.86, CH₂Cl₂). IR (film) 2973, 2929, 1743, 1700, 1397, 1364, 1267, 1175, 1027, 738 cm⁻¹. ¹H NMR (400 MHz, CDCl₃) δ 0.94 (d, *J* = 6.8 Hz, 3H), 1.27 (t, *J* = 7.1 Hz, 3H), 1.33 (m, 1H), 1.44(s, 9H), 1.78 (m, 3H), 1.96 (m, 1H), 3.36 (b, 1H), 3.59 (b, 1H), 4.18 (m, 2H), 4.35 (t, *J* = 6 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 14.14, 18.86, 25.92, 28.27, 30.73, 32.97, 53.98, 60.84, 79.99, 155.71, 172.93. HRMS (FAB): Calcd for C₁₄H₂₅NO₄: 271.1784. Found: 271.1788.

¹H NMR and ¹³C NMR of products

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reaction was purified by column chromatography (Silica gel, 80:20 petroleum ether/AcOEt as the eluent) giving the desired compound **2** as a slightly yellow oil (90% yield).

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18.89, 25.92, 28.28, 30.76, 32.99, 53.95, 60.84, 79.99, 155.71, 172.93. HRMS (FAB): Calcd for C₁₄H₂₅NO₄: 271.1784. Found: 271.1786.

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1H MNR and 13C NMR of products

1H NMR (400 MHz, CDCl₃) δ 7.2-7.6 (m, 5H), 5.1 (d, 1H), 4.3 (q, 2H), 1.2 (t, 3H).
Number of scans: 2

13C NMR (100 MHz, CDCl₃) δ 166, 141, 135, 128, 127, 126, 125, 124, 123, 122, 121, 120, 119, 118, 117, 116, 115, 114, 113, 112, 111, 110, 109, 108, 107, 106, 105, 104, 103, 102, 101, 100, 99, 98, 97, 96, 95, 94, 93, 92, 91, 90, 89, 88, 87, 86, 85, 84, 83, 82, 81, 80, 79, 78, 77, 76, 75, 74, 73, 72, 71, 70, 69, 68, 67, 66, 65, 64, 63, 62, 61, 60, 59, 58, 57, 56, 55, 54, 53, 52, 51, 50, 49, 48, 47, 46, 45, 44, 43, 42, 41, 40, 39, 38, 37, 36, 35, 34, 33, 32, 31, 30, 29, 28, 27, 26, 25, 24, 23, 22, 21, 20, 19, 18, 17, 16, 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2, 1.
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7a

7b

7b

<p> <chem>CCOC(=O)[C@H]1CC[C@@H](C)N(C1)C(=O)C2=CC=CC=C2</chem> 8a </p>	<p> <chem>CCOC(=O)[C@H]1CC[C@@H](C)N(C1)C(=O)C2=CC=CC=C2</chem> 8a </p>
<p> <chem>CCOC(=O)[C@H]1CC[C@@H](C)N(C1)C(=O)C2=CC=CC=C2</chem> 8a </p>

SpinWorks 3: AZ-152F2 03/04/2014

PP1050410302011009080705040302010.0
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file format: size: 5300000000 size: 8.0000 complex points
number of scans: 32 = 212.0009 ppm/40.0000 Hz/120954

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numberofscans:1212 1322 1336 1350 1364 1378 1392 1406 1420 1434 1448 1462
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[illegible]

11a

SpineWork83: AZ-11a-01/04-2014

[illegible]

11a

SpinWorks 3: AZ-307 01/04/2014

7.200 (m, 1H), 7.150 (m, 1H), 7.100 (m, 1H), 7.050 (m, 1H), 7.000 (m, 1H), 6.500 (d, 2H), 5.500 (s, 1H), 4.500 (q, 2H), 4.100 (t, 2H), 3.800 (s, 1H), 3.400 (d, 2H), 3.100 (s, 1H), 2.800 (d, 2H), 2.500 (s, 1H), 2.200 (d, 2H), 2.000 (s, 1H), 1.800 (d, 2H), 1.500 (s, 1H), 1.200 (d, 2H), 1.000 (s, 1H), 0.800 (d, 2H), 0.500 (s, 1H), 0.200 (d, 2H), 0.000 (s, 1H), -0.200 (d, 2H), -0.500 (s, 1H), -0.800 (d, 2H), -1.000 (s, 1H), -1.200 (d, 2H), -1.500 (s, 1H), -1.800 (d, 2H), -2.000 (s, 1H), -2.200 (d, 2H), -2.500 (s, 1H), -2.800 (d, 2H), -3.100 (s, 1H), -3.400 (d, 2H), -3.800 (s, 1H), -4.100 (q, 2H), -4.500 (d, 2H), -5.500 (s, 1H), -6.500 (d, 2H), -7.200 (m, 1H).

file: Desktop\Enterolactone\AZ-307\12a\12a-130065-1420
 file: Desktop\Enterolactone\AZ-307\12a\12a-130065-1420
 file: Desktop\Enterolactone\AZ-307\12a\12a-130065-1420
 number of scans: 16

SpinWorks 8: AZ-30701-004/2014

PPM 8.0 6.0 4.0 2.0 0

file: Desktop\Entregando 004-12a-125652788.Mkmg30>
file format: 16-bit, 200 MHz, 128K, 3.000000 complex points
number of scans: 32 = 12800001, pH 4.90, 400 MHz, 125652788

PM 8016014012010080 60 40 20 0
le: ers Dr. Teran Denizci AA 0001135 75782 MHz 30
ns 0.001 sec: 6.5 3000000 5.42 33.000 complex points
ns: 0.076 sec: 1.5 2500000 4.2 49999 Hz 0.57151
umber of Scans: 32

```

Pp=8.455284135282445284(R)
file = n\Desktop\Entire program\ppn\ppn_00_13\0010_14\0010_15\
transmittance=500
date_of_run=5-2-2006
number_of_points=12
number_of_gauss=125
ppn=3.1ppn
ppn_r=0.31058

```

13b

[illegible]