Expedient synthesis of bicyclo[3.2.1]octanes and bicyclo[3.3.1]nonanes via the Double Michael Addition to cyclic dienones

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**Supplementary Information**

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I) Experimental Section

**Experimental Data for Compounds**

**General Procedures.** All reactions were carried out under a nitrogen or argon atmosphere with dry solvents under anhydrous conditions, unless otherwise noted. Dry tetrahydrofuran (THF), hexane, diethyl ether (Et$_2$O), methylene chloride (CH$_2$Cl$_2$), and toluene were obtained by passing commercially available pre-dried, oxygen-free formulations through activated alumina columns. Methanol (MeOH), benzene, and N,N'-dimethylformamide (DMF) were purchased in anhydrous form and used without further purification. Water, ethyl acetate (EtOAc), diethyl ether (Et$_2$O), methylene chloride (CH$_2$Cl$_2$), and hexanes were purchased at the highest commercial quality and used without further purification, unless otherwise stated. Reagents were purchased at the highest commercial quality and used without further purification, unless otherwise stated. Yields refer to chromatographically and spectroscopically ($^1$H NMR) homogeneous materials, unless otherwise stated. Reactions were monitored by thin-layer chromatography (TLC) carried out on 0.25 mm E. Merck silica gel plates (60F-254) using UV light as visualizing agent and an ethanolic solution of ammonium molybdate, anisaldehyde, potassium permanganate and heat as developing agents. E. Merck silica gel (60, particle size 0.040–0.063 mm) was used for flash column chromatography. NMR spectra were recorded on a Bruker AV-600 instrument and calibrated using residual undeuterated solvent as an internal reference. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet,
quint = quintet, m = multiplet, pent = pentet, hex = hexet, br = broad. IR spectra were recorded on a Perkin-Elmer Spectrum One FTIR spectrometer with diamond ATR accessory. Optical rotation ([α]25D) were recorded on a Perkin-Elmer Model 341 polarimeter at 25 °C using thermostable optical glass cell (100 mm path length). Melting points (m.p.) are uncorrected, and recorded on a Buchi B-540 melting point apparatus. High-resolution mass spectra (HRMS) were recorded on an Agilent ESI TOF (time of flight) mass spectrometer at 3500 V emitter voltage.

**Ketones 15a/15’a:** To a stirred solution of 2,7-cyclooctadien-1-one (8) (1 g, 8.19 mmol) in DMSO (80 mL) at room temperature were added nitromethane (10a) (500 µL, 9.3 mmol) and DBU (120 µL, 0.80 mmol). The resulting mixture was stirred for 3 h before H2O (100 mL) and AcOEt (100 mL) were added. The layers were separated and the aqueous layer was extracted with AcOEt (100 mL). The combined organic layers were washed with HCl (1.0 N aq., 100 mL), dried (Na2SO4) and concentrated in vacuo to afford a 2/1 mixture of bicycles 15a and 15’a (940 mg, 63%) as a white solid. For analytical purposes, a fraction of the crude mixture was purified by silica gel chromatography and the structure of the major diastereoisomer was assigned to ketone 15a by 2D NMR experiments (Note: 15a is the most stable isomer, 15’a isomerizes to 15a when treated with silica gel and/or upon prolonged storage).

**15a:** Rf = 0.5 (silica gel, hexanes/EtOAc 80:20); IR (film) νmax 2938, 1703, 1536, 1465, 1453, 1408, 1385, 1362, 1317, 1255, 1230, 1190, 1134, 1106, 1071, 992, 952, 931, 892, 869, 834, 753 cm⁻¹; 1H NMR (600 MHz, CDCl3) δ = 4.46 (s, 1H), 3.13 (s, 2H), 2.69 (dd, J = 17.8, 6.0 Hz, 2H), 2.37 (dq, J = 17.0, 1,4 Hz, 2H), 1.91 (ddq, J = 15.3, 4.5, 2.1 Hz, 2H), 1.78–1.68 (m, 2H), 1.59–1.49 (m, 1H), 1.43–1.20 (m, 1H); 13C NMR (150 MHz, CDCl3): δ = 208.9, 85.3, 42.0 (2C), 33.8 (2C), 32.2 (2C), 16.7 ppm; HRMS (ESI): calcd for C9H14NO3⁺ [M + H]⁺ 184.0974, found 184.0972.

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**Ketone 15b:** To a stirred solution of 2,7-cyclooctadien-1-one (8) (200 mg, 1.64 mmol) in CH$_3$CN (10 mL) at room temperature were added malononitrile (10b) (135 mg, 2.04 mmol) and DBU (49 µL, 0.33 mmol). The resulting mixture was stirred at room temperature for 16 h before the medium was concentrated under reduced pressure. The crude residue was dissolved in EtOAc (20 mL) and washed with HCl (1.0 N aq., 10 mL) and H$_2$O (10 mL). The organic layer was then dried (Na$_2$SO$_4$) and concentrated in vacuo to afford pure bicycle 15b (269 mg, 87%) as a light yellow solid.

