Supporting Information

Synthesis of highly substituted 2-spiropiperidines

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3-Oxo-5-phenyl-5-(toluene-4-sulfonylamino)-pentanoic acid methyl ester (2)

To a solution of diisopropylamine (824 µL, 5.89 mmol) in THF (10 mL) at -78 °C was added n-BuLi (2.41 mL, 5.79 mmol) dropwise. The mixture was warmed to 0 °C for 15 mins, then re-cooled to -78 °C. A solution of methyl acetoacetate (312 µL, 2.90 mmol) in THF (2 mL) was added via syringe pump over 20 mins. The mixture was warmed to -50 °C, and a solution of N-Benzylidene-4-methylbenzenesulfonylamide (250 mg, 0.965 mmol) in THF (2 mL) was added fast. The reaction was stirred for 40 mins, then quenched with sat. aq. NH₄Cl (4 mL). The mixture was warmed to rt, and layers were separated. The aqueous was extracted with EtOAc (2 x 20 mL). Organics were combined, washed with water (10 mL), and brine (10 mL), dried (MgSO₄), filtered, and concentrated in vacuo. The residue was purified by column chromatography (10-30% EtOAc/hexane) to afford the title compound (225 mg, 0.600 mmol, 62% yield) as a colourless oil. Spectroscopic data was identical to that previously reported.¹

¹H NMR (400 MHz, CDCl₃): δ 7.59-7.54 (m, 2H), 7.20-7.11 (m, 5H), 7.09-7.04 (m, 2H), 5.69 (d, J = 7.2 Hz, 1H), 4.73 (dt, J = 7.2, 6.3 Hz, 1H), 3.65 (s, 3H), 3.36 (d, J = 15.5 Hz, 1H), 3.31 (d, J = 15.5 Hz, 1H), 3.17 (dd, J = 17.4, 6.3 Hz, 1H-4), 2.36 (s, 3H) ppm.

Isopropylidene-3-oxo-5-phenyl-5-(toluene-4-sulfonylamino)-pentanoic acid methyl ester (3)

To a 0.5 M solution of TiCl₄ in THF (2 mL, 1.07 mmol) at 0 °C was added a solution of 2 (400 mg, 1.07 mmol), acetone (156 µL, 2.13 mmol), and pyridine (345 µL, 4.26 mmol) in THF (2 mL). The reaction was stirred overnight at rt. The reaction mixture was partitioned between water (10 mL) and EtOAc (30 mL). The aqueous was extracted with EtOAc (2 x 15 mL). Organics were combined, washed with NaHCO₃ (30 mL), water (30 mL), and brine (30 mL), dried (MgSO₄), filtered, and concentrated in vacuo. The residue was purified by column chromatography (15% EtOAc/hexane) to afford the title compound (115 mg, 0.277 mmol, 26% yield) as a yellow oil. Spectroscopic data was identical to that previously reported.¹

¹H NMR (400 MHz, CDCl₃): δ 7.59-7.54 (m, 2H), 7.19-7.12 (m, 5H), 7.11-7.05 (m, 2H), 5.69 (d, J = 7.2 Hz, 1H), 4.73 (dt, J = 7.2, 6.3 Hz, 1H), 3.65 (s, 3H), 3.36 (d, J = 15.5 Hz, 1H), 3.31 (d, J = 15.5 Hz, 1H), 3.17 (dd, J = 17.4, 6.3 Hz, 1H-4), 2.36 (s, 3H) ppm; ¹³C NMR (101 MHz, CDCl₃): δ 201.1, 165.5, 156.1, 143.3, 139.8, 137.4, 130.9, 129.5, 128.5, 127.3, 126.8, 54.3, 51.9, 49.4, 23.5, 23.1, 21.6 ppm; IR (ATR): νmax 3278, 2952, 1726, 1694, 1156 cm⁻¹; HRMS (ESI) 438.1338 (M + Na⁺). C₂₂H₂₅NNaO₅S requires 438.1346.

Isopropylidene-3-oxo-5-phenyl-4-enoic acid methyl ester (4)

To a 0.5 M solution of TiCl₄ in THF (1.5 mL, 0.735 mmol) at 0 °C was added a solution of 5 (150 mg, 0.735 mmol), acetone (108 µL, 1.47 mmol), and pyridine (240 µL, 2.94 mmol) in THF (1 mL). The reaction was stirred overnight at rt. The reaction mixture was partitioned between water (5 mL) and EtOAc (30 mL). The aqueous was extracted with EtOAc (2 x 15 mL). Organics were combined, washed with NaHCO₃ (30 mL), water (30 mL), and brine (30 mL), dried (Na₂SO₄), filtered, and concentrated in vacuo. The residue was purified by column chromatography (5% EtOAc/hexane) to afford the title compound (23 mg, 0.0942 mmol, 13% yield) as a yellow oil.

