Regioselective Single and Double Conjugate Additions to Substituted Cyclohexa-2,5-dienone Monoacetals

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Supporting Information

Experimental Section
Copies of $^1$H and $^{13}$C NMR spectra of listed compounds

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Preparation of Substituted Cyclohexa-2,5-dienone Monoacetals.

Methyl 5-ethoxy-2-hydroxy benzoate. Oxalyl chloride (1.3 mL, 15 mmol) was added dropwise to a solution of 5-ethoxysalicylic acid (Aldrich, 1.3 g, 7.1 mmol) in 35 mL of THF. A few drops of DMF were added and the reaction was stirred at room temperature for 30 min at which time it was concentrated to a yellow solid. The residue was dissolved in 10 mL of methanol and the reaction stirred for an additional 15 min, followed by quenching with water (30 mL). The aqueous layer was extracted with ethyl acetate (2 × 50 mL), washed with a solution of saturated aqueous NaHCO₃ (1 × 60 mL), and the combined organic layers were dried (MgSO₄), filtered, and concentrated. Chromatography (5-15% EtOAc/hex) provided the product as a white solid (1.24 g, 89%). Rf = 0.60 (40% EtOAc/hex); mp 45-47 °C; IR (neat) 3400 (br), 1680, 1610 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.25 (d, J = 3.1 Hz, 1H), 7.04 (dd, J = 5.9, 3.1 Hz, 1H), 6.87 (d, J = 9.0 Hz, 2H), 3.94 (q, J = 7.0 Hz, 2H), 3.90 (s, 3H), 1.37 (t, J = 7.0 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 170.2, 155.9, 151.2, 124.4, 118.3, 112.7, 111.7, 64.0, 52.1, 14.7; MS (FAB) m/z (relative intensity) 196 (M⁺, 20), 154 (100); HRMS calcd for C₁₃H₁₂O₅ (MH⁺): 197.0814, found: 197.0810.

Methyl 3,3-diethoxy-6-oxocyclohexa-1,4-dienecarboxylate (I). Prepared according to the procedure developed by Pelter et al.¹ Thus, iodobenzene diacetate (1.96 g, 6.1 mmol) was added to a solution of methyl 5-ethoxy-2-hydroxy benzoate (1.2 g, 6.1 mmol) in 50 mL of EtOH with stirring at room temperature. The reaction was complete (TLC) within 30 min at which time the reaction mixture was concentrated and

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chromatographed (10-35% EtOAc/hex) to give a yellow oil (1.18 g, 80%). Rf = 0.30 (20% EtOAc/hex); IR (neat) 3400 (br), 1680, 1440 cm\(^{-1}\); \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.41 (t, \(J = 3.2\) Hz, 1H), 6.82 (dd, \(J = 10.4, 1.9\) Hz, 1H), 6.24 (dd, \(J = 10.4, 3.5\) Hz, 1H), 3.82 (d, \(J = 3.6\) Hz, 3H), 3.63 (m, 4H), 1.20 (m, 6H); \(^13\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 180.9, 163.9, 148.1, 142.9, 131.3, 129.6, 91.9, 58.5, 52.4, 15.4; MS (FAB) m/z (relative intensity) 240 (M\(^+\), 45), 209 (34); HRMS calc'd for C\(_{12}\)H\(_{16}\)O\(_5\): 240.0998, found: 240.1000.