15b: R$_f$ = 0.5 (silica gel, hexanes/EtOAc 70:30); IR (film) $\nu$ max 3423, 2950, 2882, 2214, 1717, 1567, 1455, 1413, 1361, 1344, 1268, 1183, 1122, 1099, 973, 954, 893, 822, 735 cm$^{-1}$; $^1$H NMR (600 MHz, CDCl$_3$) $\delta$ = 2.96 (ddd, $J$ = 18.3, 6.1, 1.4 Hz, 2H), 2.87 (d, $J$ = 4.6 Hz, 2H), 2.66–2.49 (m, 2H), 2.14 (m, 2H), 1.90–1.82 (m, 2H), 1.67 (ddt, $J$ = 15.5, 5.1, 2.7 Hz, 1H), 1.48–1.38 (m, 1H); $^{13}$C NMR (150 MHz, CDCl$_3$): $\delta$ = 204.9, 115.5, 115.1, 43.2 (2C), 37.9, 37.2 (2C), 26.0 (2C), 15.8 ppm; HRMS (ESI): calcd for C$_{11}$H$_{13}$N$_2$O$^+$ [M + H]$^+$ 189.1028, found 189.1022.

**Ketone 17b:** To a stirred solution of 2,6-cycloheptadien-1-one (9) (66 mg, 0.61 mmol) in CH$_3$CN (30 mL) at room temperature were added malononitrile (10b) (40 mg, 0.61 mmol) and DBU (18 µL, 0.120 mmol). The resulting mixture was stirred at room temperature for 3 days under argon atmosphere. After concentration under reduce pressure, the mixture was dissolved in EtOAc (15 mL) and washed with HCl (1.0 N aq., 10 mL). The layers were separated and the organic layer was washed with H$_2$O (2 x 10 mL), dried (Na$_2$SO$_4$) and concentrated in vacuo to afford pure bicycle 27 (90 mg, 84%) as a light yellow solid.
**17b**: $R_f = 0.6$ (silica gel, hexanes/EtOAc 70:30); IR (film) $\nu_{\text{max}}$ 2967, 2909, 2243, 1725, 1567, 1473, 1456, 1426, 1410, 1345, 1317, 1261, 1227, 1201, 1137, 998, 982, 943, 890, 864, 796, 734 cm$^{-1}$; $^1$H NMR (600 MHz, CDCl$_3$) $\delta = 3.13$ (dd, $J = 4.3, 2.5$ Hz, 2H), 2.92–2.86 (m, 2H), 2.54–2.49 (m, 2H), 2.36–2.31 (m, 2H), 1.90–1.85 (m, 2H); $^{13}$C NMR (150 MHz, CDCl$_3$): $\delta = 204.3, 114.9, 114.0, 46.1$ (2C), 44.7, 41.6, 27.4 (2C) ppm; HRMS (ESI): calcd for C$_{10}$H$_{11}$N$_2$O$^+$ [M + H]$^+$ 175.0871, found 175.0876.

**Ketone 15c**: To a stirred solution of 2,7-cyclooctadien-1-one (8) (260 mg, 2.13 mmol) in CH$_3$CN (19 mL) at room temperature were added methylecyanoacetate (10c) (211 µL, 2.40 mmol) and DBU (60 µL, 0.40 mmol). The resulting mixture was stirred for 48 h before DBU (160 µL, 1.07 mmol) was added to the mixture in order to get the reaction to completion. After 24 h, the medium was concentrated under reduced pressure and the residue was dissolved in EtOAc (20 mL) and washed with HCl (1.0 N aq., 20 mL) and H$_2$O (2 x 20 mL). The organic layer was then dried (Na$_2$SO$_4$) and concentrated in vacuo to afford pure bicycle 15c (409 mg, 87%) as a yellow oil.

