Ketene Dithioacetals in the aza-Diels-Alder Reaction with *N*-Arylimines: a Versatile Approach to Tetrahydroquinolines, 2,3-Dihydro-4-quinolones and 4-Quinolones

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Supporting Information

General Description. NMR spectra were recorded on either a Varian Mercury-300 (^1H : 300 MHz, ^{13}C : 75 MHz) NMR spectrometer or a Varian Mercury-400 (^1H : 400 MHz, ^{13}C : 100 MHz) NMR spectrometer for 2-D and NOE experiments at ambient temperature. Chemical shift data are reported in units of δ (ppm) relative to solvents (CDCl_3 δ 7.26 for ^1H NMR and CDCl_3 δ 77.00 for ^{13}C NMR) or to tetramethylsilane (δ 0.00 for ^1H NMR) as internal standards. *Anti*-product alone was fully characterized for examples **3a**, **3b**, **3c**, **3e**, **4a** and **5** where this isomer predominated. Both *anti*- and *syn*-product were characterized in case **3d** where the two diastereomers were separated by reverse-phase HPLC. In the case of **3f**, the 1:1 mixture of diastereomers was characterized directly. The ratios between *syn*- and *anti*-isomers were determined from the ratios of the signal integrations in the ^1H NMR spectra of the products **3c-g**. High-resolution mass spectra were recorded on a Micromass Q-TOF2 mass spectrometer. Column chromatography (low-pressure) was performed with EM Science silica gel 60 (230-400 mesh ASTM). TLC analysis was carried out on Anatech 250 micron glass-backed silica gel GF plates. Plates were visualized by using either UV light or from developing solutions of either 7% phosphomolybdic acid or 5% *p*-anisaldehyde in ethanol. All reactions were performed under magnetic stirring. Acetonitrile (anhydrous from Aldrich) was further dried with CaH_2 and filtered with a Whatman PuradiscTM 13mm syringe filter prior to use for the cyclization reaction (protocols A, B, C, and D). Other chemicals were obtained from commercial sources and were used freshly without further

purification, unless otherwise stated.

Preparation of Starting Materials. 1,3-Dithiolane **1a**^{1a} and 1,3-dithiane **1b**^{1b}, 1,4-benzodithiafulvenes **1c-e**² and imine **2a**³ were prepared according to literature procedures. Imine **2c** was purchased from Aldrich. Imines **2b,d** and 1,4-dithiofulvene **1f** were generated *in situ* (see protocols B, C and D).

Reaction of 1a or 1b with 2a. Scandium triflate (1200 mg, 2.41 mmol) was quickly weighed and added to a flask containing a mixture of imine **2a** (2.0 mmol) and 1,3-dithiolane **1a** or 1,3-dithiane **1b** (2.2 mmol). The flask was evacuated and then purged with dry nitrogen before the addition of anhydrous acetonitrile (10 mL). The reaction mixture was warmed to 64 °C and maintained at this temperature for 3 hours before cooling to room temperature. Ethyl acetate (50 mL) and aqueous solution of hydrogen chloride (1%, 60 mL) was introduced and the mixture was stirred for 30 min. This mixture was shaken in a separatory funnel and hexanes (10 mL) was added. The organic phase was separated, washed with saturated sodium hydrogencarbonate solution, and dried over sodium sulfate. After evaporation of the filtrate, the residue was subjected to column chromatography to give product **3a** or **3b**.

Compound 3a (eluent: ethyl acetate /hexanes = 1/11, 329 mg, 38%, *anti*:-: *syn*- = 58:1): ¹H NMR (CDCl₃) δ 8.02-7.92 (m, 1 H), 7.88-7.78 (m, 2 H), 7.78-7.20 (m, 4 H), 7.20-7.00 (m, 4 H), 6.86-6.74 (m, 1 H), 6.56-6.46 (m, 1 H), 5.02 (d, *J* = 10.5 Hz, 1 H, 2-), 4.19 (bs, 1 H, *N*-), 3.83 (s, 3 H, CH₃), 3.79 (d, 10.8 Hz, 1 H, 3-), 3.35-3.17 (m, 2 H), 2.60-2.30 (m, 2 H); ¹³C NMR (CDCl₃) δ 166.7, 146.9, 142.9, 137.2, 130.3, 129.4, 129.2, 128.6, 128.3, 127.0, 126.8, 125.2, 117.9, 114.1, 71.6, 60.4, 58.5, 52.0, 42.1, 40.7 (one carbon unresolved); exact mass calcd. for (C₂₅H₂₃NO₂S₂ + H⁺) 434.1248, found 434.1260.

