Supporting information

for

The Development of a Complementary Pathway for the Synthesis of Aliskiren

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**General methods:** Unless otherwise noted, all solvents were purified according to the standard procedures. Allyl bromide, (COCl)$_2$, and (EtO)$_2$POH were distilled prior to use. Other reagents were reagent grade and were used without purification. The $^1$H-NMR spectra were recorded at 600, 400, or 300 MHz (Bruker AV) in CDCl$_3$ or DMSO-d$_6$. The $^{13}$C-NMR spectra were recorded at 150 or 100 MHz in CDCl$_3$ or DMSO-d$_6$. The $^{31}$P-NMR spectra were recorded at 162 MHz in CDCl$_3$. Chemical shifts were given in ppm relative to TMS or the appropriate solvent peak. Coupling constants ($J$ values) were reported in Hertz (Hz). High resolution mass spectra (HRMS) were measured using an IonSpec Ultima 7.0 TFT-ICR-MS instrument (IonSpec, USA) with a Waters Z-spray source. HPLC analysis was performed on Shimadzu (LC 20AD, UV detection monitored at 254 nm) or Shimadzu (LC 6AD, UV detection monitored at 254 nm). C18 column for E/Z selectivity measurements (Hypersil ODS 5 μm, 4.6 mm × 250 mm) was purchased from Dalian Elite Analytical Instruments Co., Ltd. Chiralpak AD-H column for enantiomeric excess measurements was purchased from Daicel Chemical Industries, LTD. Optical rotation value was measured by a Perkin Elmer 341LC polarimeter operating on the sodium D-line (589 nm), using a 100 mm path-length cell and are reported as: $[\alpha]_D^T$ (concentration in g/100 mL, solvent). Column chromatography was performed on silica gel 100-200 mesh or 200-300 mesh.

**Synthesis of 10a:** To a round-bottom flask was added 9 (2.61 g, 10 mmol, 1.0 equiv) and dried THF (30 mL) under N$_2$ atmosphere. After being cooled to -78 °C, LiHMDS solution (1 M in THF, 12 mL, 1.2 equiv) was added dropwise. The cooling bath was then replaced with an ice-water bath and the reaction mixture was allowed to stir at 0 °C for 3 h. The solution was re-cooled to -78 °C and allyl bromide (1.3 mL, 15 mmol, 1.5 equiv) was added dropwise. The reaction mixture was stirred overnight at room temperature. The reaction mixture was then quenched with saturated aq. NH$_4$Cl (30 mL). The resulting solution was evaporated under reduced pressure to remove the volatile materials. The concentrated solution was extracted with CH$_2$Cl$_2$ (4 × 40 mL) and the combined organic layer was washed with brine (30 mL), dried over MgSO$_4$, filtered and evaporated under reduced pressure. Purification of the residue by column chromatography (1:10 ethyl acetate-hexane) gave 10a (2.89 g, 9.6 mmol, 96%) as a light yellow oil. $^1$H-NMR (600 MHz, CDCl$_3$) $\delta$ 7.33 (t, $J$ = 7.4 Hz, 2H), 7.27 (d, $J$ = 7.3 Hz, 1H), 7.23 (d, $J$ = 7.2 Hz, 2H), 5.86–5.79 (m, 1H), 5.09 (d, $J$ = 17.1, Hz, 1H), 5.02 (d, $J$ = 10.2 Hz, 1H), 4.71–4.67 (m, 1H), 4.15–4.11 (m, 2H), 3.88–3.85 (m, 1H), 3.31 (dd, $J$ = 13.4, 3.2 Hz, 1H), 2.64 (dd, $J$ = 13.4, 10.1 Hz, 1H), 2.51–2.45 (m, 1H), 2.41–2.37 (m, 1H), 2.02–1.97 (m, 1H), 0.98 (d, $J$ = 6.84 Hz, 6H). $^{13}$C-NMR (100 MHz, CDCl$_3$) $\delta$ 175.73, 153.28, 135.28, 135.66, 135.60, 129.47, 128.94, 127.29, 116.92, 65.77, 55.65, 48.19, 38.06, 33.68, 30.29, 20.91, 19.24.

**Synthesis of 10b:** To a round-bottom flask was added 9 (13.09 g, 50 mmol, 1.0 equiv) and dried THF (150 mL) under N$_2$ atmosphere. After being cooled to -78 °C, LiHMDS solution (1 M in THF, 63 mL) was added dropwise. The solution was stirred for 1 h at -78 °C and 3 h at 0 °C. The resulting mixture was then re-cooled to -78 °C and (E)-1,4-dibromobut-2-ene (32.10 g, 150 mmol, 3 equiv) was added. The reaction
mixture was allowed to warm to room temperature and stirred overnight. The reaction mixture was then quenched with saturated aq. NH₄Cl (100 mL). The solution was evaporated under reduced pressure to remove the volatile materials. The concentrated solution was extracted with CH₂Cl₂ (3 × 50 mL). The combined organic layer was washed with brine (50 mL), dried over MgSO₄, filtered and evaporated under reduced pressure. Puriﬁcation of the residue by column chromatography (1:10 ethyl acetate-hexane) gave 10b’ (17.82 g, 45.2 mmol, 90%) as a slightly yellow oil. 1H-NMR (600 MHz, CDCl₃) δ 7.33 (t, J = 7.4 Hz, 2H), 7.28–7.26 (m, 1H), 7.22 (d, J = 7.3 Hz, 2H), 5.78 (t, J = 5.8 Hz, 2H), 4.70–4.66 (m, 1H), 4.16–4.13 (m, 2H), 3.91 (d, J = 4.2 Hz, 2H), 3.87–3.83 (m, 1H), 3.35 (dd, J = 13.4, 3.1 Hz, 1H), 2.68 (dd, J = 13.3, 10.2 Hz, 1H), 2.53–2.48 (m, 1H), 2.40–2.36 (m, 1H), 2.02–1.96 (m, 1H), 0.97 (d, J = 6.6 Hz, 6H). 13C-NMR (100 MHz, CDCl₃) δ 175.35, 153.29, 135.59, 133.07, 129.44, 128.98, 128.64, 127.33, 65.92, 55.68, 48.21, 38.23, 32.83, 31.68, 30.31, 20.88, 19.15. HRMS (ESI-MS) Found 416.0827 [M+Na]+, C₁₉H₂₄BrNNaO₃ requires 416.0837; found 432.0562 [M+K]+, C₁₉H₂₄BrNKO₃ requires 432.0562.

To a solution of 10b’ (12.82 g, 32.5 mmol, 1 equiv) in THF (170 mL) was added NaBH₃CN (5.96 g, 95 mmol, 3 equiv). The reaction mixture was heated at 60 °C for 24 h. The mixture was evaporated under reduced pressure and purified by column chromatography (ethyl acetate:dichloromethane:hexane = 1:1:5) to give 10b (9.67 g, 30.7 mmol, 94%) as a colorless oil. 1H-NMR (600 MHz, CDCl₃) δ 7.33 (t, J = 7.4 Hz, 2H), 7.28 (d, J = 7.2 Hz, 1H), 7.23 (d, J = 7.3 Hz, 2H), 5.53–5.47 (m, 1H), 5.46–5.41 (m, 1H), 4.72–4.68 (m, 1H), 4.15–4.11 (m, 2H), 3.84–3.80 (m, 1H), 3.28 (dd, J = 13.4, 3.0 Hz, 1H), 2.63 (dd, J = 13.3, 10.0 Hz, 1H), 2.34–2.29 (m, 1H), 2.01–1.93 (m, 1H), 1.63 (d, J = 6.0 Hz, 3H), 0.96 (dd, J = 6.6, 3.7 Hz, 6H). 13C-NMR (150 MHz, CDCl₃) δ 176.07, 153.31, 135.67, 129.49, 129.02, 127.36, 65.72, 55.55, 48.79, 38.07, 32.81, 30.36, 20.98, 19.37, 18.04. HRMS (ESI-MS) Found 316.1904 [M+H]+, C₁₉H₂₆NO₃ requires 316.1913; found 338.1729 [M+Na]+, C₁₉H₂₅NNaO₃ requires 338.1732.

Compound 10c was synthesized according to the same procedure for the synthesis of 10a in 96% yield from 9 and 3,3-dimethylallyl bromide. 1H-NMR (300 MHz, CDCl₃) δ 7.36–7.21 (m, 5H), 5.19–5.13 (m, 1H), 4.73–4.65 (m, 1H), 4.17–4.09 (m, 2H), 3.85–3.78 (m, 1H), 3.22 (dd, J = 13.3, 3.2 Hz, 1H), 2.63 (dd, J = 13.3, 9.7 Hz, 1H), 2.53–2.42 (m, 1H), 2.33–2.20 (m, 1H), 2.04–1.93 (m, 1H), 1.65 (d, J = 11.5 Hz, 6H), 0.97 (dd, J = 6.7, 3.4 Hz, 6H). 13C-NMR (150 MHz, CDCl₃) δ 176.43, 153.32, 135.65, 133.60, 129.51, 129.02, 127.36, 121.43, 65.68, 55.45, 48.88, 37.90, 30.60, 28.42, 25.95, 20.99, 19.45, 17.88. HRMS (ESI-MS) Found 352.1877 [M+Na]+, C₂₀H₂₇NNaO₃ requires 352.1889; found 368.1621 [M+K]+, C₂₀H₂₇NKO₃ requires 368.1628.