**15c**: $R_f = 0.4$ (silica gel, hexanes/EtOAc 70:30); IR (film) $\nu_{\text{max}}$ 2945, 2880, 2241, 2006, 1741, 1708, 1447, 1436, 1410, 1363, 1338, 1260, 1241, 1186, 1113, 1057, 1038, 962, 892, 781 cm$^{-1}$; $^1$H NMR (600 MHz, CDCl$_3$) $\delta = 3.90$ (s, 3H), 2.92 (s, 2H), 2.72 (dd, $J = 18.1, 5.8$ Hz, 2H), 2.43 (d, $J = 17.9$ Hz, 2H), 2.23–2.13 (m, 2H), 1.79 (d, $J = 13.8$ Hz, 2H), 1.64 (d, $J = 15.2$ Hz, 1H), 1.39 (tdd, $J = 18.7, 9.6, 4.7$ Hz, 1H); $^{13}$C NMR (150 MHz, CDCl$_3$): $\delta = 208.2, 167.9, 118.8, 54.3, 48.1, 43.3$ (2C), 35.6 (2C), 29.6 (2C), 16.6 ppm; HRMS (ESI): calcd for C$_{12}$H$_{15}$NNaO$_3$$^+$ [M + Na]$^+$ 244.0950, found 244.0948.
**Ketone 17c:** To a stirred solution of 2,6-cycloheptadien-1-one (9) (244 mg, 2.26 mmol) in CH$_3$CN (18 mL) at room temperature were added methylcyanoacetate (10c) (219 µL, 2.49 mmol) and DBU (61 µL, 0.41 mmol). The resulting mixture was stirred for 48 h before DBU (34 µL, 2.273 mmol) was added to the mixture in order to get the reaction to completion. After 24 h, the medium was concentrated under reduced pressure and the residue was dissolved in EtOAc (20 mL) and washed with HCl (1.0 N aq., 20 mL) and H$_2$O (2 x 20 mL). The organic layer was then dried (Na$_2$SO$_4$) and concentrated in vacuo to afford pure bicycle 17c (361 mg, 77%) as a yellow oil.

17c: $R_f = 0.4$ (silica gel, hexanes/EtOAc 70:30); IR (film) $\nu_{\text{max}}$ 2956, 2887, 1745, 1718, 1449, 1435, 1341, 1251, 1236, 1195, 1114, 1037, 966, 915, 746 cm$^{-1}$; $^1$H NMR (600 MHz, CDCl$_3$) $\delta = 3.87$ (s, 3H), 3.09 (dd, $J = 4.0$, 2.6 Hz, 2H), 2.94 (d, $J = 17.6$ Hz, 2H), 2.47–2.42 (m, 2H), 2.03–1.98 (m, 2H), 1.71–1.66 (m, 2H); $^{13}$C NMR (150 MHz, CDCl$_3$): $\delta = 207.9$, 167.2, 117.7, 54.3, 53.4, 47.2 (2C), 42.2 (2C), 27.7 (2C) ppm; HRMS (ESI): calcd for C$_{11}$H$_{13}$NNaO$_3$ $^+$ [M + Na]$^+$ 230.0793, found 230.0782.

**Ketone 16d:** To a stirred solution of 2,7-cyclooctadien-1-one (8) (112 mg, 0.918 mmol) in CH$_3$CN (30 mL) at room temperature were added ethyl nitroacetate (10d) (122 µL, 1.10 mmol) and DBU (137 µL, 0.92 mmol). The resulting mixture was stirred at 80 °C for 26 h before it was concentrated under reduced pressure. The residue was then dissolved in EtOAc (10 mL) and washed with HCl (1.0 N aq., 10 mL) and H$_2$O (2 x 10 mL). The layers were separated and the organic layer was dried (Na$_2$SO$_4$) and concentrated in vacuo to afford pure bicycle 16d (225 mg, 96%) as a light yellow oil.
**16d**: \( R_f = 0.6 \) (silica gel, hexanes/EtOAc 70:30); IR (film) \( \nu_{\text{max}} \) 2942, 2882, 1746, 1712, 1547, 1471, 1454, 1411, 1372, 1338, 1266, 1232, 1208, 1124, 1109, 1095, 1080, 1062, 1039, 979, 926, 906, 856, 781, 767, 729 cm\(^{-1}\); \(^1\)H NMR (600 MHz, CDCl\(_3\)) \( \delta = 4.30 \) (q, \( J = 7.1 \) Hz, 2H), 3.40 (dd, \( J = 5.8, 2.9 \) Hz, 2H), 2.70 (dd, \( J = 18.4, 5.7 \) Hz, 2H), 2.43 (d, \( J = 18.3 \) Hz, 2H), 1.98–1.86 (m, 2H), 1.86–1.77 (m, 2H), 1.53–1.46 (m, 1H), 1.37–1.27 (m, 4H); \(^{13}\)C NMR (150 MHz, CDCl\(_3\)): \( \delta = 208.7, 164.8, 96.0, 63.7, 43.4 \) (2C), 35.5 (2C), 30.2 (2C), 16.1, 14.1 ppm; HRMS (ESI): calcd for C\(_{12}\)H\(_{17}\)NNaO\(_5\)\(^+\) [M + Na]\(^+\) 278.1004, found 278.0993.

**Ketone 18d**: To a stirred solution of 2,6-cycloheptadien-1-one (9) (59 mg, 0.55 mmol) in CH\(_3\)CN (15 mL) at room temperature were added ethynitroacetate (10d) (73 µL, 0.65 mmol) and DBU (81 µL, 0.543 mmol). The resulting mixture was stirred at 50 °C for 24 h before it was concentrated under reduced pressure. The residue was then dissolved in EtOAc (10 mL) and washed with HCl (1.0 N aq., 10 mL) and H\(_2\)O (2 x 10 mL). The layers were separated and the organic layer was dried (Na\(_2\)SO\(_4\)) and concentrated in vacuo to afford pure bicycle 18d (97 mg, 74%) as a light yellow oil.

