**Ammonia Free Partial Reduction of Pyridinium Salts as a
Versatile Route to Dihydropyridones**

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SUPPLEMENTARY MATERIAL

Key experimental procedures are included.

4-Methoxypyridine-2-carboxylic acid methyl ester 5⁶

Picolinic acid (9.92 g, 80.7 mmol) and sodium bromide (0.90 g, 8.7 mmol) were added to thionyl chloride (70 mL). The mixture was heated at reflux for 16 h. The reaction was concentrated *in vacuo* and cooled to 0 °C. MeOH (30 mL) was added cautiously and the reaction was heated at reflux for 36 h. The solvent was removed *in vacuo* and the residue was dissolved in CH₂Cl₂ (100 mL). Sodium carbonate (12.8 g, 121 mmol) was added and the mixture stirred for 3 h. H₂O (100 mL) was added and the reaction was extracted with CH₂Cl₂ (5 x 50 mL). The combined organic extracts were dried (MgSO₄) and concentrated *in vacuo*. The crude residue was purified via flash column chromatography (SiO₂, eluting with Et₂O, followed by 5:95 MeOH-CH₂Cl₂) and re-crystallised (hexane) to furnish the product **5** (9.03 g, 67%) as white needles. δ_{H} (400 MHz; CDCl₃) 8.50-8.46 (1 H, m, NCH), 7.63-7.59 (1 H, m, C(OCH₃)CH), 6.94-6.90 (1 H, m, NCH=CH), 3.94 (3 H, s, OCH₃), 3.85 (3 H, s, OCH₃); δ_{C} (100 MHz; CDCl₃) 166.5 (CO₂CH₃), 165.7

(NCCO₂CH₃), 150.9 (NCH), 149.5 (COCH₃), 113.0 (NCH=CH), 111.1 (C(OCH₃)CH), 55.5 (OCH₃), 52.9 (OCH₃).

4-Methoxy-2-methoxycarbonyl-1-methylpyridinium iodide 6

A solution of pyridine **5** (2.57 g, 15.4 mmol) in methyl iodide (10.2 ml, 164 mmol) was heated for 16 h at reflux. Et₂O (20 ml) was added and the suspension formed was filtered to give the product **6** (4.36 g, 92%) as a powdery yellow solid which was washed with Et₂O (2 × 10 ml) and dried under high vacuum. m.p. 113–115 °C (dec.); $\nu_{\max}(\text{KBr})/\text{cm}^{-1}$ 3009, 1731, 1636, 1559, 1529, 1413, 1332, 1306, 1105; δ_{H} (400 MHz; CDCl₃) 9.49 (1 H, d, *J* 7.2, NCH), 7.89 (1 H, d, *J* 3.1, C(OCH₃)CH), 7.79 (1 H, dd, *J* 7.2 and 3.1, NCH=CH), 4.53 (3 H, s, NCH₃), 4.21 (3 H, s, OCH₃), 4.05 (3 H, s, OCH₃); δ_{C} (100 MHz; CDCl₃) 171.5 (CO₂CH₃), 159.5 (NCCO₂CH₃), 152.0 (NCH), 143.0 (COCH₃), 118.0 (C(OCH₃)CH), 114.6 (NCH=CH), 59.3 (OCH₃), 54.9 (OCH₃), 48.0 (NCH₃); *m/z* (C.I.) 182 (M⁺, 100%); HRMS (C.I.) for C₉H₁₂NO₃ requires 182.0817, found (M⁺) 182.0814.

4-Methoxy-1-(4-methoxybenzyl)-2-methoxycarbonylpyridinium iodide 7

Pyridine **5** (635 mg, 3.80 mmol) was added to a stirred solution of 4-methoxybenzyl iodide (932 mg, 3.76 mmol) in Et₂O (7 mL) and stirred for 48 h under an atmosphere of argon at r.t. The solvent was removed *in vacuo*, a further portion of Et₂O (20 mL) was added and the reaction stirred for

another 5 h. The reaction was filtered and the precipitate was washed with Et₂O (2 x 10 mL). The resulting solid was dried under high vacuum to furnish the *pyridinium salt 7* (1.45 g, 92%) as a pale yellow solid. m.p. 93-95 °C (Et₂O); ν_{max} (KBr)/cm⁻¹ 1743, 1628, 1513, 1306, 1251; δ_{H} (400 MHz; CDCl₃) 9.93 (1 H, d, *J* 7.3, NCH), 7.89 (1 H, dd, *J* 7.3 and 3.1, NCH=CH), 7.68 (1 H, d, *J* 3.1, C(OCH₃)CH), 7.37 (2 H, d, *J* 8.4, ArH), 6.90 (2 H, d, *J* 8.4, ArH), 6.12 (2 H, s, NCH₂), 4.23 (3 H, s, OCH₃), 4.02 (3 H, s, OCH₃), 3.81 (3 H, s, OCH₃); δ_{C} (100 MHz; CDCl₃) 171.5 (CO₂CH₃), 160.5 (ArC), 160.0 (CCO₂CH₃), 150.9 (NCH), 143.4 (COCH₃), 130.6 (ArC), 124.9 (ArC), 117.8 (C(OCH₃)CH), 114.8 (ArC), 113.1 (NCH=CH), 60.8 (NCH₂), 59.4 (OCH₃), 55.4 (OCH₃), 54.9 (OCH₃); *m/z* (E.S.I.) 288 (M⁺, 100%); HRMS (E.S.I.) for C₁₆H₁₆NO₄ requires 288.1236, found (M⁺) 288.1228.

