Supporting information for:

Concise and Very Efficient Synthesis of the N-Methylwelwistatin Tetracyclic Core Based on an Anionic Domino Process

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1. General experimental information

All reagents were of commercial quality (Aldrich, Fluka, SDS, Probus) and were used as received. Potassium carbonate (97%) was purchased from Panreac. Solvents (from SDS and Scharlau) were dried and purified using standard techniques. Reactions were monitored by thin layer chromatography, on aluminium plates coated with silica gel with fluorescent indicator (SDS CCM221254). Separations by flash chromatography were performed on silica gel (SDS 60 ACC, 230-40 mesh) or on grade III neutral alumina from Merck. Melting points were measured with a Reichert 723 hot stage microscope, and are uncorrected. Infrared spectra were recorded on a Perkin Elmer Paragon 1000 FT-IR spectrophotometer, with all compounds examined as films on a NaCl disk. NMR spectra were obtained on a Bruker Avance instrument (250 MHz for $^1$H, 62.9 MHz for $^{13}$C), maintained by the Servicio de RMN, Universidad Complutense, with CDCl$_3$ as solvent. NMR assignments were supported by 2D-NMR experiments (COSY, NOESY, HMBC, HMQC). Combustion elemental analyses were determined by the Servicio de Microanálisis Elemental, Universidad Complutense, using a Leco 932 CHNS microanalyzer.
2. Synthesis of Kornfeld’s ketone (5)

2.1. 3-(1’-Pivaloyl-3-indolyl)propionic acid and its chloride

To a cooled (-78 ºC) solution of 3-(3-indolyl)propionic acid (2.5 g, 13.2 mmol) in dry THF (75 mL), under an argon atmosphere, was added a 1.6 M solution of BuLi in hexane (16.5 mL, 26.4 mmol, 2 eq). After stirring for 5 min, pivaloyl chloride (1.6 mL, 26.4 mmol, 1 eq) was added. Stirring at -78 ºC was maintained for 15 min and the reaction mixture was then stirred at -50 ºC for 15 min and at -20 ºC for 15 min. It was then poured onto saturated aqueous ammonium chloride (50 mL) and extracted with ethyl acetate (3 x 100 mL). The combined organic layers were dried over anhydrous sodium sulfate and evaporated, yielding the title compound (3.587 g, 99 %) as a white solid.

Mp 124-126 ºC (Lit.1 126-127 ºC).

IR (NaCl): 1689.5 (CO); 1707 (CO2H) cm⁻¹.

¹H-NMR (CDCl₃, 250 MHz) δ: 8.52 (d, 1H, J = 8.2 Hz, H-7’); 7.56 (s, 1H, H-2’); 7.49 (d, 1H, J = 10.6 Hz, H-4’); 7.36 (d, 1H, J = 7.8 Hz, H-6’); 7.19 (d, 1H, J = 8.3 Hz, H-5’); 3.06 (t, 2H, J = 7.1 Hz, H-2); 3.09 (t, 2H, J = 7.1 Hz, H-3); 1.48 (s, 9H, C(CH₃)₃).

¹³C-NMR (CDCl₃, 63 MHz) δ: 179.43 (CO₂H); 177.27 (CO) 137.57 (C-7’a); 129.42 (C-3a’); 125.88 (C-4’); 123.87 (C-5’); 123.16 (C-7’); 120.16 (C-3’); 118.61 (C-2’); 118.01 (C-6’); 41.54 (C(CH₃)₃); 33.98 (C(CH₃)₃); 29.01 (C(CH₃)₃); 20.49 (C-3).

Analysis: Calculated for C₁₆H₁₉NO₃ (M 273.3): C, 70.31; H, 7.01; N, 5.12. Found: C, 70.04; H, 6.96; N, 5.16.

A solution of this acid (3.6 g, 13.18 mmol) in thionyl chloride (4.9 mL, 67.7 mmol, 5.1 eq) was stirred at room temperature for 20 min, under an argon atmosphere. Excess thionyl chloride was removed by heating under reducer pressure. The golden, viscous

residue (3.84 g) was used immediately for the next step. When checked by IR, it showed the expected band due to the chlorocarbonyl function (1799 cm\(^{-1}\)).