$^1$H NMR (500 MHz, CDCl$_3$): δ 7.58 – 7.49 (m, 2H), 7.42 – 7.35 (m, 3H), 7.42 (d, J = 16.2 Hz, 1H), 6.80 (d, J = 16.2 Hz, 1H), 3.69 (s, 3H), 2.26 (s, 3H), 1.87 (s, 3H) ppm; $^{13}$C-NMR (101 MHz, CDCl$_3$): δ 195.5, 165.5, 154.8, 145.6, 134.5, 130.9, 129.5, 129.1, 128.6, 127.6, 51.9, 24.2, 22.5 ppm; IR (ATR): ν$_{max}$ 3063, 2912, 1708, 1641, 1620, 1596, 1435, 1301, 1238, 1217, 1201, 1097, 1033 cm$^{-1}$; HRMS (ESI) 267.0992 (M + Na$^+$). C$_{16}$H$_{16}$NaO$_3$ requires 267.0992.

3-Hydroxy-5-phenyl-penta-2,4-dienoic acid methyl ester (5)

To a solution of 6$^2$ (500 mg, 2.25 mmol) in CH$_2$Cl$_2$ (3 mL) was added acetic anhydride (223 µL, 2.36 mmol), Et$_3$N (470 µL, 3.38 mmol) and DMAP (cat.). The reaction was stirred for 2h at rt. MeOH (400 µL) was added, and the mixture stirred for 15 mins. The mixture was diluted with CH$_2$Cl$_2$ (8 mL) and partitioned with 0.1 M HCl (10 mL). Organics were combined, washed with water (10 mL), CuSO$_4$ (10 mL), and brine (10 mL), dried (MgSO$_4$), filtered, and concentrated in vacuo. The residue was purified by column chromatography (5% EtOAc/hexane) to afford title compound (201 mg, 0.905 mmol, 44% yield) as a white solid.

mp 93-96 °C; $^1$H NMR (400 MHz, CDCl$_3$): δ 11.9 (s, 1H), 7.51-7.47 (m, 2H), 7.44 (d, J = 16.0 Hz, 1H), 7.39-7.31 (m, 3H), 6.44 (dd, J = 16.0, 1.5 Hz, 1H), 5.18 (s, 1H), 3.77 (s, 3H) ppm; $^{13}$C-NMR (101 MHz, CDCl$_3$): δ 173.4, 169.4, 137.1, 135.4, 129.5, 128.9, 127.7, 121.9, 91.7, 51.5 ppm; IR (ATR): ν$_{max}$ 3027, 2953, 1634, 1590, 1445, 1202 cm$^{-1}$; HRMS (ESI) 227.0695 (M + Na$^+$). C$_{14}$H$_{16}$NNaO$_5$ requires 227.0679.

[Benzenesulfonyl-4-trifluoromethyl-phenyl]-methyl]-carbamic acid tert-butyI ester (7k)

Following the general procedure: 4-(Trifluoromethyl)benzaldehyde (6.00 g, 34.5 mmol), tert-butyI carbamate (2.69 g, 23.0 mmol) and benzenesulfinic acid sodium salt (7.54 g, 46.0 mmol). The white precipitate was triturated by stirring in diethyl ether (50 mL) for 1h at rt. Filtration gave the title compound (6.87 g, 16.6 mmol, 72% yield) as a white solid. Spectroscopic data was identical to that previously reported.$^3$

$^1$H NMR (400 MHz, CDCl$_3$): δ 7.94 (d, J = 7.8 Hz, 2H), 7.70-7.65 (m, 3H), 7.63-7.53 (m, 4H), 6.02 (d, J = 10.5 Hz, 1H), 5.93 (d, J = 10.5 Hz, 1H), 1.23 (s, 9H) ppm.