General Procedures:

Sodium-Naphthalene Ammonia-free Birch reduction.

Sodium (5 eq.) and naphthalene were added to THF (40 mL) at r.t. and sonicated for 4 h forming a dark green solution under an atmosphere of argon. The reaction was cooled to -78 °C and the pyridinium salt **6** (1 eq.) was added *via* solid addition and the remains were rinsed in with THF (10 mL). After stirring for 1 h at -78°C, the electrophile (5 eq.) was added and the reaction stirred for a further 1 h. NH₄Cl (10 mL, saturated solution) was added and stirred for 15 min, followed by HCl (10 mL, 3 M) and the reaction was

allowed to warm up to r.t. over 16 h. The aqueous layer was washed with Et₂O (3 x 50 mL), basified with Na₂CO₃ (saturated solution) until the pH was >9 and extracted with CH₂Cl₂ (6 x 25 mL). The combined organic extracts were dried (MgSO₄) and concentrated *in vacuo*. The crude residue was purified via flash column chromatography (SiO₂, eluting with 1:9 acetone-CH₂Cl₂).

Lithium-DBB Ammonia-free Birch reduction.

Sliced lithium wire (4 eq.) and DBB (4 eq.) were added to a Schlenk tube containing glass anti-bumping granules under an atmosphere of argon. The mixture was stirred vigorously for 2-4 h until the lithium was reduced to a fine powder. THF (30 mL) was added and the resultant deep blue-green solution was cooled to -78 °C and stirred for 30 min. Pyridinium salt **7** (1 eq.) was added via solid addition and the reaction stirred for a further 15 min. Dibromoethane (filtered through K₂CO₃ and MgSO₄) was added dropwise until the blue-green colour was quenched. The electrophile (4 eq.) was added dropwise and the reaction stirred for 3 h before NH₄Cl (5 mL, saturated solution) was added, followed by stirring for a further 15 min. HCl (10 mL, 1 M) was added and the reaction was warmed to r.t. and stirred for 16 h. The reaction was extracted with Et₂O (3 x 50 mL) and the combined organic extracts were washed with brine (50 mL, saturated solution), dried (MgSO₄) and concentrated *in vacuo*. The crude residue was purified via flash column chromatography

(SiO₂, eluting first with 500 mL 1:99 Et₂O-Petrol, followed by a gradient of Et₂O to 1:4 acetone-Et₂O).

(2-*RS*)-1,2-Dimethyl-5,6-dihydropyridone-2-carboxylic acid methyl ester 8

Sodium (116 mg, 5.05 mmol), naphthalene (710 mg, 5.53 mmol) and pyridinium salt **6** (310 mg, 1.00 mmol) were subjected to the general sodium-naphthalene reduction procedure using methyl iodide (0.35 mL, 5.62 mmol) as the electrophile. *Dihydropyridone 8* (130 mg, 71%) was isolated as a colourless solid. m.p. 107-110 °C (Et₂O); ν_{max} (KBr)/cm⁻¹ 1730, 1622, 1578; δ_{H} (400 MHz; CDCl₃) 6.99 (1 H, d, *J* 7.6, NCH=CH), 4.92 (1 H, d, *J* 7.6, NCH=CH), 3.71 (3 H, s, CO₂CH₃), 3.06 (3 H, s, NCH₃), 2.83 (1 H, d, *J* 16.9, CH_AH_B), 2.52 (1 H, d, *J* 16.9, CH_AH_B), 1.53 (3 H, s, CCH₃); δ_{C} (100 MHz; CDCl₃) 189.9 (C(O)CH₂), 173.0 (CO₂CH₃), 155.5 (NCH), 99.0 (NCH=CH), 64.8 (CCH₃), 52.9 (OCH₃), 46.4 (NCH₃), 39.1 (C(O)CH₂), 22.2 (CCH₃); *m/z* (E.S.I.) 184 (M+H⁺, 100%); HRMS (E.S.I.) for C₉H₁₄NO₃ requires 184.0974, found (M+H⁺) 184.0981.

(2-*RS*)-1-Methyl-5,6-dihydropyridone-2-carboxylic acid methyl ester 9

Sodium (105 mg, 4.57 mmol), naphthalene (560 mg, 4.38 mmol) and pyridinium salt **6** (271 mg, 0.88 mmol) were subjected to the general sodium-naphthalene reduction procedure without the addition of an electrophile.

Dihydropyridone 9 (111 mg, 65%) was isolated as an oil. $\nu_{\max}(\text{film})/\text{cm}^{-1}$ 2956, 1738, 1630, 1591; δ_{H} (400 MHz; CDCl_3) 7.01 (1 H, dd, J 7.6 and 1.0, $\text{NCH}=\text{CH}$), 4.93 (1 H, dd, J 7.6 and 1.0, $\text{NCH}=\text{CH}$), 4.06 (1 H, ddd, J 7.9, 2.9 and 1.0, $\text{NCH}(\text{CO}_2\text{CH}_3)$), 3.73 (3 H, s, CO_2CH_3), 3.10 (3 H, s, NCH_3), 2.87 (1 H, dd, J 16.8 and 7.9, $\text{CH}_\text{A}\text{H}_\text{B}$), 2.62 (1 H, ddd, J 16.8, 2.9 and 1.0, $\text{CH}_\text{A}\text{H}_\text{B}$); δ_{C} (100 MHz; CDCl_3) 188.4 ($\text{C}(\text{O})\text{CH}_2$), 170.2 (CO_2CH_3), 154.5 (NCH), 98.8 ($\text{NCH}=\text{CH}$), 60.9 ($\text{NCH}(\text{CO}_2\text{CH}_3)$), 52.8 (OCH_3), 42.7 (NCH_3), 37.8 ($\text{C}(\text{O})\text{CH}_2$); m/z (C.I.) 170 ($\text{M}+\text{H}^+$, 100%); HRMS (C.I.) for $\text{C}_8\text{H}_{12}\text{NO}_3$ requires 170.0817, found ($\text{M}+\text{H}^+$) 170.0817.

