Titanium catalysis in the Ugi reaction of α -aminoacids with aromatic aldehydes

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Experimental protocols. Unless otherwise indicated, ^1H and ^{13}C NMR spectra were recorded at room temperature in CDCl_3 solutions at 300 and 75 MHz, respectively. Chemical shifts are reported on the δ scale and coupling constants J are in Hz. Multiplicities are described as s (singlet), d (doublet), dd, ddd, etc. (doublet of doublets, doublet of doublets of doublets, etc.), t (triplet), q (quartet); sept (septuplet), m (multiplet), and further qualified as a (apparent), br (broad), c (complex). IR spectra (cm^{-1}) were recorded from thin films. Low resolution mass spectra (m/e) were obtained in the CI (reagent gas: isobutane) or electrospray (ESI) mode. High resolution mass spectra (HR) were obtained in the CI mode (isobutane). Optical rotation, $[\alpha]_D^{25}$, were obtained from MeOH solutions. Melting points are uncorrected. Commercial reagents (Aldrich or Acros) were used without further purification.

Compounds 6 and 7: Thick yellow oil. ^1H :

7.99 (br, 1H), 7.38 (d, $J = 8.7$, 1H, 6), 7.21 (d, $J = 8.6$, 1H, 7), 7.07-6.98 (m, 3H), 6.69 (d, $J = 8.7$, 1H, 6), 6.63 (d, $J = 8.6$, 1H, 7), 4.72 (s, 1H, 6), 4.62 (s, 1H, 7), 3.83 (s, 1H), 3.79 (s, 1H), 3.72 (s, 1H), 3.63 (s, 1H), 3.81 (m, 1H), 3.26 (td, $J = 6.0$, 1.3, 2H), 2.43 (td, $J = 7.2$, 1.3, 2H), 2.16 (s, 6H), 2.07 (s, 3H); ^{13}C : 174.3, 173.1, 169.9, 158.3, 156.7, 134.9, 134.8, 133.5, 127.9, 127.7, 126.6, 125.3, 123.7, 119.6, 106.4, 61.2, 60.8, 58.0, 57.9, 55.3, 51.6, 30.5, 30.2, 28.1, 27.8, 18.3, 17.9, 9.3; IR: 2950-2905, 1741, 1683, 1502, 1484, 1435, 1267, 1102, 1062, 773; CIMS 487 (MH^+ , 100), 455 ($\text{MH}^+ - \text{MeOH}$, 8), 338 ($\text{MH}^+ - \text{HCONHAr}$, 12); HRMS calcd for $\text{C}_{26}\text{O}_7\text{N}_2\text{H}_{35}$ (MH^+) 487.2444, found 487.2452.

Compound 8: White powder. ^1H : 8.72 (br, 1H), 7.48 (d, $J = 8.5$, 1H, minor isomer), 7.21 (d, $J = 8.5$, 1H, major isomer), 7.07-6.98 (m, 3H), 6.63 (d, $J = 8.5$, 1H, major isomer), 6.62 (d, $J = 8.5$, 1H, minor isomer), 6.41 (s, 1H, minor isomer), 5.96 (s, 1H, major isomer), 4.77 (d, $J = 6.8$, 1H), 4.04 (dd, $J = 8.4$, 1.7, 1H), 3.82 (s, 3H), 3.81 (s, 3H), 3.62 (s, 3H), 2.66-2.29 (m, 4H), 2.24 (s, 6H), 2.19 (s, 3H), 2.16-1.93 (m, 1H); ^{13}C : 175.6, 173.0, 168.6, 159.3, 157.6, 135.3, 133.2, 127.8, 127.2, 127.0, 119.9, 119.0, 106.0, 105.4, 60.8, 58.5, 55.5, 52.4, 52.0, 51.6, 29.3, 23.9, 18.2, 9.2; CIMS 455 (MH^+ , 100), 306 ($\text{MH}^+ - \text{HCONHAr}$, 12); HRMS calcd for $\text{C}_{25}\text{O}_6\text{N}_2\text{H}_{31}$ (MH^+) 455.2182, found 455.2187.