2.2. Kornfeld's ketone (5)

To a suspension of aluminium trichloride (7 g, 53 mmol, 4 eq) in dry 1,2-dichloroethane (90 mL), under an argon atmosphere, was added 4.2 mL (53 mmol, 4 eq) of chloroacetyl chloride. After stirring for 5 min, this suspension was added onto a solution of the previously mentioned acid chloride (3.36 g, 13.17 mmol) in dry 1,2-dichloroethane (130 mL). After stirring the reaction mixture for 3 h at room temperature, it was poured onto a stirred mixture of crushed ice (15 mL) and dichloromethane (15 mL). The aqueous phase was extracted with dichloromethane (3 x 15 mL). The combined organic layers were washed with 10% aqueous potassium bicarbonate (3 x 30 mL), dried over anhydrous sodium sulfate and evaporated, yielding the title compound (2.8 g, 90%) as a pale brown viscous oil that is sufficiently pure for the next reaction. An analytical sample was obtained, as a pale yellow solid, by silica gel chromatography, eluting with 4:1 petroleum ether-ethyl acetate.

Mp 166-167 °C (Lit.\(^1\) 168-169 °C).

IR (NaCl): 1685.5 (2 CO) cm\(^{-1}\).

\(^1\)H-NMR (CDCl\(_3\), 250 MHz) \(\delta\): 8.54 (dd, 1H, \(J = 7.9\) and 0.6 Hz, H-8); 7.73 (dd, 1H, \(J = 7.6\) and 0.6 Hz, H-6); 7.60 (s, 1H, H-2); 7.43 (t, 1H, \(J = 7.9\) Hz, H-7); 3.22 (td, 2H, \(J = 7.3\) and 0.8 Hz, H-3); 2.88 (t, 2H, \(J = 7.3\) Hz, H-4); 1.52 (s, 9H, (CH\(_3\))\(_3\)).

\(^13\)C-NMR (CDCl\(_3\), 63 MHz) \(\delta\): 197.74 (C-5); 177.51 (NCO); 136.10 (C-8a); 133.91 (C-8b); 126.62 (C-7); 126.13 (C-5a); 123.15 (C-8); 121.61 (C-2); 119.96 (C-6); 116.50 (C-2a); 41.42 (C(CH\(_3\))\(_3\)); 38.86 (C-4); 28.98 (C(CH\(_3\))\(_3\)); 20.90 (C-3).

Analysis: Calculated for C\(_{16}\)H\(_{17}\)NO\(_2\) (M 255.13): C, 75.27; H, 6.71; N, 5.49. Found: C, 74.97; H, 6.57; N, 5.60.
3. Synthesis of ethyl 3,4,5,6-tetrahydro-5-oxo-1-(2',2'-dimethylpropionyl)cyclohepta[cd]indole-6-carboxylate (4)

![Chemical structure](image)

To a cooled (0 °C) solution of compound 5 (0.6 g, 2.35 mmol) in dry dichloromethane (10 mL), kept under an argon atmosphere, was added triethylxonium tetrafluoroborate (0.9 g, 4.7 mmol, 2 eq). After stirring for 5 min, ethyl diazoacetate (0.49 mL, 4 mmol, 1.8 eq) was added dropwise. The reaction mixture was stirred at 0 °C for 24 h and then it was treated with saturated aqueous sodium bicarbonate solution (10 mL). The two-phase system was vigorously stirred at room temperature for at least 4 h. The organic layer was separated and the aqueous phase was extracted with dichloromethane (2 x 10 mL). The combined organic layers were dried over anhydrous sodium sulphate and evaporated, yielding 0.722 g (90%) of essentially pure compound 4, as a pale brown viscous oil. An analytical sample of 4, as a pale yellow viscous oil, was obtained by silica gel chromatography, eluting with 7:1 petroleum ether-ethyl acetate.

IR (NaCl): 3399 (OH), 1693 (NCO) cm⁻¹.