Synthesis of 11a: To a THF/H₂O (275 mL/70 mL) solution of 10a (20.72 g, 68.75 mmol, 1 equiv) was added dropwise 30% H₂O₂ (30 mL, 275 mmol, 4 equiv) and LiOH•H₂O (5.77 g, 137.5 mmol, 2 equiv) at room temperature. After being stirred for 5 h, Na₂SO₃ (43.22 g, 343 mmol, 5 equiv) was added slowly and the reaction mixture was stirred for a few hours. The resulting solution was evaporated under reduced
pressure to remove the volatile materials. The concentrated solution was adjusted to ca. pH 14 with 1.5 Maq. NaOH and extracted with CH₂Cl₂ (6 × 100 mL). The aqueous layer was acidified to pH 1 with 6 M aq. HCl and extracted with EtOAc (6 × 100 mL). The combined organic layer was washed with brine (100 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give 11a (8.94 g, 62.9 mmol, 91%) as a slightly yellow oil, which was used in the next transformation without further purification. ¹H-NMR (600 MHz, CDCl₃) 11a: δ 11.19 (s, 1H), 5.81–5.75 (m, 1H), 5.09 (d, J = 17.1 Hz, 1H), 5.02 (d, J = 10.1 Hz, 1H), 2.37–2.27 (m, 2H), 2.26–2.22 (m, 1H), 1.96–1.89 (m, 1H), 0.98 (dd, J = 6.7, 4.2 Hz, 6H). ¹³C-NMR (100 MHz, CDCl₃) δ 181.88, 135.72, 116.78, 52.43, 33.69, 30.16, 20.34, 20.17.

Synthesis of 11b was carried out according to the same procedure as the synthesis of 11a. 10b (12.55 g, 40 mmol, 1 equiv) afforded 11b (5.48 g, 35.0 mmol, 88%) as a slightly yellow oil. ¹H-NMR (600 MHz, CDCl₃) 11b: δ 9.60 (s, 1H), 5.53–5.47 (m, 1H), 5.41–5.36 (m, 1H), 2.29–2.16 (m, 3H), 1.92–1.87 (m, 1H), 1.64 (d, J = 6.3 Hz, 3H), 0.97 (dd, J = 6.7, 4.4 Hz, 6H). ¹³C-NMR (150 MHz, CDCl₃) δ 181.98, 128.09, 127.39, 52.96, 32.61, 30.10, 20.35, 20.24, 18.03. HRMS (ESI-MS) Found 155.1073 [M-H]−, C₉H₁₅O₂ requires 155.1072.

Synthesis of 11c was carried out according to the same procedure as the synthesis of 11a. The two-step yield was 85% from starting material 9. ¹H-NMR (300 MHz, CDCl₃) 11c: δ 5.09 (t, J = 7.1 Hz, 1H), 2.35–2.12 (m, 3H), 1.97–1.92 (m, 1H), 1.68 (s, 3H), 1.61 (s, 3H), 0.98 (dd, J = 6.7, 3.8 Hz, 6H). ¹³C NMR (100 MHz, CDCl₃) δ 182.24, 133.69, 121.39, 53.00, 30.20, 28.20, 25.89, 20.40, 20.30, 17.81. HRMS (ESI-MS) Found 169.1230 [M-H]−, C₁₀H₁₇O₂ requires 169.1229.

Synthesis of 12a: To a dried CH₂Cl₂ solution (80 mL) of 11a (2.27 g, 16 mmol, 1 equiv) was added (COCl)₂ (4.1 mL, 48 mmol, 3 equiv) dropwise and a few drops of DMF at room temperature. After being stirred at the same temperature for 12 h, the resulting solution was evaporated to remove the volatile materials. The residue was dissolved in CH₂Cl₂ (80 mL) and then dimethylamine hydrochloride (2.65 g, 32 mmol, 2 equiv) and DMAP (97.6 mg, 0.8 mmol, 0.05 equiv) were added and stirred for 5 min. Then Et₃N (8.9 mL, 64 mmol, 4 equiv) was added slowly and the resulting reaction mixture was stirred at room temperature overnight. The reaction mixture was washed with brine (3×100 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure. Purification of the residue by column chromatography (CH₂Cl₂) gave 12a (2.34 g, 13.8 mmol, 86%) as a colorless oil. ¹H-NMR (600 MHz, CDCl₃) δ 5.76–5.69 (m, 1H), 5.06–5.03 (m, 1H), 4.96–4.93 (m, 1H), 3.00 (s, 6H), 2.50–2.47 (m, 1H), 2.41–2.36 (m, 1H), 2.28–2.24 (m, 1H), 1.95–1.87 (m, 1H), 0.96 (d, J = 6.7 Hz, 3H), 0.90 (d, J = 6.7 Hz, 3H). ¹³C-NMR (100 MHz, CDCl₃) δ 175.29, 136.47, 116.08, 48.12, 37.65, 35.48, 34.56, 30.84, 21.10, 19.87. HRMS (ESI-MS) Found 170.1544 [M+H]^+; C₁₀H₁₉NO requires 170.1545; found 192.1362 [M+Na]^+, C₁₀H₁₉NNaO requires 192.1364.

Synthesis of 12b was carried out according to the same procedure as the synthesis of 12a. 11b (3.96 g, 25.35 mmol, 1 equiv) afforded 12b (2.54 g, 17.3 mmol, 69%) as a
colorless oil. $^1$H-NMR (300 MHz, CDCl$_3$) $\delta$ 5.52–5.41 (m, 1H), 5.37–5.27 (m, 1H), 3.02 (s, 3H), 2.97 (s, 3H), 2.47–2.39 (m, 1H), 2.33–2.15 (m, 2H), 1.94–1.83 (m, 1H), 1.61 (d, $J = 6.1$ Hz, 3H), 0.95 (d, $J = 6.7$ Hz, 3H), 0.88 (d, $J = 6.7$ Hz, 3H). $^{13}$C-NMR (100 MHz, CDCl$_3$) $\delta$ 175.62, 128.82, 126.57, 48.64, 37.63, 35.52, 33.44, 30.78, 21.18, 19.95, 17.92. HRMS (ESI-MS) Found 184.1697 [M+H]$^+$, C$_{11}$H$_{22}$NO requires 184.1701.

Synthesis of 12c was carried out according to the same procedure as the synthesis of 12a. 11c (3.39 g, 19.9 mmol, 1 equiv) afforded 12c (2.84 g, 14.4 mmol, 72%) as a colourless oil. $^1$H-NMR (300 MHz, CDCl$_3$) $\delta$ 5.07–5.01 (m, 1H), 3.01 (s, 3H), 2.96 (s, 3H), 2.40 (dd, $J = 15.1$, 7.2 Hz, 1H), 2.25 (t, $J = 7.2$ Hz, 2H), 1.96–1.84 (m, 1H), 1.65 (s, 3H), 1.61 (s, 3H), 0.96 (d, $J = 6.7$ Hz, 3H), 0.88 (d, $J = 6.7$ Hz, 3H). $^{13}$C-NMR (100 MHz, CDCl$_3$) $\delta$ 175.97, 132.85, 122.09, 48.44, 37.71, 35.65, 30.95, 29.04, 25.84, 21.26, 20.12, 17.77. HRMS (ESI-MS) Found 198.1853 [M+H]$^+$, C$_{12}$H$_{24}$NO requires 198.1858.

Synthesis of 14: To a round-bottom flask equipped with a condenser and a nitrogen balloon was charged 5-bromo-2-methoxyphenol (20.30 g, 0.1 mol, 1.0 equiv) and a magnetic stirrer. The reaction vessel was then flushed with nitrogen and dried acetonitrile (160 mL) was introduced via a glass syringe. Then potassium carbonate (41.47 g, 0.3 mol, 3 equiv), KI (33.2 g, 0.2 mol, 2 equiv) and 1-bromo-3-methoxypropane (17 mL, 0.15 mol, 1.5 equiv) were added. The resulting solution was stirred under reflux for 24 h. The reaction mixture was then diluted with water (200 mL) and the bulk of acetonitrile was removed under reduced pressure. The resulting solution was extracted with Et$_2$O (4 × 200 mL) and the combined organic layer was washed with brine (200 mL), dried over MgSO$_4$, filtered and concentrated under reduced pressure. Purification of the residue by column chromatography (CH$_2$Cl$_2$) gave 14 (27.12 g, 99 mol, 99%) as a lightly yellow solid. $^1$H-NMR (600 MHz, CDCl$_3$) $\delta$ 7.02–7.00 (m, 2H), 6.72 (d, $J = 8.3$ Hz, 1H), 4.08 (t, $J = 6.5$ Hz, 2H), 3.82 (s, 3H), 3.55 (t, $J = 6.1$ Hz, 2H), 3.34 (d, $J = 2.9$ Hz, 3H), 2.11–2.07 (m, 2H). $^{13}$C-NMR (100 MHz, CDCl$_3$) $\delta$ 149.37, 148.78, 123.53, 116.52, 113.07, 113.07, 112.77, 69.14, 66.33, 58.72, 56.18, 29.53.