Compound 3b (eluent: ethyl acetate /hexanes = 1/11, 312 mg, 35%, *anti*:-: *syn*- = 21:1): ¹H NMR (CDCl₃) δ 8.18-8.10 (m, 1 H), 8.00-7.50 (m, 3 H), 7.48-7.00 (m, 7 H), 6.84-6.74 (m, 1 H), 6.58-6.50 (m,

1 H), 5.18 (d, $J = 10.5$ Hz, 1 H, 2-), 4.26 (bs, 1 H, N -), 3.84 (s, 3 H, CH_3), 3.83 (d, 9.9 Hz, 1 H, 3-), 2.60-2.37 (m, 3 H), 2.00-1.70 (m, 3 H); ^{13}C NMR (CDCl_3) δ 166.7, 147.1, 143.5, 137.8, 132.8, 130.5, 129.4, 129.10, 129.05, 128.3, 127.7, 127.2, 124.6, 117.3, 114.2, 60.3, 58.1, 52.7, 52.0, 29.8, 28.2, 23.5; exact mass calcd. for ($\text{C}_{26}\text{H}_{25}\text{NO}_2\text{S}_2 + \text{H}^+$) 448.1405, found 448.1411.

Protocol A. Scandium triflate (1200 mg, 2.41 mmol) was quickly weighed and added to a flask containing a mixture of imine **2** (**2a** or **2c**) (2.0 mmol) and 1,4-benzodithiafulvene (2.2 mmol) **1** (**1c**, **1d** or **1e**). The flask was evacuated and then purged with dry nitrogen before the addition of anhydrous acetonitrile (10 mL). The reaction mixture was warmed to 64 °C and maintained at this temperature for the time indicated in Table 2 of the text. At this time the reaction was cooled to room temperature before the addition of ethyl acetate (50 mL) and aqueous solution of hydrogen chloride (1%, 60 mL). After 30 min of stirring, the mixture was shaken in a separatory funnel before the addition of hexanes (10 mL). The organic phase was separated, washed with saturated sodium hydrogencarbonate solution and dried over sodium sulfate. After evaporation of the filtrate, the residue was chromatographed to give the purified products **3c**, **3e** or **3g**.⁴

Compound 3c (eluent: ethyl acetate /hexanes = 1/11, 777 mg, 81%, *anti*-: *syn*- = 23:1): ^1H NMR (CDCl_3) δ 8.32 (dd, $J = 1.2, 7.8$ Hz, 1 H), 7.84-7.74 (m, 2 H), 7.50-6.96 (m, 5 H), 6.88-6.60 (m, 8 H), 6.54 (dd, $J = 1.2, 8.1$ Hz, 1 H), 5.18 (d, $J = 10.2$ Hz, 1 H, 2-), 4.26 (bs, 1 H, N -), 3.80 (s, 3 H, CH_3), 3.79 (d, 10.2 Hz, 1 H, 3-); ^{13}C NMR (CDCl_3) δ 166.6, 146.5, 143.6, 138.2, 138.1, 135.6, 130.6, 129.54, 129.48, 129.3, 129.2, 128.3, 126.9, 126.4, 124.9, 124.8, 120.9, 120.8, 120.0, 117.5, 114.4, 72.4, 59.5, 57.5, 52.0; exact mass calcd. for ($\text{C}_{29}\text{H}_{23}\text{NO}_2\text{S}_2 + \text{H}^+$) 482.1248, found 482.1247.