Analysis: Calculated for C₂₀H₂₃NO₄ (M 341.4): C, 70.36; H, 6.79; N, 4.10. Found: C, 70.19; H, 6.97; N, 3.96.

NMR data for the oxo tautomer 4a: ¹H-NMR (CDCl₃, 250 MHz) δ: 8.39 (dd, 1H, J = 8.4 and 0.7 Hz, H-9); 7.47 (d, 1H, J = 1.3 Hz, H-2); 7.27-7.15 (m, 1H, H-8); 7.0 (d, 1H, J = 7.2 Hz, H-7); 4.71 (s, 1H, H-6); 4.30-3.98 (m, 2H, CO₂CH₂CH₃); 3.12-2.95 (m, 2H, H-4 and H-3); 2.85-2.62 (m, 2H, H-4 and H-3); 1.39 (s, 9H, C(CH₃)₃); 1.14 (t, 3H, J = 7.1 Hz, CO₂CH₂CH₃) ppm. ¹³C-NMR (CDCl₃, 63 MHz) δ: 202.81 (C-5); 177.18 (NCO); 169.57 (CO₂CH₂CH₃); 137.05 (C-9a); 128.35 (C-9b); 126.53 (C-8); 125.67 (C-7); 124.00 (C-6a); 122.44 (C-2); 120.37 (C-9b); 118.09 (C-9); 66.47 (C-6); 62.53

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If this step is omitted or shorter hydrolysis times are employed, compound 4 is accompanied by side products arising from the O-alkylation of its two possible enol tautomers with excess ethyl diazoacetate.
(CO₂CH₂CH₃); 42.99 (C-4); 41.62 (C(CH₃)₃); 29.086 (C(C(CH₃)₃); 20.60 (C-3); 14.49 (CO₂CH₂CH₃) ppm.

NMR data for the enol tautomer 4b: ¹H-NMR (CDCl₃, 250 MHz) δ: 13.67 (s, 1H, OH); 8.28 (dd, 1H, J = 8.0 and 1.1 Hz, H-9); 7.37 (s, 1H, H-2); 7.33 (dd, 1H, J = 8.0 and 1.1 Hz, H-7); 7.18 (t, 1H, J = 8 Hz, H-8); 4.30-3.98 (m, 2H, CO₂CH₂CH₃); 2.95-2.85 (m, 2H, H-3); 2.62-2.5 (m, 2H, H-4); 1.38 (s, 9H, C(CH₃)₃); 1.195 (m, 3H, CO₂CH₂CH₃) ppm. ¹³C-NMR (CDCl₃, 63 MHz) δ: 178.59 (C-5); 177.23 (NCO); 173.81 (CO₂CH₂CH₃); 137.99 (C-9a); 126.77 (C-8); 126.72 (C-9b); 126.36 (C-6a); 124.88 (C-7); 122.35 (C-2a); 121.65 (C-2); 115.57 (C-9); 101.40 (C-6); 61.65 (CO₂CH₂CH₃); 41.62 (C(CH₃)₃); 35.60 (C-4); 29.06 (C(CH₃)₃); 25.74 (C-3); 14.53 (CO₂CH₂CH₃) ppm.
4. Synthesis of ethyl 1-(2',2'-dimethylpropionyl)-5-oxo-6-(3'-oxopropyl)-3,4-dihydrocyclohepta[cd]indole-5-carboxylate (6)

![Chemical Structure]

A mixture of compound 4 (600 mg, 1.75 mmol) and potassium carbonate (1.93 g, 13.98 mmol, 8 eq) was suspended in anhydrous tetrahydrofuran (16 mL) under an inert atmosphere. The suspension was stirred at room temperature for 5 min and acrolein (0.23 mL, 0.19 moles, 2 eq) was then added. Stirring was maintained for 1 h and the reaction was then filtered through celite and washed with ethyl acetate (5 x 30 mL). The combined organic layers were washed with water (2 x 10 mL), dried over sodium sulfate and evaporated, giving 0.656 g (94%) of compound 6 as a pale yellow solid.

Mp 187-188 °C.

IR (NaCl): 1717, 1697 (CO) cm\(^{-1}\).