Synthesis of 16a: To a dried CH$_2$Cl$_2$ solution (100 mL) of 11a (2.85 g, 20 mmol, 1 equiv) was added dropwise (COCl)$_2$ (5.1 mL, 60 mmol, 3 equiv) and a few drops of DMF at room temperature. After being stirred for 10 h, the resulting solution was evaporated under reduced pressure to remove the volatile materials. The residue was dissolved in CH$_2$Cl$_2$ (100 mL) and $N,O$-dimethylhydroxylamine hydrochloride (3.9 g, 40 mmol, 2 equiv) and DMAP (122 mg, 1 mmol, 0.05 equiv) were added. Then, Et$_3$N (11.2 mL, 80 mmol, 4 equiv) was added slowly and the resulting reaction mixture was stirred overnight. The reaction mixture was washed with brine (3 × 100 mL), dried over Na$_2$SO$_4$, filtered and concentrated under reduced pressure. Purification of the residue by column chromatography (CH$_2$Cl$_2$) gave 13a as a colorless oil. $^1$H-NMR (600 MHz, CDCl$_3$) $\delta$ 5.78–5.71 (m, 1H), 5.07–5.04 (m, 1H), 4.98–4.96 (m, 1H), 3.66 (s, 3H), 3.18 (s, 3H), 2.70 (s, 1H), 2.40–2.34 (m, 1H), 2.30–2.26 (m, 1H), 1.94–1.86 (m, 1H), 0.97 (d, $J = 6.8$Hz, 3H), 0.92 (d, $J = 6.7$Hz, 3H). $^{13}$C-NMR (100 MHz,
CDCl₃) δ 176.81, 136.57, 116.22, 61.36, 47.43, 34.31, 32.01, 30.61, 21.09, 20.00. HRMS (ESI-MS) Found 186.1487 [M+H]^+, C₁₀H₂₀NO₂ requires 186.1494; found 208.1308 [M+Na]^+, C₁₁H₁₉NNaO₂ requires 208.1314.

To a round-bottom flask equipped with a condenser and a magnetic stirrer was charged 14 (11.01 g, 40 mmol, 2.0 equiv). Then dried THF (120 mL) was introduced via a glass syringe. The solution was cooled to -78 °C. n-butyl lithium solution (1.6 M in hexane, 25 mL, 40 mmol, 2 equiv) was added. The solution was stirred for 3 h at -78 °C. Then Weinreb amide 13a (1 equiv) was dissolved in a minimal amount of THF and was added dropwise. The resulting solution was further stirred at -78 °C and then room temperature for 1 h, respectively. The reaction mixture was quenched with saturated aq. NH₄Cl. The THF solvent was evaporated under reduced pressure. The solution was extracted with CH₂Cl₂ (4 × 100 mL) and the combined organic layer was washed with brine (100 mL), dried over MgSO₄, filtered and concentrated under reduced pressure. Purification of the residue by column chromatography (1:20 ethyl acetate-hexanes) gave 15a as a slight yellow oil. ¹H-NMR (300 MHz, CDCl₃) δ 7.57–7.55 (m, 2H), 6.88 (d, J = 8.9 Hz, 1H), 5.76–5.62 (m, 1H), 5.00 (dd, J = 17.0 Hz, 1H), 4.90 (d, J = 10.0 Hz, 1H), 4.18 (t, J = 6.5 Hz, 2H), 3.93 (s, 3H), 3.57 (t, J = 6.1 Hz, 2H), 3.36 (s, 3H), 3.32–3.25 (m, 1H), 2.60–2.49 (m, 1H), 2.35–2.27 (m, 1H), 2.17–1.99 (m, 3H), 0.93 (dd, J = 6.6, 4.6 Hz, 6H). ¹³C-NMR (100 MHz, CDCl₃) δ 202.27, 153.58, 148.54, 148.54, 136.47, 131.52, 122.80, 116.17, 112.19, 110.32, 69.25, 66.13, 58.71, 56.06, 51.75, 33.48, 30.77, 29.51, 21.29, 19.67. HRMS (ESI-MS) Found 321.2047 [M+H]^+, C₁₉H₂₉O₄ requires 321.2066; found 343.1861 [M+Na]^+, C₁₉H₂₈NaO₄ requires 343.1885. The enantiomeric excess of 97% ee was determined by HPLC (Daicel Chiralpak AD-H, hexane/isopropanol = 98/2, flow rate 1.0 mL/min, T = 30 °C, 254 nm, tR (minor) 16.481 min, tR(major) 13.257 min).

To a dried Et₂O (60 mL) suspension of AlCl₃ (5.40 g, 40 mmol, 2 equiv) was added slowly LiAlH₄ (759 mg, 20 mmol, 1 equiv) and a Et₂O solution of 15a at room temperature. The reaction mixture was stirred for 1 h. Then EtOAc (20 mL), H₂O (40 mL), saturated aq. potassium tartrate (40 mL) and 1 M aq. NaOH (40 mL) were added sequentially. The mixture was extracted with Et₂O (3 × 50 mL) and the combined organic layers were washed with brine (50 mL), dried over MgSO₄, filtered and concentrated under reduced pressure. Purification of the residue by column chromatography (1:20 ethyl acetate-hexanes) gave 16a (4.30 g, 14 mmol, 70% for three steps from 11a) as a colorless oil. ¹H-NMR (600 MHz, CDCl₃) δ 6.78 (d, J = 8.1 Hz, 1H), 6.70–6.67 (m, 2H), 5.78–5.70 (m, 1H), 5.00–4.97 (m, 2H), 4.10 (t, J = 6.5 Hz, 2H), 3.83 (s, 3H), 3.58 (t, J = 6.2 Hz, 2H), 3.36 (s, 3H), 2.52 (dd, J = 13.8, 6.6 Hz, 1H), 2.38 (dd, J = 13.8, 8.0 Hz, 1H), 2.10 (m, J = 6.3 Hz, 2H), 2.06–2.02 (m, 1H), 1.96–1.91 (m, 1H), 1.76–1.70 (m, 1H), 1.58–1.53 (m, 1H), 0.91 (d, J = 6.9 Hz, 3H), 0.88 (d, J = 6.9 Hz, 3H). ¹³C-NMR (100 MHz, CDCl₃) δ 148.33, 147.63, 138.27, 134.71, 121.44, 115.76, 114.61, 111.84, 69.53, 66.19, 58.78, 56.18, 45.99, 37.57, 36.24, 34.51, 29.79, 28.41, 19.21, 18.96. HRMS (ESI-MS) Found 307.2261 [M+H]^+, C₁₉H₃₁O₃ requires 307.2273; found 329.2077 [M+Na]^+, C₁₉H₃₀NaO₃ requires 329.2093.
Synthesis of 16b was carried out according to the same procedure for the synthesis of 16a. 16b was afforded in 38% overall yield via a three-step transformation from 11b as a colorless oil.

13b: $^1$H-NMR (300 MHz, CDCl$_3$) $\delta$ 5.53–5.30 (m, 2H), 3.65 (s, 3H), 3.18 (s, 3H), 2.65 (s, 1H), 2.33–2.17 (m, 2H), 1.93–1.81 (m, 1H), 1.62 (d, $J = 6.0$ Hz, 3H), 0.93 (dd, $J = 16.3$, 6.7 Hz, 6H). 13C-NMR (150 MHz, CDCl$_3$) $\delta$ 177.13, 129.01, 126.68, 61.32, 47.88, 33.13, 32.03, 30.59, 21.09, 20.09, 17.90. HRMS (ESI-MS) Found 222.1477 [M+Na$^+$], C$_{11}$H$_{21}$NNaO$_2$ requires 222.1470.

15b: $^1$H-NMR (300 MHz, CDCl$_3$) $\delta$ 7.55 (dd, $J = 4.3$, 2.5 Hz, 2H), 6.90–6.87 (m, 1H), 5.48–5.24 (m, 2H), 4.18 (t, $J = 6.5$ Hz, 2H), 3.93 (s, 3H), 3.58 (t, $J = 6.1$ Hz, 2H), 3.36 (s, 3H), 3.26–3.19 (m, 1H), 2.50–2.40 (m, 1H), 2.17–2.08 (m, 2H), 2.06–1.97 (m, 1H), 1.53 (dd, $J = 6.1$ Hz, 3H), 0.92 (dd, $J = 6.7$, 4.4 Hz, 6H).

13C-NMR (150 MHz, CDCl$_3$) $\delta$ 202.69, 153.52, 148.54, 131.74, 128.89, 126.71, 122.82, 112.32, 110.36, 69.33, 66.21, 58.78, 56.12, 52.37, 32.33, 30.70, 29.58, 21.33, 19.77, 17.96. HRMS (ESI-MS) Found 335.2218 [M+H$^+$], C$_{20}$H$_{31}$O$_4$ requires 335.2222; found 357.2035 [M+Na$^+$], C$_{20}$H$_{30}$NaO$_4$ requires 357.2042; found 373.1770 [M+K$^+$], C$_{20}$H$_{30}$KO$_4$ requires 373.1781.

