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SUPPORTING INFORMATION

Title: Regioselective Domino Metathesis of 7-Oxanorbornenes and Its Application to the Synthesis of Biologically Active Glutamate Analogues

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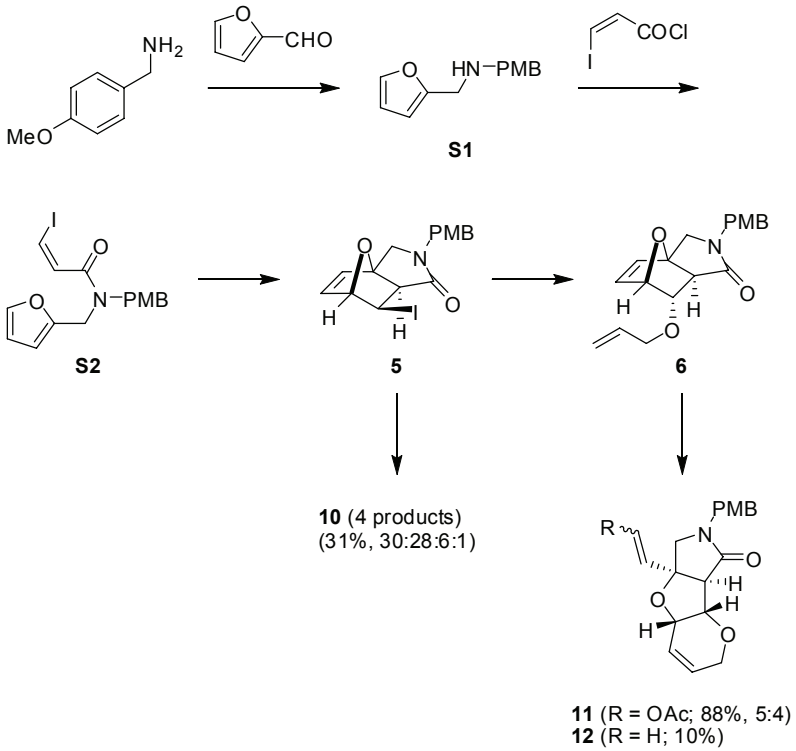
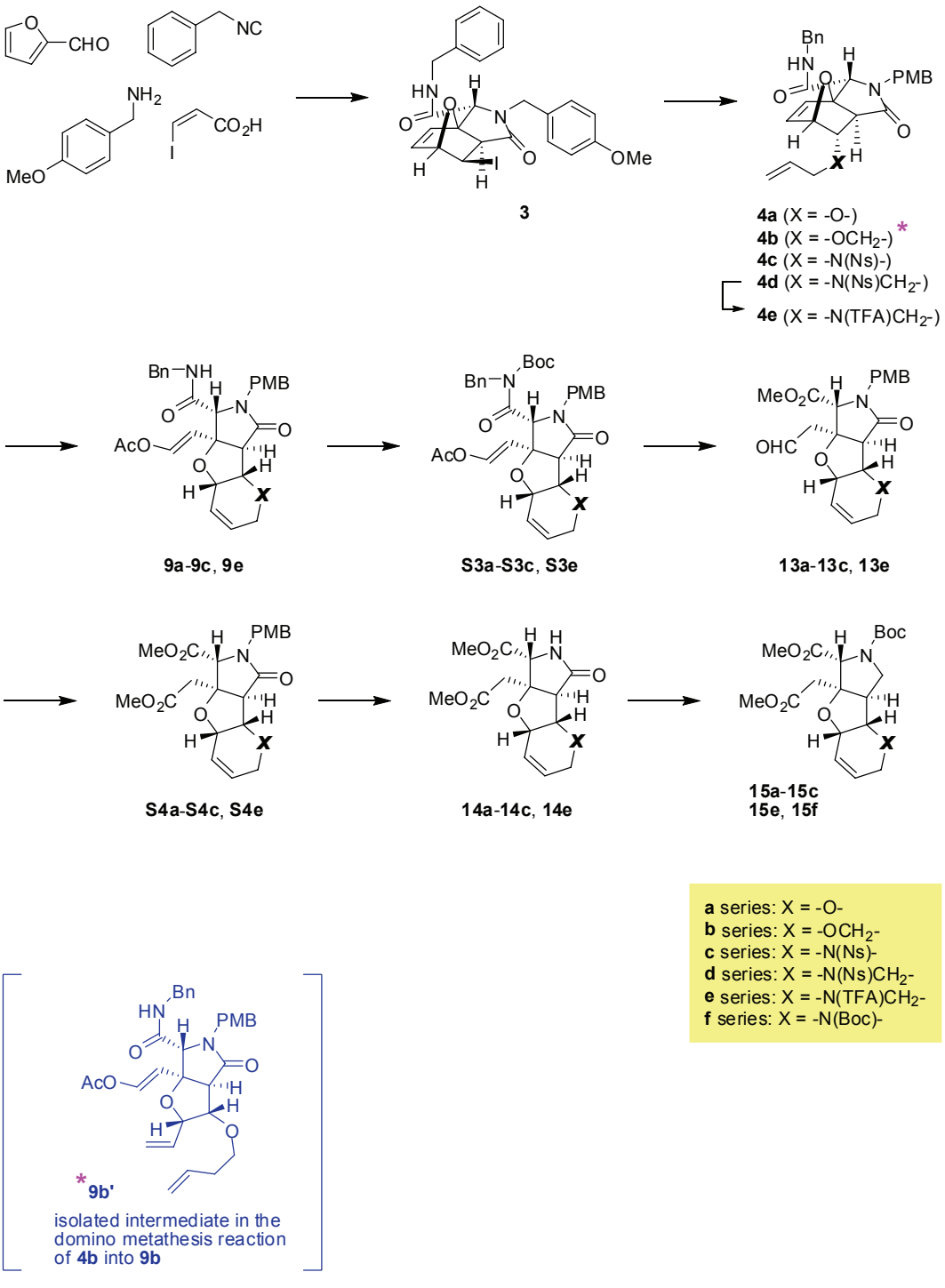
Ref. No.: O200800704

Contents:

Synthetic Scheme for the 7-Oxanorbornenes 5 and 6 and Their Metathesis Reactions Leading to 10 and 11



Synthetic Scheme for the Key Intermediates 15a-15c, 15e, and 15f

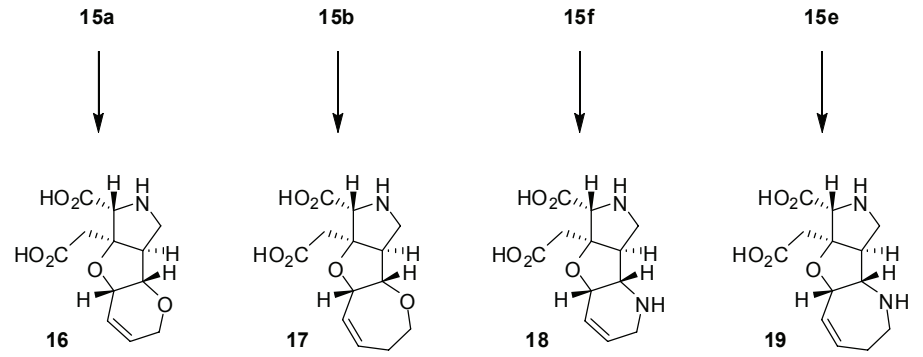


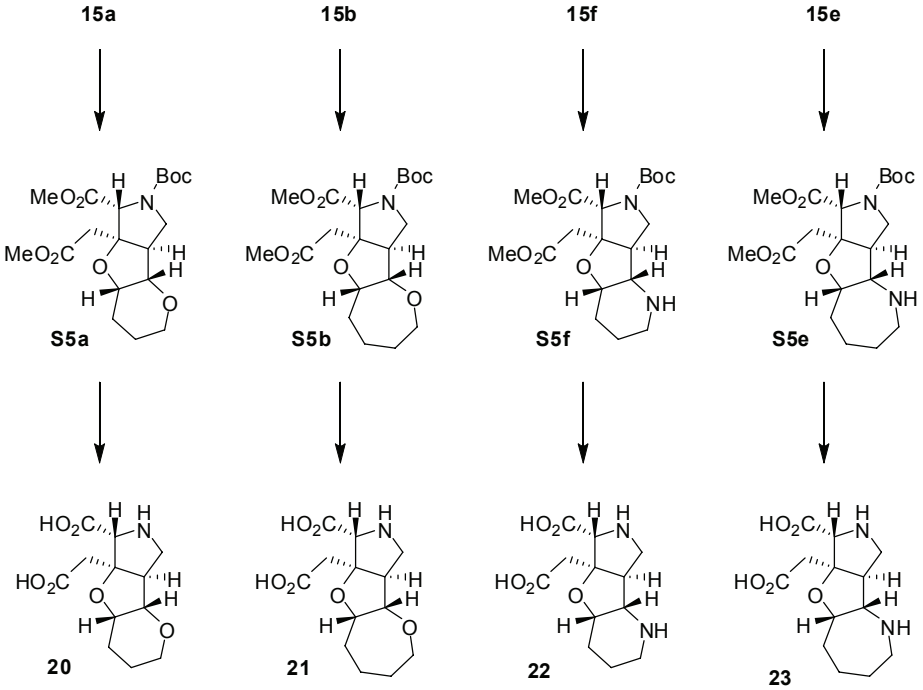
a series: X = -O-
b series: X = $-OCH_2-$
c series: X = -N(Ns)-
d series: X = $-N(Ns)CH_2-$
e series: X = $-N(TFA)CH_2-$
f series: X = -N(Boc)-

*9b'

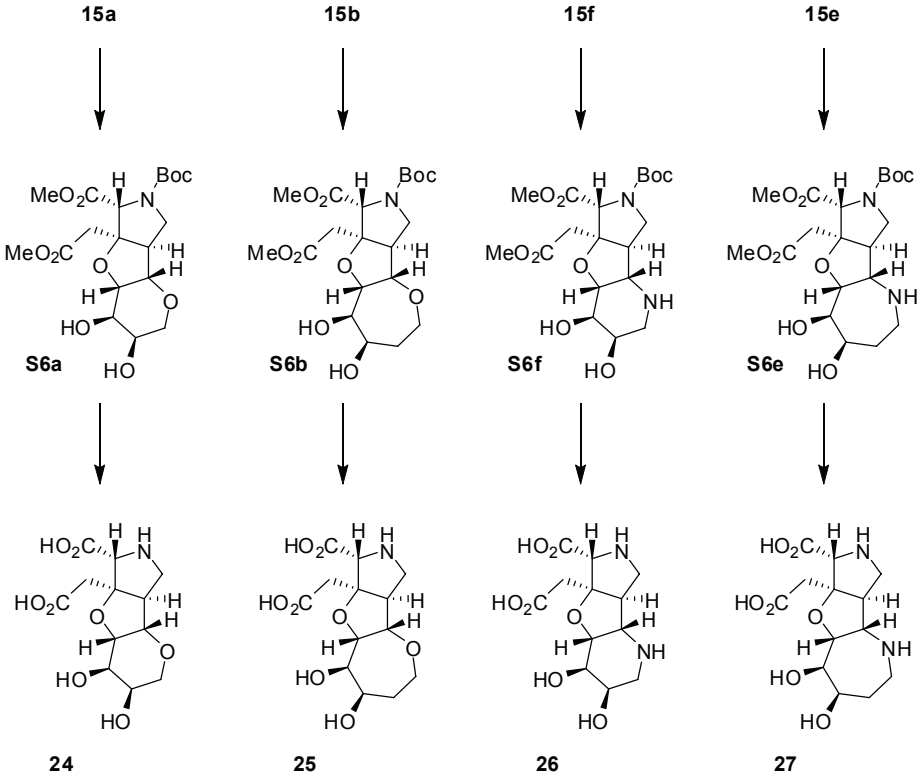
isolated intermediate in the domino metathesis reaction of **4b** into **9b**

Synthetic Scheme for the Glutamate Analogues 16-23

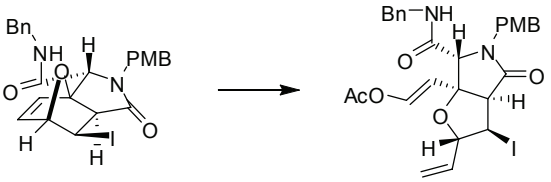




Synthetic Scheme for the Glutamate Analogues 24-27



Synthetic Scheme for the Metathesis Reaction of 3 into the Heterobicycle 8



3

8 (87%, *E*/*Z* = 13:1)

General Methods. All reactions sensitive to air or moisture were carried out under argon atmosphere in oven-dried glassware unless otherwise noted. Anhydrous dichloromethane (CH_2Cl_2), acetonitrile (MeCN) and tetrahydrofuran (THF) were purchased from Kanto Chemical Co., Inc., Wako Pure Chemical Industries, Ltd. or Aldrich Chemical Co., and used without further drying. All other reagents were used as supplied unless otherwise stated. Analytical thin-layer chromatography (TLC) was performed using E. Merck silica gel 60 F_{254} pre-coated plates (0.25-mm thickness). For column chromatography, Fuji Silysia silica gel BW-300 (200-400 mesh) was used. For reversed-phase column chromatography, Wako gel ®100C18 (63-212 μm) was used. IR spectra were recorded on a JASCO FT/IR-4100 spectrometer. ^1H and ^{13}C NMR spectra were recorded on Varian Gemini2000, Unity INOVA500 or INOVA600 spectrometers. Chemical shifts are reported in ppm from tetramethylsilane with reference to internal residual solvent [^1H NMR: $CHCl_3$ (δ 7.24), C_6HD_5 (δ 7.15), HDO (δ 4.70); ^{13}C NMR: $CDCl_3$ (δ 77.0), C_6D_6 (δ 128.0)]. The following abbreviations are used to designate the multiplicities; s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, and br = broad peak. High-resolution mass spectrometry (HRMS) for ESI (electrospray ionization) was recorded on a Bruker Daltonics microTOF focus mass spectrometer equipped with Agilent HPLC system (1100 series).

***N*-(4-Methoxybenzyl)furfurylamine (S1).** To a stirred solution of 4-methoxybenzylamine (6.5 mL, 50 mmol) in benzene (100 mL) was added furfural (5.0 mL, 50 mmol) and the mixture was heated to reflux with Dean-Stark condenser. After 12 h, the mixture was cooled to rt and concentrated under reduced pressure. To a stirred solution of the residue in methanol (50 mL) at 0 °C were added $NaBH_4$ (3.0 g, 74 mmol) in one portion and TFA (4.1 mL, 55 mmol) successively. After 1 h, the mixture was concentrated under reduced pressure, diluted with EtOAc (200 mL), washed with aqueous NaOH (2 M, 100 mL) and brine (100 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (20 g, hexane/EtOAc = 7:3) to give *N*-(4-methoxybenzyl)furfurylamine (**S1**, 10.4 g, 97%) as a colorless oil; IR (film) 3324, 1512, 1456, 1247, 1174, 1035, 919, 813, 737 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.35 (dd, *J* = 1.8 Hz, 0.9 Hz, 1 H), 7.22 (d, *J* = 8.7 Hz, 2 H), 6.84 (d, *J* = 8.7 Hz, 2 H), 6.30 (dd, *J* = 3.0, 1.8 Hz, 1 H), 6.16 (d, *J* = 2.4 Hz, 1 H), 3.78 (s, 3 H), 3.75 (s, 2 H), 3.70 (s, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.5, 153.7, 141.6, 131.8, 129.3, 113.6, 109.9, 106.8, 55.0, 52.0, 45.1; HRMS (ESI, positive) calcd for $C_{13}H_{16}NO_2$ [$(M+H)^+$] 218.1176, found 218.1182.

The Iodoacrylamide S2. To a stirred solution of *N*-(4-methoxybenzyl)furfurylamine (**S1**, 596 mg, 2.77 mmol) in THF (30 mL) at 0 °C were added (*Z*)-3-iodoacryl chloride (629 mg, 2.92 mmol)[1] and Cs_2CO_3 (1.43 mg, 4.38 mmol), and allowed to warm to rt. After 3 h, the mixture was poured into saturated aqueous NH_4Cl (30 mL) and extracted with EtOAc (50 mL). Organic layer was washed with brine (50 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (20 g, hexane/EtOAc = 8:2) to give the iodoacrylamide **S2** (840 mg, 74%) as a pale yellow oil, which was unstable and used immediately for the next reaction without characterization.