5-Ethoxy-2-hydroxy-N-phenylbenzamide.\(^2\) Prepared according to the procedure developed by Herz et. al.\(^3\) 5-Ethoxy-2-hydroxy benzoic acid (1.18 g, 6.5 mmol) was placed in a round bottom flask fitted with a reflux condenser. Toluene was added (10 mL) followed by the addition of triphenyl phosphate (2.0 mL, 7.8 mmol) and aniline (0.71 mL, 7.8 mmol) The mixture was then heated to reflux with stirring for 3 h. After cooling to room temperature, a voluminous solid formed, which was washed with two portions of ice-cold chloroform (15 mL each). The resulting solid was dried (P\(_2\)O\(_5\)) to give a white solid (1.54 g, 92%). Rf = 0.48 (40% EtOAc/hex); mp 157-158 °C; IR (neat) 3180 (br), 1635 cm\(^{-1}\); \(^1\)H NMR (500 MHz, acetone-d\(_6\)) \(\delta\) 9.79 (s, 1H), 7.77 (d, \(J = 8.2\) Hz, 2H), 7.54 (d, \(J = 3.0\) Hz, 1H), 7.39 (m, 2H), 7.18 (t, \(J = 5.0\) Hz, 1H), 7.11 (dd, \(J = 9.0, 3.1\) Hz, 1H), 6.92 (d, \(J = 9.0\) Hz, 1H), 4.04 (q, \(J = 6.9\) Hz, 2H), 1.37 (t, \(J = 6.9\) Hz, 3H); \(^13\)C NMR (125 MHz, acetone-d\(_6\)) \(\delta\) 167.9, 154.8, 151.4, 137.9, 128.6, 124.4, 121.7, 121.2, 118.4, 115.2, 112.0, 63.9, 14.2; MS (FAB) m/z (relative intensity) 258 (MH\(^+\), 100), 165 (48); HRMS calc'd for C\(_{12}\)H\(_{16}\)NO\(_5\)(MH\(^+\)): 258.1135, found: 258.1130.
3,3-Diethoxy-6-oxo-N-phenylcyclohexa-1,4-diene carboxamide (2). Oxidation of 5-ethoxy-2-hydroxy-N-phenylbenzamide (0.50 g, 1.9 mmol) according to the procedure developed by Peiter et al.\textsuperscript{1} afforded a yellow solid (0.48 g, 83\%) after chromatography (20\% EtOAc/hex); R\textsubscript{f} = 0.63 (40\% EtOAc/hex); mp 62-64 °C; IR (neat) 3270, 2975, 1695 cm\textsuperscript{-1}; \textsuperscript{1}H NMR (500 MHz, acetone-d\textsubscript{6}) \delta 10.65 (s, 1H), 8.03 (d, J = 3.3 Hz, 1H), 7.77 (d, J = 7.6 Hz, 2H), 7.38 (t, J = 7.6 Hz, 2H), 7.17 (m, 2H), 6.34 (d, J = 10.2 Hz, 1H), 3.77 (q, J = 7.0 Hz, 4H), 1.22 (t, J = 7.0 Hz, 6H); \textsuperscript{13}C NMR (125 MHz, acetone-d\textsubscript{6}) \delta 185.8, 159.5, 151.4, 145.4, 138.3, 129.4, 128.8, 128.7, 124.2, 120.0, 92.0, 58.2, 15.1; MS (FAB) m/z (relative intensity) 302 (MH\textsuperscript{+}, 62), 256 (67), 209 (100); HRMS calc'd for C\textsubscript{13}H\textsubscript{20}N\textsubscript{2}O\textsubscript{4}(MH\textsuperscript{+}): 302.1392, found: 302.1392.

4,4-Dimethoxy-2-(2'-nitrophenyl)cyclohexa-2,5-diene (3). Iodobenzene diacetate (3.1 g, 9.6 mmol) was added to a solution of 2-hydroxy-2'-nitrobenzophenyl\textsuperscript{1} (1.08 g, 4.70 mmol) in 50 mL of dry methanol.\textsuperscript{1} The reaction was stirred at room temperature for 3 h then concentrated to an oil, which was chromatographed (10-40\% EtOAc/hex) to give a yellow solid (0.75 g, 74\%). R\textsubscript{f} = 0.35 (40\% EtOAc/hex); mp 97-100 °C; IR (neat) 1680, 1660, 1350 cm\textsuperscript{-1}; \textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}) \delta 8.14 (dd, J = 3.1, 1.0 Hz, 1H), 7.69 (dt, J = 5.0, 1.3 Hz, 1H), 7.59 (dt, J = 8.3, 1.5 Hz, 1H), 7.37 (dd, J = 7.6, 1.4 Hz, 1H), 6.92 (dd, J = 10.4, 3.1 Hz, 1H), 6.84 (d, J = 3.17 Hz, 1H), 6.42 (d, J = 10.3 Hz, 1H), 3.49 (s, 6H); \textsuperscript{13}C NMR (125 MHz, CDCl\textsubscript{3}) \delta 182.4, 148.6, 143.5, 140.3, 139.5, 133.6, 131.6, 130.3, 130.2, 129.7, 124.4, 93.1, 50.7; MS (FAB) m/z (relative intensity)
276 (MH+, 68), 244 (100); HRMS calcld for C₁₄H₁₄NO₃ (MH⁺): 276.0872, found: 276.0872.