Compound 3e (eluent: ethyl acetate /hexanes=1/50, 716 mg, 82%, *anti*-: *syn*- = 28:1): ^1H NMR (CDCl_3) δ 8.04 (dd, $J = 1.5, 8.1$ Hz, 1 H), 7.24-7.02 (m, 8 H), 7.02-6.90 (m, 5 H), 6.78-6.64 (m, 3 H), 6.45 (dd, $J = 1.2, 8.4$ Hz, 1 H), 4.42 (d, $J = 9.0$ Hz, 1 H, 2-), 4.11 (bs, 1 H, N -), 3.38 (dd, $J = 2.4, 14.7$

Hz, 1 H, CH₂), 3.06 (ddd, $J = 2.4, 9.0, 8.4$ Hz, 1H, 3-), 2.45 (dd, $J = 8.1, 14.7$ Hz, 1 H, CH₂); ¹³C NMR (CDCl₃) δ 142.4, 141.0, 140.7, 137.3, 131.2, 129.2, 128.6, 128.5, 128.3, 128.2, 128.1, 127.7, 125.4, 125.3, 125.0, 123.6, 121.1, 120.3, 117.7, 114.1, 72.8, 59.6, 55.3, 35.7; exact mass calcd. for (C₂₈H₂₃NS₂ + H⁺) 438.1350, found 438.1350.

Compound 3g (eluent: ethyl acetate /hexanes = 1/11, 339 mg, 38%, *anti*- only): ¹H NMR (CDCl₃) δ 8.05 (d, $J = 8.7$ Hz, 2 H), 7.69 (dd, $J = 1.2, 7.5$ Hz, 1 H), 7.62 (d, $J = 8.1$ Hz, 2 H), 7.28-6.92 (m, 5 H), 6.70-6.50 (m, 2 H), 4.74 (d, $J = 4.7$ Hz, 1 H), 4.17 (bs, 1 H), 3.93 (s, 3 H), 3.06 (dd, $J = 1.8, 4.5$ Hz, 1 H), 2.60-2.40 (m, 1 H), 1.00 (d, $J = 7.2$ Hz, 3 H), 0.78 (d, $J = 7.2$ Hz, 3 H); ¹³C NMR (CDCl₃) δ 166.9, 149.7, 141.2, 138.5, 136.7, 129.7, 129.3, 129.2, 127.8, 127.5, 125.5, 125.3, 125.0, 121.9, 121.1, 117.9, 113.6, 72.2, 56.3, 54.3, 52.1, 31.7, 24.4, 17.4; exact mass calcd. for (C₂₆H₂₅NO₂S₂ + H⁺) 448.1405, found 448.1411.

Protocol B. To a mixture of 1,4-benzodithiafulvene **1** (**1c** or **1d**) (1.0 mmol), anhydrous magnesium sulfate (800 mg, 6.67 mmol), aniline (186 mg, 2.0 mmol) and scandium triflate (1200 mg, 2.41 mmol) under dry nitrogen was added anhydrous acetonitrile (5.0 mL). The mixture was heated to 65 °C and isovaleraldehyde (172 mg, 2.0 mmol) in anhydrous acetonitrile (1.0 mL) was added dropwise over 15 minutes. After 60 minutes at 64 °C, the reaction mixture was allowed to cool before work up according to the protocol described in protocol A. Products **3d** or **3f** were obtained following chromatography.

Compound 3d (eluent: ethyl acetate/hexanes = 1/100, 258 mg, 64%, *anti*-: *syn*- = 2:1). Reverse-phase HPLC separation afforded two diastereomers. *Anti*-**3d** ¹H NMR (CDCl₃) δ 8.27 (dd, $J = 1.5, 7.8$ Hz, 1 H), 7.56-7.28 (m, 2 H), 7.14-7.06 (m, 1 H), 7.05-6.90 (m, 3 H), 6.78-6.62 (m, 5 H) 6.54 (dd, $J = 1.2, 8.4$ Hz, 1 H), 4.13 (bs, 1 H, *N*-), 4.09 (ddd, $J = 3.3, 9.6, 10.2$ Hz, 1 H, 2-), 3.29 (d, $J = 10.5$ Hz, 1 H, 3-), 1.85-1.65 (m, 1H), 1.45-1.15 (m, 2 H, CH₂), 0.94 (d, $J = 6.3$ Hz, 3 H, CH₃), 0.85 (d, $J = 6.3$ Hz, 3 H,