The 7-Oxanorbornene 5. A solution of the iodoacrylamide **S2** (268 mg, 0.65 mmol) in toluene (7.0 mL) was heated to reflux. After 12 h, the mixture was cooled to rt and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (20 g, hexane/EtOAc = 2:8) to give **5** (232 mg, 87 %) as a white solid; IR (film) 2932, 1684, 1512, 1246, 1175, 1032, 707 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.19 (d, *J* = 8.7 Hz, 2 H), 6.86 (d, *J* = 8.7 Hz, 2 H), 6.50 (d, *J* = 5.7 Hz, 1 H), 6.34 (dd, *J* = 5.7, 2.1 Hz, 1 H), 5.27 (d, *J* = 1.2 Hz, 1 H), 4.54 (d, *J* = 14.4 Hz, 1 H), 4.42 (d, *J* = 14.4 Hz, 1 H), 3.86 (d, *J* = 8.1 Hz, 1 H), 3.78 (s, 3 H), 3.70 (d, *J* = 12.0 Hz, 1 H), 3.49 (d, *J* = 12.0 Hz, 1 H), 2.43 (d, *J* = 7.5 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.9, 159.0, 136.1, 135.3, 129.3, 127.7, 114.1, 90.3, 88.7, 55.2, 50.1, 47.2, 46.2, 18.4; HRMS (ESI, positive) calcd for $C_{16}H_{17}INO_3$ [$(M+H)^+$]

[1] Prepared from (*Z*)-3-iodoacrylic acid by treatment with oxalyl chloride and DMF in benzene. For the synthesis of (*Z*)-3-iodoacrylic acid, see: R. Takeuchi, K. Tanabe, S. Tanaka, *J. Org. Chem.* **2000**, *65*, 1558-1561.

398.0248, found 398.0252.

The Allyl Ether 6. To a stirred solution of allyl alcohol (20.6 μL, 0.30 mmol) in DMF (1.0 mL) at rt was added NaH (60% in mineral oil, 12 mg, 0.3 mmol). After 30 min, a solution of **5** (19.9 mg, 0.05 mmol) in DMF (1.0 mL) was added *via* a cannula, and the mixture was stirred at -10 °C for 1.5 h. The mixture was then poured into saturated aqueous NH_4Cl (10 mL) and was extracted with EtOAc (20 mL). The extract was washed with water (3 × 10 mL) and brine (10 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (0.5 g, hexane/EtOAc = 5:5) to give the allyl ether **6** (633 mg, 73%) as a yellow solid: IR (film) 2910, 1686, 1513, 1470, 1247, 1112, 1032, 839, 720 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.14 (d, *J* = 8.5 Hz, 1 H), 6.84 (d, *J* = 8.5 Hz, 1 H), 6.51 (d, *J* = 6.0 Hz, 1 H), 6.42 (dd, *J* = 11.5, 2.0 Hz, 1 H), 5.89 (ddd, *J* = 16.8, 11.0, 10.5 Hz, 1 H), 5.31 (dd, *J* = 17.0, 1.5 Hz, 1 H), 5.19, (dd, *J* = 10.5, 1.5 Hz, 1 H), 4.99 (dd, *J* = 4.5, 2.0 Hz, 1 H), 4.50 (d, *J* = 14.5 Hz, 1 H), 4.35 (d, *J* = 14.5 Hz, 1 H), 4.35 (d, *J* = 5.0, 2.0 Hz, 1 H), 4.13 (dd, *J* = 12.5, 5.5 Hz, 1 H), 4.05 (dd, *J* = 12.5, 5.5 Hz, 1 H), 3.77 (s, 3 H), 3.75 (d, *J* = 11.5 Hz, 1 H), 3.42 (d, *J* = 11.5 Hz, 1 H), 2.23 (d, *J* = 2.0 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.1, 159.1, 134.8, 133.9, 129.3, 128.0, 117.7, 114.1, 90.1, 79.6, 78.3, 71.6, 55.3, 55.2, 49.2, 46.0; HRMS (ESI, positive) calcd for $C_{19}H_{22}NO_4$ $[(M+H)^+]$ 328.1549, found 328.1542.

Metathesis Reaction of 5. To a stirred solution of the 7-oxanorbornene **5** (50.0 mg, 0.122 mmol) in DCM (3.0 mL) at rt were added vinyl acetate (56.7 μL, 0.611 mmol) and Hoveyda-Grubbs catalyst 2nd generation (3.80 mg, 6.11 μmol) under argon atmosphere. After stirring for 14 h, the mixture was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (4 g, hexane/EtOAc = 7:3) to give the heterobicycle **10** (a brown oil, 18.5 mg, 31%) as a mixture four diastereomers as judged from LC-MS and ^1H NMR spectra.

The Heterotricycle 11. To a stirred solution of the 7-oxanorbornene **6** (295.3 mg, 0.86 mmol) in DCM (331 mL) at rt were added vinyl acetate (2.7 mL, 4.3 mmol) and Hoveyda-Grubbs catalyst 2nd generation (2.7 mg, 4.3 μmol) under argon atmosphere. After 6 h, the mixture was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (4 g, hexane/EtOAc = 6:4) to give the heterotricycles **11** (291.6 mg, 88%, *E/Z* = 5:4) and **12** (29.5 mg, 10%) as colorless oils.

Data for 11. IR (film) 2935, 1757, 1684, 1513, 1247, 1213, 1088, 1035, 818, 763 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.33 (d, *J* = 12.2 Hz, 1.3 H), 7.16 (d, *J* = 9.0 Hz, 2 H), 7.13 (d, *J* = 9.0 Hz, 2 H), 6.97 (d, *J* = 7.0 Hz, 1 H), 6.85 (d, *J* = 9.0 Hz, 2.6 H), 6.83 (d, *J* = 9.0 Hz, 2 H), 6.05 (dd, *J* = 10.8, 3.0 Hz, 2.6 H), 5.96 (m, 1 H), 5.57 (d, *J* = 12.3 Hz, 1.3 H), 5.27 (d, *J* = 7.0

Hz, 1 H), 4.51-4.45 (m, 2.3 H), 4.37-4.31 (m, 4.6 H), 4.19-3.96 (m, 6.9 H), 3.78 (s, 3.9 H), 3.77 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.3, 170.2, 167.7, 166.5, 159.2, 159.2, 137.4, 133.1, 131.4, 131.0, 129.6, 129.5, 127.9, 127.6, 122.0, 121.9, 116.5, 115.6, 114.2, 114.1, 85.4, 82.9, 82.5, 78.6, 76.6, 73.4, 72.6, 64.4, 64.1, 60.5, 59.9, 58.6, 57.2, 55.3, 46.1, 46.0, 20.6, 20.5; HRMS (ESI, positive) calcd for $C_{19}H_{22}NO_4$ [$(M+H)^+$] 386.1604, found 386.1602.
Data for 12. IR (film) 2935, 1684, 1512, 1246, 1090, 1032, 764 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.13 (d, *J* = 8.4 Hz, 2 H), 6.82 (d, *J* = 8.4 Hz, 2 H), 6.05 (dd, *J* = 10.1, 3.6 Hz, 1 H), 5.98 (m, 1 H), 5.96 (dd, *J* = 16.7, 10.5 Hz, 1 H), 5.29 (d, *J* = 16.7 Hz, 1 H), 5.28 (s, 1 H), 5.11 (d, *J* = 10.5 Hz, 1 H), 4.49 (d, *J* = 14.7 Hz, 1 H), 4.34 (d, *J* = 3.0 Hz, 1 H), 4.33 (d, *J* = 14.7 Hz, 1 H), 4.15 (dd, *J* = 16.4, 3.9 Hz, 1 H), 4.08-4.00 (m, 2 H), 3.78 (s, 3 H), 3.42 (d, *J* = 11.1 Hz, 1 H), 3.31 (d, *J* = 11.1 Hz, 1 H), 3.15 (br s, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.4, 159.2, 138.6, 131.0, 129.4, 127.7, 122.1, 114.9, 84.9, 78.7, 73.3, 64.2, 59.8, 57.0, 55.3, 46.0; HRMS (ESI, positive) calcd for $C_{19}H_{22}NO_4$ [$(M+Na)^+$] 328.1543, found 328.1550.

The 7-Oxanorbornene 3 (Tandem Ugi/Diels-Alder Reaction). To a stirred solution of furfural (500 μL, 5.31 mmol) in methanol (25 mL) at rt were added 4-methoxybenzylamine (459 μL, 3.54 mmol), (*Z*)-iodoacrylic acid (750 mg, 3.54 mmol), and benzyl isocyanide (647 μL, 5.31 mmol). After stirring at 50 °C for 8.5 h, the mixture was concentrated under reduced pressure and the residue was diluted with chloroform (200 mL). The solution was washed with saturated aqueous $NaHCO_3$ (100 mL), saturated aqueous NH_4Cl (100 mL), and brine (100 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (20 g, hexane/EtOAc = 6:4) to give the 7-oxanorbornene **3** (1.29 g, 68%) as a white solid: IR (film) 2921, 1684, 1512, 1384, 1247, 1029, 701 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36-7.30 (m, 3 H), 7.22 (d, *J* = 7.0 Hz, 2 H), 7.09 (d, *J* = 8.0 Hz, 2 H), 6.81 (d, *J* = 8.0 Hz, 2 H), 6.35 (d, *J* = 6.0 Hz, 1 H), 5.96 (br s, 1 H), 5.25 (d, *J* = 1.5 Hz, 1 H), 5.04 (d, *J* = 15.5 Hz, 1 H), 5.96 (br s, 1 H), 5.25 (d, *J* = 1.5 Hz, 1 H), 5.04 (d, *J* = 15.5 Hz, 1 H), 4.45 (dd, *J* = 14.5, 5.5 Hz, 1 H), 4.36 (dd, *J* = 14.5, 5.5 Hz, 1 H), 3.94 (s, 1 H), 3.89 (d, *J* = 15.5 Hz, 1 H), 3.86 (d, *J* = 15.5 Hz, 1 H), 3.76 (s, 3 H), 2.62 (d, *J* = 7.5 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.9, 166.8, 159.3, 137.3, 135.2, 135.0, 129.4, 128.9, 128.0, 128.0, 126.8, 114.3, 92.0, 88.8, 61.6, 55.3, 49.2, 45.4, 43.9, 18.2; HRMS (ESI, positive) calcd for $C_{24}H_{24}IN_2O_4$ [$(M+H)^+$] 531.0775, found 531.0782.

The 7-Oxanorbornene Allyl Ether 4a. To a stirred solution of allyl alcohol (7.80 mL, 11.3 mmol) in DMF (22 mL) at rt was added NaH (60% in mineral oil, 452 mg, 11.3 mmol). After 30 min, a solution of the iodide **3** (1.011 g, 1.89 mmol) in DMF (44 mL) was added *via* a cannula, and the mixture was stirred at same temperature for 1.5 h. The mixture was poured into saturated aqueous NH_4Cl (100 mL) and extracted with EtOAc (100 mL). The extract

was washed with water (3 × 30 mL) and brine (50 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (20 g, hexane/EtOAc = 7:3) to give the allyl ether **4a** (633 mg, 73%) as a yellow solid: IR (film) 3298, 2921, 1669, 1513, 1247, 1055, 701 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.35-7.28 (m, 3 H), 7.18 (d, *J* = 6.5 Hz, 2 H), 7.06 (d, *J* = 8.5 Hz, 2 H), 6.39 (s, 2 H), 6.03 (br t, *J* = 5.0 Hz, 1 H), 5.87 (m, 1 H), 5.30 (dd, *J* = 17.5, 1.5 Hz, 1 H), 5.19 (d, *J* = 10.0 Hz, 1 H), 4.98 (d, *J* = 4.0 Hz, 1 H), 4.80 (d, *J* = 15.0 Hz, 1 H), 4.40 (dd, *J* = 14.8, 6.0 Hz, 1 H), 4.33 (s, 1 H), 4.32 (dd, *J* = 14.8, 6.0 Hz, 1 H), 4.10 (dd, *J* = 12.8, 5.0 Hz, 1 H), 4.03 (d, *J* = 14.5 Hz, 1 H), 4.02 (dd, *J* = 12.8, 5.0 Hz, 1 H), 3.97 (s, 1 H), 3.75 (s, 3 H), 2.45 (d, *J* = 2.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.4, 166.8, 159.1, 137.5, 134.6, 133.7, 133.5, 129.3, 128.7, 127.8, 127.7, 126.9, 117.6, 91.7, 79.4, 78.5, 71.3, 63.4, 55.1, 54.3, 45.3, 43.7; HRMS (ESI, positive) calcd for $C_{27}H_{29}N_2O_5$ [$(M+H)^+$] 461.2074, found 461.2071.

The 7-Oxanorbornene Butenyl Ether 4b. With the same procedure for the synthesis of **4a**, **4b** (407 mg, 49%) was obtained as a yellow solid starting from **3** (900 mg, 1.75 mmol), NaH (430 mg, 10.41 mmol), and 3-buten-1-ol (903 mL, 10.41 mmol).

Data for 4b. IR (film) 3074, 2912, 1667, 1513, 1247, 1031, 820, 713 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.35-7.27 (m, 3 H), 7.18 (d, *J* = 10.0 Hz, 2 H), 7.06 (d, *J* = 9.0 Hz, 2 H), 6.78 (d, *J* = 9.0 Hz, 2 H), 6.37 (dd, *J* = 8.5, 6.5 Hz, 2 H), 6.11 (br t, *J* = 5.5 Hz, 1 H), 5.74 (m, 1 H), 5.05 (dd, *J* = 17.0, 2.0 Hz, 1 H), 5.00 (d, *J* = 10.5 Hz, 1 H), 4.96 (dd, *J* = 4.5, 1.5 Hz, 1 H), 4.80 (d, *J* = 15.0 Hz, 1 H), 4.39 (dd, *J* = 14.1, 6.0 Hz, 1 H), 4.33 (dd, *J* = 14.1, 6.0 Hz, 1 H), 4.27 (dd, *J* = 4.5, 2.0 Hz, 1 H), 4.02 (d, *J* = 15.0 Hz, 1 H), 3.97 (s, 1 H), 3.74 (s, 3 H), 3.60-3.53 (m, 2 H), 2.42 (d, *J* = 2.0 Hz, 1 H), 2.29 (dd, *J* = 7.0, 6.8 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.5, 166.8, 159.2, 137.5 (× 2), 134.6, 133.5, 129.4, 128.7, 127.9, 127.8, 127.0, 116.6, 114.1, 91.7, 79.5, 79.0, 69.9, 63.5, 55.2, 54.2, 45.4, 43.7, 33.9; HRMS (ESI, positive) calcd for $C_{28}H_{31}N_2O_5$ [$(M+H)^+$] 475.2223, found 475.2215.

The 7-Oxanorbornene *N*-Allyl *N*-Ns Amide 4c. To a stirred solution of the iodide **3** (201.1 mg, 0.38 mmol) in DMF (5.0 mL) at rt were added *N*-allyl 2-nitrobenzenesulfonamide (138 mg, 0.57 mmol) and Cs_2CO_3 (1.14 mmol). After stirring at 50 °C for 10 h, the mixture was cooled to rt, poured into saturated aqueous NH_4Cl (20 mL), and extracted with EtOAc (50 mL). The extract was washed with water (3 × 10 mL) and brine (30 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (4 g, hexane/EtOAc = 5:5) to give the Ns amide **4c** (244.5 mg, 100%) as a yellow solid: IR (film) 3087, 2933, 1695, 1541, 1513, 1359, 1247, 1173, 1031, 737, 589 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.15 (dd, *J* = 7.3, 2.0 Hz, 1 H), 7.76-7.70 (m, 2 H), 7.64 (dd, *J* = 7.3, 2.0 Hz, 1 H), 7.35-7.29 (m, 3 H), 7.19 (d, *J* = 7.0 Hz, 1 H), 7.03 (d, *J* =

9.0 Hz, 2 H), 6.79 (d, *J* = 9.0 Hz, 2 H), 6.50 (dd, *J* = 6.0, 1.5 Hz, 1 H), 6.35 (d, *J* = 6.0 Hz, 1 H), 5.98 (br t, *J* = 5.5 Hz, 1 H), 5.68 (m, 1 H), 5.18 (d, *J* = 11.5 Hz, 1 H), 5.16 (s, 1 H), 5.07 (d, *J* = 11.5 Hz, 1 H), 4.83 (d, *J* = 15.0 Hz, 1 H), 4.46 (t, *J* = 3.5 Hz, 1 H), 4.43 (dd, *J* = 15.0, 6.5 Hz, 1 H), 4.31 (dd, *J* = 15.0, 6.5 Hz, 1 H), 3.94 (d, *J* = 15.0 Hz, 1 H), 3.92 (s, 1 H), 3.88 (br s, 2 H), 3.75 (s, 3 H), 2.93 (d, *J* = 3.5 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.7, 166.7, 159.3, 128.5, 137.2, 135.7, 134.0, 133.9, 133.5, 132.1, 132.0, 130.8, 129.5, 128.9, 128.0, 127.8, 126.6, 124.3, 117.9, 114.2, 91.2, 81.9, 62.9, 59.8, 55.2, 50.4, 49.8, 45.4, 43.8; HRMS (ESI, positive) calcd for $C_{33}H_{33}N_4O_8$ [$(M+H)^+$] 645.2014, found 645.2018.