2,5-Dihydroxy-N-phenylbenzamide. 2,5-Dihydroxybenzoic acid (8.0 g, 52 mmol) was dissolved in toluene (45 mL), followed by the addition of triphenyl phosphite (16.4 mL, 62 mmol) and aniline (5.7 mL, 62 mmol) according to the procedure developed by Herz et al. The mixture was heated to reflux for 3 h. After cooling to room temperature, a voluminous solid formed, which was washed with ice-cold chloroform (2 × 35 mL). The resulting solid was dried (P₂O₅) to give a white solid (11.5 g, 96%). \( R_f = 0.64 \) (60% EtOAc/hex); mp 160-163 °C; IR (neat) 3050, 1640, 1590 cm⁻¹; \(^1\)H NMR (500 MHz, DMSO-d₆) δ 9.10 (s, 1H), 7.70 (d, \( J = 9.4 \) Hz, 2H), 7.37 (m, 3H), 7.13 (t, \( J = 7.4 \) Hz, 1H), 6.90 (dd, \( J = 8.8, 2.19 \) Hz, 1H), 6.83 (d, \( J = 8.8 \) Hz, 1H), 3.37 (s, 1H); \(^{13}\)C NMR (125 MHz, DMSO-d₆) δ 166.2, 150.9, 150.1, 138.7, 129.1, 124.4, 121.5, 121.0, 118.4, 118.2, 115.0; MS (FAB) m/z (relative intensity) 230 (MH⁺, 47), 192 (100); HRMS calcld for C₁₄H₁₄NO₃ (MH⁺): 230.0817, found: 230.0823.

2-Ethoxy-5-hydroxy-N-phenylbenzamide. 2,5-Dihydroxy-N-phenylbenzamide (1.5 g, 6.5 mmol) was placed in a round-bottom flask fitted with a reflux condenser. Acetone (40 mL) was added, followed by potassium carbonate (0.9 g, 6.5 mmol) and ethyl iodide (0.5 mL, 6.5 mmol). The mixture was heated to reflux and stirred for 15 h, then cooled to room temperature and quenched with a saturated solution of NH₄Cl (40 mL) and extracted with ethyl acetate (4 × 40 mL). The organic extracts were combined, dried (MgSO₄), filtered and concentrated to give yellow crystals which were
recrystallized from boiling acetone to give light yellow crystals (1.15 g, 68%). R$_f$ = 0.33 (40% EtOAc/hex); mp 180-182 °C; IR (neat) 3315 (br), 1650 cm$^{-1}$; $^1$H NMR (500 MHz, acetone-d$_6$) δ 10.26 (s, 1H), 8.27 (s, 1H), 7.79 (d, J = 9.6 Hz, 2H), 7.68 (d, J = 3.9 Hz, 1H), 7.37 (t, J = 10.4 Hz, 2H), 7.10 (m, 2H), 7.01 (dd, J = 11.1, 3.9 Hz, 1H), 4.28 (q, J = 8.7, 2H), 1.59 (t, J = 8.7 Hz, 3H); $^{13}$C NMR (125 MHz, acetone-d$_6$) δ 162.7, 151.5, 150.2, 139.2, 128.9, 123.6, 122.9, 119.7, 119.6, 117.4, 114.6, 65.4, 14.3; MS (FAB) m/z (relative intensity) 258 (MH$^+$, 100); HRMS calcd for C$_{15}$H$_{16}$NO$_3$ (MH$^+$): 258.1130, found: 258.1116.