(2-*RS*)-2-Ethyl-1-methyl-5,6-dihydropyridone-2-carboxylic acid methyl ester 10

Sodium (115 mg, 5.00 mmol), naphthalene (706 mg, 5.52 mmol) and pyridinium salt **6** (312 mg, 1.01 mmol) were subjected to the general sodium-naphthalene reduction procedure using ethyl iodide (0.40 mL, 5.00 mmol) as the electrophile. *Dihydropyridone 10* (118 mg, 59%) was isolated as a yellow solid. m.p. 58–60°C (Et_2O); $\nu_{\max}(\text{KBr})/\text{cm}^{-1}$ 2954, 1734, 1636, 1585; δ_{H} (400 MHz; CDCl_3) 6.99 (1 H, d, J 7.6, $\text{NCH}=\text{CH}$), 4.91 (1 H, d, J 7.6, $\text{NCH}=\text{CH}$), 3.70 (3 H, s, CO_2CH_3), 3.08 (3 H, s, NCH_3), 2.70 (1 H, d, J 16.5, $\text{CH}_\text{A}\text{H}_\text{B}$), 2.64 (1 H, d, J 16.3, $\text{CH}_\text{A}\text{H}_\text{B}$), 1.90 (2 H, q, J 7.6, CH_2CH_3), 0.99 (3 H, t, J 7.5 CH_2CH_3); δ_{C} (100 MHz; CDCl_3) 190.7 ($\text{C}(\text{O})\text{CH}_2$), 173.1 (CO_2CH_3), 156.3

(NCH), 99.0 (NCH=CH), 68.4 ((CH₃CH₂)C(CO₂CH₃)), 52.8 (OCH₃), 42.4 (C(O)CH₂), 39.1 (NCH₃), 27.7 (CH₂CH₃), 8.4 (CH₂CH₃); *m/z* (C.I.) 198 (M+H⁺, 100%); HRMS (C.I.) for C₁₀H₁₆NO₃ requires 198.1130, found (M+H⁺) 198.1133.

(2-*RS*)-1-(4-Methoxybenzyl)-2-methyl-5,6-dihydropyridone-2-carboxylic acid methyl ester 11

Lithium (62 mg, 8.8 mmol), DBB (2.14 g, 8.04 mmol) and pyridinium salt **7** (824 mg, 1.99 mmol) were subjected to the general lithium-DBB reduction procedure using methyl iodide (0.50 mL, 8.10 mmol) as the electrophile. *Dihydropyridone 11* (426 mg, 74%) was isolated as a white solid. m.p. 123-125 °C (Et₂O); *v*_{max}(KBr)/cm⁻¹ 2954, 1737, 1643, 1582, 1514, 1249; *δ*_H (400 MHz; CDCl₃) 7.22 (2 H, d, *J* 8.6, ArH), 6.99 (1 H, d, *J* 7.7, NCH), 6.91 (2 H, d, *J* 8.6, ArH), 5.01 (1 H, d, *J* 7.7, NCH=CH), 4.47 (1 H, d, *J* 15.3, NCH_AH_B), 4.36 (1 H, d, *J* 15.3, NCH_AH_B), 3.82 (3 H, s, OCH₃), 3.75 (3 H, s, CO₂CH₃), 2.93 (1 H, d, *J* 16.4, C(O)CH_AH_B), 2.62 (1 H, d, *J* 16.4, C(O)CH_AH_B), 1.54 (3 H, s, CCH₃); *δ*_C (100 MHz; CDCl₃) 190.0 (C(O)CH₂), 173.3 (CO₂CH₃), 159.4 (ArC), 154.2 (NCH), 129.0 (ArC), 128.9 (ArC), 114.4 (ArC), 99.7 (NCH=CH), 65.8 (CCH₃), 55.3 (OCH₃), 54.3 (NCH₂), 53.0 (CO₂CH₃), 47.0 (C(O)CH₂), 22.5 (CCH₃); *m/z* (C.I.) 290 (M+H⁺, 100%), 170 (M-PMB+2H⁺, 82) 121 (PMB, 81); HRMS (C.I.) for C₁₆H₂₀NO₄ requires 290.1392, found (M+H⁺) 290.1404.