\(^1\)H-NMR (CDCl\(_3\), 250 MHz) \(\delta\): 9.62 (s, 1H, CHO); 8.46 (dd, 1H, \(J = 8.0 \text{ and } 1.0 \text{ Hz, H-9}\)); 7.51 (s, 1H, H-2); 7.30 (t, 1H, \(J = 8.0 \text{ Hz, H-8}\)); 7.13 (dd, 1H, \(J = 8.0 \text{ and } 1.0 \text{ Hz, H-7}\)); 4.09 (q, 2H, \(J = 7.0 \text{ Hz, CO}_2\text{CH}_2\text{CH}_3\)); 3.24-3.07 (m, 1H, H-4); 3.05-2.89 (m, 1H, H-3); 2.86-2.78 (m, 2H, H-4 and H-3); 2.78-2.65 (m, 1H, H-2’); 2.65-2.47 (m, 2H, H-1’ and H-2’); 2.47-2.27 (m, 1H, H-1’) 1.44 (s, 9H, C(CH_3)_3); 1.01 (t, 3H, \(J = 7.0 \text{ Hz, CO}_2\text{CH}_2\text{CH}_3\)) ppm.

\(^{13}\)C-NMR (CDCl\(_3\), 63 MHz) \(\delta\): 205.22 (C-5); 201.48 (CHO); 177.20 (CO\(_2\)CH\(_2\)CH\(_3\)); 172.17 (CO\(_{tBu}\)); 138.27 (C-9a); 128.66 (C-6a); 128.30 (C-9b); 126.26 (C-8); 122.72 (C-2); 122.39 (C-7); 119.84 (C-2a); 117.76 (C-9) 67.19 (C-6); 62.52 (CO\(_2\)CH\(_2\)CH\(_3\)); 43.47 (C-4); 41.75 (C(CH\(_3\))\(_3\)); 40.39 (C-1”); 29.10 (C(CH\(_3\))\(_3\)); 28.27 (C-2’); 21.57 (C-3); 14.29 (CO\(_2\)CH\(_2\)CH\(_3\)) ppm.

Analysis: Calculated for C\(_{23}\)H\(_{27}\)NO\(_5\) (M 397.5): C, 69.50; H, 6.85; N, 3.52. Found: C, 69.29; H, 6.61; N, 3.47.
5. Synthesis of compounds (8)

5.1. Intramolecular aldol reaction of compound (6) and N-depivaloylation

To a solution of compound 6 (0.133 g, 0.33 mmol) in tetrahydrofuran (6 mL) was added DBU (0.075 mL, 0.5 mmoles, 1.7 eq). After stirring the solution at room temperature for 1.5 h,3 water (23 µL, 1.32 mmol, 4 eq) and an additional amount of DBU (0.075 mL, 0.5 mmoles, 1.7 eq) were added. Stirring at room temperature was maintained for 18 h and the reaction mixture was then poured on water (3 mL) and extracted with ethyl acetate (3 x 6 mL). The combined organic layers were dried over anhydrous sodium sulfate and evaporated, yielding compound 8 as a pale brown solid (0.094 g, 90%). An analytical sample of the 14-S* diastereoisomer \(8a\) was obtained by chromatography on grade III neutral alumina, eluting with a 2:1 petroleum ether-ethyl acetate mixture.

5.2. One-pot procedure from compound (4)

To a stirred solution of compound 4 (0.530 g, 1.55 mmol) in tetrahydrofuran (15 mL) was added DBU (0.34 mL, 2.32 mmol, 1.7 eq.). The solution was stirred at room temperature for 5 min and acrolein (0.2 mL, 3.11 mmol, 1.5 eq) was added. Stirring at room temperature was maintained for an additional period of 4 h and the reaction mixture was then treated with water (55 µL, 3.11 mmol, 2 eq) and an additional amount

3 When the reaction was worked up at this stage, the crude reaction mixture was found to consist of a ca. 3:1 mixture of compounds 7 and 8, from which an analytical sample of 7a, the 14-S* diastereoisomer of compound 7, could be isolated.
of DBU (0.34 mL, 2.32 mmol, 1.5 eq). The reaction mixture was stirred at room temperature for 18 h and it was then poured onto a saturated aqueous ammonium chloride solution (8 mL) and extracted with ethyl acetate (4 x 10 mL). The combined organic layers were dried over sodium sulfate and evaporated, leaving a residue of 0.430 g (93%) of compound 8.

