Supporting Information

(Experimental Procedure and Spectral Data)

Stereocontrolled Synthesis of (+)-Methoxyphenylkainic Acid and (+)-Phenylkainic Acid

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Analysis instrument

Nuclear magnetic resonance [^{1}H NMR (270 MHz), ^{13}NMR (68 MHz)] spectra were determined on a JEOL EX-270 instrument, and [^{1}H NMR (500 MHz), ^{13}C NMR (125 MHz)] spectra were determined on JEOL ECA-500 and JEOL A-500 instrument. Chemical shifts for ^{1}H NMR were reported in parts per million downfields from tetramethylsilane (δ) as the internal standard and coupling constants are in hertz (Hz). The following abbreviations are used for spin multiplicity : s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. Chemical shifts for ^{13}C NMR were reported in ppm relative to the center line of a triplet at 77.0 ppm for deuteriochloroform.

High resolution mass spectra (HRMS) were obtained on a JEOL MStation 700. Fast atom bombardment (FAB) mass spectra were obtained with 3-nitrobenzylalcohol as the matrix and a BRUKER DALTONICS micrOTOF (ESI).

Melting points (mp), determined on a Yanaco Micro Melting Point Apparatus MP-S3, are uncorrected.

Analytical thin layer chromatography (TLC) was performed on Merck precoated analytical plates, 0.25 mm thick, silica gel 60 F_{254}. Preparative TLC separations were made on 7 x 20 cm plates prepared with a 0.25 mm layer of Merck silica gel 60 F_{254}. Compounds were eluted from the adsorbent with 10% methanol in chloroform.

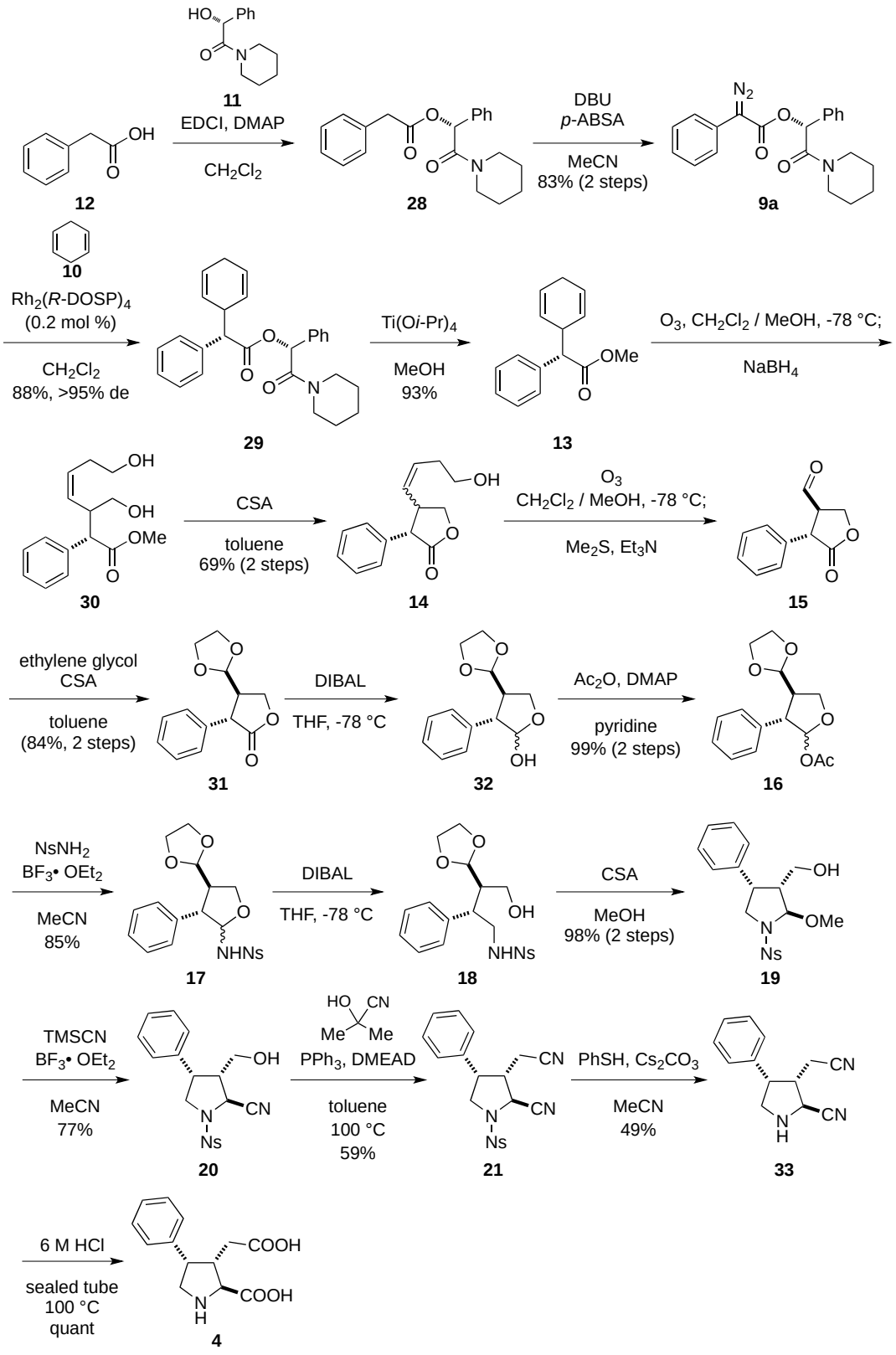
Flash chromatography separations were performed on KANTO CHEMICAL Silica Gel 60 (spherical) 40 - 50 μm, Silica Gel 60 (spherical) 63 - 210 μm or Silica Gel 60 N (spherical, neutral) 63 - 210 μm.

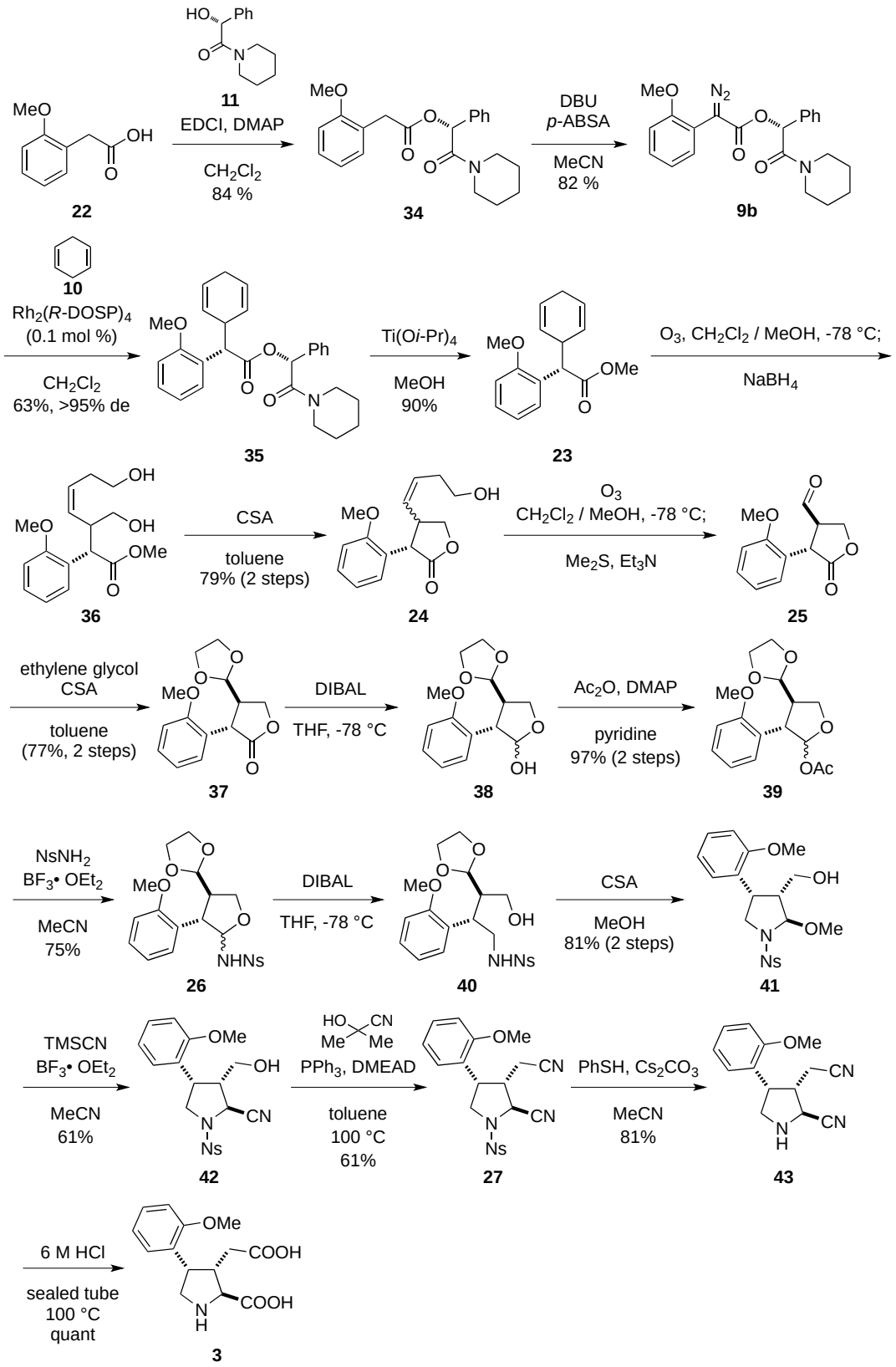
Chiral HPLC was performed on SPD-10A VP, LC-10AT VP and LC-10AT VP using 0.46 cm□ × 25 cm ChiralPak AD, AD-H, AS, AS-H, ChiralCel OB, OB-H, OD, OD-H, OJ, OJ-H from Daicel.

Reagents and solvents were commercial grades and were used as supplied with following exceptions : Dichloromethane, diethylether, *n*-hexane, tetrahydrofuran, toluene :dried over molecular sieves 4A.

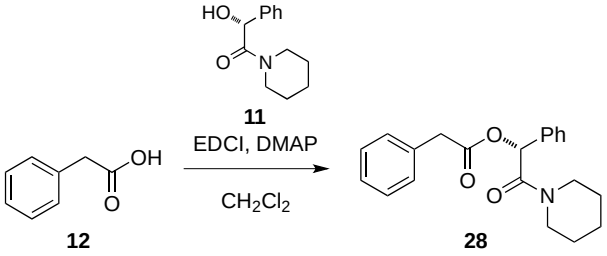
All reactions sensitive to oxygen or moisture were conducted under an argon atmosphere.