2,2-Diethoxy-5-oxo-N-phenylcyclohexa-1,3-dienecarboxamide (4). Oxidation of 2-Ethoxy-5-hydroxy-N-phenylbenzamide (0.64 g, 2.5 mmol) according to the procedure developed by Pellet et al. afforded a yellow oil (0.73 g, 97%) after chromatography (5% EtOAc/hex). R$_f$ = 0.53 (60% EtOAc/hex); IR (neat) 3331 (br), 2975, 1665 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ 9.48 (s, 1H), 7.62 (d, J = 8.0 Hz, 2H), 7.35 (t, J = 7.8 Hz, 2H), 7.23 (d, J = 2.1 Hz, 1H), 7.14 (t, J = 7.5 Hz, 1H), 6.82 (d, J = 10.3 Hz, 1H), 6.47 (dd, J = 10.3, 2.2 Hz, 1H), 3.64 (m, 2H), 3.48 (m, 2H), 1.25 (t, J = 7.0 Hz, 6H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 185.4, 160.8, 146.7, 144.5, 137.9, 134.9, 132.2, 129.6, 125.3, 120.5, 95.5, 60.5, 15.9; MS (FAB) m/z (relative intensity) 301 (M$^+$, 10), 256 (93), 228 (100); HRMS calcd for C$_{17}$H$_{20}$NO$_3$ (MH$^+$): 302.1392, found: 302.1407.

General Procedure for the Conjugate Additions of Substituted Cyclohexa-
2,5-dienone Monoacetals with Nucleophiles. The substituted cyclohexa-2,5-dienone monoacetal (1.0 equiv) was dissolved in THF (5 mL) followed by the addition of the indicated nucleophile (1.0 equiv) and potassium tert-butoxide (0.15 equiv). The reaction mixture was stirred at room temperature for 10 h at which time it was quenched with saturated aqueous solution of NH$_4$Cl (1 mL) and diluted with H$_2$O (20 mL). The aqueous
layer was then extracted with ethyl acetate (3 × 20 mL) and the organic extracts were combined and concentrated to an oil which was chromatographed to afford the indicated products.

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Methyl 2-(diethyl malonyl)-3-ethoxy-6-hydroxybenzoate (5). The crude \(^1\)H NMR showed mostly the aromatized product indicated along with a trace amount of unstable conjugate addition adduct. Thus, the residue was dissolved in benzene (5 mL) and p-toluenesulfonic acid (1.2 equiv) was added and the mixture heated to reflux according to the method described by Parker and Kang.\(^3\) After 30 min, the reaction was cooled and quenched with a saturated aqueous solution of NaHCO\(_3\) (25 mL) and extracted with ethyl acetate (3 × 20 mL). The organic extracts were combined, dried over MgSO\(_4\), filtered and concentrated to an oil, which was chromatographed (10-20% EtOAc/6:hex) to afford a clear oil (71%). \(R_F = 0.26\) (20% EtOAc/hex); IR (neat) 2975, 1740, 1620 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) δ 10.27 (s, 1H), 7.14 (d, \(J = 9.1\) Hz, 1H), 6.98 (d, \(J = 9.1\) Hz, 1H), 5.53 (s, 1H), 4.21 (q, \(J = 7.2\) Hz, 4H), 4.02 (q, \(J = 7.0\) Hz, 2H), 3.85 (s, 3H), 1.35 (t, \(J = 7.0\) Hz, 3H), 1.26 (t, \(J = 7.1\) Hz, 6H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) δ 170.4, 160.1, 155.8, 150.3, 123.5, 121.6, 118.3, 113.4, 66.5, 61.4, 51.9, 50.8, 14.8, 14.1; MS (FAB) m/z (relative intensity) 354 (M\(^+\), 100), 323 (60); HRMS calc’d for C\(_7\)H\(_{14}\)O\(_4\)(MH\(^+\)): 355.1393, found: 355.1398.
Methyl 5,5-diethoxy-6-(3-ethoxy-1-nitro-3-oxopropyl)-2-hydroxycyclohexa-
1,3-diene carboxylate (6). For this reaction, 1.2 equiv ethyl 3-nitropropanoate and 1.0
equiv potassium tert-butoxide were used. A diastereomeric ratio of ca. 10:1 was
estimated from $^1$H NMR analysis of the crude reaction mixture. Yellow oil (100% crude)
following workup. Crystallization from EtOAc/hexane (1:1) at 0 °C gave crystals suitable
for X-ray crystallographic analysis. $R_f = 0.45$ (40% EtOAc/hex). **Major isomer:** $^1$H
NMR (400 MHz, CDCl$_3$) δ 6.34 (d, $J = 10.2$ Hz, 1H), 6.12 (d, $J = 10.1$ Hz, 1H), 4.84 (dd,
$J = 10.5$, 2.6 Hz, 1H), 4.37 (m, 1H), 4.15 (m, 4H), 3.56 (m, 3H), 3.46 (m, 3H), 3.09 (dd,
$J = 17.4$, 10.5 Hz, 1H), 2.51 (dd, $J = 16.2$, 2.5 Hz, 1H), 1.28 (m, 6H), 1.14 (q, $J = 6.9$
Hz, 6H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 171.3, 166.4, 135.8, 125.6, 97.9, 94.0, 81.8,
61.4, 56.8, 52.3, 40.1, 32.7, 31.1, 15.1, 14.4, 14.0. **Minor isomer** (diagnostic peaks only):
$^1$H NMR (400 MHz, CDCl$_3$) δ 6.32 (d, $J = 10.1$ Hz, 1H), 5.05 (td, $J = 10.5$, 2.6 Hz, 1H),
3.95 (m, 1H), 3.66 (s, 3H), 2.60 (dd, $J = 17.4$, 7.2 Hz, 1H); $^{13}$C NMR (100 MHz,
CDCl$_3$) δ 171.6, 165.9, 139.7, 126.8.