Data for 7a

\[
\begin{align*}
\text{Mp: } & 182-183 ^\circ \text{C.} \\
\text{IR (NaCl): } & 3495 (\text{OH}), 1731, 1699 (\text{CO}) \text{ cm}^{-1}. \\
^1\text{H-NMR (CDCl}_3, 250 \text{ MHz}) & \delta: 8.60 (\text{dd, } 1\text{H}, J = 8.4 \text{ and } 0.8 \text{ Hz, H-7}); 7.60 (\text{d, } 1\text{H}, J = 1.8 \text{ Hz, H-2}); 7.37 (\text{t, } 1\text{H}, J = 8.4 \text{ Hz, H-6}); 6.94 (\text{dd, } 1\text{H}, J = 8.4 \text{ and } 0.8 \text{ Hz, H-5}); 4.38 \text{ and } 4.39 (\text{2 q, } 2\text{H}, J = 7.2 \text{ Hz, CO}_2\text{CH}_2\text{CH}_3); 4.34-4.27 (\text{m, } 1\text{H, H-14}); 3.58 (\text{dd, } 1\text{H}, J = 16.6 \text{ and } 3.5 \text{ Hz, H-16}); 3.46-3.44 (\text{m, } 1\text{H, H-15}); 3.05 (\text{m, } 1\text{H, OH}); 2.87 (\text{ddd, } 1\text{H}, J = 16.7, 5.0 \text{ and } 2.2 \text{ Hz, H-16}); 2.53 (\text{td, } 1\text{H}, J = 14.1 \text{ and } 3.1 \text{ Hz, H-12}); 2.08 (\text{dt, } 1\text{H}, J = 9.5 \text{ and } 3.1 \text{ Hz, H-12}); 1.76 (\text{m, } 2\text{H, H-13}); 1.54 (\text{s, } 9\text{H, COC(CH}_3)_3); 1.31 (\text{t, } 3\text{H, J = 7.2 Hz, CO}_2\text{CH}_2\text{CH}_3) \text{ ppm.} \\
^1\text{C-NMR (CDCl}_3, 63 \text{ MHz}) & \delta: 207.06 (\text{C-10}); 176.75 (\text{COC(CH}_3)_3); 172.03 (\text{CO}_2\text{CH}_2\text{CH}_3); 137.15 (\text{C-8}); 130.69 (\text{C-4}) 128,67 (\text{C-9}); 125.47 (\text{C-6}) 123.39 (\text{C-2}); 122.97 (\text{C-5}); 117.61 (\text{C-3}); 116.23 (\text{C-7}); 70.33 (\text{C-14}); 69.00 (\text{C-11}); 61.72 (\text{CO}_2\text{CH}_2\text{CH}_3); 54.53 (\text{C-15}); 41.36 (\text{COC(CH}_3)_3); 34.69 (\text{C-12}); 28.67 (\text{COC(CH}_3)_3); 27.51 (\text{C-13}); 22.36 (\text{C-16}); 14.03 (\text{CO}_2\text{CH}_2\text{CH}_3) \text{ ppm.} \\
\text{Analysis: Calculated for C}_{23}\text{H}_{27}\text{NO}_5 (M 397.4): } & \text{C, 69.50; H, 6.85; N, 3.52. Found: C, 69.68; H, 7.08; N, 3.38.}
\end{align*}
\]
**NMR data for 7b**

![Chemical Structure of 7b]

$^1$H-NMR (CDCl$_3$, 250 MHz) $\delta$: 8.33 (dd, 1H, $J = 8.0$ and 0.75 Hz, H-7); 7.64 (s, 1H, H-2); 7.36 (t, 1H, $J = 8.0$ Hz, H-6); 6.93 (dd, 1H, $J = 8.0$ and 0.75 Hz, H-5); 4.38 (m, 2H, CO$_2$CH$_2$CH$_3$); 4.26 (m, 1H, H-14); 3.25-3.00 (m, 4H, H-12, H-13, H-15, H-16); 1.90-2.10 (m, 1H, H-12); 1.81-1.44 (m, 2H, H-13, H-16); 1.24 (t, 3H, $J = 7.2$ Hz, CO$_2$CH$_2$CH$_3$) ppm.