Experimental Details



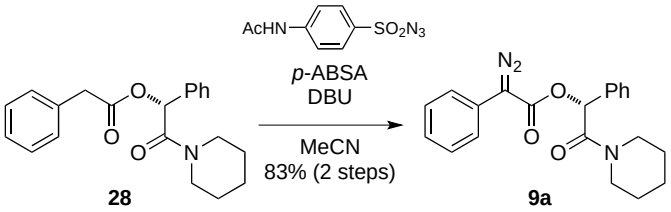

11
EDCI, DMAP
CH2Cl2
84 %
22
34
DBU
p-ABSA
MeCN
82 %
9b
10
Rh2(R-DOSP)4
(0.1 mol %)
CH2Cl2
63%, >95% de
35
Ti(Oi-Pr)4
MeOH
90%
23
O3, CH2Cl2 / MeOH, -78 °C;
NaBH4
36
CSA
toluene
79% (2 steps)
24
O3
CH2Cl2 / MeOH, -78 °C;
Me2S, Et3N
25
ethylene glycol
CSA
toluene
(77%, 2 steps)
37
DIBAL
THF, -78 °C
38
Ac2O, DMAP
pyridine
97% (2 steps)
39
NsNH2
BF3• OEt2
MeCN
75%
26
DIBAL
THF, -78 °C
40
CSA
MeOH
81% (2 steps)
41
TMSCN
BF3• OEt2
MeCN
61%
42
PPh3, DMEAD
toluene
100 °C
61%
27
PhSH, Cs2CO3
MeCN
81%
43
6 M HCl
sealed tube
100 °C
quant
3

(*R*)-2-oxo-1-phenyl-2-(piperidin-1-yl)-ethyl 2-phenylacetate (28)



To a stirred solution of **11** (2.20 g, 10.0 mmol) in CH_2Cl_2 (20 mL) were added **12** (1.50 g, 11.0 mmol), EDCI (2.88 g, 15.0 mmol) and DMAP (123 mg, 1.0 mmol) at 0 °C. The solution was stirred at room temperature for 7 h. The reaction mixture was poured into saturated aqueous NH_4Cl and extracted with CH_2Cl_2. The organic layer was washed with saturated aqueous $NaHCO_3$, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was purified by trituration with *n*-hexane. The crude **28** (pale yellow solid, 3.29 g) was used in the next step without further purification.

(*R*)-2-oxo-1-phenyl-2-(piperidin-1-yl)-ethyl 2-diazo-2-phenylacetate (9a)



To a stirred solution of crude **28** (3.29 g) in MeCN (50 mL) were added *p*-ABSA (*p*-acetamidobenzenesulfonylazide) (2.79 g, 11.6 mmol) and DBU (2.20 mL, 14.6 mmol) at 0 °C. The solution was stirred at room temperature for 1.5 h. The reaction mixture was poured into saturated aqueous NH_4Cl and extracted with Et_2O. The organic layer was washed with saturated aqueous NaCl, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography (*n*-hexane/AcOEt, 2/1) to afford **9a** (3.01 g, 83%, 2 steps from **12**) as orange needles.

mp: 119-120 °C (decomp.)

IR (film, cm^{-1}): 2938, 2857, 2089, 1703, 1659, 1501, 1443, 1352, 1246, 1153, 1051, 1011

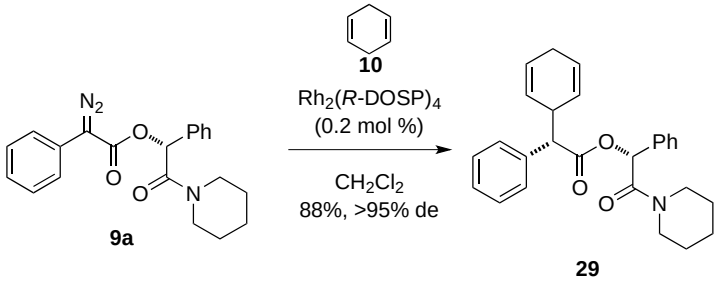
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.50-7.46 (m, 4H), 7.42-7.38 (m, 3H), 7.37-7.33 (m, 2H), 7.16 (t, *J* = 7.5 Hz, 1H), 6.46 (s, 1H), 3.72-3.63 (m, 1H), 3.52-3.31 (m, 3H), 1.63-1.40 (m, 5H), 1.12-1.02 (m, 1H)

^{13}C NMR (126 MHz, $CDCl_3$): δ 165.9, 164.8, 134.3, 129.2, 129.0, 128.8, 128.3, 125.8, 125.3, 124.1, 73.6, 46.4, 43.6, 25.6, 25.4, 24.4

ESI-MS *m/z* 386 $(M+Na)^+$

HRMS (ESI-TOF): Calcd for $C_{21}H_{21}N_3NaO_3$ $(M+Na)^+$ 386.1475, found 386.1486

(*S*)-((*R*)-2-oxo-1-phenyl-2-(piperidin-1-yl)-ethyl)-2-(cyclohexa-2,5-dienyl)-2-phenylacetate (29)



To a stirred solution of **9a** (1.29 g, 3.6 mmol) in CH_2Cl_2 (20 mL) were added 1,4-cyclohexadiene (**10**) (1.70 mL, 18.0 mmol) and Rh_2(*R*-DOSP)$_4$ (14 mg, 7.2 μmol, 0.2 mol%) at 0 °C under Ar atmosphere. The solution was stirred at room temperature for 2.5 h. The reaction mixture was concentrated under reduced pressure. The residue was purified by column chromatography (*n*-hexane/AcOEt, 5/1 to 5/2) to afford **29** (1.32 g, 88%, >95% de) as pale green amorphous. The diastereoselectivity was determined by ^{1}H NMR analysis of the crude mixture.

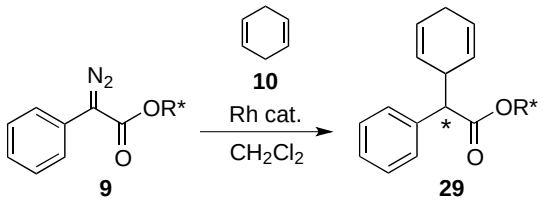
IR (film, cm^{-1}): 3030, 2938, 2857, 1730, 1661, 1651, 1454, 1445, 1150, 1003

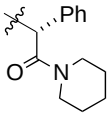
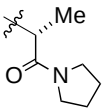
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.36-7.22 (m, 10H), 6.20 (s, 1H), 5.92 (br.d, *J* = 10.3 Hz, 1H), 5.81 (br.d, *J* = 10.3 Hz, 1H), 5.67 (br.d, *J* = 10.3 Hz, 1H), 5.31 (br.d, *J* = 10.3 Hz, 1H), 3.72-3.63 (m, 1H), 3.61-3.53 (m, 2H), 3.51-3.45 (m, 1H), 3.35-3.24 (m, 2H), 2.63-2.50 (m, 2H), 1.59-1.37 (m, 5H), 1.08-0.98 (m, 1H)
^{13}C NMR (126 MHz, $CDCl_3$): δ 172.8, 165.8, 136.4, 134.3, 129.0, 128.9, 128.8, 128.3, 128.2, 127.3, 126.8, 126.1, 125.9, 125.7, 73.9, 57.6, 46.4, 43.6, 38.7, 26.3, 25.6, 25.4, 24.4

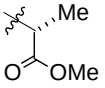
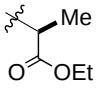
ESI-MS *m/z* 438 $(M+Na)^+$

HRMS (ESI-TOF): Calcd for $C_{27}H_{29}NNaO_3$ $(M+Na)^+$ 438.2040, found 438.2051

Table 1. Optimization of asymmetric intermolecular C-H insertion reaction.



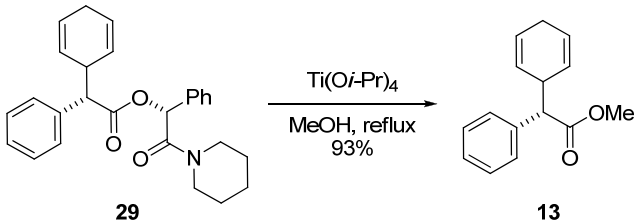
*R	Rh cat.	yield (%)	de (%) [a]
	$Rh_2(OAc)_4$	32	<20
	Rh_2(*R*-DOSP)$_4$	83	>95
	Rh_2(*S*-DOSP)$_4$	86	55
	$Rh_2(OAc)_4$	28	not determined
	Rh_2(*R*-DOSP)$_4$	39	>95
	Rh_2(*S*-DOSP)$_4$	23	not determined

*R	Rh cat.	yield (%)	de (%) [a]
	$Rh_2(OAc)_4$	69	<20
	Rh_2(*R*-DOSP)$_4$	67	>95
	Rh_2(*S*-DOSP)$_4$	28	20
	$Rh_2(OAc)_4$	8	3
	Rh_2(*R*-DOSP)$_4$	61	17
	Rh_2(*S*-DOSP)$_4$	45	85

a) de was determined by ^{1}H NMR

General procedure for Table 1: To a stirred solution of α-diazoester **9** in CH_2Cl_2 were added **10** and a catalytic amount of Rh(II) reagent (1.0 mol %) at 0 °C under Ar atmosphere. The solution was stirred at room temperature. The reaction mixture was concentrated under reduced pressure. The residue was purified by column chromatography (*n*-hexane/AcOEt, 5/1 to 5/2) to afford **29**. The diastereoselectivity was determined by ^{1}H NMR analysis of the crude mixture.

(*S*)-methyl 2-(cyclohexa-2,5-dienyl)-2-phenylacetate (13)



29 **13**

To a stirred solution of **29** (22.1 g, 53.1 mmol) in MeOH (200 mL) was added Ti(O*i*-Pr)$_4$ (90.6 g, 319 mmol) at room temperature. The solution was refluxed for 20 h. After cooling, the reaction mixture was poured into 2 M HCl and extracted with CH_2Cl_2. The organic layer was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography (*n*-hexane/AcOEt, 20/1) to afford **13** (11.3 g, 93%) as a pale yellow oil.