Methyl 3-ethoxy-2-(1'-nitro-2'-carboethoxethyl)-6-hydroxybenzoate. The
unstable adducts 6 were treated with $p$-toluenesulfonic acid according to the method
described by Parker and Kang$^b$ to give an orange oil (41% over two steps). $R_f = 0.40$
(40% EtOAc/hex); IR (neat) 2975, 1730, 1560 cm$^{-1}$; 1H NMR (400 MHz, CDCl$_3$) δ
10.18 (s, 1H), 7.12 (d, $J = 9.2$ Hz, 1H), 7.05 (d, $J = 9.2$ Hz, 1H), 6.80 (dd, $J = 9.2$, 2.8 Hz,
1H), 4.25 (m, 2H), 4.06 (m, 1H), 3.98 (s, 3H), 3.87 (m, 1H), 3.79 (dd, $J = 17.5$, 8.3 Hz,
4-Ethyl 6-methyl 9,9-diohexy-3-methyl-7-oxo-2-oxa-bicyclo[3.3.1]non-3-ene-4,6-dicarboxylate (7). Isolated as a mixture of keto and enol tautomers. Clear oil (84%). \( R_f = 0.30 \) (20% EtOAc/hex); IR (neat) 2975, 1740, 1620, cm\(^{-1}\); MS (FAB) m/z (relative intensity) 370 (M\(^+\), 15), 325 (100); HRMS calcd for C\(_{18}\)H\(_{28}\)O\(_6\): 371.1706, found 371.1697. **Keto tautomer:** \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 4.56 (q, \( J = 3.7 \) Hz, 1H), 4.19-4.11 (m, 2H), 4.01 (d, \( J = 2.9 \) Hz, 1H), 3.74 (s, 3H), 3.66-3.43 (m, 4H), 3.00 (dd, \( J = 16.6, 4.1 \) Hz, 1H), 2.66 (td, \( J = 16.5, 2.4 \) Hz, 1H), 2.59 (dd, \( J = 18.1, 1.3 \) Hz, 1H), 2.16 (s, 3H), 1.30 (t, \( J = 7.1 \) Hz, 3H), 1.20-1.10 (m, 6H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \( \delta \) 203.3, 171.6, 169.3, 167.6, 166.2, 101.7, 96.4, 74.9, 59.8, 56.8, 56.6, 52.1, 37.8, 33.0, 19.7, 15.3, 15.0, 14.2. **Enol tautomer** (diagnostic peaks only): \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) (s, 12.04, 1H), 4.45 (m, 1H) 3.85 (m, 1H), 3.40 (t, \( J = 2.1 \) Hz, 1H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \( \delta \) 167.6, 161.5, 106.4.

