Supporting Information

Synthesis of [$^{123}$I]-Iodometomidate from a Polymer-Supported Precursor with a Large Excluded Volume.

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Experimental Section

General Methods

NMR spectra were recorded on a JEOL Model EX-270 (270 MHz for $^1$H, 67.8 MHz for $^{13}$C) or a JEOL Model ECP-400 (400 MHz for $^1$H, 100 MHz for $^{13}$C, 373 MHz for $^{19}$F) in the indicated solvent. Chemical shifts were reported in parts per million (ppm) relative to the signal (0.00 ppm) for internal tetramethylsilane solutions in CDCl$_3$. $^1$H NMR spectral data are reported as follows: CDCl$_3$ (7.26 ppm), CD$_2$Cl$_2$ (5.32 ppm), Acetone-d$_6$ (2.04 ppm), DMSO-d$_6$ (2.50 ppm), CD$_3$OD (3.30 ppm) $^{13}$C NMR spectral data are reported as follows: CDCl$_3$ (77.0 ppm), CD$_2$Cl$_2$ (53.8 ppm), Acetone-d$_6$ (29.8 ppm), DMSO-d$_6$ (39.5 ppm), CD$_3$OD (49.8 ppm) or D$_2$O (Acetone-d$_6$ (206.0 ppm) as an internal standard). $^{19}$F NMR spectral data are reported as follows: CF$_3$COOH (-79.0 ppm) as an external standard. NMR multiplicities are reported using the following abbreviations.

(s: singlet, d: doublet, t: triplet, q: quartet, m: multiplet, br: broad, J: coupling constants in Hertz.)

Infrared spectra (IR) were recorded on a Perkin-Elmer Spectrum 1. Only the strongest and/or structurally important absorbances are reported as the IR data given in cm$^{-1}$.

All reactions were monitored by thin layer chromatography carried out on Merck precoated TLC plates (60F-254) using UV light and p-anisaldehyde H$_2$SO$_4$ ethanol solution or 10% ethanolic phosphomolybdic acid.

Column chromatography separations were performed using silica gel (KANTO, silica gel 60 N, spherical, neutral, 40-100 um).

High performance liquid chromatography (HPLC) for qualitative and quantitative analysis were performed on a Gilson 506C system using a SHODEX ODS column (4.6 x 250 mm). Asahipak GF-7M HQ (7.5 x 300 mm), GPC K-804L (8.0 x 300 mm), ESI-TOF Mass spectra were measured with AppliedBioSystems Mariner TK-3500 Biospectrometry Workstation mass spectrometers and Waters LCT Premier$^\text{TM}$ XE. HRMS(ESI-TOF) were calibrated with angiotensin I (SIGMA), bradykinin (SIGMA), and neurotensin (SIGMA) as an internal standard.

Dry THF, dry hexane and dry toluene were distilled from sodium wire with a catalytic amount of benzophenone. Dry CH$_2$Cl$_2$ was distilled from P$_2$O$_5$. Dry DMF was distilled from CaH$_2$. Dry MeOH and dry EtOH were distilled from magnesium turning with a catalytic amount of iodine.
Preparation of the polymer-supported IMTO precursor 2.

1-((4-(Bromobutyl)dimethylsilyl)phenyl)-1-ethanol (5)

To a stirred solution of 1-(4-bromophenyl)ethyl-1-(2-tetrahydropiranyl)ether (3) (4.70 g, 16.5 mmol) in THF (49.5 mL), BuLi (1.64 mol/L n-hexyl solution, 12.1 mL, 19.8 mmol) was added dropwise at -78 °C. After 1 h at the same temperature, the mixture was treated with (4-bromobutyl)chlorodimethylsilane 4 (4.95 g, 21.5 mmol, 1.30 eq.) was added dropwise to the reaction mixture at the same temperature. After stirring the mixture at 1 h, the mixture was gradually warmed to room temperature. The reaction mixture was poured into NH₄Cl aq. with cooling. The aqueous layer was extracted by diethyl ether twice. The combined extract was washed with saturated NaHCO₃, brine, dried over MgSO₄, filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel with hexane: ethyl acetate 92:8 to give 5 (4.60 g, 14.6 mmol, 88% in 2 steps).