(2-*RS*)-1-(4-Methoxybenzyl)-5,6-dihydropyridone-2-carboxylic acid methyl ester 12

Lithium (30 mg, 4.34 mmol), DBB (1.09 g, 4.08 mmol) and pyridinium salt **7** (415 mg, 1.00 mmol) were subjected to the general lithium-DBB reduction procedure without the addition of an electrophile. Dihydropyridone **12** (179 mg, 65%) was isolated as a pale yellow oil. $\nu_{\max}(\text{film})/\text{cm}^{-1}$ 2954, 1740, 1638, 1588, 1250; δ_{H} (400 MHz; CDCl_3) 7.22 (2 H, d, J 8.7, ArH), 7.18 (1 H, dd, J 7.6 and 1.0, NCH), 6.92 (2 H, d, J 8.7, ArH), 5.02 (1 H, d, J 7.6, NCH=CH), 4.49 (1 H, d, J 14.7, $\text{NCH}_\text{A}\text{H}_\text{B}$), 4.37 (1 H, d, J 14.7, $\text{NCH}_\text{A}\text{H}_\text{B}$), 4.06 (1 H, td, J 5.6 and 1.0, NCH(CO_2CH_3)), 3.83 (3 H, s, OCH_3), 3.77 (3 H, s, CO_2CH_3), 2.78 (2 H, d J 5.6, $\text{C}(\text{O})\text{CH}_2$); δ_{C} (100 MHz; CDCl_3) 188.9 ($\text{C}(\text{O})\text{CH}_2$), 170.4 (CO_2CH_3), 159.7 (ArC), 153.4 (NCH), 129.5 (ArC), 127.4 (ArC), 114.4 (ArC), 98.9 (NCH=CH), 58.5 (NCH₂), 58.0 (NCH(CO_2CH_3)), 55.3 (OCH_3), 52.8 (CO_2CH_3), 37.9 ($\text{C}(\text{O})\text{CH}_2$); m/z (C.I.) 276 ($\text{M}+\text{H}^+$, 100%), 156 ($\text{M}-\text{PMB}+2\text{H}^+$, 38) 121 (PMB, 82); HRMS (C.I.) for $\text{C}_{15}\text{H}_{18}\text{NO}_4$ requires 276.1236, found ($\text{M}+\text{H}^+$) 276.1237.

(2-*RS*)-2-*iso*-Butyl-1-(4-methoxybenzyl)-5,6-dihydropyridone-2-carboxylic acid methyl ester 13

Lithium (33 mg, 4.74 mmol), DBB (1.09 g, 4.08 mmol) and pyridinium salt **7** (415 mg, 1.00 mmol) were subjected to the general lithium-DBB reduction procedure using *iso*-

butyl iodide (0.50 mL, 4.05 mmol) as the electrophile. *Dihydropyridone* **13** (273 mg, 67%) was isolated as a yellow oil. $\nu_{\max}(\text{film})/\text{cm}^{-1}$ 2957, 1736, 1651, 1586, 1514, 1249; δ_{H} (400 MHz; CDCl_3) 7.22 (2 H, d, J 8.6, ArH), 6.95-6.88 (3H, m, NCH and ArH), 4.99 (1 H, d, J 7.9, NCH=CH), 4.57 (1 H, d, J 15.0, $\text{NCH}_\text{A}\text{H}_\text{B}$), 4.37 (1 H, d, J 15.0, $\text{NCH}_\text{A}\text{H}_\text{B}$), 3.83 (3 H, s, OCH_3), 3.71 (3 H, s, CO_2CH_3), 2.92 (1 H, d, J 16.2, $\text{C}(\text{O})\text{CH}_\text{A}\text{H}_\text{B}$), 2.70 (1 H, d, J 16.2, $\text{C}(\text{O})\text{CH}_\text{A}\text{H}_\text{B}$), 2.03-1.95 (1 H, m, $\text{CH}(\text{CH}_3)_2$), 1.88-1.77 (2 H, m, $\text{CH}_2\text{CH}(\text{CH}_3)_2$), 0.96 (3 H, d, J 6.5, CHCH_3), 0.93 (3 H, d, J 6.1, CHCH_3); δ_{C} (100 MHz; CDCl_3) 190.6 ($\text{C}(\text{O})\text{CH}_2$), 172.8 (CO_2CH_3), 159.3 (ArC), 153.6 (NCH), 129.3 (ArC), 128.7 (ArC), 114.3 (ArC), 99.5 (NCH=CH), 68.6 (C-*s*-Bu), 55.3 (OCH_3), 53.3 (NCH_2), 52.6 (CO_2CH_3), 43.7 ($\text{CH}_2\text{CH}(\text{CH}_3)_2$), 24.7 (CHCH_3), 23.9 ($\text{CH}(\text{CH}_3)_2$), 23.5 (CHCH_3); m/z (E.S.I.) 354 ($\text{M}+\text{MeCN}+\text{NH}_4^+$, 69%), 332 ($\text{M}+\text{H}^+$, 100); HRMS (E.S.I.) for $\text{C}_{19}\text{H}_{26}\text{NO}_4$ requires 332.1862, found ($\text{M}+\text{H}^+$) 332.1860.

(2-*RS*)-2-(4-Chlorobutyl)-1-(4-methoxybenzyl)-5,6-dihydropyridone-2-carboxylic acid methyl ester 14

Lithium (23 mg, 3.31 mmol), DBB (531 mg, 1.99 mmol) and pyridinium salt **7** (199 mg, 0.48 mmol) were subjected to the general lithium-DBB reduction procedure using 1-chloro-4-iodobutane (0.25 mL, 2.05 mmol) as the electrophile. *Dihydropyridone* **14** (114 mg, 65%) was isolated as a pale yellow oil. $\nu_{\max}(\text{film})/\text{cm}^{-1}$ 2954, 1735, 1646, 1586, 1513, 1249; δ_{H} (400 MHz; CDCl_3) 7.20 (2 H, d,