**18d**: \( R_f = 0.5 \) (silica gel, hexanes/EtOAc 70:30); IR (film) \( \nu_{\text{max}} \) 2968, 2926, 2896, 1746, 1720, 1544, 1469, 1455, 1414, 1369, 1357, 1342, 1298, 1248, 1227, 1190, 1085, 1045, 1026, 855, 799, 770, 744 cm\(^{-1}\); \(^1\)H NMR (600 MHz, CDCl\(_3\)) \( \delta = 4.32 \) (q, \( J = 7.2 \) Hz, 2H), 3.25 (d, \( J = 4.4 \) Hz, 2H), 2.84 (ddd, \( J = 18.2, 2.3, 1.5 \) Hz, 2H), 2.44–2.39 (m, 2H), 2.09–2.04 (m, 2H), 1.73–1.69 (m, 2H), 1.31 (dd, \( J = 9.2, 5.1 \) Hz, 3H); \(^{13}\)C NMR (150 MHz, CDCl\(_3\)): \( \delta = 208.0, 165.2, 99.6, 63.9, 45.9 \) (2C), 40.0 (2C), 26.8 (2C), 14.1 ppm; HRMS (ESI): calcd for C\(_{11}\)H\(_{15}\)NNaO\(_5\)\(^+\) [M + Na]\(^+\) 264.0848, found 264.0851.
Ketone 17a: To a stirred solution of 2,6-cycloheptadien-1-one (9) (103 mg, 0.952 mmol) in CH₃CN (30 mL) at room temperature were added nitromethane (10a) (62 µL, 1.15 mmol) and KF/basic Al₂O₃ (102 mg).[1] The resulting mixture was stirred at 80 °C for 18 h before the solids were removed by filtration over silica. The filtrate was concentrated under reduced pressure and the residue was dissolved in EtOAc (10 mL) and washed with HCl (1.0 N aq., 10 mL) and H₂O (2 x 10 mL). The organic layer was then dried (Na₂SO₄) and concentrated in vacuo to afford pure bicycle 17a (67 mg, 42%) as an orange oil.

17a: R_f = 0.8 (silica gel, hexanes/EtOAc 60:40); IR (film) ν_max 2959, 2926, 2887, 1712, 1668, 1538, 1470, 1455, 1412, 1377, 1341, 1312, 1271, 1259, 1192, 1153, 1081, 1016, 929, 850, 796, 771, 719 cm⁻¹; ^1H NMR (600 MHz, CDCl₃) δ = 4.88 (s, 1H), 3.19 (d, J = 1.8 Hz, 2H), 2.62 (d, J = 17.2 Hz, 2H), 2.48 (d, J = 17.5 Hz, 2H), 2.15–2.08 (m, 2H), 1.74–1.68 (m, 2H); ^13C NMR (150 MHz, CDCl₃): δ = 207.9, 93.0, 48.6 (2C), 39.8 (2C), 27.5 (2C) ppm; HRMS (ESI): calcd for C₈H₁₁NNaO₃⁺ [M + Na]^+ 192.0637, found 192.0636.

16f: R_f = 0.4 (silica gel, hexanes/EtOAc 70:30); IR (film) ν_max 2945, 2880, 1706, 1531, 1461, 1437, 1414, 1374, 1353, 1328, 1260, 1178, 1128, 967, 897, 839, 804, 714 cm⁻¹; ^1H NMR (600 MHz, CDCl₃) δ = 2.94 (dd, J = 4.9, 2.7 Hz, 2H), 2.71–2.57 (m, 2H), 2.37 (dd, J = 17.8, 1.7 Hz, 2H), 2.14 (q, J = 7.4 Hz, 2H), 2.00–1.85 (m, 2H), 1.78–1.70 (m, 2H), 1.54 (ddd, J = 15.3, 6.4, 4.0 Hz, 1H), 1.41–1.29 (m, 1H), 0.89 (t, J = 7.4 Hz, 3H); ^13C NMR (150 MHz, CDCl₃): δ = 210.1, 94.7, 44.1 (2C), 35.6 (2C), 29.8, 29.4 (2C), 16.3, 7.1 ppm; HRMS (ESI): calcd for C₁₁H₁₇NNaO₃⁺ [M + Na]^+ 234.1106, found 234.1106.
**Ketone 15g/16g:** To a stirred solution of 2,7-cyclooctadien-1-one (8) (36 mg, 0.294 mmol) in CH$_3$CN (9 mL) at room temperature were added oxindole (46 mg, 1.17 mmol) and KF/basic Al$_2$O$_3$ (41 mg). The resulting mixture was stirred at 80 °C for 4 days before the solids were removed by filtration over silica. The filtrate was concentrated under reduced pressure and the residue was dissolved in EtOAc (10 mL) and washed with HCl (1.0 N aq., 10 mL) and H$_2$O (2 x 10 mL). The organic layer was then dried (Na$_2$SO$_4$), concentrated in vacuo and purified by flash column chromatography (silica gel, hexanes:EtOAc 80/20) to afford bicycles 15g (25 mg, 33%) and 16g (14 mg, 19%) as pink and yellow solids respectively.