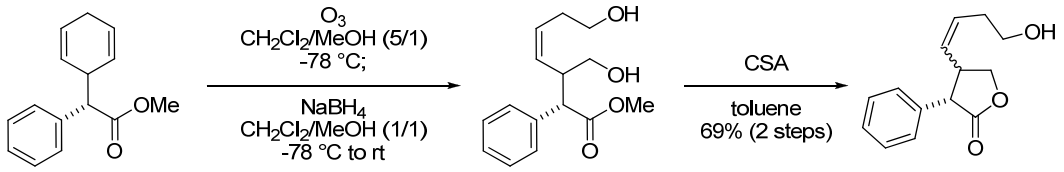
IR (film, cm^{-1}): 3030, 2951, 2862, 2818, 1736, 1495, 1454, 1433, 1329, 1273, 1225, 1192, 1157, 1078

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.35-7.30 (m, 4H), 7.28-7.25 (m, 1H), 5.83-5.78 (m, 1H), 5.74-5.66 (m, 2H), 5.28-5.23 (m, 1H), 3.67 (s, 3H), 3.52-3.45 (m, 1H), 3.42 (d, *J* = 10.9 Hz, 1H), 2.63-2.59 (m, 2H)
^{13}C NMR (126 MHz, $CDCl_3$): δ 173.4, 136.7, 128.6, 128.5, 127.4, 126.6, 126.3, 125.84, 125.78, 58.3, 51.9, 38.5, 26.3

ESI-MS *m/z* 251 $(M+Na)^+$
HRMS (ESI-TOF): Calcd for $C_{15}H_{16}NaO_2$ $(M+Na)^+$ 251.1043, found 251.1043

The enantioselectivity and absolute stereochemistry were determined by chiral HPLC according to the procedure reported by Davies.[11)]

(3*S*)-4-((*Z*)-4-hydroxybut-1-enyl)-3-phenyldihydrofuran-2(3*H*)-one (14)



A solution of **13** (5.0 g, 22 mmol) in CH_2Cl_2/MeOH (5/1, 180 mL) was stirred under ozone bubbling at −78 °C for 5 h. Ar gas was bubbled into the solution to purge of unreacted ozone. After the additions of MeOH (120 mL) and $NaBH_4$ (4.2 g, 110 mmol), the solution was stirred at 0 °C to room temperature for 5 h. The reaction mixture was poured into 2 M HCl and extracted with AcOEt. The organic layer was washed with saturated aqueous NaCl, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The crude **30** was used in the next step without further purification.

To a stirred solution of crude **30** in toluene (15 mL) was added CSA (511 mg, 2.2 mmol) at 0 °C. The solution was stirred at room temperature for 42 h. The reaction mixture was poured into saturated aqueous $NaHCO_3$ and extracted with AcOEt. The organic layer was washed with saturated aqueous NaCl, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography (*n*-hexane/ AcOEt, 1/1) to afford lactone **14** (3.0 g, 69%, 2 steps from **13**) as a mixture of diastereomers.

IR (film, cm^{-1}): 3456, 2921, 1767, 1454, 1374, 1153, 1010

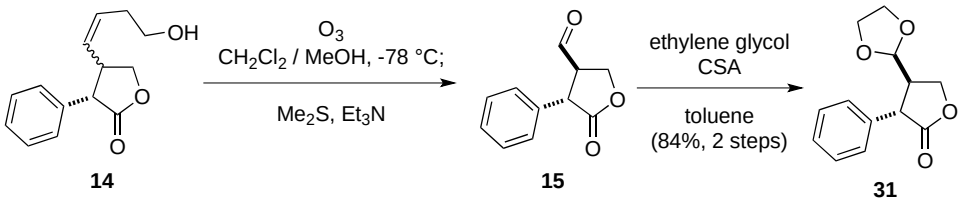
^{1}H NMR (500 MHz, $CDCl_3$): (4*R*) δ 7.36-7.32 (m, 2H), 7.32-7.29 (m, 1H), 7.22-7.19 (m, 2H), 5.60 (dt, *J* = 10.9, 7.5 Hz, 1H), 5.48 (ddd, *J* = 10.9, 9.2, 1.2 Hz, 1H), 4.48 (ddd, *J* = 9.2, 7.5, 1.2 Hz, 1H), 4.00 (ddd, *J* = 10.3, 9.2, 1.2 Hz, 1H), 3.63-3.53 (m, 1H), 3.49 (d, *J* = 11.5 Hz, 1H), 3.37-3.26 (m, 2H), 2.13-2.02 (m, 1H), 1.95-1.86 (m, 1H), (4*S*) δ 7.39-7.28 (m, 3H), 7.15-7.12 (m, 2H), 5.43 (dt, *J* = 10.9, 7.5 Hz, 1H), 5.15 (br.t, *J* = 10.9 Hz, 1H), 4.53-4.50 (m, 1H), 4.13 (ddd, *J* = 9.2, 5.7, 1.7 Hz, 1H), 3.97 (d, *J* = 7.5 Hz, 1H), 3.82-3.74 (m, 1H), 3.47-3.42 (m, 2H), 2.28-2.15 (m, 2H)

^{13}C NMR (126 MHz, $CDCl_3$): (4*R*) δ 176.5, 135.1, 131.5, 128.9, 128.6, 128.0, 127.9, 70.2, 61.6, 52.9, 44.7, 31.0, (4*S*) δ 177.2, 135.9, 130.3, 129.0, 128.4, 127.8, 127.7, 71.3, 60.7, 50.4, 47.8, 30.9

ESI-MS *m/z* 255 $(M+Na)^+$

HRMS (ESI-TOF): Calcd for $C_{14}H_{16}NaO_3$ $(M+Na)^+$ 255.0992, found 255.0990

(3*S*,4*R*)-4-(1,3-dioxolan-2-yl)-3-phenyldihydrofuran-2(3*H*)-one (31)



A solution of **14** (4.15 g, 17.8 mmol) in CH_2Cl_2/MeOH (5/1, 18 mL) was stirred under ozone bubbling at −78 °C for 1 h. Ar gas was bubbled into the reaction mixture to purge of unreacted ozone. The reaction mixture were added Me_2S (5.20 mL, 71.4 mmol) and Et_3N (3.7 mL, 26.7 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 3 h. The solution was concentrated under reduced pressure. The residue was poured into saturated aqueous NH_4Cl and extracted with CH_2Cl_2. The organic layer was washed with water, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The crude **15** was used in the next step without further purification.

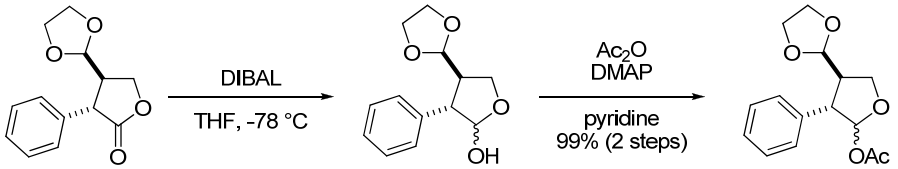
To a stirred solution of crude **15** in toluene (50 mL) were added $(HOCH_2)_2$ (5.00 mL, 89.0 mmol) and CSA (830 mg, 3.56 mmol) at room temperature. The solution was refluxed for 10 h. The reaction mixture was poured into saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The organic layer was washed with water, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography (*n*-hexane/AcOEt, 2/1) to afford **31** (3.50 g, 84%, 2 steps from **14**) as a mixture of diastereomers.

IR (film, cm^{-1}): 1774, 1764, 1170, 1143, 1021

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.39-7.34 (m, 2H), 7.32-7.28 (m, 1H), 7.27-7.24 (m, 2H), 4.98 (d, *J* = 3.4 Hz, 1H), 4.47 (dd, *J* = 9.2, 8.0 Hz, 1H), 4.33 (dd, *J* = 9.2, 6.9 Hz, 1H), 4.05-3.88 (m, 4H), 3.86 (d, *J* = 8.0 Hz, 1H), 3.02 (ddt, *J* = 8.0, 6.9, 3.4 Hz, 1H)
^{13}C NMR (126 MHz, $CDCl_3$): δ 176.8, 136.3, 129.0, 128.1, 127.7, 102.7, 66.3, 65.7, 65.3, 47.4, 47.1

ESI-MS *m/z* 235 $(M+H)^+$
HRMS (ESI-TOF): Calcd for $C_{13}H_{15}O_4$ $(M+H)^+$ 235.0965, found 235.0974

(3*S*,4*R*)-4-(1,3-dioxolan-2-yl)-3-phenyltetrahydrofuran-2-yl acetate (16)



31 **32** **16**

To a stirred solution of **31** (1.60 g, 6.8 mmol) in THF (10 mL) was added DIBAL (8.8 mL, 1.02 M in *n*-hexane, 8.8 mmol) at −78 °C. The solution was stirred at same temperature for 1 h. The reaction mixture was poured into 2M HCl at 0 °C and extracted with CH_2Cl_2. The organic layer was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The crude residue **32** was used in the next step without further purification.

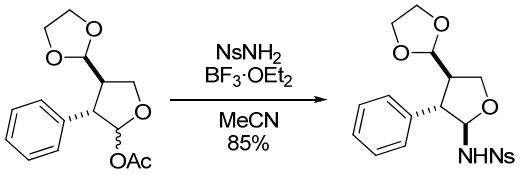
To a stirred solution of the residue **32** in pyridine (10 mL) were added acetic anhydride (1.3 mL, 13.6 mmol) and DMAP (172 mg, 1.4 mmol). The solution was stirred at room temperature for 1 h. After the addition of a small amount of toluene, the mixture was concentrated under reduced pressure to remove pyridine. The residue was purified by column chromatography (*n*-hexane/AcOEt, 4/1) to afford **16** (1.87 g, 99%, 2 steps from **31**) as a mixture of diastereomers.

IR (film, cm^{-1}): 1735, 1232, 1106, 1008

^{1}H NMR (500 MHz, $CDCl_3$): (2*S*) δ 7.34-7.30 (m, 3H), 7.25-7.23 (m, 2H), 6.20 (d, *J* = 1.7 Hz, 1H), 5.02 (d, *J* = 6.3 Hz, 1H), 4.33 (dd, *J* = 9.2, 8.6 Hz, 1H), 4.11 (dd, *J* = 9.2, 8.0 Hz, 1H), 3.97-3.85 (m, 4H), 3.49 (dd, *J* = 5.2, 1.7 Hz, 1H), 2.62 (dddd, *J* = 8.6, 8.0, 6.3, 5.2 Hz, 1H), 2.08 (s, 3H), (2*R*) δ 7.34-7.30 (m, 3H), 7.25-7.23 (m, 2H), 6.35 (d, *J* = 4.6 Hz, 1H), 4.87 (d, *J* = 3.4 Hz, 1H), 4.30 (dd, *J* = 9.2, 8.6 Hz, 1H), 4.08 (dd, *J* = 9.2, 7.6 Hz, 1H), 3.85-3.76 (m, 4H), 3.52 (dd, *J* = 10.9, 4.6 Hz, 1H), 3.19 (dddd, *J* = 10.9, 8.6, 7.6, 3.4 Hz, 1H), 1.86 (s, 3H)
^{13}C NMR (126 MHz, $CDCl_3$): (2*S*) δ 170.3, 140.7, 128.8, 127.4, 127.1, 104.6, 104.2, 69.7, 65.2, 65.1, 53.2, 51.2, 21.3, (2*R*) δ 169.7, 135.2, 129.2, 128.2, 127.1, 103.5, 99.2, 68.4, 65.4, 65.1, 51.2, 44.4, 21.0

ESI-MS *m/z* 301 $(M+Na)^+$
HRMS (ESI-TOF): Calcd for $C_{15}H_{18}NaO_5$ $(M+Na)^+$ 301.1046, found 301.1034

((2*R*, 3*S*,4*R*)-4-(1,3-dioxolan-2-yl)-3-phenyltetrahydrofuran-2-yl)-2-nitrobenzene sulfonamide (17)



16 **17**

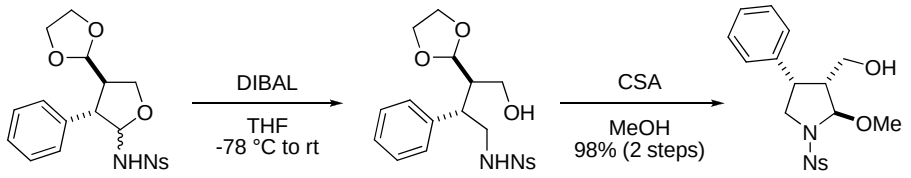
To a stirred solution of **16** (1.06 g, 3.8 mmol) in MeCN (20 mL) were added $NsNH_2$ (2-nitrobenzenesulfonamide) (1.56 g, 7.6 mmol) and $BF_3 \cdot OEt_2$ (10 μL) at room temperature. The solution was stirred at the same temperature for 20 min. After the addition of Et_3N, the reaction mixture was stirred for 15 min and concentrated under reduced pressure. The residue was purified by column chromatography (*n*-hexane/CH_2Cl_2, 1/2) to afford **17** (1.35 g, 85%) as a yellow amorphous solid.