CH₃); ¹³C NMR (CDCl₃) δ 143.8, 138.41, 138.36, 136.7, 130.7, 129.3, 127.0, 126.6, 124.73, 124.65, 120.7, 120.0, 116.9, 114.3, 72.7, 59.2, 49.5, 43.1, 24.4, 24.0, 21.0 (two carbons unresolved); exact mass calcd. for (C₂₅H₂₅NS₂ + H⁺) 404.1507, found 404.1501. *Syn*-**3d** ¹H NMR (CDCl₃) δ 8.00 (dd, *J* = 1.5, 8.4 Hz, 1 H), 7.34-6.88 (m, 10 H), 6.76-6.66 (m, 1 H), 6.55 (dd, *J* = 0.6, 8.1 Hz, 1 H), 4.16 (ddd, *J* = 3.0, 6.3, 6.0 Hz, 1 H, 2-), 3.95 (bs, 1 H, *N*-), 3.72 (d, *J* = 3.0 Hz, 1 H, 3-), 1.85-1.65 (m, 1H), 1.60-0.90 (m, 2 H, CH₂), 0.93 (d, *J* = 6.3 Hz, 3 H, CH₃), 0.90 (d, *J* = 6.6 Hz, 3 H, CH₃); ¹³C NMR (CDCl₃) δ 143.6, 138.1, 138.0, 136.8, 129.7, 129.6 128.0, 127.2, 125.8, 125.5, 121.9, 121.6, 120.9, 117.9, 114.5, 72.8, 55.6, 49.8, 42.7, 24.3, 22.9, 22.5 (one carbon unresolved); exact mass calcd. for (C₂₅H₂₅NS₂ + H⁺) 404.1507, found 404.1506.

Compound 3f (eluent: ethyl acetate/hexanes = 1/100, 274 mg, 66%, *anti*:-*syn*- = 1:1). ¹H NMR (1:1 mixture in CDCl₃) δ 8.07 (dd, *J* = 1.5, 7.8 Hz, 0.5 H), 7.87 (dd, *J* = 1.5, 8.1 Hz, 0.5 H) 7.30-6.94 (m, 10 H), 6.72-6.63 (m, 1 H), 6.51 (dd, *J* = 0.9, 7.5 Hz, 0.5 H), 6.47 (dd, *J* = 1.2, 7.8 Hz, 0.5 H), 4.20-3.50 (m, 1.5 H), 3.45 (dd, *J* = 1.8, 14.4 Hz, 0.5 H), 3.37 (ddd, *J* = 4.2, 6.0, 9.6 Hz, 0.5 H), 2.92-2.70 (m, 2 H), 2.51 (dd, *J* = 9.3, 14.4 Hz, 0.5 H), 1.68-1.18 (m, 3 H), 0.85 (d, *J* = 6.0 Hz, 1.5 H), 0.81 (d, *J* = 6.3 Hz, 1.5 H), 0.70 (d, *J* = 6.3 Hz, 1.5 H), 0.65 (d, *J* = 6.0 Hz, 1.5 H); exact mass calcd. for (C₂₆H₂₇NS₂ + H⁺) 418.1663, found 418.1664.

Protocol C. A mixture of 2-(1-chloroethyl)-1,3-benzodithiole⁵ (404 mg, 2.0 mmol) and benzyltriethylammonium chloride (100 mg, 0.37 mmol) in refluxing benzene (5 mL) was treated with potassium hydroxide (smashed to powder, 1000 mg, 17.9 mmol) for 30 minutes to generate compound **1f**. After cooling to room temperature, the solution was added, *via* a syringe equipped with a syringe filter, to a solution of imine **2c** (181 mg, 1.0 mmol) in anhydrous acetonitrile (6 mL). Scandium triflate (100 mg, 0.2 mmol) was added and the mixture was stirred at room temperature for 15 min. Work-up was as described in protocol **A** to give **3h** after chromatography.⁴