J 8.7, ArH), 6.93 (1 H, d, J 7.78, NCH), 6.89 (2 H, d, J 8.7, ArH), 4.93 (1 H, d, J 7.8, NCH=CH), 4.45 (1 H, d, J 14.9, NCH_AH_B), 4.34 (1 H, d, J 14.9, NCH_AH_B), 3.78 (3 H, s, OCH₃), 3.69 (3 H, s, CO₂CH₃), 3.44 (2 H, t, J 6.3, CH₂Cl), 2.84 (1 H, d, J 16.4, C(O)CH_AH_B), 2.66 (1 H, d, J 16.4, C(O)CH_AH_B), 1.96-1.88 (2 H, m, CH₂), 1.77-1.59 (2 H, m, CH₂), 1.53-1.48 (2 H, m, CH₂); δ_{C} (100 MHz; CDCl₃) 190.1 (C(O)CH₂), 172.8 (CO₂CH₃), 159.4 (ArC), 154.2 (NCH), 129.4 (ArC), 128.3 (ArC), 114.4 (ArC), 99.6 (NCH=CH), 68.9 (CCO₂CH₃), 55.3 (OCH₃), 53.6 (NCH₂), 52.8 (CO₂CH₃), 44.2 (CH₂), 43.5 (CH₂), 33.7 (CH₂), 32.3 (CH₂), 21.8 (CH₂); m/z (E.S.I.) 426 (M[³⁷Cl]+MeCN+NH₄⁺, 51%), 424 (M[³⁵Cl]+MeCN+NH₄⁺, 100), 368 (M[³⁷Cl]+H⁺, 36), 366 (M[³⁵Cl]+H⁺, 80); HRMS (E.S.I.) for C₁₉H₂₅NO₄Cl requires 366.1472, found (M+H⁺) 366.1471.

1-(4-Methoxybenzyl)-5,6-dihydropyridone-2,2-dicarboxylic acid dimethyl ester 15

Lithium (20 mg, 2.9 mmol), DBB (543 mg, 2.04 mmol) and pyridinium salt **15** (200 mg, 0.48 mmol) were subjected to the general lithium-DBB reduction procedure using methyl chloroformate (0.15 mL, 1.95 mmol) as the electrophile. Dihydropyridone **15** (117 mg, 70%) was isolated as a pale yellow solid. m.p. 79-81 °C (Et₂O); ν_{max} (KBr)/cm⁻¹ 2956, 1742, 1656, 1589, 1250; δ_{H} (400 MHz; CDCl₃) 7.27 (2 H, d, J 8.8, ArH), 6.93-6.89 (3 H, m, NCH and ArH), 5.02 (1 H, d, J 8.1,

NCH=CH), 4.23 (2 H, s, NCH₂), 3.81 (3 H, s, OCH₃), 3.76 (6 H, s, 2 x CO₂CH₃), 3.13 (2 H, s, C(O)CH₂); δ_c (100 MHz; CDCl₃) 188.0 (C(O)CH₂), 168.1 (CO₂CH₃), 159.6 (ArC), 152.9 (NCH), 129.7 (ArC), 127.8 (ArC), 114.2 (ArC), 100.7 (NCH=CH), 73.7 (C(CO₂CH₃)₂), 56.2 (NCH₂), 55.3 (OCH₃), 53.6 (CO₂CH₃), 42.7 (C(O)CH₂); *m/z* (E.S.I.) 392 (M+MeCN+NH₄⁺, 36%), 356 (M+Na⁺, 29), 334 (M+H⁺, 100); HRMS (E.S.I.) for C₁₇H₂₀NO₆ requires 334.1291, found (M+H⁺) 334.1297.

(5-*RS*, 10-*SR*)-*cis*-1-(4-Methoxybenzyl)-5,6,7,8,9-hexahydroquinolin-4-one-10-carboxylic acid methyl ester
16

Iron (III) chloride (5 mg, 15 mol%) was added to a stirred solution of sodium (30 mg, 1.30 mmol) in ammonia (30 mL) under an atmosphere of argon at -78 °C until the dark blue colour faded to a grey suspension. A solution of dihydropyridone **14** (76 mg, 0.21 mmol) in THF (10 mL) was added to the reaction and the mixture was stirred at -40 °C for 2 h. NH₄Cl (20 mL, saturated solution) was added and the reaction warmed to r.t. until the ammonia was removed, before extraction with Et₂O (3 x 50 mL). The combined organic extracts were washed with brine (50 mL, saturated solution), dried (MgSO₄) and concentrated *in vacuo*. The crude residue was purified via flash column chromatography (SiO₂, eluting with 1:4 petrol-Et₂O) to furnish, as a single diastereoisomer, the *product* **16** (49 mg, 71%) as an off white solid. m.p. 141-143 °C (Et₂O);