$^{13}$C-NMR (CDCl$_3$, 63 MHz) $\delta$: 208.34 (C-10); 177.17 (COC(CH$_3$)$_3$); 172.56 (CO$_2$CH$_2$CH$_3$); 137.58 (C-8); 131.58 (C-4); 128.51 (C-9); 126.01 (C-6); 124.07 (C-2); 123.60 (C-5); 117.19 (C-3); 116.58 (C-7); 73.77 (C-14); 70.20 (C-11); 62.18 (CO$_2$CH$_2$CH$_3$); 57.44 (C-15); 41.81 (COC(CH$_3$)$_3$); 34.56 (C-12); 29.11 (COC(CH$_3$)$_3$); 27.37 (C-13); 22.74 (C-16); 14.55 (CO$_2$CH$_2$CH$_3$) ppm.

**Data for 8**

Analysis: Calculated for C$_{18}$H$_{19}$NO$_4$ (M 313.3): C, 68.99; H, 6.11; N, 4.47. Found: C, 68.51; H, 5.98; N, 4.32.

**NMR data for 8a**

![Chemical Structure of 8a]

$^1$H-NMR (CDCl$_3$, 250 MHz) $\delta$: 8.33 (s, 1H, NH); 7.18 (d, 1H, $J = 8.1$ Hz, H-7); 7.08 (t, 1H, $J = 7.4$ Hz, H-6); 6.96 (s, 1H, H-2); 6.66 (dd, 1H, $J = 0.8$ and 6.52 Hz, H-5); 4.33-
4.22 (m, 2H, CO₂CH₂CH₃); 4.20-4.05 (m, 1H, H-14); 3.45 (dd, 1H, J = 16.3 and 3.6 Hz, H-16); 3.32 (m, 1H, H-15); 3.06-2.99 (m, 1H, H-13); 2.78 (dd, 1H, J = 16.3, 3.7 and 1.4 Hz, H-16); 2.42 (dt, 1H, J = 14.0 and 3.1 Hz, H-12); 2.13-1.95 (m, 1H, H-12); 1.70-1.55 (m, 1H, H-13); 1.26-1.50 (m, 3H, CO₂CH₂CH₃) ppm.

¹³C-NMR (CDCl₃, 63 MHz) δ: 208.69 (C-10); 172.51 (CO₂CH₂CH₃); 136.27 (C-8); 130.75 (C-4); 127.06 (C-9); 122.94 (C-2); 122.51 (C-6); 119.12 (C-5); 111.99 (C-3); 110.52 (C-7); 70.29 (C-14); 69.81 (C-11); 62.06 (CO₂CH₂CH₃); 55.30 (C-15); 35.39 (C-12); 28.39 (C-13); 22.19 (C-16); 14.54 (CO₂CH₂CH₃) ppm.

NMR data for 8b

¹H-NMR (CDCl₃, 250 MHz) δ: 8.41 (s, 1H, NH); 7.27 (d, 1H, J = 7.3 Hz, H-7); 6.76 (t, 1H, J = 7.3 Hz, H-6); 6.99 (s, 1H, H-2); 6.76 (dd, 1H, J = 7.3 and 1.3 Hz, H-5); 4.43-4.31 (m, 2H, CO₂CH₂CH₃); 4.23-4.17 (m, 1H, H-14); 3.21-2.90 (m, 4H, H-12, H-13, H-15, H-16); 2.06-1.94 (m, 1H, H-12); 1.58-1.51 (m, 2H, H-13, H-16); 1.35-1.28 (m, 3H, CO₂CH₂CH₃) ppm.