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Solvent: CDCl₃
Frequency: 400 Mhz
Solvent: CDCl₃
Frequency: 101 MHz
Solvent: CDCl$_3$
Frequency: 400 Mhz

$\text{MeO} - \text{O} - \text{O} - \text{HN} - \text{SO}$

$\text{3}$

$\text{MeO} - \text{O} - \text{O} - \text{HN} - \text{SO}$

$\text{3}$
Solvent: CDCl₃
Frequency: 101 Mhz
Solvent: CDCl₃
Frequency: 400 Mhz
Solvent: CDCl₃
Frequency: 101 MHz
Solvent: CDCl$_3$
Frequency: 400 Mhz
Solvent: CDCl$_3$
Frequency: 101 Mhz

![Chemical Structure Image]
Solvent: CDCl$_3$
Frequency: 400 Mhz

![Chemical Structure Image]

- 7.26 ppm
- 4.87 ppm
- 1.00 ppm
- 3.01 ppm
- 1.99 ppm
- 2.73 ppm
Solvent: CDCl$_3$
Frequency: 101 Mhz
Solvent: CDCl$_3$
Frequency: 400 Mhz
Solvent: CDCl$_3$
Frequency: 101 Mhz
Solvent: CDCl$_3$
Frequency: 400 Mhz
Solvent: CDCl$_3$
Frequency: 101 MHz
Solvent: CDCl$_3$
Frequency: 400 Mhz

[Chemical Structure Image]

7h
Solvent: CDCl$_3$
Frequency: 101 MHz
Solvent: CDCl$_3$
Frequency: 400 Mhz
Solvent: CDCl$_3$
Frequency: 101 Mhz
Solvent: CDCl$_3$
Frequency: 400 Mhz
Solvent: CDCl$_3$
Frequency: 101 MHz

![Chemical Structure](image)
Solvent: CDCl₃
Frequency: 400 Mhz
Solvent: CDCl$_3$
Frequency: 101 Mhz
Solvent: CDCl$_3$
Frequency: 400 Mhz

\[
\text{MeO}\overset{\text{O}}{\text{C}}\overset{\text{O}}{\text{C}}\overset{\text{H}}{\text{N}}_\text{Boc}
\]___9b
Solvent: CDCl$_3$
Frequency: 101 Mhz

\[
\text{MeO} \quad \begin{array}{c}
\text{O} \\
\text{O} \\
\text{HN} \quad \text{Boc}
\end{array}
\]

9b
Solvent: CDCl$_3$
Frequency: 400 Mhz
Solvent: CDCl$_3$
Frequency: 101 Mhz
Solvent: CDCl$_3$
Frequency: 400 Mhz
Solvent: CDCl₃
Frequency: 101 MHz

![Chemical structure of 9d]

- 200.8531
- 172.7625
- 167.3954
- 155.193
- 141.2317
- 128.7982
- 127.6289
- 126.3171
- 79.8885
- 77.1600
- 52.5359
- 50.4604
- 48.7788
- 28.4168
Solvent: CDCl$_3$
Frequency: 400 Mhz

\[ \text{MeO} \quad \text{HN}^\text{Boc} \quad \text{9e} \quad \text{F} \]
Solvent: CDCl$_3$
Frequency: 101 Mhz
Solvent: CDCl$_3$
Frequency: 376 Mhz
Solvent: CDCl$_3$
Frequency: 400 Mhz
Solvent: CDCl$_3$
Frequency: 101 Mhz

MeO \begin{array}{c}
\text{O} & \text{O} \\
\text{HN}^- & \text{Boc}
\end{array} \\
9f

\begin{array}{c}
\text{MeO} \\
\text{OMe}
\end{array}
Solvent: CDCl$_3$
Frequency: 400 Mhz

![Chemical structure image]

$\text{MeO}$

$\text{HN}$

$\text{Boc}$

S37
Solvent: CDCl$_3$
Frequency: 101 Mhz

![NMR spectrum of compound 9g]
Solvent: CDCl$_3$
Frequency: 400 Mhz

![Chemical Structure](attachment:structure.png)
Solvent: CDCl$_3$
Frequency: 101 Mhz
Solvent: CDCl$_3$
Frequency: 400 Mhz
Solvent: CDCl$_3$
Frequency: 101 Mhz
Solvent: CDCl₃
Frequency: 400 Mhz

![Chemical Structure](image)
Solvent: CDCl$_3$
Frequency: 101 Mhz
Solvent: CDCl$_3$
Frequency: 500 Mhz
Solvent: CDCl$_3$
Frequency: 101 Mhz