ν_{max} (KBr)/ cm^{-1} 2949, 1732, 1644, 1587, 1513, 1238; δ_{H} (400 MHz; CDCl_3) 7.28 (2 H, d, J 9.1, ArH), 6.96-6.92 (3 H, m, NCH and ArH), 4.92 (1 H, d, J 7.8, NCH=CH), 4.50 (1 H, d, J 14.1, $\text{NCH}_\text{A}\text{H}_\text{B}$), 4.42 (1 H, d, J 14.1, $\text{NCH}_\text{A}\text{H}_\text{B}$), 3.83 (3 H, s, OCH_3), 3.73 (3 H, s, CO_2CH_3), 2.73 (1 H, dd, J 8.6 and 3.6, $\text{C}(\text{O})\text{CH}$), 2.35-2.27 (2 H, m, $\text{CH}_{\text{A}1}\text{CH}_{\text{B}1}$ and $\text{CH}_{\text{A}2}\text{CH}_{\text{B}2}$), 1.89-1.20 (6 H, m, $\text{CH}_{\text{A}1}\text{CH}_{\text{B}1}$, $\text{CH}_{\text{A}2}\text{CH}_{\text{B}2}$ and 2 x CH_2); δ_{C} (100 MHz; CDCl_3) 194.5 ($\text{C}(\text{O})\text{CH}$), 173.6 (CO_2CH_3), 159.5 (ArC), 153.3 (NCH), 130.2 (ArC), 128.0 (ArC), 114.5 (ArC), 99.2 (NCH=CH), 68.9 ($\text{NC}(\text{CH}_2)_4$), 55.3 (OCH_3), 52.8 (CO_2CH_3), 52.1 (NCH₂), 50.3 ($\text{C}(\text{O})\text{CH}$), 30.1 (CH_2), 26.2 (CH_2), 24.3 (CH_2), 21.5 (CH_2); m/z (E.S.I.) 388 ($\text{M}+\text{MeCN}+\text{NH}_4^+$, 70%), 330 ($\text{M}+\text{H}^+$, 100); HRMS (E.S.I.) for $\text{C}_{19}\text{H}_{24}\text{NO}_4$ requires 330.1705, found ($\text{M}+\text{H}^+$) 330.1708.

(2-*RS*)-5-Iodo-1-(4-methoxybenzyl)-2-methyl-5,6-dihydropyridone-2-carboxylic acid methyl ester 17

Iodine (248 mg, 0.98 mmol) and potassium carbonate (211 mg, 1.53 mmol) were added to a stirred solution of dihydropyridone **11** (139 mg, 0.48 mmol) in CH_2Cl_2 (10 mL). The reaction was wrapped in foil and stirred for 16 h. After filtration, sodium thiosulphate (20 ml, saturated solution) was added and the organic layer isolated. This was washed with brine (20 ml, saturated solution), dried (MgSO_4) and concentrated *in vacuo*. The crude residue was purified via flash column chromatography (SiO_2 , eluting with 1:4 petrol-Et₂O) to furnish the product **17** (189 mg,

95%) as a yellow oil. ν_{max} (film)/ cm^{-1} 2954, 1738, 1646, 1567, 1513, 1250; δ_{H} (400 MHz; CDCl_3) 7.44 (1 H, s, NCH), 7.20 (2 H, d, J 8.6, ArH), 6.91 (2 H, d, J 8.6, ArH), 4.49 (1 H, d, J 15.2, $\text{NCH}_\text{A}\text{H}_\text{B}$), 4.41 (1 H, d, J 15.2, $\text{NCH}_\text{A}\text{H}_\text{B}$), 3.80 (3 H, s, OCH_3), 3.72 (3 H, s, CO_2CH_3), 3.17 (1 H, d, J 16.2, $\text{C}(\text{O})\text{CH}_\text{A}\text{H}_\text{B}$), 2.72 (1 H, d, J 16.2, $\text{C}(\text{O})\text{CH}_\text{A}\text{H}_\text{B}$), 1.52 (3 H, s, CCH_3); δ_{C} (100 MHz; CDCl_3) 184.0 ($\text{C}(\text{O})\text{CH}_2$), 172.6 (CO_2CH_3), 159.6 (ArC), 158.7 (NCH), 129.1 (ArC), 128.0 (ArC), 114.5 (ArC), 66.2 (NCH=CI), 62.7 (CCH_3), 55.4 (OCH_3), 54.5 (NCH_2), 53.3 (CO_2CH_3), 45.7 ($\text{C}(\text{O})\text{CH}_2$), 22.5 (CCH_3); m/z (E.S.I.) 474 ($\text{M}+\text{MeCN}+\text{NH}_4^+$, 100%), 416 ($\text{M}+\text{H}^+$, 38); HRMS (E.S.I.) for $\text{C}_{16}\text{H}_{19}\text{NO}_4\text{I}$ requires 416.0359, found ($\text{M}+\text{H}^+$) 416.0347.

(2-*RS*)-5-Allyl-1-(4-methoxybenzyl)-2-methyl-5,6-dihydropyridone-2-carboxylic acid methyl ester 18

Allyl iodide (0.50 mL, 5.40 mmol) was added to a stirred solution of *dihydropyridone 11* (91 mg, 0.31 mmol) in MeCN (0.5 mL) under an atmosphere of argon. The reaction was heated at reflux for 48 h before the addition of brine (2 mL, saturated solution). The reaction was extracted with Et_2O (3 x 10 mL) and the combined organic extracts were washed with brine (10 mL, saturated solution), dried (MgSO_4) and concentrated *in vacuo*. The crude residue was purified via flash column chromatography (SiO_2 , eluting with a gradient of Et_2O to 1:4 acetone- Et_2O) to furnish the *product*