16b: $^1$H-NMR (300 MHz, CDCl$_3$) $\delta$ 6.79–6.66 (m, 3H), 5.45–5.29 (m, 2H), 4.10 (t, $J = 6.5$ Hz, 2H), 3.84 (s, 3H), 3.58 (t, $J = 6.1$ Hz, 2H), 3.36 (s, 3H), 2.63 (s, 1H), 2.35–2.19 (m, 2H), 1.94–1.82 (m, 1H), 1.64 (d, $J = 4.7$ Hz, 3H), 1.55–1.44 (m, 1H), 0.88 (dd, $J = 10.8$, 6.9 Hz, 6H). 13C-NMR (100 MHz, CDCl$_3$) $\delta$ 148.31, 147.58, 134.96, 130.53, 126.11, 121.45, 114.65, 111.85, 69.54, 66.20, 58.76, 56.19, 46.32, 36.26, 33.12, 29.79, 28.39, 19.21, 19.02, 18.11. HRMS (ESI-MS) Found 320.2340 [M$^+$], C$_{20}$H$_{32}$O$_3$ requires 320.2351; found 343.2235 [M+Na$^+$], C$_{20}$H$_{32}$NaO$_3$ requires 343.2249.

Synthesis of 16c was carried out according to the same procedure for the synthesis of 16a. 16c was afforded in 26% overall yield via a three-step transformation from 11c as a colorless oil.

13c: $^1$H-NMR (300 MHz, CDCl$_3$) $\delta$ 5.11–5.05 (m, 1H), 3.64 (s, 3H), 3.18 (s, 3H), 2.63 (s, 1H), 2.35–2.19 (m, 2H), 1.94–1.82 (m, 1H), 1.66 (s, 3H), 0.97 (d, $J = 6.7$ Hz, 3H), 0.91 (d, $J = 6.7$ Hz, 3H). 13C-NMR (100 MHz, CDCl$_3$) $\delta$ 177.30, 132.76, 122.23, 61.18, 47.62, 32.06, 30.72, 28.57, 25.76, 21.03, 20.18, 17.72. HRMS (ESI-MS) Found 214.1802 [M+H$^+$], C$_{12}$H$_{24}$NO$_2$ requires 214.1807.

15c: $^1$H-NMR (300 MHz, CDCl$_3$) $\delta$ 7.56–7.52 (m, 2H), 6.91–6.86 (m, 1H), 5.02–4.97 (m, 1H), 4.18 (t, $J = 6.5$ Hz, 2H), 3.93 (s, 3H), 3.58 (t, $J = 6.1$ Hz, 2H), 3.36 (s, 3H), 3.21 (ddd, $J = 9.7$, 6.9, 4.2 Hz, 1H), 2.49–2.39 (m, 1H), 2.31–2.22 (m, 1H), 2.17–1.98 (m, 3H), 1.58 (d, $J = 5.0$ Hz, 6H), 0.93 (dd, $J = 7.6$, 7.0 Hz, 6H). 13C-NMR (100 MHz, CDCl$_3$) $\delta$ 203.00, 153.46, 148.48, 138.77, 131.83, 122.80, 122.21, 112.31, 110.32, 69.31, 66.19, 58.74, 56.08, 52.39, 30.79, 29.57, 27.98, 25.75, 21.34, 19.86, 17.77. HRMS (ESI-MS) Found 349.2372 [M+H$^+$], C$_{21}$H$_{33}$O$_4$ requires 349.2379.

16c: $^1$H-NMR (400 MHz, CDCl$_3$) $\delta$ 6.77 (d, $J = 8.0$ Hz, 1H), 6.70–6.67 (m, 2H), 5.09
(t, J = 6.9 Hz, 1H), 4.10 (t, J = 6.5 Hz, 2H), 3.83 (s, 3H), 3.58 (t, J = 6.1 Hz, 2H), 3.36 (s, 3H), 2.50 (dd, J = 13.7, 6.7 Hz, 1H), 2.36 (dd, J = 13.7, 7.9 Hz, 1H), 2.10 (m, J = 6.3 Hz, 2H), 1.98–1.81 (m, 2H), 1.75–1.71 (m, 1H), 1.68 (s, 3H), 1.55 (s, 3H), 1.53–1.48 (m, 1H), 0.89 (dd, J = 12.2, 6.9 Hz, 6H). 13C-NMR (100 MHz, CDCl 3) δ 148.30, 147.57, 135.07, 131.95, 123.98, 121.45, 114.65, 111.86, 69.56, 66.21, 58.77, 56.22, 46.90, 36.48, 29.79, 28.51, 28.42, 25.98, 19.34, 19.01, 17.91. HRMS (ESI-MS) Found 357.2393 [M+Na] +, C21H34NaO3 requires 357.2406; found 373.2133 [M+K] +, C21H34KO3 requires 373.2145.

General synthesis of 2a via the olefin cross-metathesis:

A round-bottom flask equipped with a condenser and a magnetic stirrer bar was charged 16 (1.0 equiv), 12 (3.0 or 4.0 equiv), additives (added or not) and 5 mol% of catalyst under nitrogen atmosphere. The reaction vessel was flushed with nitrogen. Then solvent was added via a glass syringe. The resulting reaction mixture was refluxed for 24 h under nitrogen atmosphere. The solvent was then removed under reduced pressure. The product was isolated by column chromatography on silica gel with ethyl acetate and hexane (v/v = 1:5) as eluent to gave 2a as a slightly yellow oil.

Synthesis of 18: To a THF/H2O (115/60 mL) solution of 12a (3.27 g, 19.3 mmol, 1 equiv) was added OsO4 (0.08 M in tBuOH, 2.5 mL, 0.2 mmol, 0.01 equiv) and NaIO4 (16.57 g, 77.5 mmol, 4 equiv) at 0 °C. The solution was stirred at 0 °C for 4 h and then evaporated under reduced pressure. The resulting mixture was diluted with water (200 mL) and extracted with CH2Cl2 (3 × 150 mL). The combined organic layer was washed with brine (200 mL), dried over Na2SO4, filtered and concentrated under reduced pressure. Purification of the residue by column chromatography (1:3 ethyl acetate-hexane) gave 18 (2.28 g, 13.3 mmol, 69%) as a colorless oil. 1H-NMR (300 MHz, CDCl3) δ 9.78 (s, 1H), 3.16 (s, 3H), 3.13–2.98 (m, 2H), 2.96 (s, 3H), 2.54 (dd, J = 18.0, 2.6 Hz, 1H), 1.95–1.84 (m, 1H), 0.93 (dd, J = 6.7, 3.7 Hz, 6H). 13C-NMR (100 MHz, CDCl3) δ 201.63, 174.54, 44.01, 41.20, 37.70, 35.74, 30.16, 20.74, 19.35. HRMS (ESI-MS) Found 172.1333 [M+H] +, C9H18NO2 requires 172.1338; found 212.1259 [M+H2O+Na] +, C9H19NNaO3 requires 212.1263. The enantiomeric excess of 97% ee was determined by HPLC (Daicel Chiralpak OD-H, hexane/isopropanol = 85/15, flow rate 1.0 mL/min, T = 30 °C, 215 nm, tR (minor) 7.857 min, tR(major) 5.839 min).

Synthesis of 19: To a THF/H2O (60/30 mL) solution of 16a (3.08 g, 10 mmol, 1 equiv) was added OsO4 (0.08 M in tBuOH, 1.2 mL, 0.1 mmol, 0.01 equiv), NaIO4 (8.61 g, 40.0 mmol, 4 equiv) and DABCO (4.50 g, 40 mmol, 4 equiv) at 0 °C. The solution was stirred at 0 °C for 4 h and then evaporated under reduced pressure. The resulting mixture was extracted with CH2Cl2 (3 × 100 mL). The combined organic layer was washed with brine (100 mL), dried over Na2SO4, filtered and concentrated under reduced pressure. Purification of the residue by column chromatography (1:10 ethyl acetate-hexane) gave 19 (2.76 g, 8.94 mmol, 89%) as a colorless oil. 1H-NMR (400 MHz, CDCl3) δ 9.56 (s, 1H), 6.79–6.67 (m, 3H), 4.10 (t, J = 6.4 Hz, 2H), 3.83 (s, 3H), 3.56 (t, J = 6.1 Hz, 2H), 3.36 (s, 3H), 2.70–2.65 (m, 1H), 2.37–2.09 (m, 6H),

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1.78–1.72 (m, 1H), 0.92 (dd, J = 10.1, 6.9 Hz, 6H). $^{13}$C-NMR (100 MHz, CDCl$_3$) δ 203.01, 148.56, 148.07, 133.08, 121.56, 114.52, 111.94, 69.50, 66.26, 58.79, 56.16, 45.00, 41.32, 37.39, 30.02, 29.75, 19.69, 18.74. HRMS (ESI-MS) found 331.1862 [M+Na]$^+$, C$_{18}$H$_{28}$NaO$_4$ requires 331.1885.