Methyl 9,9-diohexy-7-methyl-6-nitro-3-oxo-8-oxa-bicyclo[3.3.1]non-6-ene-4-carboxylate (8). White solid (52%). \( R_f = 0.51 \) (40% EtOAc/hex); mp 122-123 °C. IR
Methyl 5,5-diethoxy-6-([3-ethoxy-1-nitro-3-oxopropyl]-1-methyl-2-oxocyclohex-3-ene)carboxylate (10). Quinone monoacetate 1 (59 mg), ethyl 3-nitropropionate (36 mg), and potassium tert-butoxide (28 mg) were dissolved in THF (3 mL) at room temperature. After 20 min, Mel (178 mg, 80 µL) was added. After 10 h, the reaction was subjected to the usual quench, workup and purification protocol, which provided a clear oil (45%). Crystallization from hexane/EtOAc (3:1) gave crystals suitable for X-ray crystallographic analysis. A diastereomeric ratio of greater than 10:1 was estimated from $^1$H NMR analysis of the crude reaction mixture. $R_f = 0.53$ (40% EtOAc/hex); IR (neat) 2975, 1730, 1690, cm$^{-1}$; MS (TOF) m/z (relative intensity) 424 (M$^+$ + Na, 100); HRMS calcd for C$_{16}$H$_{21}$NO$_5$Na (M$^+$ + Na): 424.1584, found 424.1583.

**Major isomer:** $^1$H NMR (400 MHz, CDCl$_3$) δ 7.00 (d, $J = 10.6$ Hz, 1H), 6.24 (d, $J = 10.6$ Hz, 1H), 5.30 (d, $J = 10.8$ Hz, 1H), 4.20 (m, 2H), 3.79 (dd, $J = 8.64$, 1.5 Hz, 1H), 3.65 (s, 3H), 3.58 (d, $J = 1.5$ Hz 1H), 3.45 (m, 3H), 3.27 (broad d, $J = 17.9$ Hz, 1H), 3.18 (dd, $J = 7.0$, 1.8 Hz, 1H), 1.71 (s, 3H), 1.28 (t, $J = 7.0$ Hz, 3H), 1.15 (q, $J = 7.0$ Hz, 6H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 194.3, 172.2, 171.3, 144.8, 130.7, 97.6, 82.3, 61.0, 59.1, 58.7, 55.7, 52.5, 51.5, 34.1, 20.6, 15.2, 14.9, 14.1.
Ethyl 5-ethoxy-8-hydroxy-1,3-dioxo-2-phenyl-1,2,3,4-tetrahydroisoquinoline-4-carboxylate (11). The unstable adduct was treated with p-toluenesulfonic acid according to the method described by Parker and Kang⁶ to provide a yellow semi-solid (77%). Rf = 0.75 (40% EtOAc/hex); IR (neat) 2970, 1720, 1660 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 10.97 (s, 1H), 7.53 (m, 3H), 7.23 (m, 3H), 7.04 (dd, J = 9.2, 0.5 Hz, 1H), 5.19 (d, J = 0.5 Hz, 1H), 4.28 (q, J = 7.1 Hz, 2H), 4.09 (m, 2H), 1.44 (t, J = 7.0 Hz, 3H), 1.33 (t, J = 7.1 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 169.3, 166.5, 166.5, 155.7, 148.0, 133.8, 129.5, 129.2, 128.4, 120.5, 120.4, 118.0, 109.1, 64.8, 62.6, 50.5, 14.7, 14.1; MS (FAB) m/z (relative intensity) 370 (MH⁺, 100); HRMS calcd for C₂₅H₂₆NO₄: 369.1212, found: 369.1212.

3-Ethoxy-6-hydroxy-2-(1'-nitro-2'-carboethoxyethyl)-N-phenylbenzamide (12). tert-Butanol was used. The unstable adduct was treated with p-toluenesulfonic acid according to the method described by Parker and Kang⁶ which provided white crystals (57%) following chromatography. Rf = 0.23 (40% EtOAc/hex); mp 154-156 °C; IR (neat) 3310 (br), 1730, 1550 cm⁻¹; ¹H NMR (400 MHz, acetone-d₆) δ 9.58 (d, 1H), 8.74 (s, 1H), 7.85 (d, J = 7.8 Hz, 2H), 7.38 (t, J = 7.7 Hz, 2H), 7.14 (t, J = 7.4 Hz, 1H), 7.04 (s, 2H), 6.24 (dd, J = 10.1, 2.5 Hz, 1H), 4.18 (q, J = 7.3 Hz, 2H), 4.10 (m, 1H), 3.93 (m, 1H), 3.77 (dd, J = 17.5, 10.2 Hz, 1H), 2.91 (m, 1H) 1.30 (t, J = 7.0 Hz, 3H), 1.24 (t, J = 7.0 Hz, 3H); ¹³C NMR (100 MHz, acetone-d₆) δ 169.7, 164.3, 150.1, 147.8, 139.2, 128.7, 126.5, 123.9, 122.8, 119.7, 117.6, 115.0, 80.7, 64.6, 60.6, 36.4, 13.8, 13.5; MS (FAB)
m/z (relative intensity) 403 (MH⁺, 25), 356 (100); HRMS calecd for C₂₆H₂₃N₂O₇ (MH⁺): 403.1505, found: 403.1495.