Compound 3h (eluent: ethyl acetate/hexanes = 1/50, 320 mg, 92%): ^1H NMR (CDCl_3) δ 8.28 (dd, $J = 1.5, 7.8$ Hz, 1 H), 7.48-7.40 (m, 2 H), 7.40-7.22 (m, 3 H), 7.22-6.98 (m, 5 H), 6.80-6.70 (m, 1 H) 6.54 (dd, $J = 1.2, 8.4$ Hz, 1 H), 4.77 (dd, $J = 2.4, 11.7$ Hz, 1 H, 2-), 4.17 (bs, 1 H, *N*-), 2.95 (dd, $J = 2.4, 13.5$ Hz, 1 H), 2.62 (dd, $J = 11.4, 13.5$ Hz, 1 H); ^{13}C NMR (CDCl_3) δ 145.3, 142.1, 138.0, 136.9, 130.1, 129.8, 128.7, 128.0, 127.0, 126.0, 125.7, 122.5, 122.1, 117.5, 117.3, 115.1, 68.8, 54.0, 49.0; exact mass calcd. for ($\text{C}_{21}\text{H}_{17}\text{NS}_2 + \text{H}^+$) 348.0880, found 348.0876.

Protocol D. A mixture of 2-(1-chloroethyl)-1,3-benzodithiole⁵ (404 mg, 2.0 mmol) and benzyltriethylammonium chloride (100 mg, 0.37 mmol) in refluxing benzene (5 mL) was treated with potassium hydroxide (smashed to powder, 1000 mg, 17.9 mmol) for 30 minutes to generate compound **1f**. After cooling to room temperature, the solution was added, *via* a syringe equipped with a syringe filter, to a mixture of aniline (93 mg, 1.0 mmol), magnesium sulfate (400 mg) and scandium triflate (100 mg, 0.2 mmol) in anhydrous acetonitrile (5 mL). Isobutyraldehyde (72 mg, 1.0 mmol) in acetonitrile (1.0 mL) was added dropwise over 15 minutes and the mixture was stirred at room temperature for another 15 min. Work-up was the same as protocol A to give **3i** after chromatography.

Compound 3i (eluent: ethyl acetate/hexanes = 1/100, 200 mg, 64%): ^1H NMR (CDCl_3) δ 8.18 (dd, $J = 1.5, 7.8$ Hz, 1 H), 7.26-7.20 (m, 1 H), 7.14-7.00 (m, 4 H), 6.72-6.64 (m, 1 H) 6.51 (dd, $J = 1.2, 8.1$ Hz, 1 H), 3.90 (bs, 1 H, *N*-), 3.48 (ddd, $J = 2.1, 5.1, 11.7$ Hz, 1 H, 2-), 2.76 (dd, $J = 2.1, 13.2$ Hz, 1 H), 2.25 (dd, $J = 11.4, 13.2$ Hz, 1 H), 1.85-1.70 (m, 1H), 0.98 (d, $J = 6.6$ Hz, 6 H); ^{13}C NMR (CDCl_3) δ 145.4, 138.1, 137.0, 130.1, 129.6, 125.9, 125.7, 122.3, 122.0, 118.2, 117.1, 115.0, 69.0, 54.2, 43.2, 32.0, 18.3, 17.9; exact mass calcd. for ($\text{C}_{18}\text{H}_{19}\text{NS}_2 + \text{H}^+$) 314.1037, found 314.1034.

Reduction of Dithioacetals 3c, 3g.⁶ To a solution of **3** (**3c** or **3g**) (1.0 mmol) in methanol (25 mL) and tetrahydrofuran (8 mL) at 0 °C was added $\text{NiCl}_2 \cdot 6\text{H}_2\text{O}$ (238 mg, 1.0 mmol) followed by NaBH_4 (113 mg, 3.0 mmol) cautiously in portions. The addition of $\text{NiCl}_2 \cdot 6\text{H}_2\text{O}$ and NaBH_4 was repeated 7

times over 35 minutes. The reaction mixture was stirred for 10 minutes before it was filtered through celite and washed with ethyl acetate. The filtrate was concentrated, dissolved in ethyl acetate (60 mL) and washed with water (50 mL) and brine (50 mL). Following drying over sodium sulfate, the filtrate was evaporated and the residue obtained was chromatographed to give the products **4a** or **4b**.