Synthesis of 22: A PhMe solution (10 mL) of 19 (308.4 mg, 1 mmol, 1 equiv) and TsNHNH$_2$ (186.0 mg, 1 mmol, 1 equiv) was stirred for 45 min at room temperature and then evaporated under reduced pressure. The N-tosylhydrazone 21 thus obtained was re-dissolved in PhMe (10 mL). Then CuI (19.0 mg, 0.1 mmol, 0.1 equiv), K$_3$PO$_4$ (1.28 g, 6 mmol, 6 equiv) and HOP(OEt)$_2$ (0.65 mL, 5 mmol, 5 equiv) were added to the reaction vessel. The reaction system was flushed with nitrogen for 3 times and heated under refluxing for 12 h. The reaction mixture was filtered and the filtrate was evaporated under reduced pressure. Purification of the residue by column chromatography (2:1 ethyl acetate-hexane) gave 22 (342.4 mg, 0.80 mmol, 80%) as a colorless oil. $^1$H-NMR (400 MHz, CDCl$_3$) δ 6.79–6.67 (m, 3H), 4.11–4.00 (m, 6H), 3.83 (s, 3H), 3.58 (t, J = 6.0 Hz, 2H), 3.36 (s, 3H), 2.57 (dd, J = 13.7, 5.3 Hz, 1H), 2.33 (dd, J = 13.7, 7.5 Hz, 1H), 1.73–1.41 (m, 6H), 1.28 (td, J = 7.0, 2.6 Hz, 6H), 0.90 (dd, J = 14.0, 6.8 Hz, 6H). $^{13}$C-NMR (100 MHz, CDCl$_3$) δ 148.37, 147.68, 134.11, 121.28, 114.33, 111.87, 69.40, 66.13, 61.37, 58.68, 56.12, 46.67 (d, J = 16.0 Hz), 36.29, 29.68, 28.66, 23.80 (d, J = 14.0 Hz), 22.54 (d, J = 3.9 Hz), 19.08, 18.87, 16.48, 16.43. $^{31}$P-NMR (162 MHz, CDCl$_3$) δ 32.40. HRMS (ESI-MS) Found 431.2556 [M+H]$^+$, C$_{22}$H$_{40}$O$_6$P requires 431.2563; found 453.2378 [M+Na]$^+$, C$_{22}$H$_{39}$NaO$_6$P requires 453.2382.

Synthesis of 24: To a THF solution (1 mL) of 22 (91.9 mg, 0.21 mmol, 1 equiv) was added dropwise n-BuLi (1.6 M in hexane, 0.2 mL, 0.32 mmol, 1.5 equiv) at -78 °C. The reaction mixture was stirred at the same temperature for 40 min. Then allyl bromide 23 (0.1 mL, 1.16 mmol, 5.4 equiv) was added slowly. The mixture was allowed to reach to room temperature gradually and then evaporated under reduced pressure to remove the volatile materials. Purification of the residue by column chromatography (1:6 acetone-CH$_2$Cl$_2$) gave 24 (69.3 mg, 0.15 mmol, 69%) as a colorless oil. $^1$H-NMR (400 MHz, CDCl$_3$) δ 6.79–6.67 (m, 3H), 5.88–5.61 (m, 1H), 5.09–5.03 (m, 1H), 4.99–4.89 (m, 1H), 4.12–3.98 (m, 6H), 3.83 (d, J = 2.1 Hz, 3H), 3.58 (t, J = 6.1 Hz, 2H), 3.35 (s, 3H), 2.56–2.07 (m, 2H), 1.95–1.45 (m, 2H), 1.32–1.25 (m, 6H), 0.94–0.82 (m, 6H). $^{13}$C-NMR (100 MHz, CDCl$_3$) δ 148.37, 147.68, 134.11, 121.28, 114.33, 111.87, 69.40, 66.13, 61.37, 58.68, 56.12, 46.67 (d, J = 16.0 Hz), 36.29, 29.68, 28.66, 23.80 (d, J = 14.0 Hz), 22.54 (d, J = 3.9 Hz), 19.08, 18.87, 16.48, 16.43. $^{31}$P-NMR (162 MHz, CDCl$_3$) δ 32.40. HRMS (ESI-MS) Found 471.2862 [M+H]$^+$, C$_{25}$H$_{44}$O$_6$P requires 471.2876; found 493.2692 [M+Na]$^+$, C$_{25}$H$_{43}$NaO$_6$P requires 493.2695; found 509.2442 [M+K]$^+$, C$_{25}$H$_{43}$KO$_6$P requires 509.2434.

Synthesis of 26: To a THF solution (2 mL) of methyl 2-(diethoxyphosphoryl)acetate 25 (183 μL, 0.75 mmol, 1 equiv) was added n-BuLi (1.6 M in hexane, 0.5 mL, 0.75 mmol, 1.5 equiv) at -78 °C. The reaction mixture was stirred at the same temperature for 40 min. Then 18 (85.6 mg, 0.5 mmol, 1 equiv) in THF was added slowly. The mixture was allowed to reach to room temperature gradually and then evaporated.
under reduced pressure to remove the volatile materials. Purification of the residue by column chromatography (2:1 ethyl acetate-hexane) gave 26 (84.1 mg, 0.37 mmol, 74%) in a cis/trans mixture as a colorless oil. \(^1\)H-NMR (400 MHz, CDCl\(_3\)) for \(E\)-26: \(\delta\) 6.90–6.82 (m, 1H), 5.84 (d, \(J = 15.5\) Hz, 1H), 3.71 (s, 3H), 3.03 (s, 3H), 2.96 (s, 3H), 2.60–2.53 (m, 2H), 2.42–2.32 (m, 1H), 2.00–1.89 (m, 1H), 0.98 (dd, \(J = 10.9, 6.8\) Hz, 6H). for \(Z\)-26: \(\delta\) 6.30–6.23 (m, 1H), 5.78 (d, \(J = 11.5\) Hz, 1H), 3.72 (s, 3H), 3.18–3.11 (m, 1H), 3.02 (s, 3H), 2.97 (s, 3H), 2.69–2.60 (m, 2H), 2.00–1.89 (m, 1H), 0.93 (dd, \(J = 6.7, 2.9\) Hz, 6H). 

13C-NMR (100 MHz, CDCl\(_3\)) for \(E\)-26: \(\delta\) 174.22, 166.83, 147.17, 122.25, 51.34, 47.12, 37.61, 35.58, 32.45, 30.81, 20.95, 19.55. For \(Z\)-26: \(\delta\) 174.89, 166.59, 148.22, 120.25, 51.01, 47.43, 37.61, 35.54, 30.81, 28.93, 21.05, 19.55. HRMS (ESI-MS) Found 250.1423 [M+Na\(^+\)], \(C_{12}H_{21}NNaO_3\) requires 250.1419.

Synthesis of 27: To a THF solution (43 mL) of 19 (2.70 g, 8.75 mmol, 1 equiv) was added LiBH\(_4\) (235.4 mg, 10.8 mmol, 1.2 equiv) at room temperature. The solution was stirred at room temperature for 1 h and quenched with saturated aq. NH\(_4\)Cl (1 mL). The mixture was extracted with CH\(_2\)Cl\(_2\) for three times. The combined organic layer was dried over Na\(_2\)SO\(_4\), filtered and concentrated under reduced pressure. Purification of the residue by column chromatography (1:1 ethyl acetate-hexane) gave 27 (2.71 g, 8.74 mmol, 100%) as a colorless oil. \(^1\)H-NMR (400 MHz, CDCl\(_3\)) \(\delta\) 6.79–6.68 (m, 3H), 4.11 (t, \(J = 6.5\) Hz, 2H), 3.84 (s, 3H), 3.59–3.55 (m, 4H), 3.36 (s, 3H), 2.61–2.56 (m, 1H), 2.38–2.33 (m, 1H), 2.13–2.07 (m, 2H), 1.75–1.71 (m, 1H), 1.63–1.57 (m, 2H), 1.44–1.39 (m, 1H), 1.31 (s, 1H), 0.93–0.87 (m, 6H). 13C-NMR (100 MHz, CDCl\(_3\)) \(\delta\) 148.24, 147.60, 134.43, 121.28, 114.39, 111.78, 69.44, 66.09, 61.66, 58.70, 56.08, 42.43, 37.02, 33.30, 29.62, 29.17, 19.16, 18.60. HRMS (ESI-MS) Found 311.2206 [M+H\(^+\)], \(C_{18}H_{31}O_4\) requires 311.2222.