IR (film, cm^{-1}): 3271, 2959, 2894, 1540, 1431, 1360, 1171, 1021

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.18 (dd, *J* = 5.7, 1.7 Hz, 1H), 7.90-7.86 (m, 1H), 7.71-7.68 (m, 2H), 7.60 (d, *J* = 9.7 Hz, 1H), 7.33-7.28 (m, 2H), 7.27-7.22 (m, 1H), 7.18 (d, *J* = 8.0 Hz, 2H), 5.49 (d, *J* = 9.7 Hz, 1H), 5.03 (br.s, 1H), 4.29-4.23 (m, 1H), 4.15-3.93 (m, 4H), 3.77 (dd, *J* = 9.2, 6.9 Hz, 1H), 3.39 (br.s, 1H), 2.81-2.75 (m, 1H)
^{13}C NMR (126 MHz, $CDCl_3$): δ 147.8, 142.9, 136.3, 133.3, 133.1, 131.3, 129.1, 127.2, 126.8, 125.0, 103.2, 91.7, 66.8, 65.8, 65.6, 52.6, 49.6

ESI-MS *m/z* 443 $(M+Na)^+$
HRMS (ESI-TOF): Calcd for $C_{19}H_{20}N_2NaO_7S$ $(M+Na)^+$ 443.0883, found 443.0900

((2*R*,3*R*,4*S*)-2-methoxy-1-(2-nitrophenylsulfonyl)-4-phenylpyrrolidin-3-yl)methanol (19)



17 **18** **19**

To a stirred solution of **17** (1.67 g, 4.0 mmol) in THF (15 mL) was added DIBAL (11.5 mL, 1.04 M in *n*-hexane, 11.9 mmol) at −78 °C. The solution was stirred at −78 °C to room temperature for 2.5 h. The reaction mixture was poured into 2 M HCl and extracted with CH_2Cl_2. The organic layer was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The crude residue **18** was used in the next step without further purification.

To a stirred solution of the crude **18** in MeOH (30 mL) was added CSA (1.85 g, 8.0 mmol) at room temperature. The solution was stirred at the same temperature for 20 h. The reaction mixture was quenched with Et_3N and concentrated under reduced pressure. The residue was purified by column chromatography (*n*-hexane/AcOEt, 2/1) to afford **19** (1.53 g, 98%, 2 steps from **17**) as a yellow amorphous solid.

Optical Rotation: $[\alpha]^{25}_{D}$ +5.4 (*c* 0.45, $CHCl_3$)

IR (film, cm^{-1}): 3553, 3428, 3092, 3031, 2948, 2901, 2840, 1547, 1372, 1354, 1299, 1173, 1140, 1084, 1063, 1042

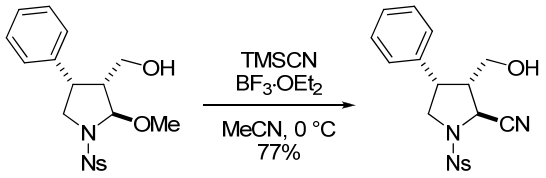
^{1}H NMR (500 MHz, $CDCl_3$): δ 8.17 (dd, *J* = 6.3, 3.4 Hz, 1H), 7.74-7.71 (m, 2H), 7.66 (dd, *J* = 6.0, 3.4 Hz, 1H), 7.30 (t, *J* = 7.5 Hz, 2H), 7.23 (t, *J* = 7.5 Hz, 1H), 7.15 (d, *J* = 7.5 Hz, 2H), 5.36 (s, 1H), 4.01 (ddd, *J* = 10.3, 8.6, 6.9 Hz, 1H), 3.85 (dd, *J* = 9.2, 8.6 Hz, 1H), 3.75 (dd, *J* = 10.3, 9.2 Hz), 3.44 (s, 3H), 3.30 (dd, *J* = 10.9, 4.6 Hz, 1H), 3.09 (t, *J* = 10.9 Hz, 1H), 2.59 (ddd, *J* = 10.9, 6.9, 4.6 Hz, 1H), 1.74 (br.s, 1H)

^{13}C NMR (126 MHz, $CDCl_3$): δ 148.4, 136.3, 133.7, 132.5, 131.7, 131.0, 128.8, 127.7, 127.3, 124.1, 94.2, 58.9, 56.2, 51.5, 49.7, 43.0

ESI-MS *m/z* 415 $(M+Na)^+$

HRMS (ESI-TOF): Calcd for $C_{18}H_{20}N_2NaO_6S$ $(M+Na)^+$ 415.0934, found 415.0933

(2*S*,3*S*,4*S*)-3-(hydroxymethyl)-1-(2-nitrophenylsulfonyl)-4-phenylpyrrolidine-2-carbonitrile (20)



19 **20**

To a stirred solution of **19** (858 mg, 2.19 mmol) in MeCN (10 mL) were added TMSCN (0.82 mL, 6.57 mmol) and $BF_3 \cdot OEt_2$ (0.30 mL, 2.41 mmol) at 0 °C. The solution stirred at same temperature for 1.5 h. The reaction mixture was poured into saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The organic layer was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography (*n*-hexane/AcOEt, 1/1) to afford **20** (652 mg, 77%) as a pale yellow amorphous solid.

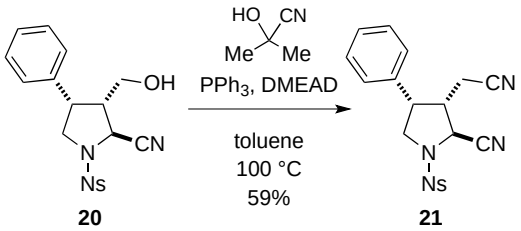
Optical Rotation: $[\alpha]^{25}_{D}$ −10.7 (*c* 0.105, $CHCl_3$)

IR (film, cm^{-1}): 3493, 2920, 2359, 1547, 1371, 1172, 1039

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.22-8.20 (m, 1H), 7.81-7.77 (m, 2H), 7.75-7.71 (m, 1H), 7.36 (t, *J* = 7.5 Hz, 2H), 7.32-7.29 (m, 1H), 7.21 (d, *J* = 7.5 Hz, 2H), 5.03 (d, *J* = 2.9 Hz, 1H), 4.09-3.94 (m, 3H), 3.48-3.43 (m, 1H), 3.34 (ddd, *J* = 10.9, 8.6, 5.2 Hz, 1H), 2.94 (dddd, *J* = 10.6, 8.6, 6.3, 2.9 Hz, 1H), 1.54 (t, *J* = 5.2 Hz, 1H)
^{13}C NMR (126 MHz, $CDCl_3$): δ 148.2, 135.0, 134.5, 132.2, 131.9, 131.2, 129.1, 127.9, 127.6, 124.4, 117.7, 59.2, 51.3, 51.1, 51.0, 44.7

ESI-MS *m/z* 410 $(M+Na)^+$
HRMS (ESI-TOF): Calcd for $C_{18}H_{17}N_3NaO_5S$ $(M+Na)^+$ 410.0781, found 410.0785

(2*S*,3*S*,4*S*)-3-(cyanomethyl)-1-(2-nitrophenylsulfonyl)-4-phenylpyrrolidine-2-carbonitrile (21)



To a stirred solution of **20** (77 mg, 0.20 mmol) in toluene (5 mL) were added PPh_3 (220 mg, 0.84 mmol), acetone cyanohydrine (70 μL, 0.80 mmol) and DMEAD (127 mg, 0.54 mmol) at 0 °C. The solution was stirred at 100 °C for 24 h. After cooling, the reaction mixture was concentrated under reduced pressure. The residue was purified by column chromatography (*n*-hexane/AcOEt, 4/1 to 2/1) to afford **21** (47 mg, 59%) as a yellow amorphous.

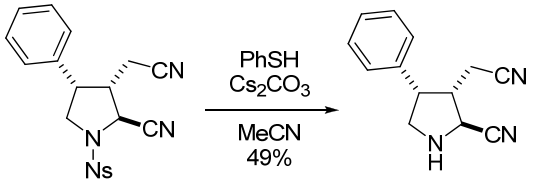
Optical Rotation: $[\alpha]^{25}_{D}$ +6.0 (*c* 0.565, $CHCl_3$)

IR (film, cm^{-1}): 3096, 3033, 2963, 2907, 2363, 2253, 1545, 1372, 1173, 1131, 1042

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.24-8.21 (m, 1H), 7.83-7.75 (m, 3H), 7.42-7.38 (m, 2H), 7.37-7.34 (m, 1H), 7.20 (d, *J* = 6.9 Hz, 2H), 4.80 (d, *J* = 4.0 Hz, 1H), 4.15 (dd, *J* = 9.7, 7.5 Hz, 1H), 4.10-4.01 (m, 2H), 3.12 (ddt, *J* = 9.2, 6.3, 4.0 Hz, 1H), 2.24 (dd, *J* = 17.2, 9.2 Hz, 1H), 2.09 (dd, *J* = 17.2, 6.3 Hz, 1H)
^{13}C NMR (126 MHz, $CDCl_3$): δ 148.0, 134.9, 133.9, 132.4, 131.6, 131.4, 129.6, 128.7, 127.6, 124.7, 116.6, 116.2, 52.6, 50.3, 46.5, 45.1, 16.3

ESI-MS *m/z* 419 $(M+Na)^+$
HRMS (ESI-TOF): Calcd for $C_{19}H_{16}N_4NaO_4S$ $(M+Na)^+$ 419.0784, found 419.0804

(2*S*,3*S*,4*S*)-3-(cyanomethyl)-4-phenylpyrrolidine-2-carbonitrile (33)



21 **33**

To a stirred solution of **21** (114 mg, 0.29 mmol) in MeCN (5 mL) were added PhSH (36 μL, 0.35 mmol) and Cs_2CO_3 (192 mg, 0.59 mmol) at room temperature. The solution was stirred at the same temperature for 1 h. The reaction mixture was concentrated under reduced pressure. The residue was purified by column chromatography (*n*-hexane/AcOEt, 2/1) to afford **33** (30 mg, 49%) as a yellow oil.