18 (52 mg, 51%) as a yellow oil. ν_{max} (film)/ cm^{-1} 2954, 1737, 1640, 1602, 1513, 1248, 1173; δ_{H} (400 MHz; CDCl_3) 7.22 (2 H, d, J 8.3, ArH), 6.95-6.87 (3 H, m, NCH and ArH), 5.77 (1 H, ddtd, J 16.9, 10.1, 6.3 and 0.8, $\text{CH}_2=\text{CH}$), 4.99-4.92 (2 H, m, $\text{CH}_2=\text{CH}$), 4.48 (1 H, d, J 15.5, $\text{NCH}_\text{A}\text{H}_\text{B}$), 4.35 (1 H, d, J 15.5, $\text{NCH}_\text{A}\text{H}_\text{B}$), 3.83 (3 H, s, OCH_3), 3.73 (3 H, s, CO_2CH_3), 2.97 (1 H, d, J 16.4, $\text{C}(\text{O})\text{CH}_\text{A}\text{H}_\text{B}$), 2.89 (1 H, dd, J 15.9 and 6.4, $\text{CH}_2=\text{CHCH}_\text{A}\text{H}_\text{B}$), 2.81 (1 H, dd, J 15.9 and 6.3, $\text{CH}_2=\text{CHCH}_\text{A}\text{H}_\text{B}$), 2.63 (1 H, d, J 16.4, $\text{C}(\text{O})\text{CH}_\text{A}\text{H}_\text{B}$), 1.51 (3 H, s, CCH_3); δ_{C} (100 MHz; CDCl_3) 188.8 ($\text{C}(\text{O})\text{CH}$), 173.6 (CO_2CH_3), 159.2 (ArC), 153.2 (NCH), 137.2 ($\text{CH}_2=\text{CHCH}_2$), 129.7 (ArC), 128.6 (ArC), 114.9 ($\text{CH}_2=\text{CH}$), 114.3 (ArC), 109.3 (NCH=C), 66.0 (CCH_3), 55.3 (OCH_3), 54.4 (NCH_2), 52.9 (CO_2CH_3), 47.1 ($\text{C}(\text{O})\text{CH}_2$), 30.4 ($\text{CH}_2=\text{CHCH}_2$), 22.5 (CCH_3); m/z (E.S.I.) 330 ($\text{M}+\text{H}^+$, 100%); HRMS (E.S.I.) for $\text{C}_{19}\text{H}_{24}\text{NO}_4$ requires 330.1705, found ($\text{M}+\text{H}^+$) 330.1705.

(2-*RS*, 6-*SR*)-1-(4-Methoxybenzyl)-2,6-dimethylpiperidone-2-carboxylic acid methyl ester 19

Dihydropyridone **11** (64 mg, 0.22 mmol) was added to a stirred solution of copper (I) bromide dimethyl sulphide (187 mg, 0.91 mmol) in THF (5 mL) and stirred for 1 h under an atmosphere of argon. The reaction was cooled to $-78\text{ }^\circ\text{C}$ and boron trifluoride diethyl etherate (0.11 mL, 0.87 mmol) was added and the mixture stirred for a further 1 h. Hexyl magnesium bromide (0.26 mL, 3 M in

Et₂O, 0.78 mmol) was added by dropwise addition and the reaction warmed to -10 °C. The reaction was stirred for 6 h before the addition of NH₄Cl (3 mL, saturated solution). The mixture was warmed to r.t. and extracted with Et₂O (3 x 10 mL). The combined organic extracts were washed with brine (20 mL), dried (MgSO₄) and concentrated *in vacuo*. The crude residue was purified via flash column chromatography (SiO₂, eluting with 3:7 Et₂O-petrol). The diastereomers α and β were isolated in a combined yield of 72% with a diastereomeric ratio of α : β of 80:20.

Diastereomer α **19**: $\nu_{\max}$ (film)/cm⁻¹ 1731, 1511, 1245; δ_{H} (400 MHz; CDCl₃) 7.35 (2 H, d, J 8.7, ArH), 6.87 (2 H, d, J 8.7, ArH), 4.03 (1 H, d, J 15.5, NCH_AH_B), 3.81 (3 H, s, OCH₃), 3.76 (1 H, d, J 15.5, NCH_AH_B), 3.64 (3 H, s, CO₂CH₃), 3.61-3.28 (1 H, m, CHCH₃), 3.03 (1 H, dd, J 13.9 and 1.5, CH_AH_BC(O)), 2.47 (1 H, ddd, J 14.1, 5.4 and 1.0, C(O)CH_AH_B), 2.38 (1 H, dd, J 13.9 and 1.5, CH_AH_BC(O)), 2.26 (1 H, ddd, J 14.1, 5.8 and 1.8, C(O)CH_AH_B), 1.47 (3 H, s, CCH₃), 0.93 (3 H, d, J 6.7, CHCH₃); δ_{C} (100 MHz; CDCl₃) 207.7 (C(O)CH₂), 175.6 (CO₂CH₃), 158.5 (ArC), 133.0 (ArC), 128.6 (ArC), 113.6 (ArC), 64.7 (CCH₃), 55.3 (OCH₃), 2 x 52.1 (CO₂CH₃ and CHCH₃), 51.2 (NCH₂), 50.2 (C(O)CH₂), 48.1 (C(O)CH₂), 23.4 (CCH₃), 17.2 (CHCH₃); m/z (E.S.I.) 328 (M+MeCN+NH₄⁺, 63%), 306 (M+H⁺, 100); HRMS (E.S.I.) for C₁₇H₂₄NO₄ requires 306.1705, found (M+H⁺) 306.1706.