15g: R$_f$ = 0.6 (silica gel, hexanes/EtOAc 60:40); IR (film) $\nu_{\text{max}}$ 3174, 3077, 3036, 2961, 2916, 2893, 1695, 1621, 1591, 1475, 1467, 1447, 1407, 1328, 1299, 1259, 1240, 1213, 1175, 1104, 1073, 1019, 977, 917, 888, 844, 801, 758, 745, 715 cm$^{-1}$; $^1$H NMR (600 MHz, CDCl$_3$) $\delta$ = 7.78 (s, 1H), 7.28–7.25 (m, 1H), 7.24 (d, $J$ = 7.8 Hz, 1H), 7.00 (td, $J$ = 7.7, 1.1 Hz, 1H), 6.93 (dd, $J$ = 7.8, 0.6 Hz, 1H), 3.17 (dd, $J$ = 19.3, 6.5 Hz, 2H), 2.92–2.83 (m, 2H), 2.51 (d, $J$ = 19.4 Hz, 2H), 2.27 (s, 2H), 1.75–1.66 (m, 1H), 1.52–1.41 (m, 3H); $^{13}$C NMR (150 MHz, CDCl$_3$): $\delta$ = 212.0, 180.1, 140.7, 133.1, 128.7, 127.2, 122.1, 110.1, 50.9, 45.5 (2C), 35.6 (2C), 26.9 (2C), 16.1 ppm; HRMS (ESI): calcd for C$_{16}$H$_{17}$NNaO$_2^{+}$ [M + Na]$^+$ 278.1157, found 278.1156.

16g: R$_f$ = 0.6 (silica gel, hexanes/EtOAc 60:40); IR (film) $\nu_{\text{max}}$ 3256, 2952, 2924, 2879, 1695, 1618, 1589, 1473, 1401, 1332, 1262, 1235, 1192, 1102, 1928, 906, 802, 757, 744, 727 cm$^{-1}$; $^1$H NMR (600 MHz, CDCl$_3$) $\delta$ = 8.68 (s, 1H), 7.71 (d, $J$ = 7.7 Hz, 1H), 7.28 (td, $J$ = 7.6, 0.7 Hz, 1H), 7.06 (td, $J$ = 7.7, 1.0 Hz, 1H), 6.95 (d, $J$ = 7.5 Hz, 1H), 3.62 (dd, $J$ = 18.0, 6.4 Hz, 2H), 2.50–2.41 (m, 2H), 2.31 (d, $J$ =
18.0 Hz, 2H), 2.21 (s, 2H), 1.82–1.76 (m, 1H), 1.72 (ddd, \(J = 20.3, 13.0, 5.4\) Hz, 1H), 1.65–1.59 (m, 2H); \(^{13}\)C NMR (150 MHz, CDCl\(_3\)); \(\delta = 212.7, 181.2, 141.0, 132.6, 128.7, 128.6, 121.9, 110.3, 51.0, 43.7 (2C), 35.2 (2C), 28.1 (2C), 16.0\) ppm; HRMS (ESI): calcd for C\(_{16}\)H\(_{17}\)NNaO\(_2\)\(^+\) [M + Na]\(^+\) 278.1157, found 278.1156.

Alcohol 19: To a stirred solution of ketone 16d (1.43 g, 5.6 mmol) in CH\(_3\)OH (50 mL) at room temperature was added NaBH\(_4\) (2.8 g, 74.1 mmol). The resulting mixture was stirred for 2 h before acetone (30 mL) was added and the medium was concentrated under reduced pressure. The residue was dissolved in CH\(_2\)Cl\(_2\) (150 mL) and washed with H\(_2\)O (2 x 70 mL). The organic layer was then dried (Na\(_2\)SO\(_4\)) and concentrated in vacuo to afford pure bicycle 19 (1.13 g, 79\%) as a light yellow solid.