Synthesis of 28: To a THF solution (60 mL) of 27 (3.67 g, 11.8 mmol, 1 equiv), TsCl (2.55 g, 13.4 mmol, 1.1 equiv) and DMAP (69.5 mg, 0.6 mmol, 0.05 equiv) was added dropwise Et\(_3\)N (5 mL, 35.8 mmol, 3 equiv) at room temperature. The solution was stirred at room temperature for 14 h and then evaporated under reduced pressure. The resulting mixture was diluted with Et\(_2\)O (150 mL), filtered and concentrated under reduced pressure. Purification of the residue by column chromatography (1:2 ethyl acetate-hexane) gave 28 (5.25 g, 11.3 mmol, 96%) as a colorless oil. \(^1\)H-NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.72 (d, \(J = 8.2\) Hz, 2H), 7.32 (d, \(J = 8.1\) Hz, 2H), 6.75 (d, \(J = 8.1\) Hz, 1H), 6.65 (s, 1H), 6.60 (d, \(J = 8.1\) Hz, 1H), 4.08 (t, \(J = 6.5\) Hz, 2H), 3.92 (t, \(J = 6.9\) Hz, 2H), 3.84 (s, 3H), 3.58 (t, \(J = 6.1\) Hz, 2H), 3.36 (s, 3H), 2.53 (dd, \(J = 13.7, 6.2\) Hz, 1H), 2.44 (s, 3H), 2.27 (dd, \(J = 13.8, 8.0\) Hz, 1H), 2.10 (m, \(J = 6.3\) Hz, 2H), 1.68–1.46 (m, 4H), 0.84 (dd, \(J = 16.3, 6.8\) Hz, 6H). 13C-NMR (100 MHz, CDCl\(_3\)) \(\delta\) 148.46, 147.83, 144.68, 133.61, 133.32, 129.86, 127.90, 121.24, 114.34, 111.94, 69.72, 69.49, 66.20, 58.76, 56.17, 42.22, 36.71, 29.75, 29.47, 29.02, 21.70, 19.07, 18.51. HRMS (ESI-MS) Found 464.2238 [M]+, \(C_{25}H_{36}O_6S\) requires 464.2233; found 487.2111 [M+Na\(^+\)], \(C_{25}H_{36}NaO_6S\) requires 487.2130.

Synthesis of 30a (Method A): A mixture of 28 (4.45 g, 9.6 mmol, 1 equiv), 29a (3.42 g, 19.2 mmol, 2 equiv) and K\(_2\)CO\(_3\) (6.63 g, 48.0 mmol, 5 equiv) in MeCN (60 mL) was heated at 50 °C for 24 h. The reaction mixture was diluted with CH\(_2\)Cl\(_2\) (120 mL),
filtered and concentrated under reduced pressure. Purification of the residue by column chromatography (1:10 ethyl acetate-hexane) gave 30a (4.27 g, 9.1 mmol, 95%) as a colorless oil.

**Method B:** To a THF solution (80 mL) of 27 (2.48 g, 7.99 mmol, 1 equiv), PPh$_3$ (3.17 g, 12 mmol, 1.5 equiv) and 29a (2.85 g, 16 mmol, 2 equiv) was added a THF solution of DEAD (2.6 mL, 16 mmol, 2 equiv) at -40 °C. The reaction mixture was stirred at -40 °C for 10 min and room temperature for 20 min, and then evaporated under reduced pressure. The resulting mixture was diluted with CH$_2$Cl$_2$ (150 mL) and washed with brine (6 × 100 mL), dried over Na$_2$SO$_4$, filtered and concentrated under reduced pressure. Purification of the residue by column chromatography (1:10 ethyl acetate-hexane) gave 30a (3.01 g, 6.39 mmol, 80%) as a colorless oil. 1H-NMR (400MHz, CDCl$_3$) $\delta$ 7.55 (s, 5H), 6.76 (d, $J$ = 8.0 Hz, 1H), 6.70–6.67 (m, 2H), 4.08 (t, $J$ = 6.4 Hz, 2H), 3.82 (s, 3H), 3.57 (t, $J$ = 6.1 Hz, 2H), 3.35–3.23 (m, 5H), 2.65–2.60 (m, 1H), 2.41–2.36 (m, 1H), 2.12–2.06 (m, 2H), 1.84–1.78 (m, 2H), 1.71–1.58 (m, 2H), 0.94–0.88 (m, 6H). 13C-NMR (100 MHz, CDCl$_3$) $\delta$ 154.36, 148.32, 147.69, 133.81, 133.73, 130.05, 129.76, 123.81, 121.26, 114.28, 111.82, 69.39, 66.11, 58.67, 56.05, 45.51, 36.59, 36.04, 35.23, 32.07, 29.76, 29.64, 29.08, 19.03, 18.80. HRMS (ESI-MS) Found 471.2424 [M+H]$^+$, C$_{25}$H$_{35}$N$_4$O$_3$S requires 471.2430; found 493.2245 [M+Na]$^+$, C$_{25}$H$_{34}$N$_4$NaO$_3$S requires 493.2249.

Synthesis of 30b was carried out according to the method A for the synthesis 30a. 30b was obtained in 60% yield from 28 as a colorless oil. 1H-NMR (400 MHz, CDCl$_3$) $\delta$ 6.78 (d, $J$ = 8.0 Hz, 1H), 6.71–6.68 (m, 2H), 4.10 (t, $J$ = 6.5 Hz, 2H), 3.84 (s, 3H), 3.58 (t, $J$ = 6.1 Hz, 2H), 3.36 (s, 3H), 3.32–3.26 (m, 2H), 2.62 (dd, $J$ = 13.8, 5.6 Hz, 1H), 2.41 (dd, $J$ = 13.8, 7.6 Hz, 1H), 2.10 (m, $J$ = 6.3 Hz, 2H), 1.85–1.73 (m, 2H), 1.70 (s, 9H), 1.67–1.59 (m, 2H), 0.91 (dd, $J$ = 16.3, 6.8 Hz, 6H). 13C-NMR (150 MHz, CDCl$_3$) $\delta$ 152.80, 148.45, 147.81, 134.03, 121.37, 114.31, 111.94, 69.52, 66.26, 60.95, 58.79, 56.19, 45.68, 36.71, 32.74, 29.78, 29.74, 29.06, 28.78, 19.20, 18.81. HRMS (ESI-MS) Found 473.2551 [M+Na]$^+$, C$_{23}$H$_{38}$N$_4$NaO$_3$S requires 473.2562; found 489.2266 [M+Na]$^+$, C$_{23}$H$_{38}$N$_4$NaO$_3$S requires 489.2294.

Synthesis of 30c was carried out according to the method A for the synthesis 30a. 30c was obtained in 85% yield from 28 as a colorless oil. 1H-NMR (300 MHz, CDCl$_3$) $\delta$ 6.77–6.65 (m, 3H), 4.10 (t, $J$ = 6.5 Hz, 2H), 3.85 (d, $J$ = 1.5 Hz, 6H), 3.58 (t, $J$ = 6.1 Hz, 2H), 3.36 (s, 3H), 3.34–3.13 (m, 2H), 2.63 (dd, $J$ = 13.7, 5.3 Hz, 1H), 2.35 (dd, $J$ = 13.7, 8.0 Hz, 1H), 2.15–2.05 (m, 2H), 1.84–1.70 (m, 2H), 1.70–1.58 (m, 2H), 0.92 (dd, $J$ = 14.8, 6.8 Hz, 6H). 13C-NMR (150 MHz, CDCl$_3$) $\delta$ 154.34, 148.41, 147.79, 133.90, 121.40, 114.41, 111.84, 69.49, 66.25, 58.78, 56.16, 45.52, 36.69, 33.32, 32.22, 30.00, 29.76, 29.28, 19.08, 18.95. HRMS (ESI-MS) Found 409.2266 [M+H]$^+$, C$_{20}$H$_{32}$N$_4$O$_3$S requires 409.2273; found 431.2089 [M+Na]$^+$, C$_{20}$H$_{32}$N$_4$NaO$_3$S requires 431.2093.

**Synthesis of 31a:** To a EtOH solution (33 mL) of 30a (1.54 g, 3.3 mmol, 1 equiv) was added a H$_2$O$_2$ solution (7 mL) of (NH$_4$)$_6$Mo$_7$O$_24$·4H$_2$O (859.7 mg, 0.7 mmol, 0.2 equiv) at room temperature. The solution was stirred at room temperature for 24 h and
evaporated under reduced pressure. Puriification of the residue by column chromatography (1:6 ethyl acetate-hexane) gave 31a (1.55 g, 3.09 mmol, 94%) as a colorless oil. 1H-NMR (400 MHz, CDCl 3) δ 7.65–7.58 (m, 5H), 6.79–6.67 (m, 3H), 4.10 (t, J = 6.5 Hz, 2H), 3.84 (s, 3H), 3.65–3.47 (m, 4H), 2.34 (dd, J = 13.7, 9.0 Hz, 1H), 2.13–2.07 (m, 2H), 1.98–1.89 (m, 1H), 1.86–1.72 (m, 2H), 1.70–1.65 (m, 1H), 0.94 (dd, J = 12.3, 6.8 Hz, 1H). 13C-NMR (100 MHz, CDCl 3) δ 153.45, 148.58, 148.00, 133.09, 133.02, 131.49, 129.73, 125.16, 121.20, 114.14, 112.04, 69.44, 66.20, 58.73, 56.13, 54.95, 45.24, 36.62, 29.65, 22.82, 19.01, 18.90. HRMS (ESI-MS) Found 503.2309 [M+H]+, C25H35N4O5S requires 503.2328; found 525.2116 [M+Na]+, C25H34N4NaO5S requires 525.2148.