Typical procedure for the catalyzed Ugi reaction: A solution of an α -amino acid (0.31 mmol, 1.2 eq.) and an aldehyde (0.25 mmol, 1 eq.) in methanol (2 mL) was stirred at RT for 20 min, then an isocyanide (0.31 mmol, 1.2 eq.) was added, followed by the catalyst (5 mol%, 0.05 mmol). The mixture was stirred at RT for 12 hours, then it was diluted with EtOAc (15 mL) and washed with water. The organic phase was dried (Na_2SO_4), filtered, and concentrated. If necessary, the resulting oil was purified by preparative TLC (1:1 cyclohexane:EtOAc).

Compounds 9a and 10a: Yellow oil (80%).

^1H : 9.08 (s, 1H), 8.81 (dd, $J = 4.9, 1.5$, 1H), 8.16 (dt, $J = 7.9, 1.9$, 1H), 7.46 (dd, $J = 7.5, 4.9$, 1H), 6.34 (br, 1H), 4.16 (s, 1H, 9a), 3.95 (s, 1H, 10a), 3.69 (s, 3H), 3.59 (s, 3H), 3.06 (dd, 1H, $J = 7.5, 5.6$, 1H), 2.50-2.35 (m, 1H), 2.03-1.82 (m, 2H), 1.27 (s, 9H); ^{13}C : 173.9, 173.1, 169.6, 149.6, 135.2, 123.8, 63.5, 57.9, 52.0, 51.6, 51.2, 30.3, 29.4, 28.5, 27.8; IR: 3410-3250, 2970-2850, 1734, 1676, 1591, 1577, 1520, 1454, 1436, 1222, 1173, 634; ESIMS 752 ($2\text{M}+\text{Na}^+$, 6), 366 (MH^+ , 100); HRMS calcd for $\text{C}_{18}\text{O}_5\text{N}_3\text{H}_{28}$ (MH^+) 366.2029, found 366.2027.

Compounds 9b and 10b: Yellow oil (86%).

^1H : 7.45 (s, 1H), 7.27 (s, 1H), 6.57 (s, 1H), 4.02 (s, 1H, 9b), 3.91 (s, 1H, 10b), 3.78 (s, 3H), 3.71 (s, 3H), 3.13 (t, $J = 6.8$, 1H), 2.47-2.31 (m, 2H), 2.12-1.99 (m, 2H), 1.35 (s, 9H); ^{13}C : 174.4, 173.6, 170.5, 135.6, 133.2, 131.8, 111.1, 64.8, 58.5, 52.8, 52.2, 51.7, 30.8, 29.1, 28.3; IR: 3370-3250, 2990-2870, 1732, 1655, 1524, 1475, 1455, 1437, 1270, 1205, 1170, 737, 704; ESIMS 537 (MH^+ , 50); HRMS calcd for $\text{C}_{19}\text{O}_6\text{N}_2\text{H}_{27}^{79}\text{Br}_2$ (MH^+) 537.0236, found 537.0233.

Compounds 9c and 10c: Yellow oil (83%).

^1H : 7.30 (m, 2H), 6.85 (m, 2H), 6.79 (br, 1H), 4.42 (s, 1H, 9c), 4.16 (s, 1H, 10c), 3.83 (s, 3H), 3.67 (s, 3H), 3.23-3.18 (m, 1H), 2.45-2.23 (m, 2H), 2.05-1.98 (m, 2H), 1.32 (s, 9H); ^{13}C : 174.7, 173.7, 171.5, 157.3, 129.4, 129.3, 128.1, 121.5, 111.4, 60.0, 59.0, 55.7, 52.2, 52.0, 51.0, 30.9, 29.0, 28.2; IR: 3390-3290, 2990-2880, 1736, 1677, 1516, 1493, 1455, 1400, 1364, 1247, 1149, 756; ESIMS 810 ($2\text{M}+\text{Na}^+$, 3), 395 (MH^+ , 100); HRMS calcd for $\text{C}_{20}\text{O}_6\text{N}_2\text{H}_{31}$ (MH^+) 395.2182, found 395.2187.

Compounds 9d and 10d: Yellow oil (86 %).