Compound 4a (eluent: ethyl acetate/ hexanes = 1/8, 260 mg, 76%): ^1H NMR (CDCl_3) δ 7.80-7.83 (m, 2 H), 7.23-6.92 (m, 9 H), 6.69 (ddd, $J = 0.9, 7.2, 7.5$ Hz, 1 H), 6.60 (dd, $J = 0.9, 8.4$ Hz, 1 H), 4.50 (d, $J = 9.3$ Hz, 1 H), 4.20 (bs, 1 H), 3.86 (s, 3 H), 3.30-2.94 (m, 3 H); ^{13}C NMR (CDCl_3) δ 166.9, 147.9, 143.9, 142.0, 129.4, 129.2, 129.1, 128.3, 127.9, 127.5, 127.2, 126.6, 121.1, 117.3, 113.6, 62.3, 52.0, 46.5, 34.8; exact mass calcd. for ($\text{C}_{23}\text{H}_{21}\text{NO}_2 + \text{H}^+$) 344.1650, found 344.1641.

Compound 4b (eluent: ethyl acetate/ hexanes = 1/8, 229 mg, 74%): ^1H NMR (CDCl_3) δ 8.01 (d, $J = 8.4$ Hz, 2 H), 7.41 (d, $J = 8.4$ Hz, 2 H), 7.06-6.98 (m, 2 H), 6.66 (ddd, $J = 0.9, 7.5, 7.2$ Hz, 1 H) 6.53 (dd, $J = 0.6, 8.1$ Hz, 1 H), 4.39 (d, $J = 7.5$ Hz, 1 H), 4.03 (bs, 1 H, *N*-), 3.92 (s, 3 H), 2.80-2.50 (m, 2 H), 1.95-1.80 (m, 1 H), 1.60-1.40 (m, 1 H), 0.98 (d, $J = 6.9$ Hz, 3 H), 0.86 (d, $J = 6.9$ Hz, 3 H); ^{13}C NMR (CDCl_3) δ 166.9, 149.8, 143.9, 129.8, 129.5, 129.3, 127.3, 126.9, 120.7, 117.1, 113.1, 58.5, 52.1, 44.1, 27.0, 25.7, 21.4, 17.2; exact mass calcd. for ($\text{C}_{20}\text{H}_{23}\text{NO}_2 + \text{H}^+$) 310.1807, found 310.1795.

Hydrolysis of Dithioacetal 3e to 2,3-Dihydro-4-quinolone 5. To compound **3e** (254 mg, 0.58 mmol) was added ethanol (10 mL) and ethyl acetate (84 mg, as co-solvent) and the resulting mixture stirred for 5 minutes. Mercuric oxide (530 mg, 2.45 mmol) was added and the mixture stirred for 5 minutes before the addition of tetrafluoroboric acid (54 wt. % solution in diethyl ether, 424 mg). After stirring for 130 minutes at room temperature, the mixture was filtered through celite, washed with ethyl acetate and the filtrate diluted further with ethyl acetate (60 mL). The organic phase was washed with sodium hydrogencarbonate (saturated aqueous solution, 50 mL), water (50 mL), and brine (50 mL) and dried over sodium sulfate. After evaporation of the filtrate, column chromatography of the residue gave

compound **5** (eluent: ethyl acetate/hexanes = 1/6, 106 mg, 58%, *anti*-): ^1H NMR (CDCl_3) δ 7.85-7.76 (m, 1 H), 7.40-7.10 (m, 11 H), 6.78-6.68 (m, 2 H), 4.43 (d, $J = 6.9$ Hz, 1 H, 2-), 3.98 (s, 1 H, *N*-), 3.14-2.86 (m, 3 H); ^{13}C NMR (CDCl_3) δ 195.7, 150.4, 140.3, 138.9, 135.6, 129.0, 128.4, 128.1, 127.6, 127.4, 126.7, 126.0, 117.6, 117.3, 115.1, 58.7, 54.2, 34.0; exact mass calcd. for ($\text{C}_{22}\text{H}_{19}\text{NO} + \text{H}^+$) 314.1545, found 314.1540.