**(2-*RS*)-1-*H*-2-methyl-5,6-dihydropyridone-2-carboxylic acid
methyl ester 20**

Dihydropyridone 11 (50 mg, 0.17 mmol) in trifluoroacetic acid (5 mL) was heated at reflux for 16 h. The reaction was concentrated *in vacuo* and the residue was dissolved in CH₂Cl₂. Potassium carbonate (46.9 mg, 0.34 mmol) was added and the reaction mixture stirred for 16 h before being filtered and concentrated *in vacuo*. The crude residue was purified via flash column chromatography (SiO₂, eluting with 1:9 acetone-Et₂O) to furnish the *product 20* (30 mg, quant.) as an oil. $\nu_{\max}(\text{film})/\text{cm}^{-1}$ 3239, 2955, 1737, 1651, 1575, 1237; δ_{H} (400 MHz; CDCl₃) 7.14 (1 H, dd, *J* 7.6 and 6.3, NCH), 5.50 (1 H, br. s, NH), 5.04 (1 H, d, *J* 7.6, NCH=CH), 3.77 (3 H, s, CO₂CH₃), 2.89 (1 H, d, *J* 16.3, C(O)CH_AH_B), 2.57 (1 H, d, *J* 16.3, C(O)CH_AH_B), 1.51 (3 H, s, CCH₃); δ_{C} (100 MHz; CDCl₃) 190.8 (C(O)CH₂), 174.2 (CO₂CH₃), 149.4 (NCH), 99.6 (NCH=CH), 60.3 (CCH₃), 53.1 (CO₂CH₃), 44.8 (C(O)CH₂), 23.9 (CCH₃); *m/z* (E.S.I.) 228 (M+MeCN+NH₄⁺, 100%); HRMS (E.S.I.) for C₈H₁₂NO₃ requires 170.0817, found (M+H⁺) 170.0816.

4-Methoxy-2-methoxycarbonyl-1-methylpyridinium iodide 6

4-Methoxy-2-methoxycarbonyl-1-methylpyridinium iodide 6

4-Methoxy-1-(4-methoxybenzyl)-2-methoxycarbonylpyridinium
iodide 7

4-Methoxy-1-(4-methoxybenzyl)-2-methoxycarbonylpyridinium
iodide 7

(2-*RS*)-1,2-Dimethyl-5,6-dihydropyridone-2-carboxylic acid

methyl ester 8

(2-*RS*)-1,2-Dimethyl-5,6-dihydropyridone-2-carboxylic acid
methyl ester 8

(2-*RS*)-1-Methyl-5,6-dihydropyridone-2-carboxylic acid
methyl ester 9

(2-*RS*)-1-Methyl-5,6-dihydropyridone-2-carboxylic acid
methyl ester 9

(2-*RS*)-2-Ethyl-1-methyl-5,6-dihydropyridone-2-carboxylic
acid methyl ester 10

(2-*RS*)-2-Ethyl-1-methyl-5,6-dihydropyridone-2-carboxylic
acid methyl ester 10

(2-*RS*)-1-(4-Methoxybenzyl)-2-methyl-5,6-dihydropyridone-2-carboxylic acid methyl ester 11

(2-*RS*)-1-(4-Methoxybenzyl)-2-methyl-5,6-dihydropyridone-2-carboxylic acid methyl ester 11

(2-*RS*)-1-(4-Methoxybenzyl)-5,6-dihydropyridone-2-carboxylic acid methyl ester 12

(2-*RS*)-1-(4-Methoxybenzyl)-5,6-dihydropyridone-2-carboxylic acid methyl ester 12

(2-*RS*)-2-*iso*-Butyl-1-(4-methoxybenzyl)-5,6-dihydropyridone-
2-carboxylic acid methyl ester 13

(2-*RS*)-2-*iso*-Butyl-1-(4-methoxybenzyl)-5,6-dihydropyridone-
2-carboxylic acid methyl ester 13

COc1ccc(cc1)CN2C(=O)C(CCCCl)C(=O)OC2

(2-*RS*)-2-(4-Chlorobutyl)-1-(4-methoxybenzyl)-5,6-dihydropyridone-2-carboxylic acid methyl ester 14

1-(4-Methoxybenzyl)-5,6-dihydropyridone-2,2-dicarboxylic
acid dimethyl ester 15

1-(4-Methoxybenzyl)-5,6-dihydropyridone-2,2-dicarboxylic
acid dimethyl ester 15

(5-*RS*, 10-*SR*)-*cis*-1-(4-Methoxybenzyl)-5,6,7,8,9-hexahydroquinolin-4-one-10-carboxylic acid methyl ester
16

(5-*RS*, 10-*SR*)-*cis*-1-(4-Methoxybenzyl)-5,6,7,8,9-hexahydroquinolin-4-one-10-carboxylic acid methyl ester
16

(2-*RS*)-5-Iodo-1-(4-methoxybenzyl)-2-methyl-5,6-dihydropyridone-2-carboxylic acid methyl ester 17

(2-*RS*)-5-Iodo-1-(4-methoxybenzyl)-2-methyl-5,6-dihydropyridone-2-carboxylic acid methyl ester 17

(2-*RS*)-5-Allyl-1-(4-methoxybenzyl)-2-methyl-5,6-dihydropyridone-2-carboxylic acid methyl ester 18

(2-*RS*)-5-Allyl-1-(4-methoxybenzyl)-2-methyl-5,6-dihydropyridone-2-carboxylic acid methyl ester 18

(2-*RS*, 6-*SR*)-1-(4-Methoxybenzyl)-2,6-dimethylpiperidone-2-carboxylic acid methyl ester 19

(2-*RS*, 6-*SR*)-1-(4-Methoxybenzyl)-2,6-dimethylpiperidone-2-carboxylic acid methyl ester 19

(2-*RS*)-1-*H*-2-methyl-5,6-dihydropyridone-2-carboxylic acid
methyl ester 20

(2-*RS*)-1-*H*-2-methyl-5,6-dihydropyridone-2-carboxylic acid
methyl ester 20