Synthesis of 31b was carried out according to the same procedure for the synthesis 31a. 31b was obtained in 90% yield from 30b as a colorless oil. 1H-NMR (600 MHz, CDCl 3) δ 6.79 (d, J = 8.0 Hz, 1H), 6.73–6.69 (m, 2H), 4.11 (t, J = 6.5 Hz, 2H), 3.84 (s, 3H), 3.74–3.69 (m, 1H), 3.66–3.61 (m, 1H), 3.58 (t, J = 6.2 Hz, 2H), 3.36 (s, 3H), 2.69 (dd, J = 13.9, 5.9 Hz, 1H), 2.38 (dd, J = 13.9, 8.7 Hz, 1H), 2.10 (m, J = 6.3 Hz, 2H), 1.99–1.94 (m, 1H), 1.87–1.84 (m, 1H), 1.83 (s, 9H), 1.80–1.75 (m, 1H), 1.73–1.66 (m, 1H), 0.95 (dd, J = 15.2, 6.8 Hz, 6H). 13C-NMR (150 MHz, CDCl 3) δ 154.11, 148.62, 148.04, 133.22, 121.29, 114.28, 112.10, 69.54, 66.27, 65.47, 58.80, 56.21, 55.68, 45.39, 36.72, 29.78, 29.58, 22.96, 19.18, 18.88. HRMS (ESI-MS) Found 505.2445 [M+Na]+, C23H38N4NaO5S requires 505.2461; found 521.2181 [M+K]+, C23H38N4KO5S requires 521.2200.

Synthesis of 31c was carried out according to the same procedure for the synthesis 31a. 31c was obtained in 98% yield from 30c as a colorless oil. 1H-NMR (300 MHz, CDCl 3) δ 6.79–6.64 (m, 3H), 4.29 (s, 3H), 4.10 (t, J = 6.5 Hz, 2H), 3.85 (s, 3H), 3.58 (t, J = 6.2 Hz, 2H), 3.53–3.34 (m, 5H), 2.70 (dd, J = 13.8, 5.4 Hz, 1H), 2.39–2.27 (m, 1H), 2.15–2.07 (m, 2H), 2.14–1.64 (m, 4H), 0.94 (dd, J = 11.1, 6.8 Hz, 6H). 13C-NMR (150 MHz, CDCl 3) δ 153.22, 148.65, 148.09, 132.99, 121.21, 114.18, 112.09, 69.48, 66.28, 58.79, 56.20, 54.78, 45.21, 36.70, 36.09, 29.83, 29.72, 22.86, 19.01. HRMS (ESI-MS) Found 441.2157 [M+H]+, C20H33N4O5S requires 441.2172; found 463.1971 [M+Na]+, C20H33N4NaO5S requires 463.1991; found 479.1711 [M+K]+, C20H33N4KO5S requires 479.1730.

General Synthesis of 2a via the Julia-Kocienski olefination: A dried tube equipped with a magnetic stirrer was charged 31 (0.2 mmol, 1.0 equiv) and flushed with nitrogen. Then dried solvent (2.5 mL) was added via a glass syringe. Unless otherwise noted, the solution was cooled to -70 °C and a solution of MHMDS base (0.4 mmol in solvent (1mL), where M= Li, Na, or K) was added dropwise. After being stirred at -70 °C for 1 h, aldehyde 18 (0.8 mmol in solvent (1 mL)) was added dropwise. The resulting reaction mixture was stirred at -70 °C and then allowed to warm gradually to room temperature and stirred for a few hours until 31 has disappeared as monitored by TLC. The reaction mixture was quenched with brine and diluted with CH2Cl2. The organic layer was separated, dried over Na2SO4, filtered, concentrated and purified by flash column chromatography on silica gel with a mixed ethyl acetate
and hexane (v/v = 1:2) as eluent to gave 2a as a light yellow oil. $^1$H-NMR (600 MHz, CDCl$_3$) $\delta$ 6.77 (d, $J = 8.1$ Hz, 1H), 6.68–6.65 (m, 2H), 5.41–5.37 (m, 1H), 5.32–5.27 (m, 1H), 4.09 (t, $J = 6.5$ Hz, 2H), 3.83 (s, 3H), 3.58 (t, $J = 6.2$ Hz, 2H), 3.36 (s, 3H), 2.99 (s, 3H), 2.91 (s, 3H), 2.48–2.41 (m, 2H), 2.35–2.28 (m, 2H), 2.22–2.18 (m, 1H), 2.10 (p, $J = 6.3$ Hz, 2H), 1.96–1.90 (m, 1H), 1.89–1.80 (m, 2H), 1.71–1.64 (m, 1H), 1.51–1.45 (m, 1H), 0.95 (d, $J = 6.7$ Hz, 3H), 0.88 (d, $J = 6.9$ Hz, 6H), 0.84 (d, $J = 6.8$ Hz, 3H). $^1$H-NMR (600 MHz, DMSO) $\delta$ 6.83 (d, $J = 8.1$ Hz, 1H), 6.70 (s, 1H), 6.64 (d, $J = 8.1$ Hz, 1H), 5.34–5.29 (m, 1H), 5.27–5.22 (m, 1H), 3.97 (t, $J = 6.4$ Hz, 2H), 3.71 (s, 3H), 3.47 (t, $J = 6.3$ Hz, 2H), 3.24 (s, 3H), 2.54–2.51 (m, 1H), 2.42 (dd, $J = 13.7$, 6.7 Hz, 1H), 2.28 (dd, $J = 13.7$, 8.0 Hz, 1H), 2.12 (t, $J = 6.8$ Hz, 2H), 1.94–1.86 (m, 3H), 1.77–1.68 (m, 2H), 1.63–1.56 (m, 1H), 1.48–1.42 (m, 1H), 0.86 (dd, $J = 21.1$, 6.8 Hz, 6H), 0.81 (dd, $J = 9.5$, 7.0 Hz, 6H). $^{13}$C-NMR (100 MHz, DMSO) $\delta$ 174.05, 147.78, 147.11, 134.00, 130.31, 129.02, 120.99, 114.20, 112.09, 68.58, 65.37, 57.91, 55.55, 46.93, 45.46, 37.06, 35.37, 34.89, 32.93, 32.38, 30.28, 29.11, 27.72, 20.70, 19.57, 19.06, 18.68. HRMS (ESI-MS) Found 448.3408 [M+H]$^+$, C$_{27}$H$_{46}$NO$_4$ requires 448.3427; found 470.3216 [M+Na]$^+$, C$_{27}$H$_{45}$NNaO$_4$ requires 470.3246.

Synthesis of Aliskiren HCl salt: The synthesis of 33 from 2a was carried out according to the reported procedures in ref. 3p and 3s.

**Compound 32:** $^1$H-NMR (600 MHz, CDCl$_3$) $\delta$ 6.79 (d, $J = 8.1$ Hz, 1H), 6.72 (s, 1H), 6.69 (d, $J = 8.2$ Hz, 1H), 4.34 (q, $J = 6.7$ Hz, 1H), 4.11 (t, $J = 6.2$ Hz, 2H), 4.03–4.00 (m, 1H), 3.85 (s, 3H), 3.58 (t, $J = 6.1$ Hz, 2H), 3.36 (s, 3H), 2.74 (dd, $J = 13.8$, 4.4 Hz, 1H), 2.63–2.59 (m, 1H), 2.24–2.08 (m, 6H), 1.95–1.90 (m, 1H), 1.88–1.78 (m, 2H), 1.62–1.57 (m, 1H), 1.01 (t, $J = 7.8$ Hz, 6H), 0.93 (d, $J = 6.8$ Hz, 3H), 0.86 (d, $J = 6.9$ Hz, 3H). $[^\alpha]_D^{20} = 39.2$ (c 1, CHCl$_3$).

**Compound 33:** $^1$H-NMR (600 MHz, CDCl$_3$) $\delta$ 6.79 (d, $J = 8.1$ Hz, 1H), 6.73 (s, 1H), 6.70 (d, $J = 8.1$ Hz, 1H), 6.38 (t, $J = 6$ Hz, 1H), 5.98 (s, 1H), 5.37 (s, 1H), 4.10 (t, $J = 6.4$ Hz, 2H), 3.84 (s, 3H), 3.58 (t, $J = 6.2$ Hz, 2H), 3.47–3.42 (m, 2H), 3.36 (s, 3H), 3.35–3.26 (m, 1H), 3.02 (d, $J = 4.8$ Hz, 1H), 2.90–2.87 (m, 1H), 2.55–2.51 (m, 1H), 2.49–2.46 (m, 1H), 2.12–2.06 (m, 3H), 1.90–1.84 (m, 1H), 1.78–1.70 (m, 2H), 1.68–1.55 (m, 3H), 1.38–1.32 (m, 1H), 1.23 (s, 6H), 0.93–0.87 (m, 12H). $^{13}$C-NMR (100 MHz, CDCl$_3$) $\delta$ 180.32, 176.02, 148.44, 147.79, 133.94, 121.32, 114.35, 111.97, 72.21, 69.44, 66.55, 66.17, 58.66, 56.13, 50.80, 47.31, 43.10, 42.59, 37.48, 34.37, 31.78, 30.29, 29.91, 29.61, 24.20, 24.06, 21.22, 20.37, 19.99, 17.50.