Hydrolysis and Oxidation of Dithioacetal 3e to 4-Quinolone 6. To a mixture of mercuric oxide (895 mg, 4.1 mmol), tetrafluoroboric acid (54 wt. % solution in diethyl ether, 724 mg) and ethanol (10 mL) was added dithioacetal **3e** (437 mg, 1.0 mmol) in portions and the mixture was heated to 60 °C and this temperature was maintained overnight. The resulting mixture was allowed to cool to room temperature and filtered. The filtrate was partitioned between ethyl acetate (80 mL) and water (60 mL). The organic layer was further washed with sodium hydrogencarbonate (saturated aqueous solution, 60 mL) and brine (60 mL), and dried over anhydrous sodium sulfate. After evaporation of the filtrate, the residue was chromatographed to give 4-quinolone **6** (eluent: ethyl acetate/hexanes = 2/3, 262 mg, 84%): ^1H NMR ($\text{CDCl}_3\text{-CD}_3\text{OD}$) δ 8.32 (ddd, $J = 0.6, 1.5, 8.1$ Hz, 1 H), 7.62-7.28 (m, 8 H), 7.18-6.98 (m, 5 H), 3.89 (s, 2 H), 3.69 (s, 1 H, *N*-); ^{13}C NMR ($\text{CDCl}_3\text{-CD}_3\text{OD}$) δ 178.2, 150.0, 141.3, 139.2, 134.8, 131.6, 129.4, 128.3, 127.9, 127.8, 125.6, 125.2, 124.1, 123.4, 119.0, 117.5, 31.4 (one carbon unresolved); exact mass calcd. for ($\text{C}_{22}\text{H}_{17}\text{NO} + \text{H}^+$) 312.1388, found 312.1384.

Characterization of the Stereochemistry. The coupling constants between 2- and 3-H in the major diastereomers of **3c-e** and **4a,b** are 10.2, 10.5, 9.0, 9.3, 7.5 Hz respectively. In compound *syn*-**3d**, NOE effects were observed between protons **c** and **e**, and protons **d** and **e** while no NOE effects were observed between protons **a** and **e**. In compound *anti*-**3d** (the major isomer), NOE effects were observed between protons **a** and **e** but no NOE effects were observed between either **c** and **e**, or **d** and **e**. In compound **4b**, NOE effects were observed between protons **a** and **f**, and between **a** and **g**.

syn-3d

anti-3d

4b

Position	Syn-3d	Anti-3d	4b
a	b, c, c, d, f, g	c, e, f	c, d, f, g
b	a, c, d, e	c, e	c, d, f, g
c	a, b, c, d, e	a, b, d, g	
d	a, b, e, f, g	a, b	
e			a, b, f, g
f,g	a, b, d	a, b, d	a, b, d, e

The nuclear Overhauser effect (nOe) data were recorded on a 400MHz Varian Mercury using the double pulsed filed gradient spin echo (DPFGSE)-NOE experiment with a mixing time of 600ms, a recycle delay of 1s and 256 transients per spectrum.

References

- (1) (a) Corey, E. J.; Beams, D. J. *J. Am. Chem. Soc.* **1973**, *95*, 5829-5831; (b) Corey, E. J.; Kozikowski, A. P.; *Tetrahedron Lett.* **1975**, *122*, 925-928.
- (2) (a) Barbero, M.; Cadamuro, S.; Ceruti, M.; Degani, I.; Fochi, R.; Regondi, V. *Gazz. Chim. Ital.* **1987**, *117*, 227-235; (b) Bellesia, F.; Boni, M.; Ghelfi, F.; Pagnoni, U. M. *J. Heterocyclic Chem.* **1994**, *31*, 1721-1723.
- (3) Nose, A.; Kudo, T. *Chem. Pharm. Bull.* **1986**, *34*, 4817-4820.
- (4) In the column chromatography of **3e** or **3h**, small amounts of imine **2c** may persist which decompose during chromatography to contaminate the products **3e** or **3h** with benzaldehyde. This small amount

of benzaldehyde was conveniently removed as follows. The eluent containing the products **3e** or **3h** (2% ethyl acetate in hexanes) was concentrated to about 1~2 mL in volume at which time either **3e** or **3h** precipitated. The solvents which contained the impurity were decanted. This process was repeated 2~3 times.

(5) Bellesia, F.; Boni, M.; Ghelfi, F.; Pagnoni, U. M. *J. Heterocyclic Chem.* **1994**, *31*, 1721-1723.

(6) Back, T. G.; Baron, D. L.; Yang, K. *J. Org. Chem.* **1993**, *58*, 2407-2413.

anti-3d, ^1H -NMR

syn-3d, ¹³C-NMR

anti-3e, $^1\text{H-NMR}$

3f, mixture of diastereomers

4a, ¹H-NMR

5, 1H-NMR