11a
Solvent: CDCl$_3$
Frequency: 500 Mhz

$11b$
Mixture of diastereomers
Solvent:  CDCl₃  
Frequency:  101 Mhz
Solvent: CDCl$_3$
Frequency: 400 Mhz
Solvent: CDCl$_3$
Frequency: 101 Mhz
Solvent: CDCl₃
Frequency: 400 MHz
Solvent: CDCl$_3$
Frequency: 101 Mhz
Solvent: CDCl$_3$
Frequency: 400 Mhz
Solvent: CDCl$_3$
Frequency: 101 Mhz
Solvent: CDCl₃
Frequency: 400 Mhz

Mixture of diastereomers

11f
Solvent: CDCl$_3$
Frequency: 101 Mhz
Solvent: CDCl$_3$
Frequency: 400 Mhz

Mixture of diastereomers
Solvent: CDCl₃
Frequency: 101 Mhz
Solvent: CDCl$_3$
Frequency: 376 Mhz

11g
Solvent: CDCl$_3$
Frequency: 400 Mhz

Two-step Mixture of diastereomers
Solvent: CDCl$_3$
Frequency: 400 Mhz

11h
One-pot
Mixture of diastereomers
Solvent: CDCl$_3$
Frequency: 101 MHz
Solvent: CDCl$_3$

Frequency: 376 Mhz

![NMR Spectrum Image]
Solvent: CDCl₃
Frequency: 400 Mhz

Two-step
Solvent: CDCl$_3$
Frequency: 400 Mhz

One-pot Mixture of diastereomers
Solvent: CDCl$_3$
Frequency: 101 Mhz
Solvent: CDCl₃
Frequency: 376 Mhz
Solvent: CDCl$_3$
Frequency: 400 Mhz
Solvent: CDCl₃
Frequency: 101 Mhz
Solvent: CDCl$_3$
Frequency: 376 MHz
Solvent: CDCl$_3$
Frequency: 400 Mhz

Two-Step Mixture of diastereomers
Solvent: CDCl$_3$
Frequency: 400 Mhz

One-pot Mixture of diastereomers
Solvent: CDCl₃
Frequency: 101 Mhz
Solvent: CDCl$_3$
Frequency: 400 Mhz

11l
Mixture of diastereomers
Solvent: CDCl₃
Frequency: 101 Mhz
Solvent: CDCl₃
Frequency: 400 Mhz
Solvent: CDCl$_3$
Frequency: 101 Mhz
Solvent: CDCl$_3$
Frequency: 400 Mhz

11n
Mixture of diastereomers rotamers
Solvent: CDCl$_3$  
Frequency: 101 Mhz
Solvent: CDCl₃
Frequency: 400 Mhz

Mixture of diastereomers
Solvent: CDCl$_3$
Frequency: 101 Mhz
Solvent: CDCl$_3$
Frequency: 400 MHz

Two-step Mixture of diastereomers
Solvent: CDCl₃
Frequency: 400 Mhz

One-pot
Mixture of diastereomers
Solvent: CDCl₃
Frequency: 101 MHz

11p
Solvent: CDCl$_3$
Frequency: 400 Mhz

11q
Mixture of diastereomers
Solvent: CDCl$_3$
Frequency: 101 Mhz

11q
Solvent: CDCl$_3$
Frequency: 400 Mhz

Two-step Mixture of diastereomers
Solvent: CDCl₃
Frequency: 400 Mhz

11r
One-pot Mixture of diastereomers
Solvent: \( \text{CDCl}_3 \)
Frequency: 101 Mhz
Solvent: CDCl$_3$
Frequency: 400 MHz

11s
Mixture of diastereomers
Solvent: CDCl$_3$
Frequency: 101 MHz

![Chemical structure](image-url)
Solvent: CDCl₃
Frequency: 400 Mhz

11t
Mixture of diastereomers
Solvent: CDCl₃
Frequency: 101 MHz

11t
Solvent: CDCl$_3$
Frequency: 400 MHz

Mixture of diastereomers and rotamers
Solvent: CDCl$_3$
Frequency: 101 MHz
Solvent: CDCl$_3$
Frequency: 400 MHz

rotamers
Solvent: CDCl$_3$
Frequency: 101 MHz
Solvent: CDCl$_3$
Frequency: 400 Mhz

Mixture of diastereomers
Solvent: CDCl$_3$
Frequency: 101 MHz
Solvent: CDCl$_3$
Frequency: 376 MHz
Solvent: CDCl$_3$

Frequency: 400 MHz

Mixture of diastereomers
Solvent: CDCl$_3$
Frequency: 101 Mhz

![Chemical Structure](image)
Solvent: CDCl$_3$
Frequency: 400 Mhz
Solvent: CDCl$_3$
Frequency: 101 Mhz

![Chemical Structure](image)

12h