^1H : 7.39 (t, $J = 8.3$, 1H), 7.23 (t, $J = 8.3$, 1H), 7.00-6.83 (m, 2H), 6.25 (br, 1H), 6.15 (dd, $J = 16.2, 7.2$, 1H, 10d), 6.03 (dd, $J = 16.2, 8.3$, 1H, 9d), 4.97 (d, $J = 8.3$, 1H, 9d), 4.54 (d, $J = 7.5, 1\text{H}$, 10d), 3.82 (s, 3H, 9d), 3.81 (s, 3H, 10d), 3.71 (s, 3H, 9d), 3.69 (s, 3H, 10d), 3.68 (s, 3H, 10d), 3.61 (s, 3H, 10d), 3.52 (s, 1H), 3.36-3.30 (m, 1H, 10d), 3.29-3.20 (m, 1H, 9d), 2.44 (t, $J = 6.8$, 2H, 9d), 2.07-1.86 (m, 2H), 1.36 (s, 3H, 10d), 1.32 (s, 3H, 9d); ^{13}C : 175.1, 173.8, 173.7, 157.2, 157.2, 130.3, 129.6, 129.4, 128.0, 127.5, 127.3, 125.5, 121.0, 111.3, 65.9, 65.1, 59.8, 58.2, 55.8, 52.4, 52.0, 51.2, 30.9, 30.1, 29.1, 24.4, 14.5; IR: 3340-3320, 2980-2930, 1722, 1670, 1598, 1516, 1489, 1437,

1392, 1364, 1244, 1175, 1050, 1027, 979, 635; ESIMS 421 (MH^+ , 100); HRMS calcd for $\text{C}_{22}\text{O}_6\text{N}_2\text{H}_{33}$ (MH^+) 421.2702, found 421.2703.

Compounds 9e and 10e: Yellow oil (91%).

^1H : 7.11 (d, $J = 8.7$, 1H, 9e), 7.00 (d, $J = 8.7$, 1H, 10e), 6.86 (br, 1H), 6.60 (d, $J = 8.7$, 1H, 9e), 6.58 (d, $J = 8.7$, 1H, 10e), 4.33 (s, 1H, 9e), 4.22 (s, 1H, 10e), 3.75 (s, 3H), 3.73 (s, 3H), 3.66 (s, 3H), 3.58 (s, 3H), 3.36 (t, $J = 6.0$, 1H), 3.15 (t, $J = 6.0$, 2H), 2.21 (s, 3H), 2.05–1.85 (m, 2H), 1.28 (s, 9H); ^{13}C : 174.0, 173.0, 170.9, 158.3, 156.8, 126.3, 125.1, 119.2, 106.9, 60.5, 59.4, 58.0, 55.2, 51.8, 51.6, 50.2, 29.9, 28.2, 27.6, 8.9; IR: 3340–3300, 2970–2840, 1734, 1672, 1598, 1487, 1454, 1416, 1365, 1269, 1146, 734; CIMS 439 (MH^+ , 100), 407 (MH^+ -MeOH, 6), 338 (MH^+ -HCONH-*t*Bu, 8); HRMS calcd for $\text{C}_{22}\text{O}_7\text{N}_2\text{H}_{35}$ (MH^+) 439.2444, found 439.2442.

Compounds 9f and 10f: Yellow oil (90%).

^1H : 7.50–7.32 (m, 3H), 7.30–7.21 (m, 2H), 6.32 (br, 1H), 4.60 (s, 1H, 9f), 4.41 (s, 1H, 10f), 3.71 (s, 3H), 3.62 (s, 3H), 3.16 (t, $J = 5.6$, 1H), 2.50–2.32 (m, 2H), 2.11–1.83 (m, 2H), 1.34 (s, 9H); ^{13}C : 174.7, 174.4, 170.3, 137.4, 134.4, 130.5, 130.3, 129.8, 127.8, 62.4, 58.8, 52.4, 52.2, 51.6, 31.0, 29.0, 28.4; IR: 3350–3300, 2970–2910, 1739, 1680, 1680, 1520, 1454, 1367, 1204, 1170, 637; ESIMS 399 (MH^+ , 100); HRMS calcd for $\text{C}_{19}\text{O}_5\text{N}_2\text{H}_{28}^{35}\text{Cl}$ (MH^+) 399.1687, found 399.1683.

Compounds 9g and 10g: Orange oil (75 %).

^1H : 6.72 (s, 1H), 6.21 (br, 1H), 4.54 (s, 1H, 9g), 4.49 (s, 1H, 10g), 3.69 (s, 3H), 3.67 (s, 3H), 3.74 (s, 3H), 3.56 (s, 3H), 3.32 (s, 3H), 3.06 (dd, $J = 7.9$, 5.7 Hz, 1H), 2.46 (td, $J = 7.5$, 3.8 Hz, 2H, 10g), 2.46 (t, $J = 7.9$ Hz, 2H, 9g), 2.12 (s, 3H), 1.25 (s, 9H); ^{13}C : 176.0, 174.3, 167.5, 158.9, 156.0, 134.5, 125.6, 119.4, 61.8, 60.5, 58.9, 56.7, 52.6, 52.3, 51.7, 39.6, 38.4, 38.2, 21.8, 14.0, 9.3; LSIMS (Cs^+) 533 (MH^+ , 100); LSIHRMS calcd for $\text{C}_{23}\text{O}_{10}\text{N}_2\text{H}_{37}\text{S}_1$ (MH^+) 533.2169, found 533.2167.

Compounds 9h and 10h: Yellow oil (86 %).

^1H : 7.35–7.21 (m, 4H), 6.29 (m, 1H), 4.08 (s, 1H, 9h), 3.91 (s, 1H, 10h), 3.71 (s, 3H), 3.67 (s, 3H), 3.09 (m, 1H), 2.51–2.35 (m, 2H), 2.07–1.86 (m, 2H), 1.32 (s, 9H), 1.28 (s, 9H); ^{13}C : 174.9, 173.7, 171.3, 151.5, 135.8, 127.0, 126.0, 66.1, 58.4, 52.5, 52.2, 51.3, 34.9, 31.7, 30.9, 29.0, 28.4; IR: 3350–2990, 2950–2860, 1736, 1677, 1514, 1453, 1438, 1364, 1268, 1203, 1172, 1035, 844; ESIMS 421 (MH^+ , 100); HRMS calcd for $\text{C}_{23}\text{O}_5\text{N}_2\text{H}_{37}$ (MH^+) 421.2702, found 421.2703.

Compounds 9i and 10i: Yellow oil (85 %).

^1H : 7.17 (d, $J = 7.9$, 1H), 6.69 (br, 1H), 6.46–6.38 (m, 3H), 4.33 (s, 1H, 9i), 4.09 (s, 1H, 10i), 3.80 (s, 3H), 3.78 (s, 3H), 3.67 (s, 3H), 3.61 (s, 3H), 3.16 (t, $J = 6.0$, 1H), 2.46–2.32

(m, 2H), 2.05-1.83 (m, 2H), 1.32 (s, 9H); ^{13}C : 174.3, 173.2, 171.2, 160.4, 157.9, 129.5, 119.9, 104.6, 98.7, 59.2, 58.4, 55.2, 51.8, 51.5, 50.6, 30.2, 28.6, 27.8; IR: 3380-3320, 2980-2830, 1737, 1677, 1612, 1587, 1508, 1455, 1439, 1364, 1294, 1208, 1035, 833; ESIMS 425 (MH^+ , 100); HRMS calcd for $\text{C}_{21}\text{O}_7\text{N}_2\text{H}_{33}$ (MH^+) 425.2288, found 425.2283.

Compounds 9j and 10j: Yellow oil (86 %).

^1H : 8.21 (s, 1H), 7.93 (d, $J = 8.3$, 1H), 7.78 (d, $J = 7.9$, 1H), 7.68 (t, $J = 6.8$, 1H), 7.51 (t, $J = 7.2$, 1H), 6.68 (br, 1H), 4.59 (s, 1H, 9j), 4.41 (s, 1H, 10j), 3.62 (s, 3H), 3.49 (s, 3H), 3.31, 3.19 (m, 1H), 2.50-2.30 (m, 2H), 2.11-1.83 (m, 2H), 1.32 (s, 9H); ^{13}C : 173.9, 173.5, 172.9, 169.0, 149.8, 146.8, 138.5, 130.8, 130.5, 127.8, 127.6, 127.2, 127.0, 62.3, 58.6, 51.9, 51.1, 30.0, 28.3, 27.6; IR: 3355-3250, 2970-2900, 1731, 1661, 1590, 1517, 1489, 1435, 1393, 1364, 1334, 1281, 1138, 1037, 917, 731, 648; CIMS 450 (MH^+ , 100), 418 ($\text{MH}^+ - \text{MeOH}$, 24); HRMS calcd for $\text{C}_{22}\text{O}_5\text{N}_3\text{H}_{29}^{35}\text{Cl}$ (MH^+) 450.1796, found 450.1790.

Compounds 12a and 13a: Yellow oil (92 %).

^1H : 7.95 (d, $J = 8.3$, 1H), 7.74 (s, 1H), 7.68 (t, $J = 6.4$, 1H), 7.58 (d, $J = 6.8$, 1H), 7.50 (t, $J = 6.4$, 1H), 7.19 (m, 3H), 7.06 (m, 2H), 6.89 (br, 1H), 4.56 (s, 1H, 12a), 4.28 (s, 1H, 13a), 3.65 (s, 3H), 3.46-3.40 (m, 1H), 3.28 (s, 1H), 3.10 (dd, $J = 13.9$, 4.9, 1H), 2.80 (dd, $J = 9.8$, 3.8, 1H), 2.55 (br, 1H), 1.32 (s, 9H); ^{13}C : 173.9, 169.0, 146.8, 138.5, 136.6, 130.5, 130.2, 128.9, 128.6, 127.9, 127.5, 127.0, 126.9, 126.8, 62.9, 60.7, 52.0, 51.2, 39.0, 28.5; IR: 3350-3310, 2953, 2924, 2853, 1735, 1670, 1514, 1489, 1453, 1434, 1392, 1363, 1334, 1272, 1202, 1176, 1135; ESIMS: 929 ($2\text{M} + \text{Na}^+$, 34), 454 (MH^+ , 100); HRMS calcd for $\text{C}_{25}\text{O}_3\text{N}_3\text{H}_{29}^{35}\text{Cl}$ (MH^+) 454.1897, found 454.1896.

Compounds 12b and 13b: Yellow oil (79 %).

^1H : 7.10 (d, $J = 8.3$, 1H), 6.89 (br, 1H), 6.61 (d, $J = 8.3$, 1H), 4.45 (s, 1H, 12b), 4.36 (s, 1H, 13b), 3.79 (s, 3H), 3.76 (s, 3H), 3.71 (s, 3H), 3.34 (t, $J = 4.6$, 1H), 3.00-2.60 (br, 1H), 2.13 (s, 3H), 1.31 (s, 9H); ^{13}C : 173.3, 172.1, 159.0, 157.3, 125.7, 125.0, 120.2, 107.1, 63.3, 61.8, 61.4, 59.3, 56.0, 52.6, 51.4, 29.1, 9.8; IR: 2921, 2852, 2366, 1672, 1463, 1266, 1107, 898, 667; ESIMS 786 ($2\text{M} + \text{Na}^+$, 6), 383 (MH^+ , 100); HRMS calcd for $\text{C}_{19}\text{O}_6\text{N}_2\text{H}_{31}$ (MH^+) 383.2182, found 383.2185.

Compounds 12c and 13c: Yellow oil (84 %).

^1H : 8.71 (br, 1H), 7.49 (d, $J = 7.8$, 1H), 7.32-7.00 (m, 7H), 6.90 (s, 1H), 4.03 (s, 1H, 12c), 3.99 (s, 1H, 13c), 3.71 (s, 3H), 3.51 (dd, $J = 4.9$, 1H), 3.28 (dd, $J = 5.1$, 1H), 3.01 (dd, $J = 8.3$, 1H), 1.28 (s, 9H); ^{13}C : 174.3, 170.0, 136.4, 134.8, 127.1, 123.0, 122.2, 119.6, 118.3, 111.5, 110.2, 64.6, 61.6, 59.9, 52.1, 51.0, 28.9, 28.5, 27.9; IR: 3330-2990, 2965, 2923, 1731, 1656, 1591, 1577, 1517, 1477, 1455, 1425, 1392, 1362, 1341, 1208, 1176, 1128; ESIMS 838 ($2\text{M} + \text{Na}^+$, 29), 816 ($2\text{M} + \text{H}^+$, 31), 409 (MH^+ , 100); HRMS calcd for $\text{C}_{23}\text{O}_3\text{N}_4\text{H}_{29}$ (MH^+) 409.2239, found 409.2237.

Compounds 12d and 13d: Yellow oil (90

%). ^1H : 8.36 (br, 1H), 7.45 (d, $J = 7.9$, 1H), 7.32-7.20 (m, 1H), 7.13 (t, $J = 6.9$, 1H), 7.02 (t, $J = 7.3$, 1H), 6.87 (br, 1H), 6.74 (d, $J = 8.3$, 1H), 6.36 (d, $J = 8.3$, 1H), 4.37 (s, 1H, 12d), 4.26 (s, 1H, 13d), 3.80 (s, 3H, 13d), 3.79 (s, 3H, 12d), 3.65 (s, 3H, 12d), 3.61 (s, 3H, 13d), 3.35-3.01 (m, 3H), 2.08 (s, 3H), 1.30 (s, 9H); ^{13}C : 175.0, 172.3, 158.7, 157.5, 136.7, 127.7, 126.0, 123.5, 122.4, 119.9, 119.2, 110.9, 106.6, 61.9, 60.0, 56.0, 52.3, 51.1, 30.1, 29.1, 28.7, 9.8; IR: 3330-2990, 2961, 2923, 2852, 1736, 1658, 1600, 1520, 1488, 1456, 1415, 1363, 1270, 1225, 1176, 1107; ESIMS 984 (2M+Na⁺, 15), 482 (MH⁺, 100); HRMS calcd for C₂₇O₅N₃H₃₆ (MH⁺) 482.2655, found 482.2653.

Compounds 12e and 13e: Yellow oil (81 %).

^1H : 7.18 (d, $J = 8.7$ Hz, 1H, 12e), 7.01 (d, $J = 8.7$, 1H, 13e), 6.92 (br, 1H), 6.73 (d, $J = 8.7$, 1H, 13e), 6.60 (d, $J = 8.7$, 1H, 12e), 4.26 (s, 1H, 12e), 4.17 (s, 1H, 13e), 3.79 (s, 3H), 3.72 (s, 3H), 3.68 (s, 3H), 2.98 (d, $J = 6.4$, 1H, 13e), 2.88 (d, $J = 6.0$, 1H, 12e), 2.15 (s, 3H), 1.91 (sept, $J = 6.0$, 1H), 1.28 (s, 9H), 0.82 (dd, $J = 15.1$, 6.8, 6H); ^{13}C : 174.9, 171.6, 158.3, 157.2, 125.7, 124.5, 119.6, 106.3, 65.1, 61.0, 60.0, 55.5, 51.4, 50.6, 31.3, 28.8, 19.1, 18.5, 9.2; IR: 3320-3270, 2920, 2851, 1736, 1661, 1600, 1522, 1488, 1455, 1269, 1222, 1168, 1037, 637; ESIMS 810 (2M+Na⁺, 4), 395 (MH⁺, 100); HRMS calcd for C₂₁O₅N₂H₃₅ (MH⁺) 395.2546, found 395.2549.

Compounds 12f and 13f: Yellow oil (82 %).

^1H : 8.22 (s, 1H), 7.96 (d, $J = 8.3$, 1H), 7.78 (d, $J = 8.3$, 1H), 7.69 (t, $J = 6.8$, 1H), 7.51 (t, $J = 6.8$, 1H), 6.82 (br, 1H), 4.54 (s, 1H, 12f), 4.33 (s, 1H, 13f), 3.60 (s, 3H), 3.03 (d, $J = 5.7$, 1H, 13f), 2.96 (d, $J = 5.7$, 1H, 12f), 1.97 (sept, $J = 6.7$, 1H), 1.42 (s, 9H), 0.89 (dd, $J = 13.6$, 6.8, 6H); ^{13}C : 174.4, 169.1, 146.9, 138.9, 130.8, 130.6, 128.0, 127.6, 127.2, 127.0, 65.3, 63.0, 51.6, 51.3, 31.3, 28.5, 19.2, 18.2; IR: 3350-3290, 2962, 2930, 2872, 1735, 1675, 1517, 1477, 1455, 1425, 1392, 1362, 1341, 1275, 1201, 1179, 1138, 778, 754; ESIMS 833 (2M+Na⁺, 41), 406 (MH⁺, 100); HRMS calcd for C₂₁O₃N₃H₂₉³⁵Cl (MH⁺) 406.1897, found 406.1897.

Acid-catalyzed cyclization of 9e to 14. Compound 9e (100 mg, 0.23 mmol) was dissolved in acid (40 mL, 0.006 M) and stirred at RT or refluxed for 2 hours. The resulting solution was dissolved in ethyl acetate, washed with water and dried over Na₂SO₄. The residue was purified by preparative chromatography eluting with ethyl acetate/cyclohexane (1/1) to give 4 as yellow crystals. ^1H :

8.21 (br, 1H), 7.32 (d, $J = 8.1$, 1H), 6.63 (d, $J = 8.1$, 1H), 5.86 (s, 1H), 4.60-4.53 (m, 1H), 3.82 (s, 3H), 3.66 (s, 3H), 2.51-2.35 (m, 2H), 2.14 (s, 3H); ^{13}C : 173.1, 172.3, 170.8, 159.9, 156.6, 129.7, 121.1, 119.5, 106.2, 60.3, 55.7, 55.1, 54.7, 29.5, 20.5, 10.1; IR: 2923, 2853, 1701, 1597, 1488, 1458, 1259, 1106, 760, 633; CIMS 319 (MH⁺, 100); HRMS calcd for C₁₆O₅N₂H₁₉ (MH⁺) 319.1294, found 319.1297.

Compound 15: White powder from AcOH. ^1H : 7.18 (d, $J = 8.6$, 1H, major isomer), 7.09 (d, $J = 8.6$, 1H, minor isomer), 6.66 (d, $J = 8.6$, 1H, minor isomer), 6.63 (d, $J = 8.6$, 1H, major isomer), 6.12 (s, 1H, major isomer), 5.60 (s, 1H, minor isomer), 4.77 (d, $J = 7.7$, 1H), 3.84 (s, 3H, major isomer), 3.80 (s, 3H, major isomer), 3.72 (s, 3H, minor isomer), 3.67 (s, 3H, minor isomer), 3.22 (s, 3H), 2.71-2.36 (m, 4H), 2.12 (s, 3H), 1.37 (s, 9H, minor isomer), 1.21 (s, 9H, major isomer); ^{13}C : 173.6, 169.8, 159.8, 158.4, 127.5, 120.4, 106.0, 61.3, 59.1, 56.0, 52.8, 52.0, 30.0, 29.0, 24.5, 9.8; ESIMS 835 ($2\text{M}+\text{Na}^+$, 100), 429 ($\text{M}+\text{Na}^+$, 17), 407 (MH^+ , 47); HRMS calcd for $\text{C}_{21}\text{O}_6\text{N}_2\text{H}_{31}$ (MH^+) 407.2182, found 407.2184.

General procedure for compounds 17, 18 and 19: A solution of 2,6-dimethoxy-3-methylbenzaldehyde (100 mg, 0.56 mmol, 1 eq.), pyroglutamic acid (86 mg, 0.67 mmol, 1.2 eq.) and 2,6-dimethyl-phenylisocyanide (88 mg, 0.67 mmol, 1.2 eq.) in 2.5 mL of MeOH (compounds **17** and **19**) or of EtOH (compound **7**) was stirred at 40°C (compounds **17** and **18**) or at RT (compound **19**) for 2 days. The mixture was diluted with ethyl acetate and washed several times with water. The organic phase was dried (Na_2SO_4), filtered, and concentrated. The resulting oil was purified by preparative TLC with 1:1 cyclohexane:EtOAc.

Compound 17: pale yellow solid (114 mg, 45 %). M.p. 122 °C; $[\alpha]_{\text{D}}^{25} = -52^\circ$ ($c=0.003$, MeOH); ^1H : 8.35 (d, $J = 1.5$, 1H), 8.08 (d, $J = 12.3$, 1H), 7.73 (br, 1H), 7.12-7.08 (m, 4H), 6.61 (d, $J = 9.0$ Hz, 1H), 6.03 (s, 1H), 4.88 (dd, $J = 8.7$, 1.5, 1H), 3.81 (s, 3H), 3.79 (s, 3H), 3.44 (s, 3H), 2.88-2.82 (m, 1H), 2.40-2.35 (m, 2H), 2.30 (s, 3H), 2.23 (s, 6H); ^{13}C : 174.2, 172.9, 169.1, 165.0, 159.3, 157.8, 135.4, 135.2, 133.1, 132.5, 128.6, 128.1, 127.6, 127.5, 127.4, 126.8, 121.7, 120.0, 105.7, 78.9, 61.5, 59.4, 57.8, 55.5, 31.9, 22.6, 18.6, 18.4, 18.3, 9.2; IR: 3300-3200, 2954-2878, 1744, 1694-1655, 1521, 1473, 1384, 1229, 1110; CIMS 455 (MH^+ , 86), 423 (MH^+-MeOH , 100); HRMS calcd for $\text{C}_{25}\text{O}_6\text{N}_2\text{H}_{31}$ (MH^+) 455.2182, found 455.2183.

Compound 18: White solid (60 mg, 23 %). M.p. 158 °C; ^1H : 7.61 (s, 1H), 7.12 (d, $J = 11.5$, 1H), 7.11-7.05 (m, 3H), 6.63 (d, $J = 11.5$, 1H), 6.19 (s, 1H), 4.92 (dd, $J = 8.5$, 1.5, 1H), 3.82 (s, 3H), 3.80 (s, 3H), 3.74-3.57 (m, 2H), 2.96-2.80 (m, 1H), 2.45-2.30 (m, 2H), 2.21 (s, 6H), 2.16 (s, 3H), 1.21 (t, $J = 9.8$, 3H); ^{13}C : 174.2, 173.5, 168.8, 159.2, 135.4, 133.1, 128.2, 122.0, 120.0, 105.9, 66.1, 61.5, 59.6, 55.6, 33.8, 26.7, 22.6, 18.4, 15.3, 9.3; IR: 3350-3250, 2935-2853, 1730, 1670, 1590, 1488, 1465, 1270, 1136; ESIMS 959 ($2\text{M}+\text{Na}^+$, 45), 491 ($\text{M}+\text{Na}^+$, 100), 423 (MH^+-EtOH , 22); HRMS calcd for $\text{C}_{26}\text{O}_6\text{N}_2\text{H}_{33}$ (MH^+) 469.2338, found 469.2332.

Compound 19: Tan solid (96 mg, 50 %). ^1H : 8.20 (br, 1H), 7.26 (d, $J = 8.1$, 1H), 7.09-7.01 (m, 3H), 6.65 (d, $J = 8.1$ Hz, 1H), 5.15 (s, 1H), 3.86 (s, 3H), 3.83 (s, 3H), 3.42 (s, 3H), 3.40 (s, 3H), 2.23 (s, 6H), 2.18 (s, 3H); ^{13}C NMR (CDCl_3) δ 169.2, 159.0, 135.3, 133.2, 128.1, 127.1, 125.5, 122.7, 119.8, 106.4, 78.5, 61.8, 56.9, 55.6, 50.6, 18.5, 9.2; IR (neat): 3366, 2935-2823, 1749, 1683, 1597, 1486-1415, 1272, 1092 cm^{-1} ; ESIMS 708 ($2\text{M}+\text{Na}^+$, 100), 366 ($\text{M}+\text{Na}^+$, 10), 343 (MH^+ , 12); HRMS calcd for $\text{C}_{20}\text{O}_4\text{NH}_{26}$ (MH^+) 343.1784, found 343.1787.