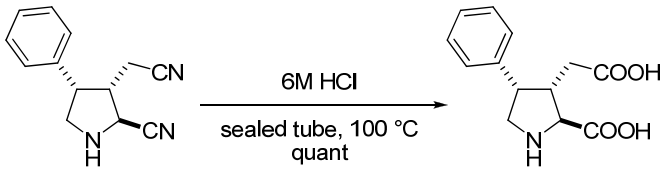
Optical Rotation: $[\alpha]^{25}_{D}$ +4.8 (*c* 0.10, $CHCl_3$)

IR (film, cm^{-1}): 3362, 2930, 2886, 2248, 1603, 1495, 1453, 1418, 1337, 1310, 1299, 1113, 1086

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.38 (t, *J* = 7.5 Hz, 2H), 7.31 (t, *J* = 7.5 Hz, 1H), 7.24 (d, *J* = 7.5 Hz, 2H), 4.08 (d, *J* = 4.0 Hz, 1H), 3.85 (ddd, *J* = 8.0, 7.5, 6.3 Hz, 1H), 3.64 (dd, *J* = 10.3, 8.0 Hz, 1H), 3.43 (dd, *J* = 10.3, 6.3 Hz, 1H), 2.99 (dddd, *J* = 8.6, 7.5, 6.3, 4.0 Hz, 1H), 2.26 (dd, *J* = 16.6, 8.6 Hz, 1H), 2.19 (br.s, 1H), 1.96 (dd, *J* = 16.6, 6.3 Hz, 1H)
^{13}C NMR (126 MHz, $CDCl_3$): δ 136.9, 129.1, 128.1, 127.9, 119.9, 117.8, 51.9, 49.4, 45.7, 45.6, 17.5

ESI-MS *m/z* 212 $(M+H)^+$
HRMS (ESI-TOF): Calcd for $C_{13}H_{14}N_3$ $(M+H)^+$ 212.1182, found 212.1181

(2*S*,3*S*,4*S*)-3-(carboxymethyl)-4-phenylpyrrolidine-2-carboxylic acid (PhKA) (4)



33 **4**

To a stirred solution of **33** (30 mg, 0.14 mmol) in 6 M HCl (5 mL) was heated at 100 °C for 5 h in a sealed tube. After cooling, the reaction mixture was concentrated under reduced pressure to afford **4** (40 mg, quant) as a colorless solid.

Optical Rotation: $[\alpha]^{25}_{D}$ +11.2 (*c* 0.50, H_2O)

mp 254-256 °C

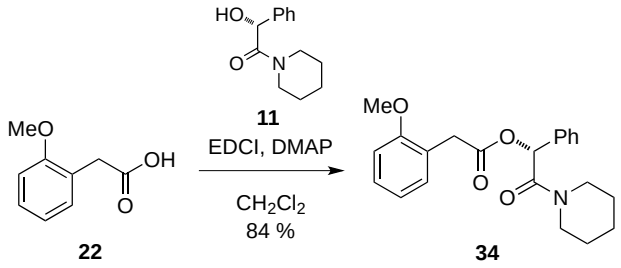
IR (film, cm^{-1}): 3402, 3146, 3048, 1715, 1634, 1416, 1173

^{1}H NMR (500 MHz, D_2O): δ 7.43-7.33 (m, 3H), 7.23 (d, *J* = 7.5 Hz, 2H), 4.00 (d, *J* = 6.9 Hz, 1H), 3.91 (dd, *J* = 12.0, 8.0 Hz, 1H), 3.83 (q, *J* = 8.0 Hz, 1H), 3.69 (dd, *J* = 12.0, 8.0 Hz, 1H), 3.09 (ddt, *J* = 8.6, 8.0, 6.9 Hz, 1H), 2.29 (dd, *J* = 16.0, 6.9 Hz, 1H), 1.91 (dd, *J* = 16.0, 8.6 Hz, 1H)
^{13}C NMR (126 MHz, D_2O): δ 181.9, 176.2, 139.1, 131.2, 131.0, 130.4, 67.9, 50.9, 47.6, 47.0, 38.9

ESI-MS *m/z* 272 $(M+Na)^+$
HRMS (ESI-TOF): Calcd for $C_{13}H_{15}NNaO_4$ $(M+Na)^+$ 272.0893, found 272.0881

DSS (sodium 3-(trimethylsilyl)-1-propanesulfonate) was used instead of tetramethylsilane as internal standard.

(*R*)-2-oxo-1-phenyl-2-(piperidin-1-yl)-ethyl 2-(2-methoxyphenyl)acetate (34)



To a stirred solution of **11** (234 mg, 1.07 mmol) in CH_2Cl_2 (3 mL) were added **22** (213 mg, 1.28 mmol), EDCI (245 mg, 1.28 mmol) and DMAP (26 mg, 0.21 mmol) at 0 °C. The solution was stirred at room temperature for 2 h. The reaction mixture was poured into saturated aqueous NH_4Cl and extracted with CH_2Cl_2. The organic layer was washed with saturated aqueous $NaHCO_3$, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography (*n*-hexane/AcOEt, 1/1) to afford **34** (329 mg, 84%) as a colorless solid.

IR (film, cm^{-1}): 2937, 1743, 1645, 1496, 1442

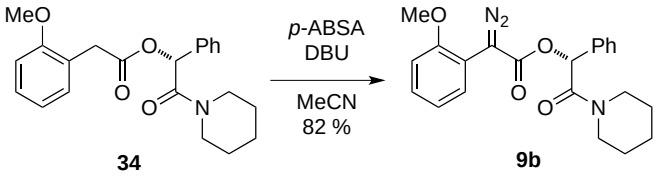
^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.46-7.33 (m, 5H), 7.26-7.21 (m, 2H), 6.91 (t, *J* = 7.5 Hz, 1H), 6.84 (d, *J* = 8.6 Hz, 1H), 6.34 (s, 1H), 3.81 (d, *J* = 16.6 Hz, 1H), 3.76 (d, *J* = 16.6 Hz, 1H), 3.75 (s, 3H), 3.61-3.50 (m, 2H), 3.39-3.33 (m, 1H), 3.29-3.23 (m, 1H), 1.59-1.49 (m, 3H), 1.48-1.38 (m, 2H), 1.13-1.04 (m, 1H)

^{13}C NMR ($CDCl_3$, 126 MHz): δ 171.5, 166.0, 157.5, 134.6, 131.1, 129.0, 128.8, 128.5, 128.2, 122.7, 120.4, 110.3, 73.4, 55.3, 46.4, 43.5, 35.5, 25.6, 25.4, 24.4

FAB-MS *m/z* 368 $(M+H)^+$

HRMS (ESI-TOF): Calcd for $C_{22}H_{25}NNaO_4$ $(M+Na)^+$ 390.1676, found 390.1694

(*R*)-2-oxo-1-phenyl-2-(piperidin-1-yl)ethyl 2-diazo-2-(2-methoxyphenyl)acetate (9b)



To a stirred solution of **34** (10.0 g, 27.2 mmol) in MeCN (40 mL) were added *p*-ABSA (*p*-acetamidobenzenesulfonylazide) (7.83 g, 32.6 mmol) and DBU (6.09 ml, 40.8 mmol) at 0 °C. The solution was stirred at room temperature for 4.5 h. The mixture was poured into saturated aqueous NH_4Cl and extracted with Et_2O. The organic layer was washed with saturated aqueous NaCl, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography (*n*-hexane/AcOEt, 4/1) to afford **9b** (8.74 g, 82%) as a yellow oil.

IR (film, cm^{-1}):2939, 2856, 2096, 1693, 1645, 1498, 1444

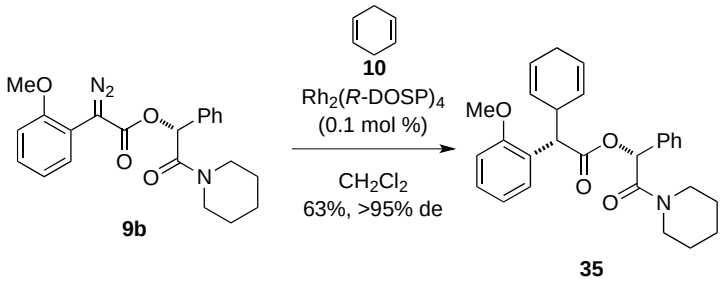
^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.69 (d, *J* = 7.5 Hz, 1H), 7.49-7.34 (m, 5H), 7.23 (t, *J* = 7.5 Hz, 1H), 7.00 (t, *J* = 7.5 Hz, 1H), 6.86 (d, *J* = 8.6 Hz, 1H), 6.44 (s, 1H), 3.83 (s, 3H), 3.70-3.63 (m, 1H), 3.53-3.46 (m, 1H), 3.44-3.31 (m, 2H), 1.62-1.51 (m, 3H), 1.51-1.39 (m, 2H), 1.12-1.02 (m, 1H)

^{13}C NMR ($CDCl_3$, 126 MHz): δ 166.2, 166.0, 155.3, 134.5, 130.4, 129.0, 128.9, 128.5, 128.2, 127.8, 121.1, 113.4, 110.7, 73.5, 55.4, 46.4, 43.5, 25.6, 25.4, 24.4

FAB-MS *m/z* 366 $(M+H)^+$

HRMS (ESI-TOF): Calcd for $C_{22}H_{23}N_3NaO_4$ $(M+Na)^+$ 416.1581, found 416.1600

(*S*)-((*R*)-2-oxo-1-phenyl-2-(piperidin-1-yl)ethyl)
2-(cyclohexa-2,5-dienyl)-2-(2-methoxyphenyl)acetate (35)



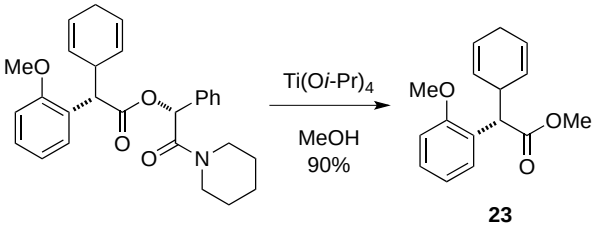
To a stirred solution of **9b** (199 mg, 506 μmol) in CH_2Cl_2 (2 mL) were added 1,4-cyclohexadiene (**10**) (0.19 ml, 2.02 mmol) and Rh_2(*R*-DOSP)$_4$ (0.96 mg, 0.51 μmol, 0.1 mol%) at 0 °C under Ar atmosphere. The solution was stirred at the same temperature for 2 h. The reaction mixture was concentrated under reduced pressure. The residue was purified by column chromatography (*n*-hexane/AcOEt, 4/1) to afford ester **35** (142 mg, 63%, >95% de) as a colorless oil. The diastereoselectivity was determined by ^{1}H NMR analysis of the crude mixture.