Conversion of 33 into the aliskiren HCl salt was performed as following: To a MeOH solution (4 mL) of 33 (21.6 mg, 0.037 mmol, 1 equiv) and 2-aminoethanol (6.7 mg, 0.11 mmol, 3 equiv) was added 10% Pd/C (24.0 mg) and stirred at room temperature under H$_2$ atmosphere for 3 h. The mixture was filtered and evaporated under reduced pressure. The residue was dissolved in CH$_2$Cl$_2$ (3 mL) and washed with de-ionized H$_2$O (6 × 1 mL), then acidified with 17% HCl in MeOH (0.14 mL). The solution was evaporated under reduced pressure and the residue was dried under vacuum at room temperature to give Aliskiren HCl salt (18.1 mg, 0.031 mmol, 82%) as a white solid.
\(^1\)H-NMR (DMSO, 400 MHz) \(\delta\) 7.70 (s, 3H), 7.59 (t, \(J = 6.0\) Hz, 1H), 7.15 (s, 1H), 6.83 (d, \(J = 7.7\) Hz, 3H), 6.71 (d, \(J = 7.2\) Hz, 1H), 3.99 (t, \(J = 6.1\) Hz, 2H), 3.72 (s, 3H), 3.47 (t, \(J = 6.2\) Hz, 2H), 3.32 (dd, \(J = 13.2, 7.3\) Hz, 1H), 3.25 (s, 4H), 3.10–3.05 (m, 1H), 2.70 (s, 1H), 2.46–2.35 (m, 2H), 2.30–2.26 (m, 1H), 1.97–1.90 (m, 2H), 1.81 (s, 1H), 1.73–1.53 (m, 3H), 1.48–1.28 (m, 3H), 1.06 (s, 6H), 0.87–0.79 (m, 12H).

\(^13\)C-NMR (DMSO, 100 MHz) \(\delta\) 178.46, 174.61, 147.89, 147.20, 133.15, 121.17, 114.27, 111.97, 68.66, 68.00, 65.41, 57.95, 55.57, 54.29, 48.76, 46.34, 42.51, 36.42, 33.89, 30.64, 30.32, 29.18, 28.12, 23.52, 20.76, 20.01, 19.09, 17.38. HRMS (ESI-MS) Found 552.3992 [M-Cl]+, C\(_{30}\)H\(_{54}\)N\(_3\)O\(_6\) requires 552.4013; found 574.3815 [M-HCl+Na]+, C\(_{30}\)H\(_{53}\)N\(_3\)NaO\(_6\) requires 574.3832. \([\alpha]_D^{20} = -5.5\) (c 1, DMSO).

Conversion of 33 into the Aliskiren Hemifumarate salt was performed as following: To a MeOH solution (3 mL) of 33 (17.3 mg, 0.03 mmol, 1 equiv) and 2-aminoethanol (5.5 mg, 0.09 mmol, 3 equiv) was added 10% Pd/C (8.0 mg) and stirred at room temperature under H\(_2\) atmosphere for 3 h. The mixture was filtered and evaporated under reduced pressure. The residue was dissolved in CH\(_2\)Cl\(_2\) (3 mL) and washed with de-ionized H\(_2\)O (6 × 1 mL), then acidified with 13.5 mM fumaric acid in MeOH (1 mL, 0.45 equiv). The solution was evaporated under reduced pressure and the residue was dried under vacuum at room temperature to give aliskiren hemifumarate salt (16.7 mg, 0.027 mmol, 91%) as a white solid. \(^1\)H-NMR (600 MHz, DMSO) \(\delta\) 7.57 (t, \(J = 5.8\) Hz, 1H), 7.16 (s, 1H), 6.82 (d, \(J = 7.4\) Hz, 2H), 6.80 (s, 1H), 6.70 (d, \(J = 7.8\) Hz, 1H), 6.39 (s, 1H), 3.97 (t, \(J = 6.1\) Hz, 2H), 3.71 (s, 3H), 3.47 (t, \(J = 6.0\) Hz, 3H), 3.30–3.26 (m, 1H), 3.24 (s, 3H), 3.16–3.07 (m, 2H), 2.57 (s, 1H), 2.49–2.43 (m, 1H), 2.40–2.33 (m, 1H), 2.31–2.24 (m, 1H), 1.97–1.89 (m, 2H), 1.78 (s, 1H), 1.71–1.51 (m, 3H), 1.37–1.24 (m, 3H), 1.04 (s, 6H), 0.89–0.75 (m, 12H). \([\alpha]_D^{20} = -20.8\) (c 1, DMSO).
Copies of NMR spectra and HPLC charts

Figure S1. $^1$H- (upper) and $^{13}$C-NMR (lower) spectra of compound 10a
Figure S2. $^1$H- (upper) and $^{13}$C-NMR (lower) spectra of compound 10b’
Figure S3. $^1$H- (upper) and $^{13}$C-NMR (lower) spectra of compound 10b
Figure S4. $^1$H- (upper) and $^{13}$C-NMR (lower) spectra of compound 10c
Figure S5. $^1$H- (upper) and $^{13}$C-NMR (lower) spectra of compound 11a
Figure S6. $^1$H- (upper) and $^{13}$C-NMR (lower) spectra of compound 11b
Figure S7. $^1$H- (upper) and $^{13}$C-NMR (lower) spectra of compound 11c
Figure S8. $^1$H- (upper) and $^{13}$C-NMR (lower) spectra of compound 12a
Figure S9. $^1$H- (upper) and $^{13}$C-NMR (lower) spectra of compound 12b
Figure S10. $^1$H- (upper) and $^{13}$C-NMR (lower) spectra of compound 12c
Figure S11. $^1$H- (upper) and $^{13}$C-NMR (lower) spectra of compound 14
Figure S12. $^1$H- (upper) and $^{13}$C-NMR (lower) spectra of compound 13a
**Figure S13.** $^1$H- (upper) and $^{13}$C-NMR (lower) spectra of compound 13b
Figure S14. $^1$H- (upper) and $^{13}$C-NMR (lower) spectra of compound 13c
Figure S15. $^1$H- (upper) and $^{13}$C-NMR (lower) spectra of compound 15a
Figure S16. $^1$H- (upper) and $^{13}$C-NMR (lower) spectra of compound 15b
Figure S17. $^1$H- (upper) and $^{13}$C-NMR (lower) spectra of compound 15c
Figure S18. $^1$H- (upper) and $^{13}$C-NMR (lower) spectra of compound 16a
Figure S19. $^1$H- (upper) and $^{13}$C-NMR (lower) spectra of compound 16b
Figure S20. $^1$H- (upper) and $^{13}$C-NMR (lower) spectra of compound 16c
Figure S21. $^1$H- (upper) and $^{13}$C-NMR (lower) spectra of compound 18
Figure S22. $^1$H- (upper) and $^{13}$C-NMR (lower) spectra of compound 19
Figure S23. $^1$H- (upper), $^{13}$C- (mid) and $^{31}$P-NMR (bottom) of 22.
Figure S24. $^1$H- (upper) and $^{13}$C-NMR (lower) spectra of compound 24
Figure S25. $^1$H- (upper) and $^{13}$C-NMR (lower) spectra of compound 26
Figure S26. $^1$H- (upper) and $^{13}$C-NMR (lower) spectra of compound 27
Figure S27. $^1$H- (upper) and $^{13}$C-NMR (lower) spectra of compound 28
Figure S28. $^1$H- (upper) and $^{13}$C-NMR (lower) spectra of compound 30a
Figure S29. $^1$H- (upper) and $^{13}$C-NMR (lower) spectra of compound 30b
Figure S30. $^1$H- (upper) and $^{13}$C-NMR (lower) spectra of compound 30c
Figure S31. $^1$H- (upper) and $^{13}$C-NMR (lower) spectra of compound 31a
Figure S32. $^1$H- (upper) and $^{13}$C-NMR (lower) spectra of compound 31b
Figure S33. $^1$H- (upper) and $^{13}$C-NMR (lower) spectra of compound 31c
Figure S34. $^1$H- (upper) and $^{13}$C-NMR (lower) spectra of compound 2a
Figure S35. $^1$H-NMR spectra of compound 32
Figure S36. $^1$H- (upper) and $^{13}$C-NMR (lower) spectra of compound 33
Figure S37. $^1$H- (upper) and $^{13}$C-NMR (lower) spectra of compound Aliskiren HCl salt
Figure S38. $^1$H-NMR spectra of compound Aliskiren hemifumarate salt
Figure S39. Chiral HPLC chart of compound 15a

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Figure S40. Chiral HPLC chart of compound 18
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**Figure S41.** HPLC chart of compound 2a synthesized under the conditions of entry 14 in Table 2