¹³C-NMR (CDCl₃, 63 MHz) δ: 209.26 (CO); 172.54 (CO₂CH₂CH₃); 136.64 (C-8); 131.44 (C-4); 126.84 (C-9); 123.05 (C-2); 122.47 (C-6); 119.17 (C-5); 111.48 (C-3); 110.50 (C-7); 74.19 (C-14); 70.34 (C-11); 62.06 (CO₂CH₂CH₃); 58.03 (C-15); 34.71 (C-12); 28.05 (C-13); 27.70 (C-16); 14.06 (CO₂CH₂CH₃) ppm.
6. Synthesis of compounds (9)

\[
\begin{align*}
\text{8} & \quad \text{1.5 eq ICH}_3, \text{HSO}_4\text{BuN}^+ \\
& \quad 50\% \text{aq. KOH-CH}_2\text{Cl}_2, \text{t.a., 14h} \\
\end{align*}
\]

To a solution of compound 8 (0.100 g, 0.32 mmol) and tetrabutylammonium hydrogen sulfate (11.5 mg, 0.03 mmol, 0.09 eq) in dichloromethane (2 mL) was added a 50\% aqueous solution of potassium hydroxide (1 mL). After stirring at room temperature for 5 min and methyl iodide (40 \(\mu\)L, (0.47 mmole, 2 eq) was added. The two-phase system was vigorously stirred at room temperature for 22 h. The aqueous layer was extracted with dichloromethane (10 mL) and the combined organic layers were washed with water (3 x 2 mL), dried over anhydrous sodium sulfate and evaporated, yielding compound 9 (0.083 g, 80\%) as a pale orange oil. The separation of both diastereoisomers of 9 was carried out by chromatography on grade III neutral alumina, eluting with a 2:1 petroleum ether-ethyl acetate mixture.

\textbf{Data for 9}

IR (NaCl): 3414 (OH), 1727, 1700 cm\(^{-1}\).

Analysis: Calculated for C\(_{19}\)H\(_{21}\)NO\(_4\) (M 327.37): C, 69.71; H, 6.47; N, 4.28. Found: C, 69.35; H, 6.21; N, 3.95.

\textit{NMR data for 9a}

A higher excess of methyl iodide leads to mixtures of 9 and its O-methyl derivative.
$^1$H-NMR (CDCl$_3$, 250 MHz) $\delta$: 7.14-7.12 (m, 2H, H-6 and H-7); 6.90 (d, 1H, J = 1.3 Hz, H-2); 6.66 (m, 1H, H-5); 4.27 and 4.26 (2 q, 2H, J = 7.2 Hz, CO$_2$CH$_2$CH$_3$); 4.20-4.07 (m, 1H, H-14); 3.76 (s, 3H, NCH$_3$); 3.46 (dd, 1H, J = 16.1 and 3.5 Hz, H-16); 3.35-3.23 (m, 1H, H-15); 3.14-2.97 (m, 1H, H-13); 2.81 (dddd, 1H, J = 16.1, 3.5 and 1.7 Hz, H-16); 2.40 (dt, 1H, J = 14.1 and 3.1 Hz, H-12); 1.99 (dt, 1H, J = 14.1 and 3.1 Hz, H-12); 1.67-1.59 (m, 1H, H-13); 1.22 (t, 3H, J = 7.1 Hz, CO$_2$CH$_2$CH$_3$) ppm.

$^{13}$C-NMR (CDCl$_3$, 63 MHz) $\delta$: 208.96 (C-10); 172.98 (CO$_2$CH$_2$CH$_3$); 137.42 (C-8); 130.95 (C-4) 127.99 (C-9); 127.14 (C-2); 121.54 (C-6); 118.67 (C-5); 110.55 (C-3); 107.93 (C-7); 70.50 (C-14); 69.63 (C-11); 61.49 (CO$_2$CH$_2$CH$_3$); 54.89 (C-15); 34.86 (C-12); 32.55 (NCH$_3$); 27.95 (C-13); 22.54 (C-16); 14.06 (CO$_2$CH$_2$CH$_3$) ppm.