IR (film, cm^{-1}): 2937, 2856, 1732, 1660, 1492, 1442, 1246 cm^{-1}

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.43 (dd, *J* = 7.45, 1.72 Hz, 1H), 7.32-7.30 (m, 5H), 7.20 (dt, *J* = 8.0, 1.2 Hz, 1H), 6.91 (dt, *J* = 7.5, 1.2 Hz, 1H), 6.81 (dd, *J* = 8.0, 1.2 Hz, 1H), 6.25 (s, 1H), 5.86 (br.d, *J* = 10.3 Hz, 1H), 5.74 (brd, *J* = 10.3 Hz, 1H), 5.67 (br.d, *J* = 10.3 Hz, 1H), 5.48 (br.d, *J* = 10.3 Hz, 1H), 4.29 (d, *J* = 9.2 Hz, 1H), 3.69 (s, 3H), 3.68-3.57 (m, 2H), 3.54-3.43 (m, 1H), 3.40-3.25 (m, 2H), 2.60-2.41 (m, 2H), 1.61-1.50 (m, 3H), 1.48-1.37 (m, 2H), 1.12-1.02 (m, 1H)
^{13}C NMR ($CDCl_3$, 126 MHz): δ 172.8, 166.0, 157.4, 134.6, 129.5, 128.7, 128.6, 128.1, 127.9, 127.1, 126.0, 125.7, 125.5, 125.0, 120.4, 110.7, 73.7, 55.5, 48.6, 46.4, 43.5, 37.8, 26.2, 25.7, 25.4, 24.4

FAB-MS *m/z* 446 $(M+H)^+$
HRMS (ESI-TOF): Calcd for $C_{28}H_{31}NNaO_4$ $(M+Na)^+$ 468.2145, found 468.2167

(*S*)-methyl 2-(cyclohexa-2,5-dienyl)-2-(2-methoxyphenyl)acetate (23)



23

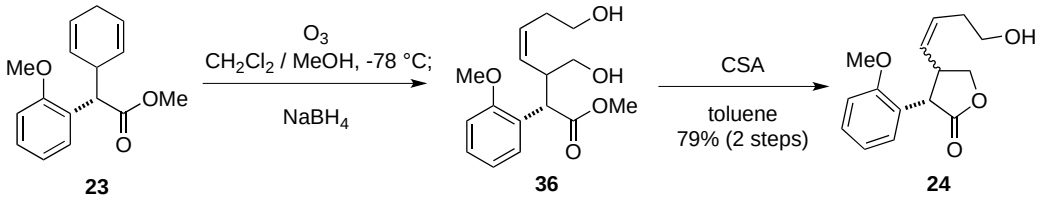
To a stirred solution of **35** (8.79 g, 19.7 mmol) in MeOH (100 mL) was added Ti(O*i*-Pr)$_4$ (34.5 mL, 118 mmol) at room temperature. The solution was refluxed for 20 h. After cooling, the reaction mixture was poured into 2 M HCl and extracted with CH_2Cl_2. The organic layer was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography (*n*-hexane/AcOEt, 10/1) to afford **23** (4.60 g, 90%) as a colorless oil.

IR (film, cm^{-1}): 2949, 2104, 1732, 1598, 1587

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.39 (dd, *J* = 7.5, 1.7 Hz, 1H), 7.23 (dt, *J* = 7.5, 1.7 Hz, 1H), 6.94 (dt, *J* = 7.5, 1.2 Hz, 1H), 6.87 (dd, *J* = 7.5, 1.2 Hz, 1H), 5.80-5.71 (m, 2H), 5.66 (br.d, *J* = 10.3 Hz, 1H), 5.34 (br.d, *J* = 10.3 Hz, 1H), 4.10 (d, *J* = 9.2 Hz, 1H), 3.80 (s, 3H), 3.66 (s, 3H), 3.53-3.46 (m, 1H), 2.55-2.55 (m, 2H)
^{13}C NMR ($CDCl_3$, 126 MHz): δ 173.7, 157.3, 128.9, 128.2, 126.9, 126.0, 125.8, 125.5, 125.3, 120.6, 110.9, 55.7, 51.8, 49.0, 37.8, 26.3

FAB-MS *m/z* 259 $(M+H)^+$
HRMS (ESI-TOF): Calcd for $C_{16}H_{18}NaO_3$ $(M+Na)^+$ 281.1148, found 281.1154

(3*S*)-4-((*Z*)-4-hydroxybut-1-enyl)-3-(2-methoxyphenyl)dihydrofuran-2(3*H*)-one (24)



A solution of **23** (322 mg, 1.25 mmol) in CH_2Cl_2/MeOH (5/1, 12 mL) was stirred under ozone bubbling at −78 °C for 15 min. Ar gas was bubbled into the solution to purge of unreacted ozone. After the additions of MeOH (8 mL) and $NaBH_4$ (263 mg, 6.95 mmol), the solution was stirred at 0 °C to room temperature for 1.5 h. The reaction mixture was poured into 2M HCl and extracted with AcOEt. The organic layer was washed with saturated aqueous NaCl, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The crude **36** was used in the next step without further purification.

To a stirred solution of crude **36** in toluene (5 mL) was added CSA (83 mg, 0.36 mmol) at room temperature. The solution was stirred at the same temperature for 2.5 h. The reaction mixture was poured into saturated aqueous $NaHCO_3$ and extracted with AcOEt. The organic layer was washed with saturated aqueous NaCl, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography (*n*-hexane/AcOEt, 1/1) to afford **24** (pale yellow oil, 258 mg, 79%, 2 steps from **23**) as a mixture of diastereomers.

IR (film, cm^{-1}): 3439, 2943, 1747, 1600, 1587

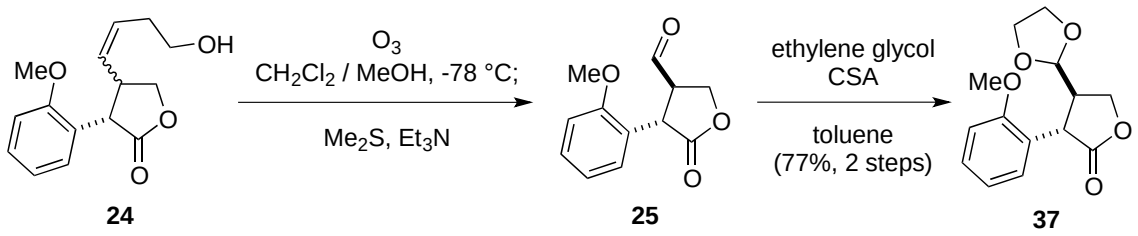
^{1}H NMR ($CDCl_3$, 500 MHz): (4*R*) δ 7.30 (t, *J* = 8.0 Hz, 1H), 7.08 (d, *J* = 7.5 Hz, 1H), 6.95-6.91 (m, 2H), 5.57-5.47 (m, 2H), 4.52 (t, *J* = 8.6 Hz, 1H), 3.99 (t, *J* = 9.5 Hz, 1H), 3.85 (s, 3H), 3.87-3.79 (m, 1H), 3.53 (d, *J* = 10.9 Hz, 1H), 3.36-3.29 (m, 1H), 3.28-3.21 (m, 1H), 2.10-2.01 (m, 1H), 1.93-1.82 (m, 1H), 0.89 (t, *J* = 5.2 Hz, 1H), (4*S*) δ 7.28 (dt, *J* = 8.0, 1.7 Hz, 1H), 7.11 (dd, *J* = 7.5, 1.7 Hz, 1H), 6.95 (dt, *J* = 7.5, 1.7 Hz, 1H), 6.88 (d, *J* = 8.0 Hz, 1H), 5.33 (dt, *J* = 11.2, 7.5 Hz, 1H), 5.17 (t, *J* = 10.3 Hz, 1H), 4.52 (dd, *J* = 8.6, 7.5 Hz, 1H), 4.28-4.20 (m, 1H), 4.15 (dd, *J* = 8.6, 6.3 Hz, 1H), 3.83 (s, 3H), 3.90-3.80 (m, 1H), 3.52-3.40 (m, 2H), 2.23-2.10 (m, 2H), 1.30 (t, *J* = 5.2 Hz, 1H)

^{3}C NMR ($CDCl_3$, 126 MHz): (4*R*) δ 176.6, 157.2, 131.1, 130.7, 129.5, 129.1, 123.8, 120.9, 111.6, 70.8, 61.7, 55.7, 50.0, 41.6, 31.0 (4*S*) δ 177.6, 157.0, 130.6, 129.3, 129.1, 128.5, 122.7, 120.8, 110.6, 71.8, 61.6, 55.4, 45.1, 38.1, 30.9

FAB-MS *m/z* 263 $(M+H)^+$

HRMS (ESI-TOF): Calcd for $C_{15}H_{18}NaO_4$ $(M+Na)^+$ 285.1097, found 285.1099

(3*S*,4*R*)-4-(1,3-dioxolan-2-yl)-3-(2-methoxyphenyl)dihydrofuran-2(3*H*)-one (37)



A solution of **24** (4.4 g, 19 mmol) in CH_2Cl_2/MeOH (5/1, 60 mL) was stirred under ozone bubbling at −78 °C for 35 min. Ar gas was bubbled into the reaction mixture to purge of unreacted ozone. The reaction mixture were added Me_2S (4.9 mL, 67 mmol) and Et_3N (3.5 mL, 25 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 5 h. The solution was concentrated under reduced pressure. The residue was poured into saturated aqueous NH_4Cl and extracted with CH_2Cl_2. The organic layer was washed with water, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The crude **25** was used in the next step without further purification.