19: \(R_f = 0.5\) (silica gel, hexanes/EtOAc 60:40); IR (film) \(\nu_{\text{max}}\) 3415, 2936, 2871, 1745, 1546, 1453, 1371, 1340, 1296, 1226, 1122, 1097, 1046, 1025, 957, 894, 859, 847, 707 cm\(^{-1}\); \(^1\)H NMR (600 MHz, CDCl\(_3\)) \(\delta = 4.24 (q, J = 7.1\) Hz, 2H), 3.89 (ddd, \(J = 7.7, 5.0, 2.6\) Hz, 1H), 3.14 (ddd, \(J = 5.8, 3.6, 1.7\) Hz, 2H), 2.40 (dt, \(J = 15.5, 7.8\) Hz, 2H), 2.23 (qt, \(J = 13.7, 5.9\) Hz, 1H), 1.82–1.75 (m, 2H), 1.73–1.66 (m, 2H), 1.53 (ddd, \(J = 15.7, 5.1, 1.7\) Hz, 2H), 1.39–1.30 (m, 1H), 1.27 (t, \(J = 7.1\) Hz, 3H); \(^{13}\)C NMR (150 MHz, CDCl\(_3\)); \(\delta = 165.7, 97.5, 63.1, 61.4, 35.5 (2C), 32.7 (2C), 30.1 (2C), 14.6, 14.1\) ppm; HRMS (ESI): calcd for C\(_{12}\)H\(_{19}\)NNaO\(_5\)\(^+\) [M + Na]\(^+\) 280.1161, found 280.1158.

Amino-alcohol 20: A suspension of Ra/Ni in water was washed three times with CH\(_3\)OH before alcohol 19 (115 mg, 0.47 mmol) was added in solution in CH\(_3\)OH (8 mL). The resulting mixture was stirred under a hydrogen atmosphere for 2 h before the solution was filtered over a short
pad of silica. The filtrate was concentrated in vacuo to afford pure bicycle 20 (80 mg, 75%) as a light yellow solid. 

20: Rf = 0.2 (silica gel, hexanes/EtOAc 50:50); IR (film) νmax 3638, 2919, 1713, 1590, 1452, 1366, 1296, 1263, 1224, 1196, 1164, 1127, 1112, 1080, 1036, 956, 921, 902, 858, 836, 770, 718 cm⁻¹; ¹H NMR (600 MHz, CD₃OD) δ = 4.28 (ddd, J = 7.7, 4.8, 2.9 Hz, 1H), 4.20 (q, J = 7.1 Hz, 2H), 2.51 (dt, J = 15.3, 7.6 Hz, 2H), 2.46–2.39 (m, 1H), 2.24–2.13 (m, 2H), 1.76–1.64 (m, 2H), 1.60–1.52 (m, 2H), 1.48–1.43 (m, 2H), 1.31 (t, J = 7.1 Hz, 3H), 1.21 (ddddd, J = 13.3, 7.5, 3.6, 1.7 Hz, 1H); ¹³C NMR (150 MHz, CD₃OD): δ = 178.3, 63.7, 62.4, 61.6, 36.3 (2C), 35.5 (2C), 31.2 (2C), 16.8, 15.3 ppm; HRMS (ESI): calcd for C₁₂H₂₂NO₃⁺ [M + H]⁺ 228.1600, found 228.1592.

Amino-acid 21: To a stirred solution of amino-ester 20 (9 mg, 0.04 mmol) in THF/CH₃OH/H₂O (3:1:1, 2.5 mL) at room temperature was added LiOH (10 mg, 0.42 mmol). The resulting mixture was stirred for 16 h before HCl (1.0 N aq., 2 mL) was added. The medium was concentrated under reduced pressure and the residue was dissolved in H₂O and purified on Dowex 50 WX8-100 to afford amino-acid 21 (9 mg, quant.) as a white solid.

21: Rf = 0.4 (silica gel, CH₂Cl₂/CH₃OH 90:10); IR (film) νmax 3369, 1652, 1452, 1143, 1046, 1023, 989, 826, 763 cm⁻¹; ¹H NMR (600 MHz, D₂O) δ = 4.14 (t, J = 6.7 Hz, 1H), 2.51–2.21 (m, 5H), 1.90 (dq, J = 13.0, 6.5, 4.9 Hz, 2H), 1.76 (d, J = 15.4 Hz, 2H), 1.61 (dd, J = 14.2, 6.1 Hz, 2H), 1.37–1.21 (m, 1H); ¹³C NMR (150 MHz, DMSO-d₆): δ = 174.4, 64.7, 60.4, 35.7 (2C), 33.0 (2C), 29.7 (2C), 15.9 ppm; HRMS (ESI): calcd for C₁₀H₁₈NO₃⁺ [M + H]⁺ 200.1287, found 200.1278.
**Diol 23:** To a stirred solution of ester 19 (87 mg, 0.34 mmol) in CH₂Cl₂ (10 mL) at −78 °C was added Dibal-H (1.0 M in CH₂Cl₂, 1.7 mL, 1.7 mmol). The resulting mixture was allowed to warm to room temperature and stirred for 16 h before it was quenched with sodium potassium tartrate (10 mL, sat. aq.) The layers were separated and the aqueous layer was extracted with CH₂Cl₂ (2 × 10 mL). The combined organic layers were dried (Na₂SO₄) and concentrated in vacuo. Flash column chromatography (silica gel, hexanes:EtOAc 7:3) afforded alcohol 23 (37 mg, 50%) as a white solid.