**Ethyl 9,9-dioethoxy-3-methyl-7-oxo-6-(phenylcarbamoyl)-2-oxa-bicycle[3.3.1]non-3-ene-4-carboxylate (13).** Light yellow crystals (42%) suitable for X-ray crystallographic analysis were obtained from recrystallization in hexanes/CHCl₃ (3:1). Rf = 0.58 (40% EtOAc/hex); mp 125-127 °C; IR (KBr pellet) 2975, 1650 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 14.78 (s, 1H), 10.09 (s, 1H), 7.69 (d, J = 8.1 Hz, 2H), 7.35 (t, J = 7.8 Hz, 2H), 7.11 (t, J = 7.4 Hz, 1H), 4.58 (m, 1H), 4.34-4.30 (m, 2H), 3.80 (d, J = 2.5 Hz, 1H), 3.62-3.47 (m, 4H), 2.91 (dd, J = 19.2, 5.2 Hz, 1H), 2.67 (d, J = 19.2 Hz, 1H), 2.24 (s, 3H), 1.36 (t, J = 7.1 Hz, 3H), 1.18 (q, J = 6.8 Hz, 6H); ¹³C NMR (125 MHz, CDCl₃) δ 170.8, 170.6, 170.5, 165.3, 138.4, 128.7, 123.8, 120.4, 105.3, 101.7, 96.5, 71.0, 61.3, 57.0, 56.4, 38.0, 33.2, 21.0, 15.3, 15.1, 14.3; MS (FAB) m/z (relative intensity) 432 (MH⁺, 65), 386 (100); HRMS calecd for C₂₆H₂₃NO₇ (MH⁺): 432.2022, found: 432.2005.

**5-(Diethylmalonyl)-4,4-dimethoxy-2-(2'-nitrophenyl)-2-cyclohexenone (14).** Yellow oil (ca. 100%). Rf = 0.34 (40% EtOAc/hex); IR (neat) 2930, 1730, 1530 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 8.11 (dd, J = 8.1, 0.9 Hz, 1H), 7.67 (dt, J = 7.5, 1.0 Hz, 1H), 7.56 (dt, J = 7.9, 1.3 Hz, 1H), 7.33 (dd, J = 7.4, 1.3 Hz, 1H), 6.85 (d, J = 1.0 Hz, 1H), 4.22 (m, 4H), 3.82 (d, J = 7.6 Hz, 1H), 3.77 (s, J = 6.4 Hz, 2H), 3.49 (t, J = 7.0 Hz, 1H), 3.12.
3.40 (s, 3H), 3.36 (s, 3H), 2.98 (dd, J = 17.5, 4.9 Hz, 1H) 2.78 (dd, J = 17.5, 5.7 Hz, 1H), 1.87 (p, J = 3.3 Hz, 2H), 1.30 (t, J = 7.1 Hz, 3H), 1.22 (t, J = 7.1 Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 194.3, 168.7, 168.5, 148.9, 142.2, 142.0, 134.0, 131.9, 130.8, 130.1, 124.8, 98.8, 62.0, 62.0, 51.7, 50.9, 50.0, 40.8, 38.7, 14.4, 14.3; MS (FAB) m/z (relative intensity) 435 (M$^+$, 20), 330 (100); HRMS calcd for C$_{31}$H$_{29}$N$_2$O$_8$ (M$^+$ + NH$_4^+$): 453.1873, found: 453.1864.