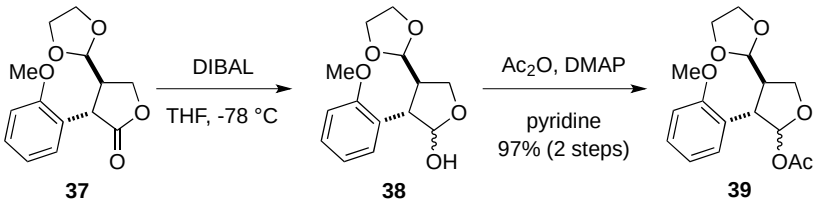
To a stirred solution of crude **25** in toluene (80 mL) were added $(HOCH_2)_2$ (4.7 mL, 84 mmol) and CSA (780 mg, 3.4 mmol) at room temperature. The solution was refluxed for 16 h. The reaction mixture was poured into saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The organic layer was washed with water, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography (*n*-hexane/AcOEt, 2/1) to afford **37** (3.44 g, 77%, 2 steps from **24**) as a mixture of diastereomers.

IR (film, cm^{-1}): 2962, 2920, 1766, 1600, 1587

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.29 (dt, *J* = 8.0, 1.7 Hz, 1H), 7.16 (dd, *J* = 7.5, 1.7 Hz, 1H), 6.95-6.88 (m, 2H), 4.95 (d, *J* = 3.4 Hz, 1H), 4.49 (t, *J* = 9.2 Hz, 1H), 4.30 (dd, *J* = 9.2, 7.5 Hz, 1H), 4.03-3.86 (m, 4H), 3.83 (s, 3H), 3.81 (d, *J* = 8.0 Hz, 1H), 3.13-3.06 (m, 1H)
^{13}C NMR ($CDCl_3$, 126 MHz): δ 177.3, 156.8, 131.0, 129.3, 125.6, 120.9, 111.2, 103.3, 66.6, 65.6, 65.2, 55.5, 45.1, 44.9

FAB-MS *m/z* 265$(M+H)^+$
HRMS (ESI-TOF): Calcd for $C_{14}H_{16}NaO_5$ $(M+Na)^+$ 287.0890, found 287.0893

(3*S*,4*R*)-4-(1,3-dioxolan-2-yl)-3-(2-methoxyphenyl)tetrahydrofuran-2-yl acetate (39)



37 **38** **39**

To a stirred solution of **37** (3.44 g, 13.0 mmol) in THF (20 mL) was added DIBAL (18.9 mL, 1.03 M in *n*-hexane, 19.5 mmol) at −78 °C. The solution was stirred at the same temperature for 30 min. The reaction mixture was poured into 2 M HCl and extracted with CH_2Cl_2. The organic layer was washed with saturated aqueous NaCl, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The crude residue **38** was used in the next step without further purification.

To a stirred solution of the crude **38** in pyridine (15 mL) were added acetic anhydride (2.45 mL, 26.0 mmol) and DMAP (318 mg, 2.60 mmol). The solution was stirred at room temperature for 1 h. After the addition of a small amount of toluene, the mixture was concentrated under reduce pressure to remove pyridine. The residue was purified by column chromatography (*n*-hexane/AcOEt, 3/1) to afford **39** (pale yellow oil, 3.89 g, 97%, 2 steps from **37**) as a mixture of diastereomers.

IR (film, cm^{-1}): 3639, 3537, 2958, 1745, 1600, 1587, 1487 cm^{-1}

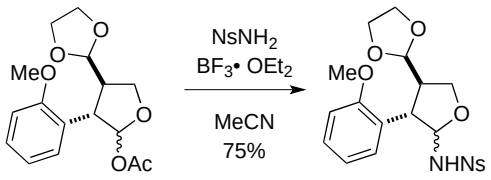
^{1}H NMR (CDCl$_3$, 500 MHz): (2*S*) δ 7.24 (t, *J* = 7.5 Hz, 1H), 7.17 (d, *J* = 7.5 Hz, 1H), 6.93 (t, *J* = 7.5 Hz, 1H), 6.88 (d, *J* = 7.5 Hz, 1H), 6.24 (d, *J* = 2.3 Hz, 1H), 5.03 (d, *J* = 5.7 Hz, 1H), 4.30 (t, *J* = 8.6 Hz, 1H), 4.12 (t, *J* = 8.6 Hz, 1H), 3.97-3.85 (m, 4H), 3.84 (s, 3H), 3.80 (dd, *J* = 6.3, 1.7 Hz, 1H), 2.84-2.77 (m, 1H), 2.07 (s, 3H), (2*R*) δ 7.33 (dd, *J* = 7.5, 1.7 Hz, 1H), 7.24 (dt, *J* = 7.5, 1.7 Hz, 1H), 6.93 (dt, *J* = 7.5, 1.7 Hz, 1H), 6.84 (d, *J* = 7.5 Hz, 1H), 6.50 (d, *J* = 4.6 Hz, 1H), 4.92 (d, *J* = 4.0 Hz, 1H), 4.30 (t, *J* = 8.6 Hz, 1H), 4.08 (t, *J* = 8.6 Hz, 1H), 3.82 (s, 3H), 3.99-3.77 (m, 5H), 3.31-3.24 (m, 1H), 1.76 (s, 3H)

^{13}C NMR (CDCl$_3$, 126 MHz): (2*S*) δ 170.4, 156.9, 128.7, 128.3, 127.9, 120.7, 110.8, 104.5, 103.4, 69.5, 65.2, 65.0, 55.4, 48.9, 47.9, 21.4, (2*R*) δ 169.8, 157.7, 128.1, 123.3, 119.9, 110.1, 103.8, 98.3, 68.2, 65.4, 65.1, 55.4, 44.1, 41.9, 21.0

ESI-MS *m/z* 331 $(M+Na)^+$

HRMS (ESI-TOF): Calcd for $C_{16}H_{20}NaO_6$ $(M+Na)^+$ 331.1152, found 331.1150.

((2*R*,3*S*,4*R*)-4-(1,3-dioxolan-2-yl)-3-(2-methoxyphenyl)tetrahydrofuran-2-yl)-2-nitrobenzenesulfonamide (26)



39 **26**

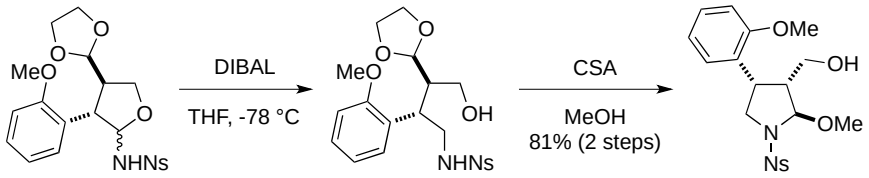
To a stirred solution of the acetal **39** (2.84 g, 9.21 mmol) in MeCN (20 mL) were added $NsNH_2$ (2.79 g, 13.8 mmol, 1.5 equiv) and $BF_3 \cdot OEt_2$ (50 μL, 0.40 □mol, 0.004 mol%) at 0 °C, and the reaction mixture was stirred for 2.5 h at room temperature. After stirring, the mixture was quenched with Et_3N and concentrated under reduced pressure. The residue was purified by column chromatography (*n*-hexane / CH_2Cl_2 = 2:1) to afford the aminal **26** (3.12 g, 75 %) as a mixture of diastereomers.

IR (film, cm^{-1}): 3265, 2958, 2891, 1737, 1598, 1548, 1494, 1354, 1246

^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.18 (d, *J* = 7.5 Hz, 1H), 7.87 (d, *J* = 7.5 Hz, 1H), 7.73-7.65 (m, 3H), 7.22 (t, *J* = 7.5 Hz, 1H), 7.12 (d, *J* = 7.5 Hz, 1H), 6.91 (t, *J* = 7.5 Hz, 1H), 6.86 (d, *J* = 8.6 Hz, 1H), 5.50 (dd, *J* = 10.3, 1.7 Hz, 1H), 5.12 (d, *J* = 2.9 Hz, 1H), 4.29-4.24 (m, 1H), 4.10-3.92 (m, 4H), 3.87-3.85 (m, 1H), 3.83 (s, 3H), 3.79 (dd, *J* = 9.2, 6.3 Hz, 1H), 2.75-2.71 (m, 1H)
^{13}C NMR ($CDCl_3$, 126 MHz): δ 156.2, 147.6, 136.3, 133.0, 132.9, 131.2, 130.4, 128.1, 126.4, 124.9, 120.8, 110.4, 103.6, 90.9, 66.4, 65.7, 65.5, 55.5, 48.1, 45.4

FAB-MS *m/z* 450 $(M)^+$
HRMS (ESI-TOF): Calcd for $C_{20}H_{22}N_2NaO_8S$ $(M+Na)^+$ 473.0989, found 473.1010

((2*R*,3*R*,4*S*)-2-methoxy-4-(2-methoxyphenyl)-1-(2-nitrophenylsulfonyl)pyrrolidin-3-yl) methanol (41)



To a stirred solution of **26** (2.21 g, 4.91 mmol) in THF (20 mL) was added DIBAL (14.4 mL, 1.02 M in *n*-hexane, 14.7 mmol) at −78 °C. The solution was stirred at −78 °C to room temperature for 1 h. The reaction mixture was poured into 2 M HCl and extracted with CH_2Cl_2. The organic layer was washed with saturated aqueous NaCl, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The crude **40** used in the next step without further purification.

To a stirred solution of the crude **40** in MeOH (50 mL) was added CSA (2.28 g, 9.82 mmol) at room temperature. The solution was stirred at the same temperature for 18 h. The reaction mixture was guenched with Et_3N and concentrated under reduced pressure. The residue was purified by column chromatography (*n*-hexane/AcOEt, 2/1) to afford **41** (1.67 g, 81%, 2 steps from **26**) as a colorless amorphous solid.

Optical Rotation: $[\alpha]^{25}_{D}$ −79.4 (*c* 1.00, $CHCl_3$)

IR (film, cm^{-1}): 3520, 3093, 2941, 1712, 1587, 1556

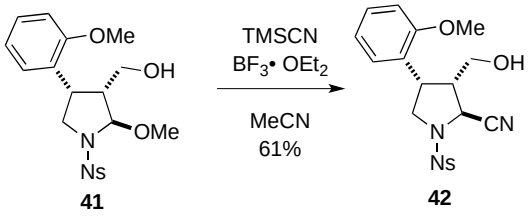
^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.21-8.17 (m, 1H), 7.75-7.70 (m, 2H), 7.68-7.65 (m, 1H), 7.24 (t, *J* = 8.0 Hz, 1H), 7.06 (d, *J* = 7.5 Hz, 1H), 6.91-6.85 (m, 2H), 5.32 (s, 1H), 4.25-4.19 (m, 1H), 3.83 (s, 3H), 3.91-3.76 (m, 2H), 3.43 (s, 3H), 3.16 (dd, *J* = 11.5, 5.2 Hz, 1H), 3.08 (dd, *J* = 11.5, 9.2 Hz, 1H), 2.84-2.79 (m, 1H)

^{13}C NMR ($CDCl_3$, 126 MHz): δ 157.3, 148.4, 133.6, 132.8, 131.7, 130.9, 128.3, 127.2, 124.6, 124.0, 120.6, 110.4, 94.2, 59.5, 56.0, 55.4, 49.5, 49.3, 37.2

FAB-MS *m/z* 423 $(M+H)^+$

HRMS (ESI-TOF): Calcd for $C_{19}H_{22}N_2NaO_7S$ $(M+Na)^+$ 445.1040, found 445.1060

(2*S*,3*S*,4*S*)-3-(hydroxymethyl)-4-(2-methoxyphenyl)-1-(2-nitrophenylsulfonyl) pyrrolidine-2-carbonitrile (42)



41 **42**

To a stirred solution of **41** (21.5 mg, 50.9 μmol) and TMSCN (12.6 μL, 102 μmol) in MeCN (1 mL) were added $BF_3 \cdot OEt_2$ (12.8 μL, 102 μmol) at 0 °C. The reaction mixture was stirred at room temperature for 1.5 h. The reaction mixture was quenched with Et_3N and concentrated under reduced pressure. The residue was purified by preparative TLC to afford **42** (13 mg, 61%) as a colorless amorphous solid.