**23:** Rf = 0.4 (silica gel, hexanes/EtOAc 50:50); IR (film) νmax 3147, 2931, 2871, 1709, 1534, 1471, 1450, 1343, 1311, 1260, 1218, 1122, 1052, 1004, 957, 933, 844, 799, 752, 708 cm⁻¹; ¹H NMR (600 MHz, CDCl₃) δ = 4.77 (s, 1H), 4.02 (s, 2H), 3.86 (tt, J = 7.6, 5.7 Hz, 1H), 2.82 (dt, J = 5.3, 2.4 Hz, 2H), 2.37 (dt, J = 15.5, 7.8 Hz, 2H), 2.31–2.14 (m, 1H), 1.88–1.75 (m, 2H), 1.70–1.61 (m, 2H), 1.52–1.40 (m, 3H), 1.26 (d, J = 6.3 Hz, 1H); ¹³C NMR (150 MHz, CDCl₃): δ = 96.1, 66.4, 62.0, 35.8 (2C), 30.7 (2C), 29.5 (2C), 14.4 ppm; HRMS (ESI): calcd for C₁₀H₁₇NNaO₄⁺ [M + Na]⁺ 238.1055, found 238.1049.

**Alcohol 24:** To a stirred solution of ketone 15c (220 mg, 1.0 mmol) in CH₃OH (12 mL) at room temperature was added NaBH₄ (378 g, 10.0 mmol). The resulting mixture was stirred for 2 h before acetone (10 mL) was added and the medium was concentrated under reduced pressure. The residue was dissolved in CH₂Cl₂ (50 mL) and washed with H₂O (2 x 20 mL). The organic layer was then dried (Na₂SO₄) and concentrated in vacuo to afford pure bicycle 24 (165 g, 75%) as a light yellow solid.

**24:** Rf = 0.5 (silica gel, hexanes/EtOAc 50:50); IR (film) νmax 3416, 2935, 2869, 1743, 1435, 1265,
1239, 1123, 1061, 891, 786 cm\(^{-1}\); \(^1\)H NMR (600 MHz, CDCl\(_3\)) \(\delta = 3.82\) (s, 3H), 3.81–3.72 (m, 1H), 2.83–2.59 (m, 2H), 2.29 (ddd, \(J = 15.4, 8.5, 7.2\) Hz, 2H), 2.17 (tt, \(J = 13.7, 5.4\) Hz, 1H), 2.02 (tdd, \(J = 13.8, 5.4, 3.9\) Hz, 2H), 1.80–1.74 (s, 1H), 1.62 (ddt, \(J = 14.4, 3.4, 1.6\) Hz, 2H), 1.53–1.45 (m, 1H), 1.42 (ddd, \(J = 15.0, 6.3, 2.0\) Hz, 2H); \(^13\)C NMR (150 MHz, CDCl\(_3\)): \(\delta = 168.9, 119.6, 61.7, 54.0, 48.0, 34.4\) (2C), 32.2 (2C), 29.5 (2C), 14.9 ppm; HRMS (ESI): calcd for C\(_{12}\)H\(_{17}\)NNaO\(_3\)\(^+\) [M + Na]\(^+\) 246.1106, found 246.1108.

**Amino-alcohol 25:** A suspension of Ra/Ni in water was washed three times with CH\(_3\)OH before alcohol 24 (20 mg, 0.09 mmol) was added in solution in CH\(_3\)OH (3 mL). The resulting mixture was stirred under a hydrogen atmosphere for 16 h before the solution was filtered over a short pad of silica. The filtrate was concentrated in vacuo to afford pure bicycle 25 (17 mg, 85%) as a light yellow solid.

25: \(R_f = 0.2\) (silica gel, hexanes/EtOAc 50:50); IR (film) \(\nu_{\text{max}}\) 3368, 2921, 2870, 1717, 1595, 1448, 1379, 1268, 1237, 1167, 1121, 1057, 954, 919, 814, 712 cm\(^{-1}\); \(^1\)H NMR (600 MHz, CD\(_3\)OD) \(\delta = 3.75\) (s, 3H), 3.75–3.70 (m, 1H), 2.92 (s, 2H), 2.47–2.29 (m, 4H), 2.09 (qt, \(J = 13.3, 5.6\) Hz, 1H), 1.87–1.75 (m, 2H), 1.47–1.28 (m, 5H); \(^13\)C NMR (150 MHz, CD\(_3\)OD): \(\delta = 179.4, 64.8, 53.3, 51.6, 47.1, 37.8\) (2C), 31.5 (2C), 28.9 (2C), 16.4 ppm; HRMS (ESI): calcd for C\(_{12}\)H\(_{22}\)NO\(_3\)\(^+\) [M + H]\(^+\) 228.1600, found 228.1586.