NMR data for 9b

![9b diagram]

$^1$H-NMR (CDCl$_3$, 250 MHz) $\delta$: 7.14 (m, 2H, H-6 and H-7); 6.86 (s, 1H, H-2); 6.68 (m, 1H, H-5); 4.26-4.21 (m, 2H, CO$_2$CH$_2$CH$_3$); 4.20-4.12 (m, 1H, H-14); 3.67 (s, 3H, NCH$_3$); 3.17-2.99 (m, 4H, H-12, H-13, H-15, H-16); 1.97-1.87 (m, 1H, H-12); 1.70-1.40 (m, 2H, H-13, H-16); 1.24 (t, J = 7.1 Hz, CO$_2$CH$_2$CH$_3$) ppm.

$^{13}$C-NMR (CDCl$_3$, 63 MHz) $\delta$: 209.25 (C-10); 172.88 (CO$_2$CH$_2$CH$_3$); 137.33 (C-8); 131.81 (C-4) 127.31 (C-9); 127.60 (C-2); 122.17 (C-6); 118.83 (C-5); 110.23 (C-3); 108.41 (C-7); 74.32 (C-14); 70.21 (C-11); 61.93 (CO$_2$CH$_2$CH$_3$); 58.17 (C-15); 34.67 (C-12); 33.24 (NCH$_3$); 27.70 (C-16); 27.71 (C-13); 14.56 (CO$_2$CH$_2$CH$_3$) ppm.
7. Synthesis of compound 10

To a solution of alcohol 9 (110 mg, 0.33 mmol) in dry dichloromethane (1.5 mL) was added 4 Å activated powdered molecular sieves (65 mg). After establishing an oxygen atmosphere, the suspension was stirred at room temperature while solid tetrapropylammonium perruthenate, TPAP (10 mg, 10 mol%) was added in small portions. The resulting suspension was stirred at room temperature under an oxygen atmosphere for 24 h and filtered through a pad of celite, which was washed with dichloromethane (10 mL). Evaporation of the solvent afforded 109 mg (90%) of compound 10, as a pale yellow viscous oil.

IR (NaCl): 1729.4, 1702.5 (CO) cm⁻¹.

¹H-NMR (CDCl₃, 250 MHz) δ: 7.27 (t, 1H, J = 3.4 Hz, H-6); 7.24 (d, 1H, J = 4.8 Hz, H-7); 6.96 (s, 1H, H-2); 6.85 (m, 1H, H-5); 4.37 (q, 2H, J = 7.2 Hz, CO₂CH₂CH₃); 3.45 (s, 3H, NCH₃); 3.64 (m, 1H, H-15); 3.58 (dd, 1H, J = 15.0 and 4.8 Hz, H-16); 3.22 (ddd, 1H, J = 15.0, 3.8 and 1.3 Hz, H-16); 2.74 (td, 1H, J = 15.0 and 5.4 Hz, H-13); 2.50 (m, 2H, H-13 and H-12); 1.95 (m, H, H-12); 1.30 (t, 3H, J = 7.2 Hz, CO₂CH₂CH₃) ppm.

¹³C-NMR (CDCl₃, 63 MHZ) δ: 210.62 (C-10); 205.19 (C-14); 171.73 (CO₂CH₂CH₃); 137.04 (C-8); 128.32 (C-11); 127.69 (C-2); 126.24 (C-9); 121.87 (C-6); 117.99 (C-5); 108.77 (C-7); 108.34 (C-3); 68.26 (C-11); 62.53 (C-15); 61.75 (CO₂CH₂CH₃); 36.15 (C-12); 32.80 (NCH₃); 31.34 (C-13); 29.30 (C-16); 14.04 (CO₂CH₂CH₃) ppm.

Analysis: Calculated for C₁₉H₁₉NO₄ (M C₁₉H₁₉NO₄): C, 70.14; H, 5.89; N, 4.31. Found: C, 69.81; H, 5.82; N, 4.28.
8. Representative spectra
**Supplementary Material (ESI) for Organic & Biomolecular Chemistry**

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Supplementary Material (ESI) for Organic & Biomolecular Chemistry
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8a (major component)
9a (major component)

![Chemical Structure](image)

[Graph of NMR Spectra]

[Graph of NMR Spectra (detail)]
9b (major component)