1H NMR (400MHz, CDCl₃) δ 7.50 (d, 2H, J = 8.2 Hz), 7.37 (d, 2H, J = 7.7 Hz), 4.88 (q, 1H, J = 6.6 Hz), 3.39 (t, 2H, J = 6.8 Hz), 1.90-1.83 (m, 2H), 1.50 (d, 3H, J = 6.7 Hz), 1.50-1.43 (m, 3H), 0.77-0.73 (m, 2H), 0.28 (s, 6H); 13C NMR (100 MHz, CDCl₃) δ 146.44, 138.23, 133.76, 124.80, 70.31, 36.19, 33.42, 25.00, 22.44, 14.81, -3.10; FT-IR (neat): 3371, 2958, 2930, 1602, 1391, 1271, 70.31, 36.19, 33.42, 25.00, 22.44, 14.81, -3.10; FT-IR (neat): 3371, 2958, 2930, 1602, 1391, 1271, 1249, 1111, 1083, 1007, 821839, 552 (cm⁻¹)

Methyl 1-((1-(4-bromobutyl)dimethylsilylphenyl)ethyl)-1H-imidazole-5-carboxylate (7)

To a stirred solution of 4-methoxycarbonyl-1H-imidazole (6) (1.68 g, 13.3 mmol) and triphenylphosphine (4.32 g, 16.6 mmol) in dry THF (40.0 mL) was added a solution of the alcohol 6 (4.60 g, 14.6 mmol) in dry THF (15.0 mL) at -40 °C, dropwise under argon. After a solution of di-tert-butyl azodicarboxylate (3.82 g, 16.6 mmol) in dry THF (25.0 mL) was added dropwise to the reaction mixture at the same temperature, the mixture was warmed from -40 °C to 0 °C within 2 h. After removal of the solvents in vacuo, the residue was solved with diethyl ether and stirred for 10 min. The mixture was filtered through a pad of Celite® with diethyl ether. After the filtrate was concentrated in vacuo, the residue was purified by column chromatography on silica gel with hexane: ethyl acetate 7:30 to give 7 (3.70 g, 8.74 mmol, 66%).

1H NMR (400 MHz, CDCl₃) δ 7.92 (s, 1H), 7.82 (s, 1H), 7.49 (d, 2H, J = 7.7 Hz), 7.20 (d, 2H, J = 7.7 Hz), 6.40 (q, 1H, J = 6.9 Hz), 3.86 (s, 3H), 3.39 (t, 2H, J = 6.8 Hz), 1.89-1.82 (m, 5H), 1.49-1.43 (m, 2H), 0.76-0.72 (m, 2H), 0.26 (s, 6H); 13C NMR (100 MHz, CDCl₃) δ 160.27, 141.40, 139.56, 138.63, 137.80, 125.29, 54.88, 51.04, 35.80, 33.03, 22.06, 21.76, 14.37, -3.43; FT-IR (neat): 2953, 2175, 1601, 1539, 1436, 1362, 1213, 1113, 1052, 954, 840 (cm⁻¹); HRMS (ESI-TOF) calcd. for C₁₉H₂₃BrN₂O₂Si [M+H]^+ 423.1103, found 423.1135.

Methyl 1-((4-((Azidobutyl)dimethylsilyl)phenyl)ethyl)-1H-imidazole-5-carboxylate (8)
To a solution of 7 (1.68 g, 3.97 mmol) in DMF (27.8 mL), sodium azide (1.29 g, 19.8 mmol) and a catalytic amount of sodium iodide was added. After stirring the mixture for 6 h at 80 °C, the mixture was cooled down and washed with H2O and the aqueous layer was extracted by diethyl ether, dried over MgSO4, filtered and concentrated in vacuo. The residue was purified by short pass of column chromatography on silica gel with dichloromethane : methanol : 98 : 2 to give 8 (1.35 g, 3.50 mmol, 89%).