**Diketone 28:** To a stirred solution of bicycles 15a/15’a (15a/15’a = 2:1, 50 mg, 0.27 mmol) in CH\(_3\)CN (4 mL) at room temperature were added methyl vinyl ketone (28) (45 \(\mu\)L, 0.55
mmol) and DBU (40 µL, 0.27 mmol). The resulting mixture was stirred for 2.5 h before the medium
was concentrated under reduced pressure. The residue was dissolved in AcOEt (20 mL) and washed
with HCl (1.0 N aq., 10 mL) and H₂O (10 mL), dried (Na₂SO₄) and concentrated in vacuo to afford
diketone 29 (69 mg, quant.) as an orange oil.

29: Rₜ = 0.5 (silica gel, hexanes/EtOAc 50:50); IR (film) νₘₐₓ 3483, 2947, 2878, 1708, 1531, 1459,
1438, 1412, 1376, 1346, 1301, 1258, 1222, 1176, 1121, 1102, 1068, 975, 940, 862, 836, 792, 714 cm⁻¹;
¹H NMR (600 MHz, CDCl₃) δ = 2.91 (s, 2H), 2.64 (dd, J = 18.4, 5.8 Hz, 2H), 2.50–2.33 (m, 6H), 2.17
(s, 3H), 1.99–1.90 (m, 2H), 1.75 (dt, J = 13.7, 3.3, 1.6 Hz, 2H), 1.60–1.51 (m, 1H), 1.43–1.31 (m, 1H);
¹³C NMR (150 MHz, CDCl₃); δ = 209.4, 206.3, 93.6, 44.0 (2C), 37.5, 36.0 (2C), 30.5, 30.2, 29.4 (2C),

II) Abbreviations

DMSO = dimethyl sulfoxide

DBU = 1,8-Diazabicyclo[5.4.0]undec-7-ene

Dibal-H = diisobutylaluminium hydride

III) References

IV) $^1$H and $^{13}$C NMR Spectra of Compounds

$^{13}$C NMR spectrum (151 MHz, CDCl$_3$)

$^1$H NMR spectrum (600 MHz, CDCl$_3$)

$^{13}$C NMR spectrum (151 MHz, CDCl$_3$)
$^{15a}$ + $^{15'a}$

$^{1}$H NMR spectrum (600 MHz, CDCl$_3$)

$^{13}$C NMR spectrum (151 MHz, CDCl$_3$)
$^{13}$C NMR spectrum (151 MHz, CDCl$_3$)

$^1$H NMR spectrum (600 MHz, CDCl$_3$)
$^1$H NMR spectrum (600 MHz, CDCl$_3$)

$^{13}$C NMR spectrum (151 MHz, CDCl$_3$)
$^{1}H$ NMR spectrum (600 MHz, CDCl$_3$)

$^{13}C$ NMR spectrum (151 MHz, CDCl$_3$)
$^{13}$C NMR spectrum (151 MHz, CDCl$_3$)

$^1$H NMR spectrum (600 MHz, CDCl$_3$)
$\text{EtO}_2\text{C}\begin{aligned}\text{NO}_2 \\ 16\text{d}\end{aligned}$

$^1\text{H NMR spectrum (600 MHz, CDCl}_3\text{)}$

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$^1$H NMR spectrum (600 MHz, CDCl$_3$)

$^{13}$C NMR spectrum (151 MHz, CDCl$_3$)

Electronic Supplementary Material (ESI) for RSC Advances
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$^1$H NMR spectrum (600 MHz, CDCl$_3$)

$^{13}$C NMR spectrum (151 MHz, CDCl$_3$)
1H NMR spectrum (600 MHz, CDCl3)

13C NMR spectrum (151 MHz, CDCl3)
$^{1}H$ NMR spectrum (600 MHz, CDCl$_3$)

$^{13}C$ NMR spectrum (151 MHz, CDCl$_3$)
$^{1}H$ NMR spectrum (600 MHz, CDCl$_3$)

$^{13}C$ NMR spectrum (151 MHz, CDCl$_3$)
1H NMR spectrum (600 MHz, CDCl₃)

13C NMR spectrum (151 MHz, CDCl₃)
$^{1}$$\text{H}$ NMR spectrum (600 MHz, CD$_3$OD)

$^{13}$$\text{C}$ NMR spectrum (151 MHz, CD$_3$OD)
$^1$H NMR spectrum (600 MHz, D$_2$O)

$^{13}$C NMR spectrum (151 MHz, DMSO-$d_6$)
$^{1}H$ NMR spectrum (600 MHz, CDCl$_3$)

$^{13}C$ NMR spectrum (151 MHz, CDCl$_3$)

Electronic Supplementary Material (ESI) for RSC Advances
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$^1$H NMR spectrum (600 MHz, CDCl$_3$)

$^1$C NMR spectrum (151 MHz, CDCl$_3$)
$^1$H NMR spectrum (600 MHz, CDCl$_3$)

$^{13}$C NMR spectrum (151 MHz, CDCl$_3$)
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$^{13}$C NMR spectrum (151 MHz, CDCl$_3$)