Ethyl 9,9-dimethoxy-6-(2-nitrophenyl)-3,7-dioxobicyclo[3.3.1]nonane-2-carboxylate (15). Light yellow crystals (71%) suitable for X-ray crystallographic analysis were obtained from recrystallization in hexanes/CHCl$_3$ (5:1). $R_f$ = 0.63 (30% EtOAc/hex); IR (KBr pellet) 2955, 1720, 1655 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ 7.91 (dd, J = 8.2, 0.9 Hz, 1H), 7.65 (dt, J = 7.7, 1.3 Hz, 1H), 7.46 (dt, J = 7.7, 1.3 Hz, 1H), 7.28 (m, 1H), 4.73 (d, J = 5.6 Hz, 1H), 3.51 (s, 3H), 3.29 (s, 3H), 3.09 (m, 1H), 2.94 (dd, J = 15.5, 4.5 Hz, 1H), 2.61-2.52 (m, 2H), 2.30 (d, J = 18.4 Hz, 3H), 1.33 (t, J = 7.1 Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 207.0, 171.1, 170.7, 150.2, 134.0, 132.0, 129.8, 128.2, 124.8, 99.3, 98.8, 60.8, 51.6, 48.6, 48.2, 43.7, 37.0, 34.8, 29.9, 14.2; MS (CI) m/z (relative intensity) 423 (M$^+$ + NH$_4^+$, 65), 374 (100); HRMS calcd for C$_{30}$H$_{27}$N$_2$O$_8$ (M$^+$ + NH$_4^+$): 423.1767, found: 423.1794.
6,6-Diethoxy-5-diethyl malonyl-3-oxo-N-phenyl-1-cyclohexenetetraoxamidé (16). Clear oil (58%). Rf = 0.53 (40% EtOAc/hex); IR (neat) 2975, 1675 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 9.72 (s, 1H), 7.63 (d, J = 7.6 Hz, 2H), 7.37 (t, J = 7.6 Hz, 2H), 7.16 (t, J = 7.4 Hz, 1H), 6.76 (s, 1H), 4.29 (m, 1H), 4.18-4.00 (m, 3H), 3.80 (m, 1H), 3.68 (d, J = 4.8 Hz, 1H), 3.65-3.50 (m, 4H), 3.06 (dd, J = 18.8, 6.0 Hz, 1H), 2.81 (d, J = 18.8 Hz, 1H), 1.39 (t, J = 7.0 Hz, 3H), 1.24 (t, J = 7.1 Hz, 3H), 1.18 (dt, J = 7.1, 2.4 Hz, 6H); ¹³C NMR (100 MHz, CDCl₃) δ 196.7, 168.6, 168.1, 162.3, 149.0, 137.9, 134.1, 129.2, 124.7, 119.8, 99.9, 62.1, 59.5, 56.7, 41.3, 37.6, 15.0, 14.9, 13.9, 13.6; MS (FAB) m/z (relative intensity) 461 (M⁺, 31), 416 (100); HRMS calcd for C₂₄H₂₃NO₄ (MH⁺): 462.2128, found: 462.2122.

Ethyl 9,9-diethoxy-3,7-dioxo-5-(phenylcarbamoyl)bicyclo[3.3.1]nonane-2-carboxylate (17). White crystals (69%) suitable for X-ray crystallographic analysis were obtained from recrystallization in hexanes/CHCl₃ (5:1). Rf = 0.45 (40% EtOAc/hex); mp 152-154 °C; IR (neat) 3330, 2975, 1720, 1660 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 9.59 (s, 1H), 7.51 (dd, J = 8.7, 1.1 Hz, 2H), 7.36 (t, J = 7.5, 2H), 7.14 (t, J = 3.4 Hz, 1H), 4.34-4.18 (m, 2H), 3.80-3.71 (m, 3H), 3.62-3.57 (m, 3H), 3.41 (q, J = 2.7 Hz, 1H), 3.1 (dd, J = 19.3, 2.0 Hz, 1H), 3.02 (dd, J = 16.2, 2.0 Hz, 1H), 2.91 (dd, J = 15.0, 4.6 Hz, 1H), 2.62 (d, J = 2.9 Hz, 1H) 2.58 (d, J = 2.5 Hz, 1H) 2.41 (d, J = 15.0, 2.6 Hz, 1H)
1.37-1.30 (m, 9H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 208.0, 172.1, 170.6, 169.6, 138.0, 129.2, 124.3, 119.4, 101.0, 98.0, 61.0, 58.0, 57.5, 50.8, 49.2, 43.2, 40.1, 37.4, 15.5, 15.3, 14.3; MS (FAB) m/z (relative intensity) 432 (MH$^+$, 20), 385 (39), 340 (100); HRMS calcd for C$_{25}$H$_{30}$NO$_7$ (MII$^+$): 432.2022, found: 432.2029.

References:
