Supporting Information

Synthesis of isoxazoles *en route* to semi-aromatized polyketides: dehydrogentation of benzonitrile oxide/*para*-quinone acetal cycloadducts

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General Experimental Procedures

All reactions utilizing air- or moisture-sensitive reagents were performed in dried glassware under an atmosphere of dry argon. Activated manganese oxide (IV) (~85%, <5 μm) was purchased from Aldrich Chemical Co. and was used as received. Chlorobenzene and toluene were distilled prior to use according to the standard protocols. For thin-layer chromatography (TLC) analysis, Merck pre-coated plates (TLC silica gel 60 F_{254}, Art 5715, 0.25 mm) were used. Silica-gel preparative thin-layer chromatography (PTLC) was performed using plates prepared from Merck silica gel 60 PF_{254} (Art 7747). For flash column chromatography, silica gel 60N (Spherical, neutral, 63–210 μm) from Kanto Chemical was used. Melting point (m.p.) determinations were performed using a Yanaco MP-500 instrument or a METTLER TOLEDO MP70 melting point system, and are uncorrected. ^{1}H- and ^{13}C-NMR were measured on a JEOL JNM Lambda-300, a JEOL JNM Lambda-400, a JEOL JNM AL-400, a JEOL JNM ECX-400, and a JEOL JNM ECX-500 spectrometer. Chemical shifts are expressed in parts per million (PPM) downfield from internal standard (tetramethylsilane, 0.00 ppm), and coupling constants are reported as hertz (Hz). Splitting patterns are indicated as follows: br, broad; s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. Infrared (IR) spectra were recorded on a Perkin-Elmer Spectrum 100 FTIR spectrometer. Elemental analyses were recorded on an Elementar vario MICRO CUBE analyzer. High-resolution mass spectra (HRMS) were obtained with JEOL JMS-700 spectrometer.

Isoxazoline 4

A suspension of nitrile oxide **2a** (200 mg, 0.754 mmol) and *p*-quinone mono-acetal **3a** (380 mg, 2.26 mmol) in chlorobenzene (0.75 mL) was stirred at room temperature for 2 days. The reaction mixture was condensed under reduced pressure, and the residue was purified by flash column chromatography (silica gel, hexane/EtOAc = 3/2 to 1/3) to afford a mixture of isoxazolines **4-6** (276 mg, 84%, **4/5/6** = 90/5/5) and bisisoxazoline **7** (12.8 mg, 5%) both as a white solid. Unreacted quinone mono-acetal **3a** was recovered (253 mg, 67%) as yellow oil.

Isoxazolines **4**, **5**, and **6** were isolated by the following procedure. A mixture of isoxazolines **4-6** (201 mg, **4/5/6** = 87/8/5) was purified by flash column chromatography (silica gel, hexane/Et_2O/THF = 2/4/1) to afford isoxazoline **4** (127 mg) as a colorless solid, and a mixture of isoxazolines **4-6** (74 mg), which was repurified by PTLC (hexane/tolene/THF = 2/2/1 (3x)) to afford isoxazoline **4** (42 mg) as a colorless solid and a mixture of **5** and **6** (30 mg). The mixture was further purified by PTLC (Et_2O) to afford isoxazoline **5** (18.1 mg) and isoxazoline **6** (6.0 mg) both as a colorless solid.

R*f* 0.33 (hexane/EtOAc = 1/1); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 1.36 (brd, 1H, *J* = 13.7 Hz), 2.07–2.24 (m, 1H), 2.12 (d, 3H, *J* = 1.5 Hz), 3.20 (s, 3H), 3.52 (s, 3H), 3.70–3.82 (m, 1H), 3.79 (s, 3H), 3.83 (s, 3H), 3.89 (td, 1H, *J* = 11.5, 2.4 Hz), 4.06 (dd, 1H, *J* = 11.2, 5.1 Hz), 4.21 (dd, 1H, *J* = 11.5, 5.1 Hz), 4.55 (d, 1H, *J* = 9.6 Hz), 5.22 (d, 1H, *J* = 9.6 Hz), 5.70 (s, 1H), 6.05 (d, 1H, *J* = 1.5 Hz), 6.46 (d, 1H, *J* = 2.3 Hz), 6.88 (d, 1H, *J* = 2.3 Hz); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 20.8, 25.6, 48.9, 49.5, 55.4, 55.7, 61.2, 67.1, 67.2, 78.8, 96.7, 98.7, 99.3, 102.3, 107.9, 129.6, 140.1, 153.7, 157.0, 159.0, 161.9, 187.6; **IR** (ATR) 3000, 2904, 2845, 1668, 1609, 1459, 1338, 1110, 1078, 1054, 996, 866 cm^{-1}; **Anal.** Calc'd for $C_{22}H_{27}NO_8$: C, 60.96; H, 6.28; N, 3.23; Found: C, 61.02; H, 6.45; N, 3.18; **mp** 182 °C (decomp.) (acetone/hexane, colorless prisms); **Crystallographic data**: $C_{22}H_{27}NO_8$, MW = 433.45, 0.35 x 0.25 x 0.20 mm, space group *P* –1, *Z* = 2, *T* = 173 K, a = 8.549(4), b = 8.811(4), c = 14.226(6) Å, V = 1066.7(8) Å^3, λ(Mo Kα) = 0.71075 Å, μ = 0.103 mm^{-1}; Intensity data were collected on Rigaku R-AXIS RAPID IP area detector system. The structure was solved by direct methods and refined by the full-matrix least-squares on F^2 (SHELXL-97). A total of 10501 reflections were measured and 4848 were independent. Final *R*1 = 0.0611, *wR*2 = 0.2191 (4286 refs; $I > 2\sigma(I)$), and GOF = 1.990 (for all data, *R*1 = 0.0660, *wR*2 = 0.2317); CCDC 859931 contains the supplementary crystallographic data for this paper.

These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; Fax: +44 1223 336033.

Regioisomer 5

R*f* 0.32 (hexane/EtOAc = 1/1); **^{1}H NMR** (acetone-d_6, 400 MHz, the ratio between two rotamers was 69:31, and the probable peaks from the minor rotamer are marked with an asterisk) δ 1.41 (brd, 1H, *J* = 13.2 Hz), 1.48* (brd, 1H, *J* = 11.7 Hz), 1.92 (s, 3H), 1.98–2.19 (m, 1H), 3.06 (s, 6H), 3.09* (s, 6H), 3.65–3.92 (m, 2H), 3.65–4.30* (m, 4H), 3.85 (s, 6H), 3.90* (s, 6H), 3.95–4.30 (m, 2H), 4.68* (brd, 1H, *J* = 10.7 Hz), 4.91* (brd, 1H, *J* = 10.7 Hz), 4.91 (d, 1H, *J* = 10.5 Hz), 5.06 (d, 1H, *J* = 10.5 Hz), 5.38 (s, 1H), 5.48* (brs, 1H), 6.20* (brs, 1H), 6.39 (brs, 1H), 6.59* (brs, 1H), 6.62 (brs, 1H), 6.83* (brs, 1H), 6.85 (brs, 1H); **^{13}C NMR** (acetone-d_6, 100 MHz) δ 20.7, 21.0, 26.6, 49.1, 50.0, 55.8, 56.0, 56.1, 58.8, 67.9, 81.8, 82.4, 98.3, 98.9, 99.2, 100.1, 103.6, 104.5, 110.3, 128.9, 130.0, 141.2, 153.9, 158.9, 160.1, 161.4, 162.4, 189.7; **IR** (ATR) 2967, 2843, 1691, 1613, 1593, 1459, 1433, 1330, 1081, 1057, 996, 853, cm^{-1}; **HRMS (FAB)** *m*/*z* Calc'd for $C_{22}H_{28}NO_8$ $[M+H]^+$: 434.1815; Found: 434.1801; **mp** 216 °C (decomp.) (EtOAc/hexane, colorless prisms); **Crystallographic data**: $C_{22}H_{27}NO_8$, MW = 433.45, 0.40 x 0.38 x 0.20 mm, monoclinic, space group *P* 21/n, *Z* = 4, *T* = 169 K, a = 8.5986(8), b = 9.3898(10), c = 26.681(3) Å, V = 2154.0(4) Å^3, λ(Mo Kα) = 0.71075 Å, μ = 0.102 mm^{-1}; Intensity data were collected on Rigaku R-AXIS RAPID IP area detector system. The structure was solved by direct methods and refined by the full-matrix least-squares on F^2 (SHELXL-97). A total of 19156 reflections were measured and 4910 were independent. Final $R1$ = 0.0564, $wR2$ = 0.1369 (3719 refs; $I > 2\sigma(I)$), and GOF = 1.082 (for all data, $R1$ = 0.0719, $wR2$ = 0.1436); CCDC 859932 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; Fax: +44 1223 336033.

Regioisomer 6

R*f* 0.31 (hexane/EtOAc = 1/1); **^{1}H NMR** (CDCl$_3$, 400 MHz) δ 1.37 (brd, 1H, *J* = 13.7

Hz), 1.64 (s, 3H), 2.09–2.26 (m, 1H), 3.37 (s, 3H), 3.54 (s, 3H), 3.74–3.97 (m, 2H), 3.75 (s, 3H), 3.84 (s, 3H), 4.13 (dd, 1H, J = 11.4, 5.0 Hz), 4.15 (s, 1H), 4.19 (dd, 1H, J = 11.9, 5.0 Hz), 5.68 (s, 1H), 6.20 (d, 1H, J = 11.0 Hz), 6.44 (d, 1H, J = 2.3 Hz), 6.89 (d, 1H, J = 11.0 Hz), 6.89 (d, 1H, J = 2.3 Hz); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 21.3, 25.6, 50.4, 51.6, 55.5, 55.6, 67.2, 67.3, 67.5, 90.0, 97.0, 98.7, 99.4, 102.1, 108.4, 132.1, 140.0, 148.0, 152.4, 159.1, 161.8, 188.4; **IR** (ATR) 2951, 2842, 1691, 1604, 1463, 1330, 1154, 1079, 1050, 850 cm^{-1}; **HRMS (FAB)** *m*/*z* Calc'd for $C_{22}H_{28}NO_8$ $[M+H]^+$: 434.1815; Found: 434.1822; **mp** 135–138 °C (EtOAc/hexane, colorless prisms).

Bisisoxazoline 7

R_f 0.17 (hexane/EtOAc = 1/1); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 1.41 (brd, 2H, J = 14.1 Hz), 1.70 (brs, 3H), 1.96–2.44 (m, 2H), 3.25–4.35 (m, 4H), 3.41 (brs, 3H), 3.55 (brs, 3H), 3.62 (s, 3H), 3.80 (s, 3H), 3.82 (s, 3H), 3.83–4.03 (m, 4H), 4.08–4.35 (m, 4H), 5.25–5.90 (m, 2H), 5.64 (brs, 1H), 5.74 (brs, 1H), 6.32 (s, 1H), 6.35 (d, 1H, J = 2.4 Hz), 6.88 (s, 1H), 6.92 (d, 1H, J = 2.4 Hz); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 25.6, 25.7, 51.8, 55.2, 55.4, 55.5, 67.2, 67.28, 67.33, 67.4, 97.7, 99.2, 99.3, 102.56, 102.63, 140.3, 140.4, 151.8, 158.6, 158.7, 161.7, 161.8; **IR** (ATR) 2921, 2850, 1730, 1605, 1461, 1328, 1202, 1155, 1079, 996, 843 cm^{-1}; **Anal.** Calc'd for $C_{35}H_{42}N_2O_{13}$: C, 60.16; H, 6.06; N, 4.01; Found: C, 60.33; H, 6.36; N, 3.72.

Isoxazole 8a

To a solution of isoxazoline **4** (86.7 mg, 0.200 mmol) in chlorobenzene (0.25 mL) was added activated manganese (IV) oxide (174 mg, 2.00 mmol). After stirring for 10 min at 80 ºC, the reaction mixture was filtered through a Celite® pad (washed with MeOH). The collected manganese residue was suspended in MeOH, which was heated under reflux for 1 min and filtered through a Celite® pad. The combined filtrate was condensed under reduced pressure. The residue was purified by PTLC (hexane/EtOAc = 1/1) to afford isoxazole **8a** (78.2 mg, 91%) as a colorless foam.

R_f 0.43 (hexane/EtOAc = 1/1); **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 1.30 (brd, 1H, J = 12.2 Hz), 2.01–2.19 (m, 1H), 2.04 (d, 3H, J = 1.5), 3.31 (s, 3H), 3.49 (s, 3H), 3.58 (ddd, 1H, J = 12.2, 11.3, 2.7 Hz) 3.69 (s, 3H), 3.85 (ddd, 1H, J = 11.9, 11.5, 2.4 Hz), 3.88 (s, 3H), 3.83–3.95 (m, 1H), 4.20 (dd, 1H, J = 11.5, 5.1 Hz), 5.57 (s, 1H), 6.15 (d, 1H, J = 1.5

Hz), 6.53 (d, 1H, J = 2.4 Hz), 6.94 (d, 1H, J = 2.4 Hz); **^{13}C NMR** ($CDCl_3$, 75 MHz) δ 15.5, 25.4, 52.0, 52.3, 55.4, 55.8, 67.0, 67.1, 95.0, 98.9, 99.2, 102.1, 106.9, 118.0, 130.4, 139.6, 152.1, 155.6, 159.1, 162.2, 172.5, 178.8; **IR** (ATR) 2945, 2843, 1678, 1612, 1433, 1377, 1333, 1286, 1201, 1161, 1120, 1076, 920 cm^{-1}; **Anal.** Calc'd for $C_{22}H_{25}NO_8$: C, 61.25; H, 5.84; N, 3.25; Found: C, 61.18; H, 5.84; N, 3.17; **mp** 143 °C (decomp.) (acetone/hexane, colorless prisms).

General procedure for the one-pot synthesis of isoxazoles

Isoxazole 8a

A suspension of nitrile oxide **2a** (200 mg, 0.754 mmol) and *p*-quinone mono-acetal **3a** (254 mg, 1.51 mmol) in chlorobenzene (0.75 mL) was stirred at room temperature for 4 days. To the mixture was added activated manganese (IV) oxide (656 mg, 7.55 mmol), and stirring for 10 min at 80 ºC. After cooling to room temperature, the reaction mixture was filtered through a Celite® pad (washed with MeOH). The collected manganese residue was suspended in MeOH, which was heated under reflux for 1 min and filtered through a Celite® pad. The combined filtrate was condensed under reduced pressure, and the residue was purified by flash column chromatography (silica gel, hexane/EtOAc = 2/1 to 3/2) to afford isoxazole **8a** (217 mg, 67%) as a colorless foam. Nitrile **9a**, contaminated with a trace amount of impurity (11.7 mg, ca. 6%) was also obtained. Unreacted *p*-quinone mono-acetal **3a** was recovered (127 mg, 50%) as yellow oil.

Nitrile 9a

R_f 0.50 (hexane/EtOAc = 1/1); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 1.47 (dd, 1H, J = 13.8, 0.9 Hz), 2.15–2.35 (m, 1H), 3.88 (s, 3H), 3.89 (s, 3H), 4.04 (ddd, 2H, J = 12.4, 12.4, 0.9 Hz), 4.27 (dd, 2H, J = 12.4, 5.0 Hz), 5.73 (s, 1H), 6.44 (d, 1H, J = 1.4 Hz), 6.86 (d, 1H, J = 1.4 Hz); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ25.5, 55.8, 56.1, 67.6, 93.0, 99.05, 99.11, 103.0, 114.9, 144.6, 162.9, 164.3; **IR** (ATR) 2858, 2220, 1611, 1152, 1074, 1003, 833, 684 cm^{-1}; **Anal.** Calc'd for $C_{13}H_{15}NO_4$: C, 62.64; H, 6.07; N, 5.62; Found: C, 62.63; H, 5.79; N, 5.39; **mp** 157–158 °C (EtOAc/hexane, colorless prisms); **Crystallographic data**: $C_{13}H_{15}NO_4$, MW =249.26, 0.35 x 0.30 x 0.10 mm, triclinic, space group $P\,{-1}$, Z =

2, T = 168 K, a = 6.8683(12), b = 9.2342(15), c = 10.5078(19) Å, V = 613.06(18) Å^3, λ(Mo Kα) = 0.71075 Å, μ = 0.101 mm^{-1}; Intensity data were collected on Rigaku R-AXIS RAPID IP area detector system. The structure was solved by direct methods and refined by the full-matrix least-squares on F^2 (SHELXL-97). A total of 5877 reflections were measured and 2771 were independent. Final $R1$ = 0.0436, $wR2$ = 0.1227 (2189 refs; $I > 2\sigma(I)$), and GOF = 1.114 (for all data, $R1$ = 0.0528, $wR2$ = 0.1339); CCDC 859933 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; Fax: +44 1223 336033.

Isoxazole 8b

Prepared according to the general procedure from nitrile oxide **2a** (200 mg, 0.754 mmol) and *p*-quinone mono-acetal **3b** (278 mg, 1.51 mmol) under the conditions indicated in Table 2. The crude product was purified by flash column chromatography (silica gel, hexane/EtOAc = 2/1 to 1/2) to afford isoxazole **8b** (258 mg, 77%) as a pink solid. Nitrile **9a**, contaminated with a trace amount of impurity (8.2 mg, ca. 4%) was also obtained. Unreacted *p*-quinone mono-acetal **3b** was recovered (156 mg, 56%) as white solid.

R*f* 0.33 (hexane/EtOAc = 1/2); **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 1.30 (brd, 1H, J = 13.4 Hz), 1.98–2.23 (m, 1H), 3.46 (d, 3H, J = 0.8 Hz), 3.53–3.66 (m, 1H), 3.58 (d, 3H, J = 0.8 Hz), 3.70 (s, 3H), 3.78–3.91 (m, 1H), 3.86 (s, 3H), 3.86–4.00 (m, 1H), 3.88 (s, 3H), 4.20 (dd, 1H, J = 11.4, 4.6 Hz), 5.55 (s, 1H), 5.57 (s, 1H), 6.54 (d, 1H, J = 2.2 Hz), 6.94 (d, 1H, J = 2.2 Hz); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 25.4, 52.6, 52.9, 55.4, 55.8, 57.0, 67.0, 67.1, 94.0, 98.9, 99.3, 102.1, 104.6, 107.0, 117.3, 139.7, 155.7, 159.1, 162.1, 167.2, 170.5, 178.2; **IR** (ATR) 2970, 2941, 2843, 1673, 1611, 1585, 1433, 1244, 1069, 850 cm^{-1}; **Anal.** Calc'd for $C_{22}H_{25}NO_9$: C, 59.06; H, 5.63; N, 3.13; Found: C, 59.27; H, 5.84; N, 3.08; **mp** 154 °C (decomp.) (acetone/hexane, colorless prisms); **Crystallographic data**: $C_{22}H_{25}NO_9$, MW = 447.43, 0.45 x 0.20 x 0.10 mm, triclinic, space group P –1, Z = 2, T = 173 K, a = 7.3141(14), b = 11.871(3), c = 12.579(2) Å, V = 1036.8(4) Å^3, λ(Mo Kα) = 0.71075 Å, μ = 0.112 mm^{-1}; Intensity data were collected on Rigaku R-AXIS RAPID IP area detector system. The structure was solved by direct methods and refined by the full-matrix least-squares on F^2 (SHELXL-97). A total of 13525 reflections were measured and 6823 were independent. Final $R1 = 0.0445$, $wR2 = 0.1155$ (5888 refs; $I > 2\sigma(I)$), and GOF = 1.068 (for all data, $R1 = 0.0536$, $wR2 = 0.1277$); CCDC 859935 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; Fax: +44 1223 336033.

Isoxazole 8c

A mixture of nitrile oxide **2a** (10.0 g, 37.7 mmol) and *p*-quinone mono-acetal **3c** (58.1 g, 377 mmol) in toluene (95 mL) was stirred at room temperature for 11 hours. To the mixture was added activated manganese (IV) oxide (26.2 g, 301 mmol), and stirring for 10 min at 80 ºC. After cooling to room temperature, the reaction mixture was filtered through a Celite® pad. The manganese residue was washed with hot MeOH (50 ºC, 100 mL). The combined filtrate was condensed under reduced pressure, and the residue was purified by flash column chromatography (silica gel, hexane/EtOAc = 3/1 to 1/1) to afford isoxazole **8c** (11.8 g, 75%) as a colorless foam. Nitrile **9a**, contaminated with a trace amount of impurity (0.331 g, ca. 4%) was also obtained. Unreacted *p*-quinone mono-acetal **3c** was recovered (50.7 mg, 87%) as yellow oil.

R*f* 0.35 (hexane/EtOAc = 1/1); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 1.30 (brd, 1H, *J* = 13.6 Hz), 2.04–2.18 (m, 1H), 3.52 (s, 3H), 3.57–3.65 (m, 1H), 3.61 (s, 3H), 3.69 (s, 3H), 3.86 (ddd, 1H, *J* = 11.8, 11.6, 2.6 Hz), 3.89 (s, 3H), 3.94 (dd, 1H, *J* = 11.4, 5.4 Hz), 4.20 (dd, 1H, *J* = 11.4, 4.6 Hz), 5.53 (s, 1H), 6.23 (d, 1H, *J* = 10.4 Hz), 6.53 (d, 1H, *J* = 2.0 Hz), 6.74 (d, 1H, *J* = 10.4 Hz), 6.94 (d, 1H, *J* = 2.0 Hz); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 25.4, 51.4, 51.6, 55.4, 55.8, 67.0, 67.1, 93.0, 98.9, 99.3, 102.1, 106.8, 115.8, 131.0, 139.6, 139.8, 155.5, 159.1, 162.2, 172.4, 179.1; **IR** (ATR) 2972, 2947, 2863, 2843, 1687, 1610, 1592, 1454, 1430, 1331, 1302, 1202, 1086, 1055, 838 cm^{-1}; **Anal.** Calc'd for $C_{21}H_{23}NO_8$: C, 60.43; H, 5.55; N, 3.36; Found: C, 60.41; H, 5.67; N, 3.28; **mp** 126.7–127.1 °C (acetone/hexane, colorless prisms); **Crystallographic data**: $C_{21}H_{23}NO_8$, MW = 417.40, 0.50 x 0.28 x 0.10 mm, monoclinic, space group *P* 21/c, *Z* = 4, *T* = 173

K, a = 10.301(5), b = 8.437(4), c = 23.760(11) Å, V = 2033.2(16) Å^3, λ(Mo Kα) = 0.71075 Å, μ = 0.105 mm^{-1}; Intensity data were collected on Rigaku R-AXIS RAPID IP area detector system. The structure was solved by direct methods and refined by the full-matrix least-squares on F^2 (SHELXL-97). A total of 19165 reflections were measured and 4651 were independent. Final $R1$ = 0.0490, $wR2$ = 0.1535 (3884 refs; $I > 2\sigma(I)$), and GOF = 1.262 (for all data, $R1$ = 0.0595, $wR2$ = 0.1622); CCDC 859934 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; Fax: +44 1223 336033.

Isoxazole 8d

Prepared according to the general procedure from nitrile oxide **2b** (200 mg, 0.850 mmol) and *p*-quinone mono-acetal **3a** (286 mg, 1.70 mmol) under the conditions indicated in Table 2. The crude product was passed through a pad of silica gel (EtOAc), and the filtrate was condensed under reduced pressure. Trituration with Et_2O followed by filtration gave isoxazole **8d** (185 mg, 54%) as an off-white solid. The mother liquor was condensed under reduced pressure, and the residue was purified by flash column chromatography (silica gel, hexane/EtOAc = 5/2 to 3/2) to afford isoxazole **8d** (45.0 mg, 13%) as a white solid. Unreacted *p*-quinone mono-acetal **3a** was recovered (146 mg, 51%) as yellow oil.

R*f* 0.50 (hexane/EtOAc = 1/1); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 1.29 (brd, 1H, J = 13.6 Hz), 2.00–2.16 (m, 1H), 2.05 (d, 3H, J = 1.0 Hz), 3.32 (s, 3H), 3.50 (s, 3H), 3.57 (td, 1H, J = 12.4, 2.5 Hz) 3.72 (s, 3H), 3.76–3.97 (m, 2H), 4.19 (dd, 1H, J = 11.7, 4.9 Hz), 5.57 (s, 1H), 6.16 (d, 1H, J = 1.0 Hz), 6.99 (d, 1H, J = 8.3 Hz), 7.38 (d, 1H, J = 8.0 Hz), 7.49 (dd, 1H, J = 8.3, 8.0 Hz); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 15.4, 25.3, 51.9, 52.3, 55.8, 66.89, 66.95, 94.9, 98.9, 111.1, 114.2, 117.9, 118.0, 130.2, 131.0, 138.6, 152.2, 155.6, 157.8, 172.4, 178.6; **IR** (ATR) 2968, 1682, 1596, 1478, 1432, 1385, 1277, 1076, 782 cm^{-1}; **Anal.** Calc'd for $C_{21}H_{23}NO_7$: C, 62.83; H, 5.78; N, 3.49; Found: C, 62.65; H, 5.80; N, 3.48; **mp** 164 °C (decomp.) (acetone/hexane, pink prisms).

Isoxazole 8e

A suspension of nitrile oxide **2b** (200 mg, 0.850 mmol) and *p*-quinone mono-acetal **3b** (188 mg, 1.02 mmol) in chlorobenzene (0.85 mL) was stirred at 60 °C for 30 hours. The mixture was diluted with chlorobenzene (0.85 mL), to which activated manganese (IV) oxide (739 mg, 8.50 mmol) was added. After stirring for 10 min at 80 ºC, the reaction mixture was filtered through a Celite® pad (washed with MeOH), and the filtrate was condensed under reduced pressure. The residue was passed through a pad of silica gel (EtOAc), and the filtrate was condensed under reduced pressure. Trituration with Et_2O followed by filtration gave isoxazole **8e** (235 mg, 66%) as an off-white solid. The mother liquor was condensed under reduced pressure, and the residue was purified by flash column chromatography (silica gel, hexane/EtOAc = 1/1 to 2/3) to afford isoxazole **8e** (23.0 mg, 6%) as an off-white solid.

R*f* 0.33 (hexane/EtOAc = 1/2); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 1.29 (brd, 1H, *J* = 13.7 Hz), 1.99–2.19 (m, 1H), 3.47 (s, 3H), 3.54–3.64 (m, 1H), 3.59 (s, 3H), 3.73 (s, 3H), 3.79–3.89 (m, 1H), 3.86 (s, 3H), 3.92 (dd, 1H, *J* = 11.5, 4.9 Hz), 4.18 (dd, 1H, *J* = 11.5, 4.9 Hz), 5.55 (s, 1H), 5.57 (s, 1H), 6.99 (d, 1H, *J* = 8.5 Hz), 7.38 (d, 1H, *J* = 7.9 Hz), 7.48 (dd, 1H, *J* = 8.5, 7.9 Hz); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 25.4, 52.6, 52.9, 55.9, 57.0, 66.95, 67.04, 94.0, 99.0, 104.5, 111.3, 114.4, 117.3, 118.1, 131.1, 138.8, 155.7, 157.9, 167.3, 170.4, 178.1; **IR** (ATR) 2941, 2863, 1674, 1582, 1439, 1237, 1076, 1063, 1003 cm^{-1}; **Anal.** Calc'd for $C_{21}H_{23}NO_8$: C, 60.43; H, 5.55; N, 3.36; Found: C, 60.27; H, 5.50; N, 3.29; **mp** 187 °C (decomp.) (acetone/hexane, colorless prisms).

Isoxazole 8f

Prepared according to the general procedure from nitrile oxide **2a** (53.1 mg, 0.226 mmol) and *p*-quinone mono-acetal **3c** (348 mg, 2.26 mmol) under the conditions indicated in Table 2. The crude product was purified by PTLC (hexane/EtOAc = 2/1 (2x)) to afford isoxazole **8f** (67.2 mg, 77%) as a pale yellow foam. Unreacted *p*-quinone mono-acetal **3c** was recovered (290 mg, 83%) as yellow oil.

R*f* 0.35 (hexane/EtOAc = 2/1); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 1.29 (brd, 1H, *J* = 14.4 Hz), 2.00–2.21 (m, 1H), 3.52 (s, 3H), 3.55–3.67 (m, 1H), 3.62 (s, 3H), 3.72 (s, 3H), 3.85 (td, 1H, *J* = 12.4, 2.7 Hz), 3.93 (dd, 1H, *J* = 11.5, 5.2 Hz), 4.19 (dd, 1H, *J* = 11.5, 5.2 Hz), 5.53 (s, 1H), 6.24 (d, 1H, *J* = 10.5 Hz), 6.75 (d, 1H, *J* = 10.5 Hz), 6.99 (d, 1H, *J*

= 8.3 Hz), 7.38 (d, 1H, *J* = 7.9 Hz), 7.49 (dd, 1H, *J* = 8.3, 7.9 Hz); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 25.4, 51.4, 51.6, 55.8, 67.0, 67.1, 93.0, 99.0, 111.2, 114.2, 115.8, 118.2, 130.9, 131.2, 138.8, 139.7, 155.6, 157.8, 172.3, 179.0; **IR** (ATR) 2949, 2842, 1688, 1593, 1435, 1271, 1113, 1073, 992, 963, 831 cm^{-1}; **Anal.** Calc'd for $C_{20}H_{21}NO_7$: C, 62.01; H, 5.46; N, 3.62; Found: C, 62.03; H, 5.17; N, 3.35.

Isoxazole 8g

Prepared according to the general procedure from nitrile oxide **2c** (200 mg, 0.754 mmol) and *p*-quinone mono-acetal **3a** (254 mg, 1.51 mmol) under the conditions indicated in Table 2. The crude product was purified by flash column chromatography (silica gel, $CHCl_3/CH_3CN$ = 40/1 to 30/1) to afford isoxazole **8g** (251 mg, 77%) as a white foam. Nitrile **9c** (9.7 mg, 5%) was also obtained. Unreacted *p*-quinone mono-acetal **3a** was recovered (136 mg, 54%) as yellow oil.

R*f* 0.37 (hexane/EtOAc = 1/1); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 1.18 (brd, 1H, *J* = 13.2 Hz), 1.64–1.83 (m, 1H), 2.04 (d, 3H, *J* = 1.0 Hz), 3.37 (s, 3H), 3.48 (s, 3H), 3.62–3.74 (m, 2H), 3.64 (s, 3H), 3.77–3.88 (m, 1H), 3.83 (s, 3H), 4.14 (dd, 1H, *J* = 11.2, 4.9 Hz), 5.96 (s, 1H), 6.14 (d, 1H, *J* = 1.0 Hz), 6.93 (d, 1H, *J* = 9.0 Hz), 6.99 (d, 1H, *J* = 9.0 Hz); **^{13}C NMR** (acetone-d_6, 100 MHz) δ 15.5, 26.3, 52.3, 52.4, 56.8, 56.9, 67.6, 67.7, 96.1, 97.5, 113.1, 114.4, 118.0, 119.6, 128.6, 131.0, 151.9, 153.32, 153.34, 156.9, 172.1, 179.5; **IR** (ATR) 2958, 2845, 1685, 1486, 1430, 1258, 1082, 1072, 994, 919, 809 cm^{-1}; **Anal.** Calc'd for $C_{22}H_{25}NO_8$: C, 61.25; H, 5.84; N, 3.25; Found: C, 61.48; H, 5.99; N, 3.23; **mp** 182 °C (decomp.) (acetone/hexane, pink prisms); **Crystallographic data**: $C_{22}H_{25}NO_8$, MW = 431.43, 0.35 x 0.30 x 0.15 mm, triclinic, space group $P\,{-1}$, $Z = 2$, T = 173 K, a = 7.573(6), b = 8.394(5), c = 18.258(12) Å, V = 1078.9(13) Å^3, λ(Mo Kα) = 0.71075 Å, μ = 0.102 mm^{-1}; Intensity data were collected on Rigaku R-AXIS RAPID IP area detector system. The structure was solved by direct methods and refined by the full-matrix least-squares on F^2 (SHELXL-97). A total of 10631 reflections were measured and 4874 were independent. Final $R1$ = 0.1503, $wR2$ = 0.4440 (3723 refs; $I > 2\sigma(I)$), and GOF = 2.821 (for all data, $R1$ = 0.1636, $wR2$ = 0.4465); CCDC 874424 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data

Centre, 12, Union Road, Cambridge CB2 1EZ, UK; Fax: +44 1223 336033.

Nitrile 9c

R_f 0.36 ($CHCl_3/CH_3CN$ = 30/1); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 1.41 (brd, 1H, *J* = 13.6 Hz), 2.37–2.55 (m, 1H), 3.81 (s, 3H), 3.88 (s, 3H), 3.96 (td, 2H, *J* = 12.6, 2.0 Hz), 4.30 (dd, 2H, *J* = 10.8, 4.9 Hz), 6.07 (s, 1H), 6.91 (d, 1H, *J* = 9.2 Hz), 7.05 (d, 1H, *J* = 9.2 Hz); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ25.3, 56.6, 56.7, 67.6, 95.0, 101.9, 112.6, 114.6, 116.9, 130.4, 150.2, 156.7; **IR** (ATR) 2854, 2227, 1492, 1269, 1082, 1071, 996, 810 cm^{-1}; **Anal.** Calc'd for $C_{13}H_{15}NO_4$: C, 62.64; H, 6.07; N, 5.62; Found: C, 62.52; H, 5.83; N, 5.54; **mp** 154–155 °C (acetone/hexane, pale yellow prisms).

Isoxazole 8h

Prepared according to the general procedure from nitrile oxide **2c** (200 mg, 0.754 mmol) and *p*-quinone mono-acetal **3b** (278 mg, 1.51 mmol) under the conditions indicated in Table 2. Trituration with Et_2O followed by filtration (washed with EtOAc) gave isoxazole **8h** (260 mg, 77%) as a pink solid.

R*_f* 0.30 (hexane/EtOAc = 1/2); **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 1.18 (brd, 1H, *J* = 13.4 Hz), 1.62–1.82 (m, 1H), 3.45–3.90 (m, 3H), 3.50 (s, 3H), 3.57 (s, 3H), 3.65 (s, 3H), 3.83 (s, 3H), 3.86 (s, 3H), 4.13 (dd, 1H, *J* = 11.0, 4.2 Hz), 5.56 (s, 1H), 5.96 (s, 1H), 6.93 (d, 1H, *J* = 9.3 Hz), 7.00 (d, 1H, *J* = 9.3 Hz); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 25.6, 52.6, 53.0, 56.56, 56.59, 57.0, 67.1, 67.3, 94.3, 96.7, 104.5, 112.5, 113.7, 116.8, 118.1, 127.2, 151.0, 152.5, 156.3, 167.4, 169.2, 178.8; **IR** (ATR) 2956, 1671, 1584, 1450, 1307, 1240, 1079, 1002, 958, 849, 817 cm^{-1}; **Anal.** Calc'd for $C_{22}H_{25}NO_9$: C, 59.06; H, 5.63; N, 3.13; Found: C, 58.81; H, 5.92; N, 2.83; **mp** 217 °C (decomp.) (CH_2Cl_2/hexane, colorless prisms).

Isoxazole 8i

Prepared according to the general procedure from nitrile oxide **2c** (53.1 mg, 0.200 mmol) and *p*-quinone mono-acetal **3c** (309 mg, 2.00 mmol) under the conditions indicated in Table 2. The crude product was purified by PTLC (hexane/EtOAc = 1/1 (2x)) to afford isoxazole **8i** (69.0 mg, 83%) as a white solid. Nitrile **9c**, contaminated with a trace amount of impurity (7.1 mg, ca. 14%) was also obtained. Unreacted *p*-quinone mono-acetal **3c** was recovered (261 mg, 84%) as yellow oil.

R*f* 0.23 (hexane/EtOAc = 1/1); **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 1.18 (brd, 1H, *J* = 13.1 Hz), 1.59–1.81 (m, 1H), 3.54 (s, 3H), 3.61 (s, 3H), 3.62–3.73 (m, 2H), 3.65 (s, 3H), 3.80 (td, 1H, *J* = 11.5, 2.4 Hz), 3.83 (s, 3H), 4.12 (dd, 1H, *J* = 11.3, 4.4 Hz), 5.95 (s, 1H), 6.22 (d, 1H, *J* = 10.2 Hz), 6.72 (d, 1H, *J* = 10.2 Hz), 6.93 (d, 1H, *J* = 9.0 Hz), 7.00 (d, 1H, *J* = 9.0 Hz); **^{13}C NMR** ($CDCl_3$, 75 MHz) δ 25.5, 51.6, 51.7, 56.56, 56.63, 67.0, 67.3, 93.3, 96.6, 112.5, 113.8, 116.7, 116.8, 127.4, 131.0, 140.2, 151.0, 152.5, 156.2, 171.2, 179.7; **IR** (ATR) 2956, 2860, 1683, 1453, 1259, 1112, 1084, 1065, 994, 806, 725 cm^{-1}; **Anal.** Calc'd for $C_{21}H_{23}NO_8$: C, 60.43; H, 5.55; N, 3.36; Found: C, 60.44; H, 5.58; N, 3.27; **mp** 170 °C (decomp.) (acetone/hexane, colorless prisms); **Crystallographic data**: $C_{21}H_{23}NO_8$, MW = 417.40, 0.60 x 0.55 x 0.20 mm, monoclinic, space group 7*P* 21/c, *Z* = 4, *T* = 173 K, a = 14.467(6), b = 9.266(3), c = 15.337(4) Å, V = 2041.4(12) Å^3, λ(Mo Kα) = 0.71075 Å, *μ* = 0.105 mm^{-1}; Intensity data were collected on Rigaku R-AXIS RAPID IP area detector system. The structure was solved by direct methods and refined by the full-matrix least-squares on *F*^{2} (SHELXL-97). A total of 19140 reflections were measured and 4652 were independent. Final *R*1 = 0.0577, *wR*2 = 0.2092 (4017 refs; *I* > 2σ(*I*)), and GOF = 1.795 (for all data, *R*1 = 0.0638, *wR*2 = 0.2153); CCDC 859936 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; Fax: +44 1223 336033.

Nitrile oxide 2a

Crystallographic data: $C_{13}H_{15}NO_5$, MW = 265.26, 0.50 x 0.30 x 0.20 mm, triclinic, space group *P* –1, *Z* = 2, *T* = 169 K, a = 8.4243(18), b = 8.6769(16), c = 9.1730(17) Å, V = 606.8(2) Å^3, λ(Mo Kα) = 0.71075 Å, *μ* = 0.112 mm^{-1}; Intensity data were collected on Rigaku R-AXIS RAPID IP area detector system. The structure was solved by direct methods and refined by the full-matrix least-squares on *F*^{2} (SHELXL-97). A total of 6003 reflections were measured and 2747 were independent. Final *R*1 = 0.0406, *wR*2 = 0.1068 (2312 refs; *I* > 2σ(*I*)), and GOF = 1.057 (for all data, *R*1 = 0.0467, *wR*2 =

0.1100); CCDC 874422 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; Fax: +44 1223 336033.

Nitrile oxide 2c

R*f* 0.35 (hexane/EtOAc = 1/1); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 1.45 (brd, 1H, *J* = 13.7 Hz), 2.32–2.50 (m, 1H), 3.80 (s, 3H), 3.83 (s, 3H), 3.96 (td, 2H, *J* = 12.0, 1.7 Hz), 4.28 (ddd, 2H, *J* = 12.0, 4.9, 1.2 Hz), 6.05 (s, 1H), 6.85 (d, 1H, *J* = 9.3 Hz), 6.94 (d, 1H, *J* = 9.3 Hz); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 25.6, 56.3, 56.4, 67.5, 95.0, 102.6, 112.2, 114.6, 130.4, 150.2, 156.1; Nitrile oxide carbon was missing; **IR** (ATR) 2859, 2294, 1336, 1260, 1078, 1056, 988, 809, 729 cm^{-1}; **Anal.** Calc'd for $C_{13}H_{15}NO_5$: C, 58.86; H, 5.70; N, 5.28; Found: C, 58.82; H, 5.85; N, 5.21; **mp** 169 °C (decomp.) ($CHCl_3$/hexane, colorless prisms); **Crystallographic data**: $C_{13}H_{15}NO_5$, MW = 265.26, 0.60 x 0.50 x 0.50 mm, orthorohmbic, space group *P* bca, *Z* = 8, *T* = 169 K, a = 13.0620(11), b = 12.0982(8), c = 16.2166(13) Å, V = 2562.7(3) Å^3, λ(Mo Kα) = 0.71075 Å, μ = 0.106 mm^{-1}; Intensity data were collected on Rigaku R-AXIS RAPID IP area detector system. The structure was solved by direct methods and refined by the full-matrix least-squares on F^2 (SHELXL-97). A total of 23309 reflections were measured and 2912 were independent. Final *R*1 = 0.0440, *wR*2 = 0.1169 (2304 refs; $I > 2\sigma(I)$), and GOF = 1.059 (for all data, *R*1 = 0.0562, *wR*2 = 0.1234); CCDC 874423 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; Fax: +44 1223 336033.