1H NMR (400 MHz, CDCl3) δ 7.85 (s, 1H), 7.79 (s, 1H), 7.48 (d, 2H, J = 8.0 Hz), 7.18 (d, 2H, J = 8.0 Hz), 6.38 (q, 1H, J = 7.2 Hz), 3.83 (s, 3H), 3.22 (t, 2H, J = 6.8 Hz), 1.87 (d, 3H, J = 7.2 Hz), 1.60 (tt, 2H, J = 7.2, 7.2 Hz), 1.42-1.34 (m, 2H), 0.76-0.72 (m, 2H), 0.24 (s, 6H); 13C NMR (100 MHz, CDCl3) δ 160.41, 141.46, 139.65, 138.80, 134.33, 133.84, 125.41, 122.11, 55.03, 51.17, 50.75, 32.19, 21.84, 20.8, 15.03, -3.38 ; FT-IR (neat): 3785, 2952, 2315, 2097, 1714, 1437, 1362, 1248, 1219, 1133, 1113, 1052, 922, 838, 767, 733, 673, 538 (cm−1); HRMS (ESI-TOF) calcd. for C23H33N3O5Si [M+H]+ 428.2369, found 428.2392.

**Methyl 1-(4-(4-(N-(2-methylprop-2-enoyl)amino)butyl)dimethylsilylphenyl)ethyl)-1H-imidazole-5-carboxylate (10)**

To a stirred solution of 8 (648 mg, 1.68 mmol, 1.00 eq.) in THF/H2O (1:1) (6.72 mL), NH4Cl (270 mg, 5.04 mmol, 3.00 eq.) and activated Zn (446 mg, 6.82 mmol, 4.06 eq.) was added at 0 °C. After assuring no azide 8 was detected by TLC, the mixture was filtered through a pad of Celite®, and the filtrate was evaporated in vacuo. The residue was used in the next reaction without further purification.

To a solution of the above residue and NaHCO3 (998 mg, 11.8 mmol) in THF/H2O (1:1) (6.72 mL), methacryloyl chloride (9) (522 mg, 5.04 mmol) was added dropwise at 0 °C. After no amine was detected, the reaction mixture was washed with saturated NaHCO3 and brine, dried over MgSO4, filtered and concentrated in vacuo. Before evaporation, the filtrate was added polymerization inhibitor. The residue was purified by column chromatography on silica gel with 98:2 dichloromethane: methanol to give 10 (590 mg, 1.38 mmol, 83%).

1H NMR (400 MHz, CDCl3) δ 7.82 (s, 1H), 7.80 (s, 1H), 7.48-7.46 (d, 2H, J = 7.2 Hz), 7.19-7.16 (d, 2H, J = 7.2 Hz), 6.40-6.35 (q, 1H, J = 7.3 Hz), 5.71 (m, 1H), 5.62 (s, 1H), 5.28 (s, 1H), 3.83 (s, 3H), 3.30-3.25 (dt, 2H, J = 6.6 Hz), 1.94 (s, 3H), 1.53-1.51 (tt, 2H, J = 7.2 Hz), 1.36-1.30 (m, 2H, J = 3.9 Hz), 0.77-0.73 (m, 2H), 0.24 (s, 6H); 13C NMR (100 MHz, CDCl3) δ 168.24, 160.38, 141.32, 140.13, 138.99, 137.73, 133.84, 125.34, 122.19, 118.64, 55.04, 51.17, 38.96, 32.92, 21.82, 18.46, 15.04, -3.35 ; FT-IR (neat): 3324, 2953, 1714, 1660, 1622, 1539, 1437, 1362, 1248, 1219, 1133, 1113, 1052, 922, 838, 767, 733, 673, 538 (cm−1); HRMS (ESI-TOF) calcd. for C23H33N3O5Si [M+H]+ 428.2369, found 428.2392.

**Polymer 2**

The solution of monomer in reaction mixture of monomer in 40wt% toluene was passed through a column of alumina without dilution to remove the polymerization inhibitor. To the solution of the monomer 10 (580 mg, 1.36 mmol) in toluene (40 wt%, 1.45 g/ 1.24mL), AIBN (11.2 mg,
0.0670 mmol) was added. The mixture was frozen by liq. N₂, then degassed, and risen to room temperature under reduced pressure. The same operation were done about three times, the mixture was stirred at 65 °C for 24 h. The reaction mixture was cooled to room temperature, the solvent was removed in vacuo, and the residue was poured into hexane. The insoluble materials was separated by the filter paper. The residue was purified by column chromatography on silica gel eluted with CH₂Cl₂. The residue was precipitated from hexane to provide polymer 2 (282 mg, 0.661 mmol, 49%). The number-averaged molecular weight of the purified polymer 2 was estimated by a size-exclusion chromatography (SEC: Asahipak GF-7M HQ) eluted with 1.0 M LiCl DMF solution to be 1.02x10⁴.

1H NMR (400 MHz, CDCl₃) δ 7.91-7.76 (br, 1H), 7.71 (s, 1H), 7.47-7.38 (br, 2H), 7.18-7.10 (br, 2H), 6.35-6.27 (br, 1H), 5.07 (m, 1H), 3.72 (s, 3H), 3.14-2.90 (br, 2H), 1.87-1.77 (br, 3H), 1.64-1.36 (br, 2H), 1.36-1.20 (br, 5H), 0.90-0.89 (br, 2H), 0.73-0.62 (br, 2H), 0.23-0.13 (br, 6H); 13C NMR (100 MHz, CDCl₃) δ 160.7, 142.2, 140.2, 139.2, 137.9, 134.1, 128.2, 125.6, 122.5, 77.6, 45.3, 39.8, 31.7, 22.7, 22.1, 21.7, 15.3, 13.9, -3.15; FT-IR (neat): 2945, 2328, 1705, 1456, 1360, 1225, 1114, 1003, 918, 659, 558 (cm⁻¹).

Preparation of standard samples

Methyl 1-[1-(4-iodophenyl)ethyl]-1H-imidazole-5-carboxylate 1

To a stirred solution of 4-methoxy-imidazole-carbonic acid 18 (694 mg, 1.00 eq. 5.50 mmol) and Triphenylphosphine (1.79 mg, 6.88 mmol, 1.25 eq.) in dry THF (14.0 mL) was added a solution of 1-(4-iodophenyl)ethanol 42 (1.50g, 6.05 mmol,1.10 eq.) in dry THF (5.50 mL) at -30 °C, dropwise under argon. Then, a solution of di-tert-butyl azodicarboxylate (1.58 mg, 6.88 mmol, 1.25 eq.) in THF (8.00 mL) was added dropwise and the mixture was warmed from -30 °C to 0 °C within 2 h. After no alcohol was detected by TLC, the solution was evaporated in vacuo. The residue was mixed with diethyl ether and stirred for 10 min. The crystal of Ph₃PO was filtered through a pad of Celite®, and washed with diethyl ether. The filtrate was evaporated in vacuo and the residue was purified by column chromatography silica gel with hexane: ethyl acetate 65:35 to give methyl 1-[1-(4-iodophenyl)ethyl]-1H-imidazole-5-carboxylate 1 (1.03 g, 2.89 mmol, 53%).

1H NMR (400 MHz, CDCl₃) δ 7.91-7.86 (m, 1H, H-a), 7.80 (s, 1H, H-b), 7.69-7.66 (d, 2H, H-g, J = 8.3 Hz), 6.93-6.91 (d, 2H, H-f, J = 8.3 Hz), 6.33-6.30 (q, 1H, H-h, J = 7.1 Hz ), 3.81 (s, 3H, H-c), 1.86-1.84 (d, 3H, H-e J = 7.2 Hz); 13C NMR (100 MHz, CDCl₃) δ 161.4, 140.9, 139.5, 138.1, 127.9, 122.2, 93.4, 54.8, 51.3, 21.9; FT-IR (neat): 3419, 3126, 2984, 2950, 1715, 1538, 1488, 1436, 1362, 1211, 1134, 1112, 1064, 1007, 660, 525 (cm⁻¹); mp: 69-71 °C; HRMS (ESI-TOF) calcd. for C₁₇H₁₃N₃O₂[M+H]⁺ 357.0100, found 357.0093.

Methyl 1-[1-(4-chlorophenyl)methyl]-1H-imidazole-5-carboxylate (11)

1H NMR (400 MHz, CDCl₃) δ 7.78 (s, 1H, H-a), 7.76 (s, 1H, H-b), 7.30 (d, 2H, H-f, J = 8.7 Hz), 7.10 (d, 2H, H-g, J = 8.7 Hz), 6.31 (q, 1H, H-h, J = 7.4 Hz ), 3.80 (s, 3H, H-c), 1.85 (d, 3H, H-e J = 6.8 Hz); 13C NMR (100 MHz, CDCl₃) δ 160.6, 139.8, 139.5, 138.3, 133.8, 129.0, 127.5, 126.2, 54.8, 51.5, 22.2; FT-IR (neat): 3713, 2952, 1715, 1538, 1494, 1437, 1363, 1219, 1133, 1112, 1053, 1015, 919,655 (cm⁻¹); HRMS (ESI-TOF) calcd. for C₁₇H₁₃ClN₃O₂[M+H]⁺ 256.0744, found 256.0753.
Methyl 1-[1-(phenyl)methyl]-1H-imidazole-5-carboxylate (13)

\[ \text{HNMR (400 MHz, CDCl}_3 \delta 7.78 (s, 1H, H-a), 7.74 (s, 1H, H-b), 7.37-7.27 (m, 3H, H-g,h), 7.19 (d, 2H, H-f, J = 7.3 Hz), 6.36 (q, 1H, H-d, J = 7.2 Hz ), 3.81 (s, 3H, H-c), 1.86 (d, 3H, H-e J = 7.2 Hz); 13C NMR (100 MHz, CDCl}_3 \delta 160.39, 140.89, 137.87, 128.60, 126.02, 122.13, 55.13, 51.15, 21.92; FT-IR (neat): 3419, 2986, 1715, 1538, 1495, 1455, 1438, 1363, 1217, 1133, 765, 702, 660 (cm}\^{-1}\); HRMS (ESI-TOF) calcd. for C\textsubscript{13}H\textsubscript{14}N\textsubscript{2}O\textsubscript{2} [M+H]\textsuperscript{+} 231.1134, found 231.1136.

Preparation of the silylated IMTO

1) nBuLi, THF -78 °C
2) PPTS, MeOH 0 °C to r.t.

2 steps 88%

\[ \text{HNMR (400 MHz, CDCl}_3 \delta 7.53 (d, 2H, J = 7.7 Hz), 7.37 (d, 2H, J = 7.9 Hz), 4.89 (q, 1H, J = 6.6 Hz), 1.63 (m, 1H), 1.50 (d, 3H), 0.26 (s, 9H); 13C NMR(100 MHz, CDCl}_3 \delta 146.3, 139.5, 133.5, 124.8, 70.2, 24.9, -1.2; FT-IR (neat): 3368, 2957, 1602, 1393, 1249, 1133, 1085, 1008, 840, 821, 758, 551 (cm}\^{-1}\)

Methyl 1-[1-(4-trimethylsilylphenyl)ethyl]-1H-imidazole-5-carboxylate (12)

To a stirred solution of 6 (177 mg, 1.40 mmol) and triphenylphosphine (473 mg, 1.82 mmol) in dry THF (3.50 mL) was added a solution of 14 (300 mg, 1.54 mmol) in dry THF (3.00 mL) at -30 °C, dropwise under argon. Then, a solution of di-tert-butyl azodicarboxylate (387 mg, 1.68 mmol) in THF (4.00 mL) was added dropwise to the reaction mixture at the same temperature. The reaction mixture was warmed from -30 °C to 0 °C within 2 h. After no alcohol was detected by TLC, the solution was evaporated in vacuo. After removal of the solvents in vacuo, the residue was solved with diethyl ether and stirred for 10 min. The mixture was filtered through a pad of Celite\textsuperscript{®} with diethyl ether. After the
filtrate was concentrated in vacuo, the residue was purified by column chromatography on silica gel with hexane:ethyl acetate, 68:32 to give 11 (225 mg, 0.784 mmol, 56%).

$1^H$ NMR (400 MHz, CDCl$_3$) $\delta$ 7.83 (s, 1H), 7.80 (s, 1H), 7.50 (d, 2H, $J = 7.8$ Hz), 7.18 (d, 2H, $J = 7.8$ Hz), 6.38 (q, 1H, $J = 7.1$ Hz), 3.84 (s, 3H), 1.87 (d, 3H, $J = 6.8$ Hz), 0.25 (s, 9H); $1^3$C NMR (100 MHz, CDCl$_3$) $\delta$ 160.62, 141.40, 140.42, 139.79, 133.83, 125.53, 122.33, 55.29, 51.39, 22.08, -1.24; FT-IR (neat): 2955, 1715, 1539, 1438, 1362, 1249, 1219, 1134, 1114, 841.8, 766, 671 (cm$^{-1}$); mp: 142-143 °C; HRMS (ESI-TOF) calcd. for C$_{16}$H$_{22}$N$_2$O$_2$Si [M+H]$^+$ 303.1529, found 303.1556.

**Reaction of 11 in the presence of NCS under acidic conditions.**

To a solution of methyl 1-[1-(4-trimethylsilylphenyl)ethyl]-1H-imidazole-5-carboxylate 10 (20.0 mg, 0.661 mmol) in TFA (500 µL) was added a solution of NCS (26.5 mg, 0.173 mmol) in TFA (661 µL). The reaction mixture was stirred at 40 or 90 °C for 60 min. Then, 100 µL of the reaction mixture was quenched by 10% Na$_2$S$_2$O$_3$ aq. and saturated NaHCO$_3$, and extracted by ethyl acetate. The organic layer was evaporated in vacuo, the residue was analyzed by HPLC based on a photo diode-array detector.

**Iodination using 2**

To a stirred solution of 2 (20.0 mg, 0.0469 mmol, 1.00 eq.) in TFA (469 µL), NaI (7.03 mg, 0.0469 mmol, 1.00 eq.) and NCS (18.8 mg, 0.141 mmol, 3.0 eq.) was added. The time was counted from the time as NCS was added. After stirring the mixture for 60 min at 40 °C, the reaction was quenched by 10% Na$_2$S$_2$O$_3$ aq. and saturated NaHCO$_3$, and extracted by ether acetate. The organic layer was evaporated in vacuo, and the residue was passed through a short pass of column chromatography on silica gel with dichloromethane: methanol 98:2 to give a mixture of iodide 1 (13.0 mg, 0.0366 mmol, 78%) and the chloride 11 (0.4 mg, 0.00094 mmol, 2.0%). The yields were estimated by $^1$H NMR spectra of the mixture.

**Synthesis of [I$^{123}$]IMTO from monomer 12**

Methyl 1-[1-(4-trimethylsilylphenyl)ethyl]-1H-imidazole-5-carboxylate 11 (1.4-3.2 mg, 4.6-10.6 µmol, 1.00 eq.) was added to [I$^{123}$]NaI in 1.0 mol/L NaOH(10-15µL, 60-145MBq), 14mg/mL NCS in solvent (138-320µL, 14-32µmol, 3.0 eq.) and solvent (80-262 µL, total volume is 410-415 µL). After being stirred at the indicated temperature for 60 min, the reaction was quenched by 30% Na$_2$S$_2$O$_3$ aq.. The mixture was diluted with water(10mL) and unreacted [I$^{123}$]NaI was removed by passage through a C18 Sep-Pak. The Sep-Pak was rinsed with 10mL water and the [I$^{123}$]IMTO was eluted with 2mL EtOH. The eluant was analyzed by Radio-TLC and HPLC.

TLC: The radioactive spots are detected and recorded by Rita Star

High performance liquid chromatography (HPLC) for qualitative and quantitative analysis were performed on a 2695 Alliance HPLC Separation Module using an Inertsil WP300 C18 column (4.6 × 250 mm, 5µm).
Synthesis of [$^{123}$I]IMTO from the polymer precursor 2.

To a stirred solution of Polymer precursor 2 (1 mg) in TFA (50 µL), [$^{123}$I]NaI in 1.0 mol/L NaOH (10 µL, 147 MBq) and then 5 mg/mL NCS in TFA (109 µL) was added at room temperature. After being stirred at 40°C for 60 min (TLC01), the mixture was diluted with methylene chloride (15 mL) and then was added to PS-DIEA (548 mg). After being stirred at room temperature for 5 min, the mixture was passed through a Silicagel Sep-pak and was rinsed with 10 mL of methylene chloride. After being connected another Silicagel Sep-pak, [$^{123}$I]IMTO was eluted with 15 mL methylene chloride/methanol (1:9). The eluant was heated at 40°C and the solvent was evaporated with the aid of Argon gas flow. Acetonitrile (2 mL) was added to the residue and [$^{123}$I]IMTO was obtained with radiochemical purity over 94% and radiochemical yield was 85% (decay collect) (TLC02).

Radioactivity analysis by a TLC Scanner

TLC01

TLC02