The 7-Oxanorbornene *N*-Butenyl *N*-Ns Amide 4d. With the same procedure for the synthesis of **4c**, **4d** (1.04 g, 85%) was obtained as a yellow solid starting from **3** (1.00 g, 1.87 mmol), Cs_2CO_3 (1.22 g, 3.74 mmol), and *N*-(3-butenyl) 2-nitrobenzenesulfonamide (719 mg, 2.81 mmol).

Data for 4d. IR (film) 3088, 2933, 1695, 1542, 1512, 1355, 1246, 1173, 1032, 681, 589 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.17 (d, *J* = 8.0 Hz, 1 H), 7.77-7.65 (m, 3 H), 7.36-7.30 (m, 3 H), 7.21 (d, *J* = 7.0 Hz, 2 H), 7.03 (d, *J* = 8.5 Hz, 2 H), 6.79 (d, *J* = 8.5 Hz, 2 H), 6.47 (d, *J* = 6.0 Hz, 1 H), 6.37 (d, *J* = 6.0 Hz, 1 H), 6.03 (br s, 1 H), 5.61 (m, 1 H), 5.21 (d, *J* = 4.0 Hz, 1 H), 5.01 (d, *J* = 5.5 Hz, 1 H), 4.99 (s, 1 H), 4.86 (d, *J* = 15.0 Hz, 1 H), 4.43 (dd, *J* = 14.5, 5.5 Hz, 1 H), 4.36 (dd, *J* = 14.5, 5.5 Hz, 1 H), 3.95 (d, *J* = 15.0 Hz, 1 H), 3.93 (s, 1 H), 3.75 (s, 3 H), 3.21 (m, 2 H), 2.81 (d, *J* = 4.0 Hz, 1 H), 2.43 (m, 1 H), 2.08 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.7, 166.8, 159.4, 137.0, 136.0, 133.9, 133.8, 133.6, 132.2, 132.1, 130.3, 129.6, 129.0 ($\times$ 2), 128.1, 127.9, 126.5, 124.4, 121.2, 117.7, 114.3, 91.1, 82.2, 62.9, 60.0, 55.3, 50.9, 47.4, 45.5, 44.0, 33.9; HRMS (ESI, positive) calcd for $C_{34}H_{35}N_4O_8S$ [$(M+H)^+$] 659.2170, found 659.2179.

The TFA amide 4e. To a stirred solution of **4d** (1.00 g, 1.50 mmol) in acetonitrile (20 mL) at 0 °C were added thiophenol (308 μL, 3.00 mmol) and Cs_2CO_3 (733 mg, 2.3 mmol). After stirring at rt for 2.5 h, the mixture was then poured into saturated aqueous $NaHCO_3$ (100 mL) and extracted with DCM (2 $\times$ 100 mL). The combined extracts were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (20 g, methanol/chloroform = 1:9) to give the amine (628 mg, 88%) as a pale yellow oil, which was used in the next reaction without characterization.

To a stirred solution of the amine thus obtained (426.8 mg, 0.099 mmol) in DCM (10 mL) at 0 °C were added TEA (137.5 μL, 0.992 mmol) and TFAA (138 μL, 0.992 mmol). After stirring at rt for 30 min, the mixture was then poured into saturated aqueous $NaHCO_3$ (50 mL) and extracted with EtOAc (2 $\times$ 100 mL). The combined extracts were washed with brine (30 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The residue was

purified by column chromatography on silica gel (8 g, hexane/EtOAc = 3:1) to give the TFA amide **4e** (379.6 mg, 74%) as a pale yellow oil: IR (film) 2934, 1697, 1540, 1513, 1417, 1246, 1204, 1146, 700 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.35-7.29 (m, 3 H), 7.20 (d, *J* = 7.5 Hz, 2 H), 7.05 (d, *J* = 8.5 Hz, 2 H), 6.79 (d, *J* = 8.5 Hz, 2 H), 6.34 (d, *J* = 5.5 Hz, 1 H), 6.21 (d, *J* = 6.0 Hz, 1 H), 6.11 (br t, *J* = 5.0 Hz, 1 H), 5.68 (m, 1 H), 5.68 (s, 1 H), 5.16 (d, *J* = 17.0 Hz, 1 H), 5.08 (d, *J* = 10.5 Hz, 1 H), 4.88 (d, *J* = 14.5 Hz, 1 H), 4.43-4.34 (m, 3 H), 3.97 (d, *J* = 17.0 Hz, 1 H), 3.95 (s, 1 H), 3.74 (s, 3 H), 3.60 (m, 1 H), 3.15 (m, 1 H), 2.88 (d, *J* = 3.5 Hz, 1 H), 2.65 (m, 1 H), 2.35 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.4, 166.9, 159.3, 157.7, 137.1, 135.3, 134.2, 132.8, 129.5, 128.8, 128.0, 127.8, 126.6, 118.3, 117.3, 114.2, 90.8, 80.7, 62.6, 58.9, 55.2, 51.7, 46.7, 45.4, 43.8, 32.6; HRMS (ESI, positive) calcd for $C_{30}H_{31}N_3O_5$ [$(M+H)^+$] 570.2210, found 570.2198.

The Heterobicycle 8. To a stirred solution of **3** (200 mg, 0.38 mmol) in benzene (5.0 mL) at rt were added vinyl acetate (173.4 μL, 1.87 mmol) and Hoveyda-Grubbs catalyst 2nd generation (2.3 mg, 3.8 μmol) under argon atmosphere. After 14 h, the mixture was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (4 g, hexane/EtOAc = 7:3) to give the heterobicycle **8** (205.7 mg, 87%, *E/Z* = 13:1) as a colorless oil: IR (film) 3042, 1759, 1683, 1557, 1540, 1513, 1212, 1028, 699 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.42 (d, *J* = 12.0 Hz, 1 H), 7.33-7.28 (m, 3 H), 7.20 (d, *J* = 7.5 Hz, 2 H), 7.02 (d, *J* = 8.5 Hz, 2 H), 6.78 (d, *J* = 8.5 Hz, 2 H), 5.78-5.71 (m, 2 H), 5.43 (d, *J* = 12.0 Hz, 1 H), 5.42 (d, *J* = 14.5 Hz, 1 H), 5.36 (d, *J* = 10.0 Hz, 1 H), 5.05 (d, *J* = 14.5 Hz, 1 H), 4.41 (dd, *J* = 10.5, 7.0 Hz, 1 H), 4.34 (dd, *J* = 14.8, 6.0 Hz, 1 H), 4.29 (dd, *J* = 10.1, 7.0 Hz, 1 H), 3.92 (dd, *J* = 10.1, 7.0 Hz, 1 H), 3.78 (d, *J* = 14.5 Hz, 1 H), 3.76 (s, 3 H), 3.52 (s, 1 H), 3.09 (d, *J* = 7.0 Hz, 1 H), 2.10 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.8, 167.5, 167.3, 159.2, 139.3, 137.3, 133.0, 129.7, 128.7, 128.0, 127.7, 127.0, 121.1, 114.1, 112.6, 87.2, 84.7, 69.9, 55.2, 53.6, 45.3, 43.7, 20.6, 20.0; HRMS (ESI, positive) calcd for $C_{28}H_{30}N_2O_6I$ [$(M+H)^+$] 617.1143, found 617.1151.

The Heterotricycle 9a. To a stirred solution of **4a** (310 mg, 0.64 mmol) in benzene (5.0 mL) were added vinyl acetate (312.0 μL, 3.37 mmol) and Hoveyda-Grubbs catalyst 2nd generation (2.1 mg, 3.2 μmol) under argon atmosphere. After 4 h, the mixture was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (4 g, hexane/EtOAc = 6:4) to give the heterotricycle **9a** (345.9 mg, 100%) as a brown liquid: IR (film) 2835, 1758, 1682, 1541, 1513, 1455, 1246, 1219, 1090, 1031, 700 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.34 (d, *J* = 12.0 Hz, 1 H), 7.33-7.27 (m, 3 H), 7.21 (d, *J* = 6.5 Hz, 2 H), 7.00 (d, *J* = 8.5 Hz, 2 H), 6.79 (d, *J* = 8.5 Hz, 2 H), 6.04 (dd, *J* = 10.0, 3.5 Hz, 1 H), 5.94 (d, *J* = 10.0, 2.5 Hz, 1 H), 5.78 (br t, *J* = 5.5 Hz, 1 H), 5.41 (d, *J* = 12.0 Hz, 1 H),

5.03 (d, *J* = 14.5 Hz, 1 H), 4.43 (dd, *J* = 14.5, 6.0 Hz, 1 H), 4.38 (d, *J* = 3.5 Hz, 1 H), 4.34 (dd, *J* = 14.5, 6.0 Hz, 1 H), 4.10 (dd, *J* = 17.0, 3.5 Hz, 1 H), 4.10 (br s, 1 H), 3.98 (d, *J* = 17.0 Hz, 1 H), 3.76 (s, 3 H), 3.71 (d, *J* = 14.5 Hz, 1 H), 3.66 (s, 1 H), 3.33 (s, 1 H), 2.05 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.6, 167.9 ($\times$ 2), 159.5, 139.2, 137.6, 131.4, 130.0, 129.9, 129.0, 128.3, 128.0, 127.4, 122.0, 114.5, 113.2, 85.6, 78.5, 74.0, 71.6, 64.2, 59.0, 55.5, 45.4, 44.1, 21.0; HRMS (ESI, positive) calcd for $C_{29}H_{31}N_2O_7$ [$(M+H)^+$] 519.2126, found 519.2119.

The Heterotricycle 9b. To a stirred solution of **4b** (298.1 mg, 0.63 mmol) in benzene (7.0 mL) at rt was added vinyl acetate (291.0 μL, 3.15 mmol) and Hoveyda-Grubbs catalyst 2nd generation (3.9 mg, 6.3 μmol) under argon atmosphere. After 46 h, the mixture was concentrated under reduced pressure. The Ru catalyst was removed by passing through a short pad of silica gel (6 g, hexane/EtOAc = 4:6). The filtrate was concentrated under reduced pressure to give a residue which was mainly composed of the triene ROM/CM product **9b'** (84% yield on isolation, *E/Z* = >20:1).

The residue thus obtained was, without purification, dissolved in benzene (7.0 mL). To the stirred mixture at 69 °C was added Hoveyda-Grubbs catalyst 2nd generation (3.9 mg, 6.3 μmol). After 21 h, the mixture was cooled to rt and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (6 g, hexane/EtOAc = 6:4) to give the heterotricycle **9b** (281.9 mg, 84%, *E/Z* = >20:1) as a brown liquid: IR (film) 2932, 1757, 1674, 1513, 1455, 1246, 1217, 1111, 1031, 699 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42 (d, *J* = 12.0 Hz, 1 H), 7.32-7.26 (m, 3 H), 7.16 (d, *J* = 7.0 Hz, 1 H), 7.00 (d, *J* = 8.5 Hz, 2 H), 6.79 (d, *J* = 8.5 Hz, 2 H), 5.79 (m, 1H), 5.74 (br s, 1 H), 5.60 (dd, *J* = 11.8, 4.0 Hz, 1 H), 5.40 (d, *J* = 12.0 Hz, 1 H), 5.01 (d, *J* = 14.5 Hz, 1 H), 4.48-4.45 (m, 2 H), 4.42 (dd, *J* = 14.5, 6.0 Hz, 1 H), 4.34 (dd, *J* = 14.5, 6.0 Hz, 1 H), 3.94 (m, 1 H), 3.76 (s, 3 H), 3.72 (d, *J* = 14.5 Hz, 1 H), 3.65 (d, *J* = 1.5 Hz, 1 H), 3.57 (m, 1 H), 3.30 (s, 1 H), 2.34-2.28 (m, 2 H), 2.06 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.8, 167.6 ($\times$ 2) 159.1, 138.8, 137.4, 129.8, 129.5, 128.5, 127.8, 127.5, 127.1, 125.7, 114.0, 112.3, 83.9, 83.0, 82.5, 71.0, 69.0, 59.9, 55.1, 44.9, 43.6, 30.6, 20.6; HRMS (ESI, positive) calcd for $C_{30}H_{33}N_2O_7$ [$(M+H)^+$] 533.2282, found 533.2281.

Data for the Intermediary Triene 9b'. IR (film) 2931, 1758, 1675, 1551, 1513, 1453, 1370, 1247, 1216, 1108, 1035, 930, 700, 649, 596 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 (d, *J* = 12.0 Hz, 1 H), 7.32-7.26 (m, 3 H), 7.21-7.20 (m, 2 H), 7.00 (d, *J* = 8.5 Hz, 2 H), 6.78 (d, *J* = 8.5 Hz, 2 H), 5.94 (m, 1 H), 5.85 (br s, 1 H), 5.72 (m, 1 H), 5.41 (d, *J* = 12.0 Hz, 1 H), 5.26 (d, *J* = 17.0 Hz, 1 H), 5.23 (d, *J* = 10.0 Hz, 1 H), 5.02-4.94 (m, 3 H), 4.43 (dd, *J* = 14.5, 6.0 Hz, 1 H), 4.31 (dd, *J* = 14.5, 6.0 Hz, 1 H), 4.28 (dd, *J* = 8.0, 3.5 Hz, 1 H), 4.21 (d, *J* = 3.5 Hz, 1 H), 3.75 (s, 3 H), 3.71 (d, *J* = 15.0 Hz, 1 H), 3.69 (s, 1 H), 3.54-3.43 (s, 1 H), 2.24 (m, 2 H), 2.08 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.9, 167.7, 167.6, 159.3, 138.7, 137.3, 135.0, 133.1, 129.7, 128.7, 128.0, 127.8, 127.1, 119.2, 116.4, 114.2, 112.7, 85.2, 84.8, 83.6, 71.5,

69.2, 57.3, 55.3, 45.1, 43.8, 34.0, 20.7; HRMS (ESI, positive) calcd for $C_{32}H_{37}N_2O_7$ [$(M+H)^+$] 561.2595, found 561.2600.

The Heterotricycle 9c. With the same procedure for the synthesis of **9a**, **9c** (1.07 g, 97%) was obtained as a brown solid starting from **4c** (1.00 g, 1.42 mmol), Hoveyda-Grubbs catalyst 2nd generation (19.6 mg, 0.032 mmol), and vinyl acetate (727 μL, 7.85 mmol).
Data for 9c. IR (film) 2940, 1758, 1696, 1542, 1513, 1370, 1245, 1172, 1031, 682, 583 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.42 (d, *J* = 8.0 Hz, 1 H), 7.81-7.68 (m, 3 H), 7.34-7.30 (m, 3 H), 7.20 (d, *J* = 7.5 Hz, 2 H), 7.05 (d, *J* = 8.5 Hz, 2 H), 6.83 (d, *J* = 8.5 Hz, 2 H), 5.91 (dd, *J* = 10.5, 5.0 Hz, 1 H), 5.80-5.77 (m, 2 H), 5.46 (d, *J* = 12.5 Hz, 1 H), 5.04 (d, *J* = 14.5 Hz, 1 H), 4.95 (t, *J* = 6.5 Hz, 1 H), 4.75 (d, *J* = 6.5 Hz, 1 H), 4.38 (dd, *J* = 14.5, 5.5 Hz, 1 H), 4.32 (dd, *J* = 14.5, 5.5 Hz, 1 H), 4.19 (dd, *J* = 18.5, 5.0 Hz, 1 H), 3.81 (s, 3 H), 3.77 (d, *J* = 14.5 Hz, 1 H), 3.16 (d, *J* = 4.0 Hz, 1 H), 2.11 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.2, 167.6, 166.9, 159.3, 128.0, 138.1, 137.4, 133.9, 132.3, 132.1, 129.7, 128.6 (× 2), 128.2, 128.0, 127.6, 127.4, 126.8, 126.1, 124.2, 114.2, 112.6, 84.5, 72.8, 70.6, 57.9, 55.2, 54.6, 45.0, 43.6, 40.3, 20.6; HRMS (ESI, positive) calcd for $C_{35}H_{35}N_4O_{10}S$ [$(M+H)^+$] 703.2068, found 703.2076.

The Heterotricycle 9d. With the same procedure for the synthesis of **9b**, **9d** (220.1 mg, 90%) was obtained as a brown solid starting from **4d** (225.9 mg, 0.343 mmol), Hoveyda-Grubbs catalyst 2nd generation (21.5 mg, 0.034 mmol), and vinyl acetate (158.9 μL, 1.720 mmol).
Data for 9d. IR (film) 3033, 2975, 1757, 1697, 1542, 1246, 1165, 681 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.43 (d, *J* = 8.0 Hz, 1 H), 7.81 (t, *J* = 7.5 Hz, 1 H), 7.72 (t, *J* = 7.5 Hz, 2 H), 7.60 (d, *J* = 8.0 Hz, 1 H), 7.31 (d, *J* = 13.0 Hz, 1 H), 7.31-7.27 (m, 3 H), 7.18 (d, *J* = 5.5 Hz, 2 H), 6.97 (d, *J* = 8.5 Hz, 2 H), 6.78 (d, *J* = 8.5 Hz, 2 H), 5.96 (dt, *J* = 11.5, 3.5 Hz, 1 H), 5.69 (br t, *J* = 5.5 Hz, 1 H), 5.60 (m, 1 H), 5.51 (d, *J* = 13.0 Hz, 1 H), 5.09 (d, *J* = 14.5 Hz, 1 H), 4.81 (d, *J* = 5.5 Hz, 1 H), 4.35 (d, *J* = 5.5 Hz, 2 H), 3.83 (s, 3 H), 3.77 (d, *J* = 9.5 Hz, 1 H), 3.77 (s, 3 H), 3.59 (d, *J* = 15.0 Hz, 1 H), 3.54 (s, 1 H), 3.45 (m, 1 H), 2.69 (s, 1 H), 2.67 (m, 1 H), 2.37 (d, *J* = 17.5 Hz, 1 H), 2.10 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.8, 167.6, 166.8, 159.4, 147.6, 138.0, 137.1, 133.8, 132.9, 132.7, 132.1, 129.9, 128.7, 128.2, 128.0, 127.8, 126.7, 123.7, 120.6, 114.3, 112.1, 84.2, 82.4, 70.8, 65.6, 59.8, 55.2, 45.0, 43.7, 42.8, 33.3, 20.6; HRMS (ESI, positive) calcd for $C_{36}H_{37}N_4O_{10}S$ [$(M+H)^+$] 717.2225, found 714.2218.

The Heterotricycle 9e. With the same procedure for the synthesis of **9b**, **9e** (363.0 mg, 94%) was obtained starting from **4e** (354.0 mg, 0.620 mmol), Hoveyda-Grubbs catalyst 2nd generation (38.8 mg, 0.062 mmol), and vinyl acetate (287.9 μL, 3.11 mmol).
Data for 9e. IR (film) 2934, 1760, 1696, 1514, 1210, 1035, 700 cm^{-1}; ^1H NMR (500 MHz,

$CDCl_3$, ca 7:3 mixture of rotamers) δ 7.41 (d, *J* = 12.5 Hz, 0.3 H), 7.35 (d, *J* = 12.5 Hz, 0.7 H), 7.31-7.18 (m, 5 H), 7.02 (d, *J* = 8.0 Hz, 0.6 H), 7.00 (d, *J* = 8.0 Hz, 1.4 H), 6.80 (d, *J* = 12.5 Hz, 0.7 H), 6.78 (d, *J* = 8.0 Hz, 0.6 H), 6.11 (br s, 1 H), 5.94 (dt, *J* = 11.5, 4.0 Hz, 0.7 H), 5.88 (dt, *J* = 11.5, 4.0 Hz, 0.3 H), 5.65 (d, *J* = 12.5, 0.7 H), 5.64 (d, *J* = 12.5 Hz, 0.3 H), 5.57 (m, 1 H), 5.19 –5.02 (m, 2 H), 4.76 (d, *J* = 5.0 Hz, 1.4 H), 4.46 (dd, *J* = 14.5, 6.0 Hz, 1 H), 4.39-4.35 (m, 2 H), 4.15 (t, *J* = 6.5 Hz, 0.7 H), 4.04-3.85 (m, 3.3 H), 3.85-3.77 (m, 6 H), 3.74-3.65 (m, 3 H), 3.55 (m, 1 H), 3.23 (d, *J* = 11.5, 1.4 H), 2.72 (m, 0.3 H), 2.50-2.22 (m, 1.7 H), 2.10 (s, 0.9 H), 2.08 (s, 2.1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.2, 170.8, 167.7, 167.6, 166.9, 166.8, 166.5, 166.3, 159.4, 159.3, 138.3, 137.9, 137.8, 137.7, 137.5, 137.3, 130.0 ($\times$ 2), 128.5, 128.4, 128.2, 128.1, 127.5, 127.2, 126.9, 126.7, 121.2, 120.4, 114.2 ($\times$ 2), 113.0, 112.6; HRMS (ESI, positive) calcd for $C_{36}H_{37}N_4O_{10}S$ [$(M+H)^+$] 717.2225, found 717.2217.

The *N*-Boc Imide S3a. To a stirred solution of the *N*-Bn amide **9a** (290.0 mg, 0.56 mmol) in DCM (5.0 mL) at 0 °C were added Boc_2O (396 μL, 1.69 mmol), TEA (310 μL, 2.24 mmol) and DMAP (34 mg, 0.28 mmol). After 2.5 h, the mixture was diluted with EtOAc (20 mL), washed with saturated aqueous NH_4Cl (20 mL) and brine (20 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (6 g, hexane/EtOAc = 7:3) to give the *N*-Boc imide **S3a** (329 mg, 95%) as a white solid: IR (film) 2892, 2836, 1697, 1513, 1250, 1147, 1032, 848, 700 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 (d, *J* = 12.0 Hz, 1 H), 7.29-7.21 (m, 5 H), 6.96 (d, *J* = 8.0 Hz, 2 H), 6.78 (d, *J* = 8.0 Hz, 1 H), 6.02-5.96 (m, 2 H), 5.41 (s, 1 H), 5.22 (d, *J* = 12.0 Hz, 2 H), 4.84 (d, *J* = 15.0 Hz, 1 H), 4.80 (d, *J* = 14.5 Hz, 1 H), 4.70 (d, *J* = 15.0 Hz, 1 H), 4.39 (d, *J* = 2.5 Hz, 1 H), 4.15 (d, *J* = 2.0 Hz, 1 H), 4.08 (dd, *J* = 13.5, 3.0 Hz, 1 H), 3.97 (d, *J* = 13.5 Hz, 1 H), 3.75 (s, 3 H), 3.74 (d, *J* = 14.5 Hz, 1 H), 3.29 (s, 1 H), 2.02 (s, 3 H), 1.30 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.1, 171.6, 167.3, 159.2, 151.9, 139.1, 137.2, 130.8, 130.0, 128.3, 127.4, 127.1, 122.1, 114.1, 112.5, 85.9, 84.8, 78.1, 73.9, 69.7, 63.9, 58.7, 55.2, 47.8, 45.3, 27.6, 20.6; HRMS (ESI, positive) calcd for $C_{34}H_{39}N_2O_9$ [$(M+H)^+$] 619.2650, found 619.2660.

The Ester Aldehyde 13a. To a stirred solution of the imide **S3a** (290.0 mg, 0.56 mmol) in methanol (15 mL) at -20 °C was added K_2CO_3 (36.6 mg, 0.27 mmol). After 5 h, the mixture was poured into saturated aqueous NH_4Cl (30 mL), and the mixture was extracted with EtOAc (50 mL). The extract was washed with brine (50 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (6 g, hexane/EtOAc = 7:3) to give the ester aldehyde **13a** (178 mg, 84%) as a white solid: IR (film) 2954, 1745, 1696, 1513, 1441, 1248, 1030, 684 cm^{-1}; ^{1}H NMR (500 MHz, C_6D_6) δ 9.67 (s, 1 H), 703 (d, *J* = 8.5 Hz, 2 H), 6.67 (d, *J* = 8.5 Hz, 2 H), 5.53 (dd, *J* = 5.5, 2.0 Hz, 1 H), 5.32 (dd, *J* = 10.0, 3.5 Hz, 1 H), 4.97 (d, *J* = 14.5 Hz, 1 H), 4.39 (d, *J* = 2.0

Hz, 1 H), 4.34 (s, 1 H), 3.94 (s, 1 H), 3.92 (d, *J* = 14.5 Hz, 1 H), 3.60 (dd, *J* = 17.0, 4.0 Hz, 1 H), 3.42 (d, *J* = 17.0 Hz, 1 H), 3.30 (s, 1 H), 3.22 (s, 3 H), 3.09 (s, 3 H), 2.87 (d, *J* = 16.5 Hz, 1 H), 2.45 (d, *J* = 16.5 Hz, 1 H); ^{13}C NMR (125 MHz, C_6D_6) δ 198.4, 170.5, 169.8, 159.8, 130.9, 130.1, 128.3, 122.0, 114.4, 85.1, 78.8, 74.1, 69.4, 63.9, 58.2, 54.7, 51.8, 49.1, 45.5; HRMS (ESI, positive) calcd for $C_{21}H_{23}NO_7Na$ [$(M+Na)^+$] 424.1367, found 424.1366.

The *N*-Boc Imide S3b. With the same procedure for the synthesis of **S3a**, **S3b** (311.7 mg, 95%) was obtained as a white solid starting from **9b** (275.0 g, 0.52 mmol), Boc_2O (363.6 μL, 1.55 mmol), DMAP (19.1 mg, 0.15 mmol), and TEA (214.9 μL, 1.55 mmol).

Data for S3b. IR (film) 2834, 1692, 1513, 1249, 1147, 847, 630 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42 (d, *J* = 12.5 Hz, 1 H), 7.28-7.21 (m, 5 H), 6.96 (d, *J* = 8.5 Hz, 2 H), 6.78 (d, *J* = 8.5 Hz, 2 H), 5.75 (dt, *J* = 12.0, 5.5 Hz, 1 H), 5.66 (dd, *J* = 12.0, 4.0 Hz, 1 H), 5.37 (s, 1 H), 5.22 (d, *J* = 12.5 Hz, 1 H), 4.83 (d, *J* = 12.5 Hz, 1 H), 4.77 (d, *J* = 14.5 Hz, 1 H), 4.69 (d, *J* = 15.0 Hz, 1 H), 4.58 (br s, 1 H), 4.47 (d, *J* = 3.0 Hz, 1 H), 3.91 (m, 1 H), 3.77-3.74 (m, 4 H), 3.58 (m, 1 H), 3.27 (s, 1 H), 2.30 (m, 2 H), 2.04 (s, 3 H), 1.30 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.2, 172.0, 167.3, 159.2, 151.8, 139.2, 137.1, 130.0, 129.1, 128.2, 128.1, 127.4, 127.0, 126.4, 114.1, 111.9, 84.7, 84.5, 83.4, 82.3, 69.5, 69.0, 60.1, 55.2, 47.8, 45.3, 30.4, 27.6, 20.6; HRMS (ESI, positive) calcd for $C_{35}H_{41}N_2O_9$ [$(M+H)^+$] 633.2807, found 633.2803.

The Ester Aldehyde 13b. With the same procedure for the synthesis of **13a**, **13b** (147.1 mg, 83%) was obtained as a white solid starting from **S3b** (270.0 mg, 0.43 mmol) and K_2CO_3 (29.5 mg, 0.21 mmol).

Data for 13b. IR (film) 2953, 1743, 1698, 1514, 1436, 1249, 1177, 1027, 683 cm^{-1}; ^{1}H NMR (500 MHz, C_6D_6) δ 9.86 (s, 1 H), 7.16 (d, *J* = 8.5 Hz, 2 H), 6.80 (d, *J* = 8.5 Hz, 2 H), 5.60 (dd, *J* = 11.8, 3.5 Hz, 1 H), 5.45 (m, 1 H), 5.06 (d, *J* = 15.0 Hz, 1 H), 4.67 (s, 1 H), 4.66 (d, *J* = 14.5 Hz, 1 H), 4.48 (s, 1 H), 4.11 (d, *J* = 14.5 Hz, 1 H), 3.65 (m, 1 H), 3.44 (s, 1 H), 3.36 (s, 3 H), 3.22 (s, 3 H), 3.21 (m, 1 H), 3.08 (d, *J* = 17.3 Hz, 1 H), 2.62 (d, *J* = 17.3 Hz, 1 H), 1.85 (m, 2 H); ^{13}C NMR (125 MHz, C_6D_6) δ 198.6, 171.0, 169.8, 159.8, 130.1, 128.9, 128.5, 126.7, 114.4, 83.8, 83.7, 82.5, 69.2, 68.8, 59.5, 54.7, 51.8, 48.7, 45.6, 30.0; HRMS (ESI, positive) calcd for $C_{22}H_{25}NO_7Na$ [$(M+H)^+$] 438.1523, found 438.1518.

The *N*-Boc Imide S3c. With the same procedure for the synthesis of **S3a**, **S3c** (1.00 g, 90%) was obtained as a pale yellow solid starting from **9c** (1.00 g, 1.42 mmol), Boc_2O (1.66 mL, 7.10 mmol), DMAP (86.7 mg, 0.71 mmol), and TEA (984 μL, 7.10 mmol).

Data for S3c. IR (film) 2930, 1696, 1544, 1370, 1147 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.52 (d, *J* = 8.0 Hz, 1 H), 7.78 (t, *J* = 8.0 Hz, 1 H), 7.71 (t, *J* = 8.0 Hz, 1 H), 7.65 (d, *J* = 8.0 Hz, 1 H), 7.25-7.13 (m, 6 H), 6.94 (d, *J* = 9.0 Hz, 2 H), 6.77 (d, *J* = 9.0 Hz, 2 H), 5.86 (dd, *J* = 10.5 Hz, 1 H), 5.78 (d, *J* = 10.5 Hz, 1 H), 5.30 (d, *J* = 12.5 Hz, 1 H), 5.25 (s, 1 H), 5.02 (dd, *J*

= 7.5, 2.5 Hz, 1 H), 4.82 (d, *J* = 14.5 Hz, 1 H), 4.76 (d, *J* = 7.5 Hz, 1 H), 4.70 (d, *J* = 14.0 Hz, 1 H), 4.48 (d, *J* = 14.5 Hz, 1 H), 4.26 (dd, *J* = 18.0, 5.5 Hz, 1 H), 3.75 (s, 3 H), 3.75 (d, *J* = 14.0 Hz, 1 H), 3.46 (d, *J* = 18,0 Hz, 1 H), 3.12 (s, 1 H), 2.02 (s, 3 H), 1.28 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.9, 171.8, 167.2, 159.2, 151.8, 148.0, 138.2, 137.1, 133.8, 132.7, 132.5, 132.1, 130.1, 128.2, 128.1, 127.9, 127.4, 126.4, 126.1, 123.9, 114.1, 113.0, 84.7, 84.4, 72.3, 68.9, 58.4, 55.8, 55.2, 47.6, 40.2, 27.6, 20.5; HRMS (ESI, positive) calcd for $C_{40}H_{43}N_4O_{12}S$ [$(M+H)^+$] 803.2593, found 803.2591.

The Ester Aldehyde 13c. With the same procedure for the synthesis of **13a**, **13c** (604.4 mg, 81%) was obtained as a pale yellow solid starting from **S3c** (1.03 g, 1.28 mmol) and K_2CO_3 (88.3 mg, 0.64 mmol).

Data for 13c. IR (film) 3002, 1748, 1698, 1541, 1508, 1362, 1248, 1172, 1030, 582 cm^{-1}; ^{1}H NMR (500 MHz, C_6D_6) δ 9.44 (s, 1 H), 8.44 (d, *J* = 8.0 Hz, 1 H), 7.02-6.97 (m, 3 H), 6.72-6.99 (m, 3 H), 6.56 (t, *J* = 7.5 Hz, 1 H), 5.18 (ddd, *J* = 10.8, 2.0, 2.0 Hz, 1 H), 5.10 (ddd, *J* = 10.8, 3.5, 3.5 Hz, 1 H), 4.93 (d, *J* = 14.5 Hz, 1 H), 4.76 (dd, *J* = 6.8, 3.5 Hz, 1 H), 4.28 (s, 1 H), 4.21 (br s, 1 H), 3.92 (d, *J* = 14.5 Hz, 1 H), 3.92 (d, *J* = 18.0 Hz, 1 H), 3.51 (d, *J* = 4.0 Hz, 1 H), 3.48 (d, *J* = 14.5 Hz, 1 H), 3.23 (s, 3 H), 3.11 (s, 3 H), 2.71 (dd, *J* = 17.5, 1.0 Hz, 1 H), 2.31 (dd, *J* = 17.5, 1.0 Hz, 1 H); ^{13}C NMR (125 MHz, C_6D_6) δ 197.7, 171.8, 169.5, 159.9, 148.8, 133.8, 132.5, 131.6, 131.2, 130.1, 127.4, 127.3, 125.5, 123.8, 114.6, 84.6, 73.7, 68.9, 59.5, 54.7, 54.4, 51.8, 48.7, 45.5, 41.5; HRMS (ESI, positive) calcd for $C_{27}H_{29}N_3O_{10}S$ [$(M+H)^+$] 586.1489, found 586.1490.

The *N*-Boc Imide S3e. With the same procedure for the synthesis of **S3a**, **S3e** (351.3 mg, 83%) was obtained as a pale yellow solid starting from **9e** (363.6 mg, 0.58 mmol), Boc_2O (407.9 mg, 1.74 mmol), DMAP (35.4 mg, 0.29 mmol), and TEA (241.1 μL, 1.74 mmol).

Data for S3e. IR (film) 2894, 1702, 1513, 1210, 1146, 848 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$, ca 1:1 mixture of rotamers) δ 7.32 (d, *J* = 13.0 Hz, 0.5 H), 7.29-7.19 (m, 5.5 H), 6.97-6.94 (m, 2 H), 6.79-6.78 (d, *J* = 8.0 Hz, 2 H), 5.94-5.86 (m, 1 H), 5.70-5.62 (m, 1 H), 5.47 (d, *J* = 13.0 Hz, 0.5 H), 5.45 (d, *J* = 13.0 Hz, 0.5 H), 5.36 (s, 0.5 H), 5.35 (s, 0.5 H), 5.35 (s, 0.5 H), 5.18 (d, 0.5 H), 4.90-4.83 (m, 3.5 H), 4.58 (d, *J* = 14.5 Hz, 0.5 H), 4.54 (d, *J* = 14.5 Hz, 0.5 H), 4.40-4.28 (m, 1 H), 3.95-3.87 (m, 1 H), 3.76 (s, 3 H), 3.73-3.62 (m, 2 H), 3.22 (d, *J* = 3.5 Hz, 1 H), 2.67 (m, 0.5 H), 2.47-2.22 (m, 1.5 H), 2.05 (s, 3 H), 1.34-1.28 (m, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$, selected) δ 171.6, 171.1, 167.2, 159.3, 159.3, 156.8, 151.7, 139.1, 137.3, 137.0, 130.3, 128.0 ($\times$ 2), 127.4, 126.4, 121.7, 120.9, 117.4, 114.1, 113.0, 84.7, 83.4, 76.1, 70.1, 64.2, 60.9, 55.1, 47.7, 45.5, 41.6, 32.6, 27.5, 20.5; HRMS (ESI, positive) calcd for $C_{37}H_{41}N_3O_9F_3$ [$(M+H)^+$] 728.2789, found 728.2787.

The Ester Aldehyde 13e. With the same procedure for the synthesis of **13a**, **13e** (219.4 mg,

91%) was obtained as a pale yellow solid starting from **S3e** (345.0 mg, 0.48 mmol) and K_2CO_3 (32.8 mg, 0.24 mmol).

Data for 13e. IR (film) 2933, 1748, 1698, 1541, 1508, 1145, 669 cm^{-1}; ^1H NMR (500 MHz, C_6D_6, ca 1:1 mixture of rotamers) δ 9.58 (br s, 0.5 H), 9.55 (br s, 0.5 H), 6.99 (d, *J* = 8.5 Hz, 1 H), 6.94 (d, *J* = 8.5 Hz, 1 H), 6.66 (d, *J* = 8.5 Hz, 1 H), 6.62 (d, *J* = 8.5 Hz, 1 H), 5.31-5.25 (m, 1 H), 5.16-5.02 (m, 3 H), 4.89 (d, *J* = 5.5 Hz, 0.5 H), 4.21 (s, 0.5 H), 4.08 (s, 0.5 H), 4.06 (dd, *J* = 7.3, 5.0 Hz, 0.5 H), 3.93 (dd, *J* = 7.3, 5.0 Hz, 0.5 H), 3.82-3.74 (m, 1.5 H), 3.41 (t, *J* = 13.5 Hz, 0.5 H), 3.31-3.22 (m, 6 H), 3.15 (s, 1.5 H), 3.10 (t, *J* = 12.0 Hz, 0.5 H), 2.90 (s. 0.5 H), 2.64 (br s, 0.5 H), 2.45-2.38 (m, 1.5 H), 2.35-2.32 (m, 1 H), 1.78 (br t, *J* = 18.0 Hz, 0.5 H), 1.66 (br d, *J* = 20.0 Hz, 0.5 H), 1.50 (br d, *J* = 20.0 Hz, 0.5 H), 0.91 (m, 0.5 H); ^{13}C NMR (125 MHz, C_6D_6) δ 197.6, 197.4, 170.4, 170.3, 169.8 ($\times$ 2), 172.1, 167.5, 161.1, 160.1, 128.8 ($\times$ 2), 137.8, 137.1, 130.6, 130.5, 127.7, 127.5, 122.0, 120.7, 114.8 ($\times$ 2), 82.9, 82.8, 77.0, 76.8, 69.5, 68.5, 65.9, 65.8, 65.0, 60.8, 60.0, 54.9, 52.1, 49.5, 45.7, 45.6, 43.4, 42.1, 32.8, 32.1, 29.9, 27.3; HRMS (ESI, positive) calcd for $C_{24}H_{25}F_3N_2O_7Na$ [$(M+Na)^+$] 533.1506, found 533.1493.

The Diester S4a. To a stirred solution of the aldehyde **13a** (222.7 mg, 0.55 mmol) in *tert*-butanol (15.0 mL) and water (5.0 mL) at rt were added 2-methyl-2-butene (290.8 μL, 2.75 mmol), $NaH_2PO_4 \cdot 2H_2O$ (94.2 mg, 0.60 mmol), and $NaClO_2$ (148.3 mg, 1.65 mmol). After 5 h, the mixture was diluted with DCM (50 mL), and the mixture was washed with hydrochloric acid (1 M, 20 mL) and brine (20 mL). The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was dissolved in methanol (15.0 mL) and cooled to 0 °C. $TMSCHN_2$ (2 M in Et_2O, 0.84 mL, 1.68 mmol) was added, and the mixture was allowed to warm to rt. After stirring for 30 min, the mixture was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (6 g, hexane/EtOAc = 4:6) to give the diester **S4a** (235.4 mg, 94 %) as a white solid: IR (film) 2953, 1744, 1698, 1513, 1437, 1248, 1178, 1049, 822, 684 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.10 (d, *J* = 8.5 Hz, 2 H), 6.82 (d, *J* = 8.5 Hz, 2 H), 6.02 (dd, *J* = 10.5, 3.5 Hz, 1 H), 5.93 (m, 1 H), 4.81 (d, *J* = 14.5 Hz, 1 H), 4.39 (d, *J* = 3.0 Hz, 1 H), 4.34 (s, 1 H), 4.15 (dd, *J* = 17.3, 3.5 Hz, 1 H), 4.03 (d, *J* = 17.3 Hz, 1 H), 4.01 (s, 1 H), 4.00 (d, *J* = 14.5 Hz, 1 H), 3.77 (s, 3 H), 3.61 (s, 3 H), 3.58 (s, 3 H), 3.37 (s, 1 H), 3.11 (d, *J* = 16.5 Hz, 1 H), 2.75 (d, *J* = 16.5 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.8, 170.3, 170.1, 159.2, 130.6, 129.7, 127.1, 122.5, 114.1, 85.1, 78.3, 73.6, 68.2, 64.1, 57.7, 55.2, 52.4, 51.7, 45.4, 40.1; HRMS (ESI, positive) calcd for $C_{22}H_{25}NO_8Na$ [$(M+Na)^+$] 454.1472, found 454.1477.

The Lactam 14a. To a stirred solution of the *N*-PMB amide **S4a** (187.3 mg, 0.43 mmol) in CH_3CN (10.0 mL) and water (2.4 mL) at -10 °C was added a solution of CAN (1.19 mg, 2.17

mmol) in water (6.6 mL) portionwise. After 5 h, the mixture was poured into saturated aqueous $Na_2S_2O_3$ (20 mL) and extracted with EtOAc (3 × 50 mL). The combined extracts were washed with saturated aqueous $NaHCO_3$ (20 mL) and brine (20 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (5 g, hexane/EtOAc = 4:6) to give the lactam **14a** (95.2 mg, 71%) as a white solid: IR (film) 2953, 1747, 1698, 1508, 1436, 1250, 1211, 1087, 848, 688 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.16 (s, 1 H), 6.05 (dd, *J* = 10.0, 4.0 Hz, 1 H), 5.98 (ddd, *J* = 10.0, 4.0, 2.0 Hz, 1 H), 4.44 (s, 1 H), 4.29 (d, *J* = 2.0 Hz, 1 H), 4.15 (s, 1 H), 4.13 (dd, *J* = 16.5, 4.0 Hz, 1 H), 4.00 (d, *J* = 16.5 Hz, 1 H), 3.67 (s, 3 H), 3.60 (s, 3 H), 3.28 (s, 1 H), 3.14 (d, *J* = 17.5 Hz, 1 H), 2.85 (d, *J* = 17.5 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.1, 170.4, 130.9, 122.0, 87.3, 78.1, 73.2, 64.7, 64.1, 56.7, 52.5, 51.6, 40.3; HRMS (ESI, positive) calcd for $C_{14}H_{17}NO_7Na$ [$(M+Na)^+$] 334.0897, found 334.0899.

The Diester S4b. With the same procedure for the synthesis of **S4a**, **S4b** (139.3 mg, 73%) was obtained as a colorless oil starting from **13b** (147.1 mg, 0.35 mmol), 2-methyl-2-butene (226.2 μL, 2.14 mmol), $NaH_2PO_4 \cdot 2H_2O$ (73.3 mg, 0.47 mmol), $NaClO_2$ (115.3 mg, 1.28 mmol), and $TMSCHN_2$ (2 M in Et_2O, 0.35 mL, 0.70 mmol).

Data for S4b. IR (film) 2953, 1744, 1698, 1513, 1437, 1248, 1047, 820 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.08 (d, *J* = 8.5 Hz, 2 H), 6.81 (d, *J* = 8.5 Hz, 2 H), 5.73 (dt, *J* = 11.5, 5.5 Hz, 1 H), 5.58 (dd, *J* = 11.5, 3.5 Hz, 1 H), 4.77 (d, *J* = 14.5 Hz, 1 H), 4.49-4.47 (m, 2 H), 4.30 (s, 1 H), 4.02 (d, *J* = 14.5 Hz, 1 H), 3.93 (m, 1 H), 3.77 (s, 3 H), 3.66 (m, 1 H), 3.62 (s, 3 H), 3.56 (s, 3 H), 3.34 (s, 1 H), 3.11 (d, *J* = 17.0 Hz, 1 H), 2.72 (d, *J* = 17.0 Hz, 1 H), 2.38-2.26 (m, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.4, 170.3, 170.0, 159.2, 129.7, 128.3, 127.2, 127.1, 114.1, 83.7, 83.3, 81.8, 68.7, 68.0, 58.9, 55.2, 52.3, 51.6, 45.3, 39.4, 29.9; HRMS (ESI, positive) calcd for $C_{23}H_{27}NO_8Na$ [$(M+Na)^+$] 468.1629, found 468.1634.

The Lactam 14b. With the same procedure for the synthesis of **14a**, **14b** (67.4 mg, 71%) was obtained as a white solid starting from **S4b** (130 mg, 0.29 mmol) and CAN (801 mg, 1.46 mmol).

Data for 14b. IR (film) 2953, 1743, 1715, 1436, 1362, 1211, 1046, 669 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.92 (br s, 1 H), 5.81 (ddd, *J* = 11.5, 5.0, 5.0 Hz, 1 H), 5.64 (dd, *J* = 11.5, 2.5 Hz, 1 H), 4.54 (br s, 1 H), 4.40 (s, 1 H), 4.37 (br s, 1 H), 3.96 (ddd, *J* = 11.5, 5.5, 4.5 Hz, 1 H), 3.69 (s, 3 H), 3.64 (s, 3 H), 3.62 (ddd, *J* = 11.5, 5.5, 4.5 Hz, 1 H), 3.29 (s, 1 H), 3.22 (d, *J* = 17.5 Hz, 1 H), 2.92 (d, *J* = 17.5 Hz, 1 H), 2.35 (dd, *J* = 5.5, 5.0 Hz, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.6, 170.4, 170.3, 129.7, 126.1, 85.8, 82.5, 82.0, 68.9, 64.6, 58.0, 52.5, 51.6, 39.6, 30.3; HRMS (ESI, positive) calcd for $C_{15}H_{19}NO_7Na$ [$(M+Na)^+$] 348.1054, found 348.1060.

The Diester S4c. With the same procedure for the synthesis of **S4a**, **S4c** (589.6 mg, 93%) was obtained as a white solid starting from **13c** (604.4 g, 1.03 mmol), 2-methyl-2-butene (547.0 μL, 5.16 mmol), $NaH_2PO_4 \cdot 2H_2O$ (177.0 mg, 1.13 mmol), $NaClO_2$ (278 mg, 3.09 mmol), and $TMSCHN_2$ (2 M in Et_2O, 1.03 mL, 2.06mmol).

Data for S4c. IR (film) 2953, 1745, 1699, 1544, 1513, 1248, 1172, 1031, 682 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.36 (dd, *J* = 7.5, 1.0 Hz, 1 H), 7.82-7.68 (m, 3 H), 7.12 (d, *J* = 8.5 Hz, 2 H), 6.88 (d, *J* = 8.5 Hz, 2 H), 6.00 (dt, *J* = 11.0, 4.0 Hz, 1 H), 5.80 (dd, *J* = 11.0, 3.0 Hz, 1 H), 4.94 (d, *J* = 14.5 Hz, 1 H), 4.70 (t, *J* = 7.5 Hz, 1 H), 4.63 (br s, 1 H), 4.19 (s, 1 H), 4.10 (dt, *J* = 16.0, 2.0 Hz, 1 H), 3.94 (d, *J* = 14.5 Hz, 1 H), 3.91 (d, *J* = 16.0 Hz, 1 H), 3.82 (s, 3 H), 3.70 (d, *J* = 5.0 Hz, 1 H), 3.67 (s, 3 H), 3.64 (s, 3 H), 2.97 (d, *J* = 16.5 Hz, 1 H), 2.82 (d, *J* = 16.5 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.5, 169.3 (× 2), 159.3, 148.2, 134.1, 132.2, 132.0, 131.4, 129.8, 129.7, 126.8, 125.9, 124.2, 11.3, 84.7, 73.1, 63.4, 58.7, 55.2, 52.8, 52.5, 51.9, 45.2, 40.9, 39.7; HRMS (ESI, positive) calcd for $C_{28}H_{29}N_3O_{11}SNa$ [$(M+Na)^+$] 638.1415, found 638.1392.

The Lactam 14c. With the same procedure for the synthesis of **14a**, **14c** (178.4 mg, 78%) was obtained as a white solid starting from **S4c** (278.4 mg, 0.45 mmol) and CAN (1.24 g, 2.26 mmol).

Data for 14c. IR (film) 2922, 1715, 1541, 1362, 1253, 1166, 683, 584 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.19 (dd, *J* = 5.5, 4.5 Hz, 1 H), 7.72-7.64 (m, 3 H), 6.02 (br s, 1 H), 5.91 (dd, *J* = 10.0, 1.0 Hz, 1 H), 5.74 (d, *J* = 10.0 Hz, 1 H), 4.91 (t, *J* = 7.5 Hz, 1 H), 4.80 (br s, 1 H), 4.41 (s, 1 H), 4.13 (d, *J* = 19.0 Hz, 1 H), 3.87 (d, *J* = 19.0 Hz, 1 H), 3.75 (s, 3 H), 3.59 (s, 3 H), 3.37 (d, *J* = 7.5 Hz, 1 H), 3.05 (d, *J* = 16.5 Hz, 1 H), 2.81 (d, *J* = 16.5 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.2, 169.3, 169.2, 148.0, 134.0, 132.4, 132.1, 131.9, 126.4, 124.5, 87.5, 73.7, 65.6, 58.0, 52.8, 52.0, 50.8, 40.8, 40.1; HRMS (ESI, positive) calcd for $C_{20}H_{22}N_3O_{10}S$ [$(M+H)^+$] 496.1020, found 496.1020.

The Diester S4e. With the same procedure for the synthesis of **S4a**, **S4e** (183.7 mg, 85%) was obtained as a pale yellow oil starting from **13e** (210.4 mg, 0.41 mmol), 2-methyl-2-butene (218.0 μL, 2.06 mmol), NaH_2PO_4-$2H_2O$ (70.7 mg, 0.46 mmol), $NaClO_2$ (111.3 mg, 1.24 mmol), and $TMSCHN_2$ (2 M in Et_2O, 0.41 mL, 0.81 mmol).

Data for S4e. IR (film) 2954, 1745, 1702, 1513, 1438, 1205, 1167, 1035 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, ca 6:4 mixture of rotamers) δ 7.12-7.01 (m, 2 H), 6.85-6.82 (m, 2 H), 5.98-5.90 (m, 1 H), 5.60-5.54 (m, 1 H), 5.07 (d, *J* = 14.5, 0.4 H), 5.00 (d, *J* = 14.5 Hz, 0.6 H), 4.99 (d, *J* = 5.5 Hz, 0.6 H), 4.72 (d, *J* = 5.5 Hz, 0.4 H), 4.15 (s, 0.6 H), 4.11-4.03 (m, 1.4 H), 3.90-3.85 (m, 2 H), 3.79-3.78 (m, 3 H), 3.70 (s, 1.2 H), 3.66-3.64 (m, 4.8 H), 3.56-3.51 (m, 0.6 H), 3.43 (s, 0.4 H), 3.37 (s, 0.6 H), 2.98-2.94 (m, 1.4 H), 2.82-2.69 (m, 1 H), 2.50-2.31 (m, 2 H); ^{13}C

NMR (125 MHz, $CDCl_3$) δ 170.3 (× 2), 169.4, 169.1, 168.9, 168.7, 159.4, 159.3, 157.1, 156.5, 137.6, 137.0, 130.0, 129.9, 126.9, 126.8, 121.6, 120.5, 117.3, 115.0, 114.2, 114.1, 82.8, 82.6, 75.9, 75.7, 68.4, 67.4, 65.3, 64.6, 59.3, 58.6, 55.2 (× 2), 52.5, 52.4, 52.1, 52.0, 45.1 (× 2), 43.0, 41.6, 39.9, 39.7, 32.7, 29.6; HRMS (ESI, positive) calcd for $C_{25}H_{27}N_2O_8F_3Na$ [$(M+Na)^+$] 563.1612, found 563.1609.

The Lactam 14e. With the same procedure for the synthesis of **14a**, **14e** (109.4 mg, 80%) was obtained as a pale yellow solid starting from **S4e** (175.5 mg, 0.33 mmol) and CAN (891 mg, 1.63 mmol).

Data for 14e. IR (film) 2930, 1716, 1436, 1209, 1146, 1046, 730 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, ca 1:1 mixture of rotamers) δ 6.15 (br s, 0.5 H), 6.09 (br s, 0.5 H), 6.03-5.97 (m, 1 H), 5.78-5.72 (m, 1 H), 5.04 (d, *J* = 6.0 Hz, 0.5 H), 4.75 (d, *J* = 6.0 Hz, 0.5 H), 4.49-4.45 (m, 2 H), 4.29 (s, 0.5 H), 4.24 (s, 0.5 H), 4.06 (dd, *J* = 13.5, 4.5 Hz, 0.5 H), 3.85 (d, J = 8.0 Hz, 1 H), 3.77 (s, 1.5 H), 3.76 (s, 1.5 H), 3.64 (s, 1.5 H), 3.63 (s, 1.5 H), 3.45 (ddd, *J* = 12.5, 10.5, 3.5 Hz, 0.5 H), 3.40 (d, *J* = 17.0 Hz, 0.5 H), 3.25-3.24 (m, 1 H), 3.24 (d, *J* = 17.0 Hz, 0.5 H), 2.96 (d, *J* = 17.0 Hz, 0.5 H), 2.94 (d, *J* = 17.0 Hz, 0.5 H), 2.82 (m, 0.5 H), 2.57-2.36 (m, 1.5 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.4, 172.9, 169.6, 169.3 (× 2), 169.1, 157.1, 156.8, 156.4, 156.1, 137.7, 136.5, 121.7, 120.3, 117.4, 117.2, 115.1, 114.9, 85.5, 85.3, 75.6, 75.3, 65.2 (× 2), 64.8, 64.3, 63.6, 59.2, 59.1, 52.7, 52.6, 52.1, 520, 42.6 (× 2), 41.2, 39.9, 39.8, 32.3, 29.1; HRMS (ESI, positive) calcd for $C_{17}H_{19}N_2O_7Na$ [$(M+Na)^+$] 443.1037, found 443.1038.

The Pyrrolidine 15a. To a stirred solution of the pyrrolidinone **14a** (65.8 mg, 0.212 mmol) in DCM (2.0 mL) at 0 °C were added $MeO_3 \cdot BF_4$ (94.1 mg, 0.636 mmol) and K_2CO_3 (117.2 mg, 0.848 mmol). After stirring at rt for 4 h, the mixture was diluted with DCM (20 mL), washed with water (10 mL) and brine (10 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The crude imidate thus obtained was used in the next reaction without purification.

To a stirred solution of the above imidate in methanol (2.0 mL) at 0 °C were added $NaCNBH_3$ (40 mg, 0.636 mmol) and TFA (31.5 μL, 0.424 mmol). After stirring at rt for 4 h, the mixture was diluted with DCM (20 mL), washed with saturated aqueous $NaHCO_3$ (20 mL), dried over Na_2SO_4, and concentrated under reduced pressure to a final volume of ca 2 mL. Boc_2O (149 μL, 0.636 mmol) and TEA (88 μL, 0.636 mmol) were added, and the mixture was stirred at rt for 2 h. The mixture was then concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (3 g, hexane/EtOAc = 8:2) to give the pyrrolidine **15a** (49.4 mg, 59 %, 3 steps) as a white solid: IR (film) 1742, 1701, 1395, 1366, 1174, 1013, 689 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, ca 7:3 mixture of rotamers) δ 6.01 (br s, 2 H), 4.74 (s, 1 H), 4.29 (br s, 0.7 H), 4.26 (br s, 0.3 H), 4.15 (d, *J* = 16.5 Hz, 1 H), 3.98 (d, *J* = 16.5 Hz, 1 H), 3.94-3.90 (m, 2 H), 3.66 (s, 2.1 H), 3.65 (s, 0.9 H), 3.37 (dd, *J* = 10.0,

4.5 Hz, 0.7 H), 3.32 (m, 0.3 H), 3.17 (d, *J* = 17.0 Hz, 0.7 H), 3.14 (d, *J* = 17.0 Hz, 0.3 H), 3.07 (br d, *J* = 6.0 Hz, 0.3 H), 3.00 (dd, *J* = 10.0, 4.5 Hz, 0.7 H), 2.68 (d, *J* = 17.0 Hz, 0.3 H), 2.62 (d, *J* = 17.0 Hz, 0.7 H); ^{13}C NMR (125 MHz, $CDCl_3$, selected) δ 171.0, 170.3, 154.0, 130.5, 122.7, 92.0, 81.1, 80.4, 73.0, 69.0, 64.0, 52.0, 51.6, 51.5, 48.7, 40.4, 28.2; HRMS (ESI, positive) calcd for $C_{19}H_{27}N_1O_8Na$ [$(M+Na)^+$] 420.1629, found 420.1622.

The Pyrrolidine 15b. With the same procedure for the synthesis of **15a**, **15b** (10.4 mg, 71%) was obtained as a white solid starting from **14b** (9.7 mg, 0.030 mmol), $MeO_3{\cdot}BF_4$ (13.2 mg, 0.090 mmol), and $NaCNBH_3$ (5.62 mg, 0.089 mmol).

Data for 15b. IR (film) 1745, 1701, 1396, 1171, 669 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$, ca 7:3 mixture of rotamers) δ 5.76 (dt, *J* = 12.0, 4.5 Hz, 1 H), 5.67 (dd, *J* = 12.0, 4.5 Hz, 1 H), 4.68-4.64 (br s, 2 H), 3.95-3.88 (m, 3 H), 3.71-3.61 (m, 6 H), 3.52-3.48 (m, 1 H), 3.32 (dd, *J* = 11.5 Hz, 0.7 H), 3.26 (m, 1 H), 3.16 (d, *J* = 17.0 Hz, 0.7 H), 3.12 (d, *J* = 17.0 Hz, 0.3 H), 3.05 (dd, *J* = 10.0, 5.0 Hz, 0.3 H), 2.97 (dd, *J* = 10.0, 5.0 Hz, 0.7 H), 2.67 (d, *J* = 17.0 Hz, 0.3 H), 2.60 (d, *J* = 17.0 Hz, 0.7 H), 2.36-2.26 (m, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$, selected) δ 171.0, 170.3, 154.0, 129.5, 126.8, 90.5, 85.5, 82.1, 80.4, 68.9, 68.8, 52.9, 52.0, 51.5, 49.5, 39.7, 30.6, 28.2; HRMS (ESI, positive) calcd for $C_{20}H_{29}NO_8Na$ [$(M+Na)^+$] 434.1785, found 434.1788.

The Pyrrolidine 15c. With the same procedure for the synthesis of **15a**, **15c** (162.1 mg, 86%) was obtained as a pale yellow solid starting from **14c** (160.1 mg, 0.323 mmol), $MeO_3{\cdot}BF_4$ (143.3 mg, 0.969 mmol), and $NaCNBH_3$ (101.5 mg, 1.615 mmol).

Data for 15c. IR (film) 2977, 1747, 1698, 1542, 1364, 1168, 682 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$, ca 1:1 mixture of rotamers) δ 8.08 (d, *J* = 8.0 Hz, 0.5 H), 8.02 (d, *J* = 8.0 Hz, 0.5 H), 7.74-7.67 (m, 3 H), 5.81 (dd, *J* = 10.8, 3.5 Hz, 0.5 H), 5.75 (dd, *J* = 10.8, 3.5, Hz, 0.5 H), 5.65-5.62 (m, 1 H), 4.63 (d, *J* = 7.0 Hz, 0.5 H), 4.56 (d, *J* = 7.0 Hz, 0.5 H), 4.52 (s, 0.5 H), 4.51-4.45 (m, 1 H), 4.37 (s, 1 H), 4.15 (br d, *J* = 18.0 Hz, 0.5 H), 4.01 (d, *J* = 11.5 Hz, 0.5 H), 3.96 (br d, *J* = 18.0 Hz, 0.5 H), 3.81-3.77 (m, 1 H), 3.69 (s, 1.5 H), 3.67 (s, 1.5 H), 3.62 (dd, *J* = 11.8, 5.5 Hz, 0.5 H), 3.59 (s, 3 H), 3.58 (d, *J* = 11.5 Hz, 0.5 H), 3.51 (dd, *J* = 11.8, 5.5 Hz, 0.5 H), 3.06 (m, 1 H), 2.83 (d, *J* = 15.5 Hz, 0.5 H), 2.77 (d, *J* = 15.5 Hz, 0.5 H), 2.72 (d, *J* = 15.5 Hz, 0.5 H), 2.67 (d, *J* = 15.5 Hz, 0.5 H), 1.46 (s, 4.5 H), 1.39 (s, 4.5 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.3, 170.0, 169.8, 169.7, 154.6, 153.7, 147.8, 147.6, 134.1, 134.0, 132.8, 132.6, 132.4, 132.0, 131.3, 131.0, 126.9, 126.7, 125.1, 124.7 (x2), 124.2, 91.3, 90.7, 80.8, 80.6, 71.9, 71.6, 70.4, 69.8, 59.1, 58.8, 52.2, 52.1, 51.8, 48.5, 48.2, 46.7, 45.4, 40.5, 39.7, 39.5, 28.2 ($\times$ 2); HRMS (ESI, positive) calcd for $C_{25}H_{31}N_3O_{11}Na$ [$(M+H)^+$] 604.1571, found 604.1566.

The Pyrrolidine 15e. With the same procedure for the synthesis of **15a**, **15c** (110.1 mg,

84%) was obtained as a pale yellow solid starting from **14c** (109.0 mg, 0.259 mmol), $MeO_3{\cdot}BF_4$ (114.9 mg, 0.777 mmol), and $NaCNBH_3$ (48.8 mg, 0.777 mmol).

Data for 15e. IR (film) 1746, 1688, 1394, 1211, 1143, 731 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, ca 6:4 mixture of rotamers) δ 5.98-5.89 (m, 1 H), 5.75-5.68 (m, 1 H), 4.70 (s, 0.6 H), 4.54-4.50 (m, 1.4 H), 4.44-4.37 (m, 1 H), 4.01-3.98 (m, 1 H), 3.92-3.78 (m, 3 H), 3.92-3.78 (m, 3 H), 3.71 (s, 3 H), 3.65 (s, 3 H), 3.45 (m, 0.6 H), 3.14 (m, 0.4 H), 3.00-2.97 (m, 1 H), 2.90-2.81 (m, 1.6 H), 2.73 (t, *J* = 16.0 Hz, 0.4 H), 2.49 (br s, 0.6 H), 2.42-2.30 (m, 1.4 H), 1.45 (br s, 3.6 H), 1.39 (s. 5.4 H); ^{13}C NMR (125 MHz, $CDCl_3$, selected) δ 170.5, 169.6, 157.3, 153.3, 136.6, 121.7, 117.5, 90.8, 81.0, 75.9, 68.6 ($\times$ 2), 54.7, 51.9, 51.0, 42.2, 39.0, 32.7, 29.6, 28.1; HRMS (ESI, positive) calcd for $C_{22}H_{29}N_2O_8Na$ [$(M+Na)^+$] 529.1768, found 529.1753.

The Pyrrolidine 15f. To a stirred solution of **15c** (141.2 mg, 0.243 mmol) in CH_3CN (3 mL) at 0 °C were added thiophenol (49.8 μL, 0.485 mmol) and Cs_2CO_3 (119.0 mg, 0.365 mmol). After stirring at rt for 1.5 h, the mixture was diluted with chloroform (50 mL), washed with saturated aqueous $NaHCO_3$ (25 mL), dried over Na_2SO_4, and concentrated under reduced pressure to a final volume of ca 3 mL. Boc_2O (170.9 μL, 0.729 mmol) and pyridine (59 μL, 79.1 mmol) were added, and the mixture was stirred at rt for 2 h. The mixture was then diluted with DCM (50 mL), washed with saturated aqueous NH_4Cl (30 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (2 g, hexane/EtOAc = 8:2) to give the *N*-Boc pyrrolidine **15f** (103.3 mg, 86%) as a colorless solid: IR (film) 2976, 1746, 1702, 1395, 1367, 1171, 681 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, ca 1:1 mixture of rotamers) δ 5.78 (d, *J* = 9.0 Hz, 1 H), 5.62 (dd, *J* = 9.0, 2.0 Hz, 1 H), 4.87 (br s, 1 H), 4.58 (br s, 1 H), 4.48 (s, 0.4 H), 4.40 (s, 0.6 H), 4.20 (br d, *J* = 19.0 Hz, 1 H), 3.93 (d, *J* = 11.0 Hz, 0.6 H), 3.84-3.82 (m, 0.4 H), 3.69 (s, 3 H), 3.67-3.58 (m, 1 H), 3.60 (s, 3 H), 3.55 (br d, *J* = 19.0 Hz, 1 H), 2.96-2.91 (m, 1 H), 2.83-2.65 (m, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$, selected) δ 170.6, 169.7, 154.3, 153.6, 125.6, 125.3, 91.2, 80.4, 72.5, 70.5, 56.8, 52.1, 52.0, 51.8, 49.3, 47.6, 46.3, 40.5, 28.2, 28.1; HRMS (ESI, positive) calcd for $C_{24}H_{36}N_2O_9Na$ [$(M+Na)^+$] 519.2313, found 519.2294.

The Tetrahydropyran S5a. To a stirred solution of **15a** (5.4 mg, 0.0136 mmol) in methanol (1.0 mL) at rt was added palladium (10 wt% on carbon, 0.55 mg). The mixture was stirred vigorously under hydrogen atmosphere (1atm) for 1 h. The catalyst was then removed by filtration and the filtrate was then concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (0.5 g, hexane/EtOAc = 8:2) to give **S5a** (5.4 mg, 100%) as a white solid: IR (film) 1742, 1701, 1391, 1250, 1169, 1105, 1041, 897 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, mixture of rotamers) δ 4.72 (br s, 1 H), 4.05 (br s, 1 H),

3.84 (m, 2 H), 3.78 (br s, 1 H), 3.67 (m, 6 H), 3.34-3.14 (m, 3 H), 2.92-2.82 (m, 1 H), 2.76-2.66 (m, 1 H), 2.10 (m, 1 H), 1.80 (m, 1 H), 1.64 (m, 1 H), 1.42-1.38 (m, 9 H), 1.32 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$, selected) δ 171.1, 170.5, 154.1, 91.7, 81.8, 80.5, 75.8, 69.5, 6.4, 52.0, 51.6, 48.6, 40.3, 28.3, 28.2, 24.9, 19.8; HRMS (ESI, positive) calcd for $C_{19}H_{29}NO_8Na$ [$(M+Na)^+$] 422.1785, found 422.1791.

The Oxepane S5b. With the same procedure for the synthesis of **S5a**, **S5b** (2.4 mg, 96%) was obtained as a white solid starting from **15b** (2.5 mg, 0.028 mmol) and palladium (10 wt% on carbon, 0.3 mg).

Data for S5b. IR (film) 1701, 1384, 1070 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$, mixture of rotamers) δ 4.67 (br s, 1 H), 3.30 (m, 1 H), 4.10 (m, 1 H), 3.91-3.86 (m, 2 H), 3.67 (m, 6 H), 3.31-3.19 (m, 2 H), 3.14-3.04 (m, 1 H), 2.99-2.89 (m, 1 H), 2.61-2.53 (m, 1 H), 2.09 (m, 1 H), 1.77-1.65 (m, 4 H), 1.42-1.37 (m, 9 H), 1.27-1.20 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$, selected) δ 171.3, 170.3, 154.0, 91.2, 90.0, 83.9, 80.4, 74.0, 68.7, 52.9, 52.0, 51.6, 49.4, 39.6, 32.1, 31.8, 28.2, 21.4; HRMS (ESI, positive) calcd for $C_{20}H_{31}NO_8Na$ [$(M+Na)^+$] 436.1941, found 436.1946.

The Piperidine S5f. With the same procedure for the synthesis of **S5a**, **S5f** (32.8 mg, 100%) was obtained as a white solid starting from **15f** (32.8 mg, 0.066 mmol) and palladium (10 wt% on carbon, 3.3 mg).

Data for S5f. IR (film) 1747, 1696, 1393, 1367, 1254, 1165, 1063, 770 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$, mixture of rotamers) δ 4.49-4.45 (m, 1 H), 4.28-4.21 (m, 2 H), 3.83-3.75 (m, 1 H), 3.73-3.69 (m, 4 H), 3.67-3.62 (m, 3 H), 3.55-3.50 (m, 1 H), 3.29-3.11 (m, 2 H), 2.76-2.64 (m, 2 H), 1.68-1.37 (m, 22 H); ^{13}C NMR (125 MHz, $CDCl_3$, selected) δ 171.2, 170.2, 156.0, 153.9, 90.9, 80.8, 74.9, 70.3, 61.0, 60.3, 52.2, 52.1, 50.3, 49.3, 41.0, 39.8, 28.6, 28.4, 26.1, 19.4; HRMS (ESI, positive) calcd for $C_{24}H_{38}N_2O_9Na$ [$(M+Na)^+$] 521.2469, found 521.2466.

The Azepane S5e. With the same procedure for the synthesis of **S5a**, **S5e** (34.8 mg, 100%) was obtained as a white solid starting from **15e** (34.7 mg, 0.069 mmol) and palladium (10 wt% on carbon, 3.5 mg).

Data for S5e. IR (film) 1747, 1692, 1393, 1209, 1016, 733 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$, ca 6:4 mixture of rotamers) δ 5.05 (m, 0.4 H), 4.45-4.40 (m, 1.6 H), 4.33-4.32 (m, 1 H), 4.07 (br d, 0.6 H), 3.98 (m, 0.4 H), 3.89 (m, 0.6 H), 3.81-3.74 (m, 3.4 H), 3.67-3.62 (m, 4 H), 3.19-3.01 (m, 1.4 H), 2.88-2.73 (m, 2.6 H), 2.22 (m, 1 H), 1.85-1.38 (m, 14 H); ^{13}C NMR (125 MHz, $CDCl_3$, selected) δ 170.4, 170.0, 153.9, 153.4, 117.7, 90.5, 81.1, 78.3, 67.7, 66.5, 53.3, 52.1, 52.0, 44.7, 37.6, 30.8, 28.2, 28.1, 27.4, 20.9; HRMS (ESI, positive) calcd for $C_{22}H_{31}N_2O_8F_3Na$ [$(M+Na)^+$] 531.1925, found 531.1936.

The Diol S6a. To a stirred solution of **15a** (5.40 mg, 0.0136 mmol) in *tert*-butanol (0.2 mL) at rt was added a solution of NMO (100 mg, 0.85 mmol) in water (0.2 mL) and OsO_4 (3.9 mM in *tert*-butanol, 33 μL, 0.0014 mmol). After 3 h, saturated aqueous $Na_2S_2O_4$ (2 mL) was added, and the mixture was extracted with chloroform (3 × 5 mL). The combined extracts were washed with brine (2 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (0.5 g, methanol/chloroform = 2:98) to give the diol **S6a** (5.9 mg, 100%) as a white solid: IR (film) 3400, 1743, 1693, 1401, 1250, 1167, 1090 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, mixture of rotamers) δ 4.71 (m, 1 H), 4.16-4.10 (m, 2 H), 4.01 (br s, 1 H), 3.92 (br s, 1 H), 3.81 (m, 1 H), 3.70-3.56 (m, 6 H), 3.44 (m, 1 H), 3.34-3.27 (m, 1 H), 3.08 (m, 1 H), 2.97-2.80 (m, 2 H), 2.64 (m, 1 H), 1.42-1.38 (m, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$, selected) δ 170.8, 170.3, 154.1, 91.9, 81.6, 80.8, 79.2, 69.3, 66.3, 64.4, 64.0, 52.1, 51.7, 50.9, 48.6, 40.2, 28.2; HRMS (ESI, positive) calcd for $C_{19}H_{29}NO_{10}Na$ [$(M+Na)^+$] 454.1684, found 454.1678.

The Diol S6b. With the same procedure for the synthesis of **S6a**, **S6b** (2.9 mg, 100%) was obtained as a white solid starting from **15b** (2.7 mg, 6.57 μmol).

Data for S6b. IR (film) 3406, 1742, 1694, 1394, 1171, 1101, 1074, 904, 756 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, mixture of rotamers) δ 4.62 (br s, 1 H), 4.38 (m, 1 H), 4.19 (br s, 1 H), 4.13-4.09 (m, 1 H), 3.91-3.84 (m, 2 H), 3.68-3.64 (m, 6 H), 3.32-3.24 (m, 1 H), 3.08-3.03 (m, 1 H), 2.98-2.90 (m, 2 H), 2.60-2.51 (m, 2 H), 1.92-1.86 (m, 1 H), 1.80-1.76 (m, 1 H), 1.42-1.38 (m, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$, selected) δ 171.1, 170.2, 153.8, 91.2, 85.5, 86.0, 80.6, 77.2, 71.8, 68.6, 67.7, 52.9, 52.1, 51.8, 49.1, 39.3, 34.7, 28.2; HRMS (ESI, positive) calcd for $C_{20}H_{31}NO_{10}Na$ [$(M+Na)^+$] 468.1840, found 468.1840.

The Diol S6f. With the same procedure for the synthesis of **S6a**, **S6f** (34.5 mg, 100%) was obtained as a white solid starting from **15f** (32.0 mg, 0.065 mmol).

Data for S6f. IR (film) 3412, 1744, 1698, 1396, 1367, 1170, 1133, 1057, 755 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, ca 7:3 mixture of rotamers) δ 4.70-4.62 (m, 1 H), 4.48 (br s, 0.3 H), 4.39 (br s, 0.7 H), 4.24 (m, 1 H), 3.96 (br s, 1 H), 3.89-3.81 (m, 1 H), 3.73 (br s, 3 H), 3.67-3.56 (m, 4 H), 3.23 (m, 1 H), 3.07-2.99 (m, 1 H), 2.68-2.65 (m, 2 H), 2.55-2.50 (m, 1 H), 2.26 (br s, 1 H), 1.47-1.44 (m, 18 H); ^{13}C NMR (125 MHz, $CDCl_3$, selected) δ 170.8, 170.2, 155.7, 153.5, 90.6, 80.7, 79.0, 70.5, 66.4, 57.7, 52.3, 52.1, 48.8, 47.6, 46.8, 43.2, 38.8, 28.2, 28.1; HRMS (ESI, positive) calcd for $C_{24}H_{38}N_2O_{11}Na$ [$(M+Na)^+$] 553.2368, found 553.2366.

The Diol S6e. With the same procedure for the synthesis of **S6a**, **S6e** (35.1 mg, 100%) was obtained as a white solid starting from **15f** (33.1 mg, 0.065 mmol).

Data for S6e. IR (film) 3413, 1744, 1690, 1395, 1210, 1144, 1049, 756 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, ca 6:4 mixture of rotamers) δ 5.28 (s, 0.6 H), 5.07 (m, 0.4 H), 4.49-4.31 (m, 3.5

H), 4.00-3.89 (m, 2.5 H), 3.75-3.61 (m, 7 H), 3.29-2.77 (m, 4 H), 2.35-1.80 (m, 4 H), 1.45 (br s, 5.4 H), 1.39 (br s, 3.6 H); ^{13}C NMR (125 MHz, $CDCl_3$, selected) δ 170.5, 170.0, 154.2, 153.6, 115.6, 91.3, 81.7, 78.0, 73.4, 69.7, 68.0, 67.0, 52.4, 52.3, 50.3, 39.6, 37.9, 29.3, 28.4, 28.3; HRMS (ESI, positive) calcd for $C_{22}H_{31}N_2O_{10}F_3Na$ [$(M+Na)^+$] 563.1823, found 563.1827.

General Procedures for the Synthesis of the Glutamate Analogues 16-27. A suspension of fully protected glutamate analogues (**15** series, **S5** series, and **S6** series) in hydrochloric acid (6 M, 0.5 mL) was heated at 65 °C for 10 h. The reaction mixture was then cooled to rt and concentrated under reduced pressure. The residue was purified by column chromatography on reversed-phase silica gel (500 mg, water). The active fractions were lyophilized to afford the glutamate analogues **16-27**.

The Glutamate Analogue 16. With the general procedure above, **15a** (13.6 mg, 0.034 mmol) was deprotected to give the glutamate analogue **16** (8.2 mg, 79%) as a white solid: IR (film) 1713, 1634, 1402, 1029 cm^{-1}; ^{1}H NMR (500 MHz, D_2O) δ 6.11 (dd, *J* = 10.0, 3.5 Hz, 1 H), 5.91 (ddd, *J* = 10.0, 3.5, 2.0 Hz, 1 H), 4.49 (s, 1 H), 4.43 (t, *J* = 1.5 Hz, 1 H), 4.11 (dd, *J* = 17.3, 3.5 Hz, 1 H), 4.05 (d, *J* = 2.5 Hz, 1 H), 4.02 (d, *J* = 17.3 Hz, 1 H), 3.93 (dd, *J* = 12.5, 10.0 Hz, 1 H), 3.20 (d, *J* = 17.0 Hz, 1 H), 3.15 (dd, *J* = 12.5, 8.5 Hz, 1 H), 3.10 (t, *J* = 8.5 Hz, 1 H), 2.88 (t, *J* = 17.0 Hz, 1 H); ^{13}C NMR (125 MHz, D_2O/CD_3OD = 15:1) δ 174.0, 168.6, 132.4, 120.4, 90.6, 79.1, 72.8, 67.3, 64.3, 52.2, 45.7, 40.5; HRMS (ESI, positive) calcd for $C_{12}H_{16}NO_6$ [$(M+H)^+$] 270,0978, found 270.0976.

The Glutamate Analogue 17. With the general procedure above, **15b** (9.4 mg, 0.023 mmol) was deprotected to give the glutamate analogue **17** (7.4 mg, 100%) as a white solid: IR (film) 1715, 1621, 1405, 1361, 1075 cm^{-1}; ^{1}H NMR (500 MHz, D_2O) δ 5.88 (ddd, *J* = 11.5, 5.5, 5.5 Hz, 1 H), 5.60 (dd, *J* = 1.5, 4.0 Hz), 4.75 (s, 1 H), 4.16 (s, 1 H), 4.14 (d, *J* = 3.0 Hz, 1 H), 3.85 (dd, *J* = 17.5, 1 H), 3.12-3.02 (m, 2 H), 2.81 (d, *J* = 17.5 Hz, 1 H), 2.37-2.21 (m, 2 H); ^{13}C NMR (125 MHz, D_2O/CD_3OD = 15:1) δ 174.6, 170.0, 132.0, 124.8, 88.8, 83.7, 81.0, 69.1, 67.6, 53.6, 46.2, 40.7, 29.7; HRMS (ESI, positive) calcd for $C_{13}H_{18}NO_6$ [$(M+H)^+$] 284.1129, found 284.1128.

The Glutamate Analogue 18. With the general procedure above, **15f** (23.7 mg, 0.048 mmol) was deprotected to give the glutamate analogue **18** (14.7 mg, 90%) as a white solid: IR (film) 1713, 1624, 1417, 1257, 1085, 967 cm^{-1}; ^{1}H NMR (500 MHz, D_2O) δ 6.11 (dd, *J* = 10.3, 4.5 Hz, 1 H), 6.07 (br d, 10.3 Hz, 1 H), 4.75 (br s, 1 H), 4.34 (s, 1 H), 3.99 (dd, *J* = 12.5, 9.0 Hz, 1 H), 3.86 (d, *J* = 4.0 Hz, 1 H), 3.78 (dd, *J* = 17.3, 4.0 Hz, 1 H), 3.65 (d, *J* = 17.3 Hz, 1 H), 3.48 (t, *J* = 9.0 Hz, 1 H), 3.32 (dd, *J* = 12.5, 9.0 Hz, 1 H), 3.08 (br s, 2 H); ^{13}C NMR (125

MHz, D_2O/CD_3OD = 15:1) δ 174.2, 168.4, 126.7, 121.7, 89.3, 70.2, 65.5, 60.3, 49.1, 46.2, 42.3, 38.3; HRMS (ESI, positive) calcd for $C_{12}H_{17}N_2O_5$ [$(M+H)^+$] 269.1131, found 269.1130.

The Glutamate Analogue 19. With the general procedure above, **15e** (31.4 mg, 0.062 mmol) was deprotected to give the glutamate analogue **19** (20.1 mg, 91%) as a white solid: IR (film) 1730, 1624, 1405, 1243, 1087, 991 cm^{-1}; ^1H NMR (500 MHz, D_2O) δ 5.92 (m, 1 H), 5.69 (d, *J* = 11.0 HZ, 1 H), 5.13 (br s, 1 H), 4.15 (s, 1 H), 4.11 (d, *J* = 4.5 Hz, 1 H), 3.97 (dd, *J* = 13.0, 10.5 Hz, 1 H), 3.51 (t, *J* = 8.5 Hz, 1 H), 3.31-3.25 (m, 3 H), 3.09 (d, *J* = 18.0 Hz, 1 H), 2.92 (d, *J* = 18.0 Hz, 1 H), 2.55 (m, 1 H), 2.27 (m, 1 H); ^{13}C NMR (125 MHz, D_2O/CD_3OD = 15:1) δ 173.3, 167.9, 127.7, 125.8, 87.9, 78.1, 65.2, 61.9, 51.1, 46.8, 45.4, 38.6, 21.4; HRMS (ESI, positive) calcd for $C_{13}H_{19}N_2O_5$ [$(M+H)^+$] 283.1288, found 283.1296.

The Glutamate Analogue 20. With the general procedure above, **S5a** (5.4 mg, 0.014 mmol) was deprotected to give the glutamate analogue **20** (2.6 mg, 63%) as a white solid: IR (film) 1717, 1704, 1419, 1199, 1104, 1050 cm^{-1}; ^1H NMR (500 MHz, D_2O) δ 4.22 (s, 1 H), 4.18 (s, 1 H), 3.90 (s, 1 H), 3.83 (dd, *J* = 12.8, 10.0 Hz, 1 H), 3.78 (d, *J* = 13.5 Hz, 1 H), 3.32 (t, *J* = 12.0 Hz, 1 H), 3.17 (d, *J* = 16.5 Hz, 1 H), 3.06 (dd, *J* = 12.8, 9.0 Hz, 1 H), 2.95 (t, *J* = 9.0 Hz, 1 H), 2.92 (d, *J* = 16.5 Hz, 1 H), 1.97 (br d, *J* = 14.0 Hz, 1 H), 1.81-1.65 (m, 2 H), 1.34 (d, *J* = 16.5 Hz, 1 H); ^{13}C NMR (125 MHz, D_2O/CD_3OD = 15:1) δ 174.2, 168.7, 89.9, 78.9, 75.4, 67.5, 66.5, 52.7, 45.2, 40.4, 23.5, 19.2; HRMS (ESI, positive) calcd for $C_{12}H_{18}NO_6$ [$(M+H)^+$] 272.1129, found 272.1133.

The Glutamate Analogue 21. With the general procedure above, **S5b** (2.4 mg, 0.014 mmol) was deprotected to give the glutamate analogue **21** (1.4 mg, 77%) as a white solid: IR (film) 1716, 1635, 1397, 1085, 1062, 979 cm^{-1}; ^1H NMR (500 MHz, D_2O) δ 4.39 (ddd, *J* = 7.0, 6.0, 3.5 Hz, 1 H), 4.22 (s, 1 H), 4.10 (d, *J* = 3.5 Hz, 1 H), 4.03 (d, *J* = 12.0 Hz, 1 H), 3.91 (t, *J* = 11.0 Hz, 1 H), 3.29 (m, 1 H), 3.11 (d, *J* = 16.5 Hz, 1 H), 3.09 (d, *J* = 7.5 Hz, 1 H), 2.93 (dd, *J* = 11.0, 7.5 Hz, 1 H), 2.82 (d, *J* = 16.5 Hz, 1 H), 2.06 (m, 1 H), 1.71 (m, 1 H), 1.64-1.60 (m, 3 H), 1.25 (m, 1 H); ^{13}C NMR (125 MHz, D_2O/CD_3OD = 15:1) δ 174.6, 170.2, 90.2, 88.9, 83.6, 74.2, 68.2, 53.4, 46.9, 41.0, 31.5, 31.0, 20.9; HRMS (ESI, positive) calcd for $C_{13}H_{19}NO_6$ [$(M+H)^+$] 286.1293, found 286.1285.

The Glutamate Analogue 22. With the general procedure above, **S5f** (18.1 mg, 0.036 mmol) was deprotected to give the glutamate analogue **22** (12.3 mg, 100%) as a white solid: IR (film) 1715, 1625, 1404, 1255, 1031, 975 cm^{-1}; ^1H NMR (500 MHz, D_2O) δ 4.47 (br s, 1 H), 4.25 (s, 1 H), 3.90 (t, *J* = 11.5 Hz, 1 H), 3.71 (s, 1 H), 3.37 (d, *J* = 12.5 Hz, 1 H), 3.32 (t, *J* = 9.0 Hz, 1 H), 3.22 (s, 1 H), 3.19 (dd, *J* = 12.5, 9.0 Hz, 1 H), 3.15 (d, *J* = 18.0 Hz, 1 H), 3.02 (d, *J* = 18.0 Hz, 1 H), 2.87 (t, *J* = 12.5 Hz, 1 H), 2.11 (d, *J* = 15.5 Hz, 1 H), 1.87 (t, *J* = 13.0 Hz,

1 H), 1.71-1.63 (m, 2 H); ^{13}C NMR (125 MHz, D_2O/CD_3OD = 15:1) δ 174.7, 168.4, 88.7, 72.4, 65.5, 59.7, 49.4, 45.6, 43.4, 37.2, 22.7, 16.5; HRMS (ESI, positive) calcd for $C_{12}H_{19}N_2O_5$ [$(M+H)^+$] 271.1288, found 271.1291.

The Glutamate Analogue 23. With the general procedure above, **S5e** (23.5 mg, 0.046 mmol) was deprotected to give the glutamate analogue **23** (16.2 mg, 98%) as a white solid: IR (film) 1731, 1624, 1417, 1258, 1084 cm^{-1}; ^{1}H NMR (500 MHz, D_2O) δ 4.59 (dt, *J* = 7.5, 6.0 Hz, 1 H), 4.33 (s, 1 H), 3.97 (dd, *J* = 12.8, 10.0 Hz, 1 H), 3.86 (d, *J* = 4.5 Hz, 1 H), 3.44 (br s, 1 H), 3.43 (t, *J* = 9.0 Hz, 1 H), 3.28 (dd, *J* = 12.5, 9.0 Hz, 1 H), 3.08 (d, *J* = 18.0 Hz, 1 H), 2.99 (d, *J* = 18.0 Hz, 1 H), 2.94 (dd, *J* = 13.5, 3.5, 3.5 Hz, 1 H), 2.26 (m, 1 H), 1.88-1.60 (m, 4 H), 1.40 (dd, *J* = 13.5, 12.3 Hz, 1 H); ^{13}C NMR (125 MHz, D_2O/CD_3OD = 15:1) δ 173.5, 168.0, 89.1, 78.4, 67.9, 65.3, 51.1, 49.4, 47.0, 38.6, 28.3, 26.4, 19.8; HRMS (ESI, positive) calcd for $C_{13}H_{21}N_2O_5$ [$(M+H)^+$] 284.1445, found 184.1449.

The Glutamate Analogue 24. With the general procedure above, **S6a** (2.4 mg, 0.014 mmol) was deprotected to give the glutamate analogue **24** (2.9 mg, 74%) as a white solid: IR (film) 3419, 1716, 1634, 1403, 1240, 1088 cm^{-1}; ^{1}H NMR (500 MHz, D_2O) δ 4.39 (s, 1 H), 4.18 (s, 1 H), 4.07 (s, 2 H), 3.86-3.82 (m, 2 H), 3.55 (dd, *J* = 11.0, 5.0 Hz, 1 H), 3.42 (t, *J* = 11.0 Hz, 1 H), 3.13 (d, *J* = 17.0 Hz, 1 H), 3.09-3.00 (m, 2 H), 2.90 (d, *J* = 17.0 Hz, 1 H); ^{13}C NMR (125 MHz, D_2O/CD_3OD = 15:1) δ 175.7, 170.3, 92.0, 82.4, 78.6, 78.5, 67.3, 65.8, 65.3, 53.2, 46.9, 42.0; HRMS (ESI, positive) calcd for $C_{12}H_{18}NO_8$ [$(M+H)^+$] 304.1027, found 304.1232.

The Glutamate Analogue 25. With the general procedure above, **S6b** (5.9 mg, 0.014 mmol) was deprotected to give the glutamate analogue **25** (4.8 mg, 100%) as a white solid: IR (film) 3420, 1748, 1623, 1375, 1223, 1036 cm^{-1}; ^{1}H NMR (500 MHz, D_2O) δ 4.34 (s, 1 H), 4.28 (dd, *J* = 7.5, 4.5 Hz, 1 H), 4.19 (d, *J* = 4.5 Hz, 1 H), 4.10 (d, *J* = 4.0 Hz, 1 H), 3.96-3.87 (m, 3 H), 3.55 (t, *J* = 13.0 Hz, 1 H), 3.12 (d, *J* = 16.5 Hz, 1 H), 3.11 (dd, *J* = 12.5, 7.0 Hz, 1 H), 2.96 (dd, 10.8, 7.0 Hz, 1 H), 2.86 (d, *J* = 16.5 Hz, 1 H), 1.89 (ddd, *J* = 18.8, 13.0, 4.5 Hz, 1 H), 1.69 (dd, *J* = 13.3, 4.5 Hz, 1 H); ^{13}C NMR (125 MHz, D_2O/CD_3OD = 15:1) δ 174.3, 170.2, 90.7, 86.7, 86.0, 77.0, 72.8, 68.4, 68.3, 53.2, 47.0, 40.4, 34.4; HRMS (ESI, positive) calcd for $C_{13}H_{20}NO_8$ [$(M+H)^+$] 318.1183, found 318.1193.

The Glutamate Analogue 26. With the general procedure above, **S6f** (20.3 mg, 0.038 mmol) was deprotected to give the glutamate analogue **26** (13.9 mg, 97%) as a white solid: IR (film) 3300, 1714, 1627, 1404, 1256, 1101, 1000 cm^{-1}; ^{1}H NMR (500 MHz, D_2O) δ 4.44 (br s, 1 H), 4.25 (s, 1 H), 4.18 (br s, 1 H), 3.98 (dd, *J* = 7.8, 3.5 Hz, 1 H), 3.89 (dd, *J* = 12.8, 10.0 Hz, 1 H), 3.85 (d, *J* = 2.5 Hz, 1 H), 3.36 (t, *J* = 8.5 Hz, 1 H), 3.22 (t, *J* = 13.5 Hz, 1 H),

2.99 (d, *J* = 17.5 Hz, 1 H); ^{13}C NMR (125 MHz, D_2O/CD_3OD = 15:1) δ 174.7, 168.4, 89.1, 77.8, 65.4, 64.9, 62.8, 57.4, 48.3, 45.6, 41.2, 37.1; HRMS (ESI, positive) calcd for $C_{12}H_{19}N_2O_7$ [$(M+H)^+$] 303.1187, found 303.1190.

The Glutamate Analogue 27. With the general procedure above, **S6e** (23.3 mg, 0.043 mmol) was deprotected to give the glutamate analogue **27** (16.7 mg, 100%) as a white solid: IR (film) 3350, 1718, 1635, 1405, 1227, 1097, 991 cm^{-1}; ^{1}H NMR (500 MHz, D_2O) δ 4.37 (t, *J* = 5.5 Hz, 1 H), 4.31 (s, 1 H), 4.13 (br s, 1 H), 3.98 (dd, *J* = 13.0, 10.0 Hz, 1 H), 3.96 (d, *J* = 5.5 Hz, 1 H), 3.92 (d, *J* = 5.5 Hz, 1 H), 3.46 (t, *J* = 8.5 Hz, 1 H), 3.31 (d, *J* = 12.5 Hz, 1 H), 3.31 (t, *J* = 13.0 Hz, 1 H), 3.16 (m, 1 H), 3.11 (d, *J* = 18.0 Hz, 1 H), 3.00 (d, *J* = 18.0 Hz, 1 H), 1.98-1.97 (m, 2 H); ^{13}C NMR (125 MHz, D_2O/CD_3OD = 15:1) δ 173.5, 168.0, 88.8, 81.3, 74.8, 71.3, 65.5, 65.2, 51.1, 47.0, 44.0, 38.7, 29.5; HRMS (ESI, positive) calcd for $C_{13}H_{21}N_2O_7$ [$(M+H)^+$] 317.1343, found 317.1352.

Experimental Procedures for Biological Study

Biological assay: Mouse behavioral assay was performed as reported previously.[2] Behavior of animals treatred with drug was monitored for 6 h. All the animals were maintained according to the National Research Council's Guide for the Care and Use of Laboratory Animals.

Electrophysiological analyses: Effects of **16** were measured in whole-cell patch clamp assays from cultured rat hippocampal neurons. Spontaneous action potentials were recorded using the current-clamp configuration in HEPES-buffered saline solution and K-gluconate internal solution. Excitatory postynaptic currents (EPSCs) were recorded in voltage-clamp in extracellular solution containing bicuculline methiodide and picrotoxin (10 μM each) to block $GABA_A$ receptors. CsF/CsCl-based internal solution was used for voltage-clamp recordings. All recordings were made at room temperature. Spontaneous action potential and EPSC frequencies were significantly reduced in the presence of **16** ($p<0.01$, Student's paired t-test, $n = 3$ for each type of recording).

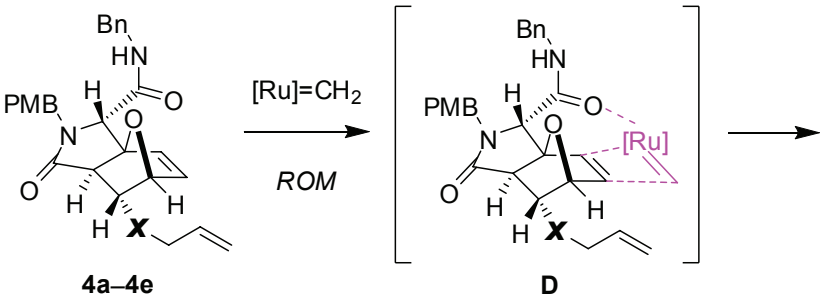
[2] R. Sakai, G. T. Swanson, K. Shimamoto, T. Green, A. Contractor, A. Ghetti, Y. Tamura-Horikawa, C. Oiwa, H. Kamiya H. *J. Pharmacol. Exp. Ther.* **2001**, *296*, 650-658.

Proposed Pathway and Its Computational Rationalization for Domino Metathesis Reaction of 7-Oxanorbornenes

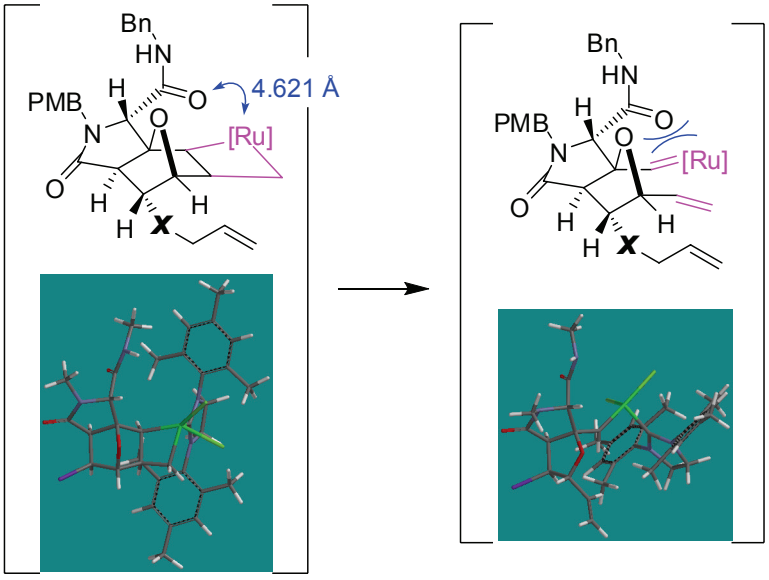
The plausible reaction mechanism is shown in the scheme below. To rationalize this pathway, the geometry of two intermediates **E** and **F** were optimized by the semiempirical level of theory employing the PM3 method. First, the distance between the *upper* exocyclic amide carbonyl group and the Ru metal center in **E** was calculated to be 4.621 Å, indicating the association is rather loose and is expected to allow conversion into the alkylidene intermediate **F** smoothly.

Second, formation of a metal-alkylidene group (intermediate **F**) causes the same group moves closer to the *upper* exocyclic amide group, and the steric environment around the alkylidene group of **F** is getting crowded by their interactions. This effect controls the approaching trajectory of the CM substrate (vinyl acetate) to the metal-alkylidene group in **F**, to generate the kinetically favorable *trans*-metallacyclobutane **F'**. The four-membered ring then stereospecifically cleaved to provide the *trans*-vinylic acetate **G**. *Trans*-olefin is usually obtained selectively in the olefin metathesis reaction, and the steric interaction in the intermediate **F** further enhance the selectivity.

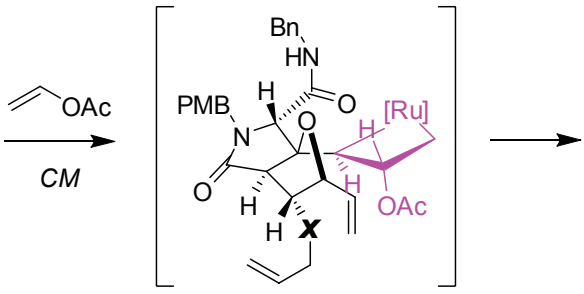
Finally, the triene **G** undergoes cyclization by RCM, giving rise to the heterotricycle **9a**–**9e**.



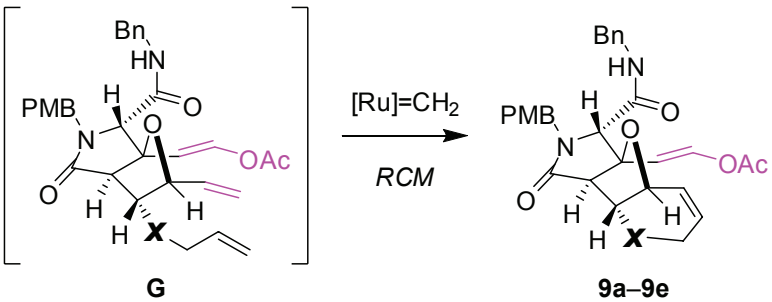
4a–4e **D**



E **F**



F'



G **9a–9e**

Scheme. The proposed pathway for the domino metathesis reaction of 7-oxanorbornenes. Chauvin's mechanism (J. L. Herisson, Y. Chauvin, *Makromol. Chem.* **1971**, *141*, 161-176) is modified here to account for our reactions. Structural optimization for the intermediates **E** and **F** was performed under high vacuum at PM3 level of theory. Benzyl (Bn) and 4-methoxybenzyl (PMB) groups were omitted in the calculation for simplicity. All calculations were performed using Spartan software. Spartan, version '06; Wavefunction, Inc., 18401 Von Karman Ave., Suite 370, Irvine, CA 92612 USA.