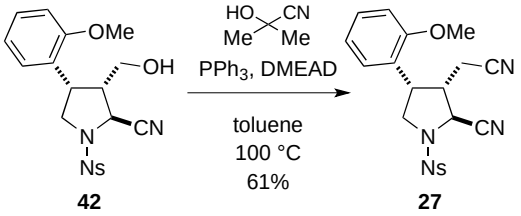
Optical Rotation: $[\alpha]^{25}_{D}$ −173.5 (*c* 0.16, $CHCl_3$)

IR (film, cm^{-1}): 2954, 2839, 2372, 2345, 1544, 1373

^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.24-8.20 (m, 1H), 7.80-7.76 (m, 2H), 7.74-7.70 (m, 1H), 7.29 (t, *J* = 8.0 Hz, 1H), 7.12 (d, *J* = 7.5 Hz, 1H), 6.95 (t, *J* = 7.5 Hz, 1H), 6.91 (d, *J* = 8.0 Hz, 1H), 4.91 (d, *J* = 3.4 Hz, 1H), 4.20 (dd, *J* = 15.3, 7.9 Hz, 1H), 4.09 (t, *J* = 9.1 Hz, 1H), 3.99 (dd, *J* = 9.1, 7.9 Hz, 1H), 3.86 (s, 3H), 3.29 (t, *J* = 6.9 Hz, 2H), 3.20-3.14 (m, 1H), 1.75 (t, *J* = 5.2 Hz, 1H)
^{13}C NMR ($CDCl_3$, 126 MHz): δ 157.0, 148.2, 134.4, 132.1, 132.0, 131.2, 129.0, 127.2, 124.4, 123.5, 121.0, 117.7, 110.6, 59.7, 55.5, 51.0, 50.8, 49.8, 38.6

FAB-MS *m/z* 418 $(M+H)^+$
HRMS (ESI-TOF): Calcd for $C_{19}H_{19}N_3NaO_6S$ $(M+Na)^+$ 440.0887, found 440.0907

(2*S*,3*S*,4*S*)-3-(cyanomethyl)-4-(2-methoxyphenyl)-1-(2-nitrophenylsulfonyl) pyrrolidine-2-carbonitrile (27)



To a stirred solution of **42** (224 mg, 537 μmol) in toluene (4 mL) were added PPh_3 (564 mg, 2.15 mmol), DMEAD (504 mg, 2.15 mmol) and acetone cyanohydrine (200 μL, 2.15 mmol) at 0 °C. The solution was stirred at 100 °C for 6 h. The reaction mixture was poured into saturated aqueous NaCl and extracted with AcOEt. The organic layer was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography (*n*-hexane/AcOEt, 2/1) to afford **27** (141 mg, 61%) as a colorless amorphous solid.

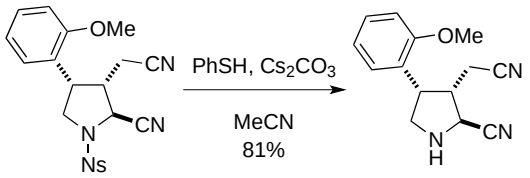
Optical Rotation: $[\alpha]^{25}_{D}$ −159.2 (*c* 0.20, $CHCl_3$)

IR (film, cm^{-1}): 2954, 2378, 2249, 1544, 1496

^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.23-8.21 (m, 1H), 7.83-7.79 (m, 2H), 7.77-7.74 (m, 1H), 7.34 (t, *J* = 8.0 Hz, 1H), 7.08 (d, *J* = 8.0 Hz, 1H), 6.97 (t, *J* = 8.0 Hz, 1H), 6.93 (d, *J* = 8.0 Hz, 1H), 4.84 (d, *J* = 2.3 Hz, 1H), 4.32-4.26 (m, 1H), 4.09-4.02 (m, 2H), 3.87 (s, 3H), 3.41-3.35 (m, 1H), 2.13 (dd, *J* = 17.2, 9.2 Hz, 1H), 2.06 (dd, *J* = 17.2, 5.7 Hz, 1H)
^{13}C NMR ($CDCl_3$, 126 MHz): δ 157.1, 148.1, 134.8, 132.4, 131.5, 131.3, 129.8, 127.5, 124.6, 121.7, 121.0, 116.9, 116.5, 110.8, 55.5, 52.9, 48.9, 44.4, 40.2, 16.4

FAB-MS *m/z* 427 $(M+H)^+$
HRMS (ESI-TOF): Calcd for $C_{20}H_{18}N_4NaO_5S$ $(M+Na)^+$ 449.0890, found 449.0912

(2*S*,3*S*,4*S*)-3-(cyanomethyl)-4-(2-methoxyphenyl)pyrrolidine-2-carbonitrile (43)



27 **43**

To a stirred solution of **27** (65.4 mg, 153 μmol) in MeCN (5 mL) were added PhSH (19 μL, 184 μmol) and Cs_2CO_3 (100 mg, 306 μmol) at room temperature. The solution was stirred at the same temperature for 3 h. The reaction mixture was poured into saturated aqueous $NaHCO_3$ and extracted with AcOEt. The organic layer were dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was purified by preparative TLC to afford **43** (30 mg, 81%) as a colorless amorphous solid.

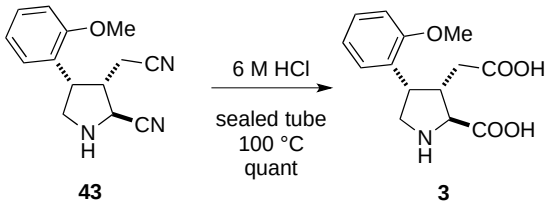
Optical Rotation: $[\alpha]^{25}_{D}$ −34.1(*c* 1.00, $CHCl_3$)

IR (film, cm^{-1}): 2953, 2841, 2247, 2223, 1600, 1585, 1494, 1462

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.29 (t, *J* = 7.5 Hz, 1H), 7.16 (d, *J* = 7.5 Hz, 1H), 6.95 (t, *J* = 7.5 Hz, 1H), 6.91 (d, *J* = 7.5 Hz, 1H), 4.10-4.05 (m, 2H), 3.86 (s, 3H), 3.52-3.43 (m, 2H), 3.21-3.15 (m, 1H), 2.11 (dd, *J* = 17.2, 9.2 Hz, 1H), 1.98 (dd, *J* = 17.2, 5.7 Hz, 1H)
^{13}C NMR ($CDCl_3$, 126 MHz): δ 157.2, 128.9, 127.9, 124.7, 120.7, 120.1, 118.1, 110.4, 55.3, 52.2, 48.2, 43.6, 40.0, 17.6

FAB-MS *m/z* 242 $(M+H)^+$
HRMS (ESI-TOF): Calcd for $C_{14}H_{16}N_3O$ $(M+H)^+$ 242.1288, found 242.1290

(2*S*,3*S*,4*S*)-3-(Carboxymethyl)-4-(2-methoxyphenyl)pyrrolidine-2-carboxylic acid (MFPA) (3)



43 **3**

To a stirred solution of **43** (5.7 mg, 23.6 μmol) and 6 M HCl (1.0 mL) was heated at 100 °C for 6h in a sealed tube. After cooling, the reaction mixture was concentrated under reduced pressure to afford HCl salt of **3** (7.2 mg, quant) as a colorless solid.

Optical Rotation: $[\alpha]^{25}_{D}$ +5.5 (*c* 0.23, H_2O);

mp 250 °C (decomp.)

IR (film, cm^{-1}): 3416, 2943, 1730, 1715, 1603, 1495, 1248

^{1}H NMR (D_2O, 500 MHz): δ 7.27 (t, *J* = 7.5 Hz, 1H), 6.99 (d, *J* = 7.5 Hz, 1H), 6.95 (d, *J* = 7.5 Hz, 1H), 6.87 (t, *J* = 7.5 Hz, 1H), 4.36 (d, *J* = 9.2 Hz, 1H), 3.95-3.88 (m, 1H), 3.73 (s, 3H), 3.76-3.64 (m, 2H), 3.23-3.15 (m, 1H), 2.56 (dd, *J* = 17.2, 5.2 Hz, 1H), 2.06 (dd, *J* = 17.2, 9.7 Hz, 1H)
^{13}C NMR (D_2O, 126 MHz): δ 175.1, 170.8, 157.2, 130.5, 129.8, 123.6, 120.9, 111.3, 63.3, 55.1, 48.2, 41.5, 41.0, 33.3

ESI-MS *m/z* 280 $(M+H)^+$
HRMS (ESI-TOF): Calcd for $C_{14}H_{17}NNaO_5$ $(M+Na)^+$ 302.0999, found 302.1006

Lit. (Hashimoto, K. Horikawa, M. Shirahama, H. *Tetrahedron Lett*. **1990**, *31*, 7047-7050.)
Optical Rotation: $[\alpha]^{24}_{D}$ = +4.99 (*c* 0.30, H_2O)
mp >300 °C
^{1}H-NMR (D_2O, 500 MHz) δ 7.30 (dd, *J* = 8.3, 7.3 Hz, 1H), 7.04 (d, *J* = 7.3 Hz, 1H), 7.00 (d, *J* = 8.3 Hz, 1H), 6.92 (t, *J* = 7.3 Hz, 1H), 4.00 (d, *J* = 7.3 Hz, 1H), 3.89 (ddd, *J* = ～8, 8.3, 7.8 Hz, 1H), 3.79 (s, 3H), 3.75 (dd, *J* = 11.7, 7.8 Hz, 1H), 3.67 (dd, *J* =11.7, 8.3 Hz, 1H), 3.08 (dddd, *J* = ～8, 9.8, 7.3, 5.4 Hz, 1H), 2.30 (dd, *J* = 16.1, 5.4 Hz, 1H), 1.85 (dd, *J* = 16.1, 9.8 Hz, 1H)