Interested Behavior of α,β -Unsaturated Oximes in Intramolecular [4 + 2] Cycloaddition Reactions

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Supporting Information

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I – General

All moisture and/or air sensitive experiments were performed under a positive pressure of nitrogen in dried glassware equipped with a rubber septum inlet and stirred magnetically. Solvents and liquid reagents were transferred by nitrogen flushed syringe. All solvents and reagents were purchased from commercial sources and were used without further purification.

NMR (^1H and ^{13}C) spectra were recorded at ambient temperature on a Bruker nuclear magnetic resonance spectrometer at the frequency indicated. Chemical shifts for NMR spectra are reported as δ in units of parts per million (ppm) relative to residual CHCl_3 for proton (δ 7.26, singlet) and CDCl_3 for carbon (δ 77.0, triplet). The data are reported as follows: chemical shift, multiplicities (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad), coupling constants (reported as a J value in Hertz (Hz)), integration. The number of protons (n) for a given resonance is indicated by nH.

High-resolution mass spectra (HRMS) were performed by M-Scan Inc. Low-resolution mass spectra (LRMS) were performed on an Agilent 1100 LCMSD single quadrupole using electrospray ionization. Infrared (IR) spectra were recorded on Perkin-Elmer 1000 PC FT-IR spectrophotometer and are reported in cm^{-1} . Optical rotations were measured using a Perkin-Elmer 341 polarimeter in a 1 dm cell at ambient temperature with a sodium lamp (wavelength of 589 nm).

Thin layer chromatography (TLC) was performed on glass baked plates coated with silica gel 60 with an F 254 indicator. Plates were visualized under UV light and/or by staining with phosphomolydic acid or an ethanolic solution of *p*-anisaldehyde. Flash column chromatography was performed with 40-63 mm silica gel (Merck) and with the indicated solvent system.

II – Experimental section

A – General procedure for oximes preparation and separation

To a suspension of the ketone **2b** (9.94 g, 24.5 mmol) in ethanol (75 mL) was added a solution of hydroxylamine hydrochloride (2.22 g, 31.9 mmol) and sodium bicarbonate (3.5 g, 41.72 mmol) in water (75 mL). The mixture was stirred for 20 h at r.t., then the limpid solution was concentrated *in vacuo* (keep temperature below 30 °C). The crude product was taken up and extracted three times with CH_2Cl_2 (100 mL). The combined organic phases were washed successively with water and brine, dried over Na_2SO_4 , filtered and concentrated *in vacuo* to give a residual solid. After purification of the crude material by careful flash chromatography on silica gel using hexanes/EtOAc (75:25), the desired oximes **3b** and **4b** were obtained (5.25 g, 51%). The following fractions by order of increasing polarity were obtained: the *E*-oxime **3b** (1.18 g, 22.4%), a mixture of *Z* and *E*-oximes **3b** and **4b** (1.61 g, 30.6%) and the *Z*-oxime **4b** (2.46 g, 47%). The above treatment was applied to ketone **2a** (5.64 g, 15.80 mmol). The desired oximes **3a** and **4a** were obtained (3.75 g, 64%). The following fractions by order of increasing polarity were obtained: the *E*-oxime **3a** (0.84 g, 22.4%), a mixture of *Z* and *E*-oximes **3a** and **4a** (1.05 g, 28%) and the *Z*-oxime **4a** (1.86 g, 49.6%).

***E*-Oxime 3b:**

Due to its instability this isomer has to be kept at $-78\text{ }^\circ\text{C}$ right after being chromatographed.

Molecular formula $\text{C}_{25}\text{H}_{28}\text{N}_2\text{O}_4$

Colorless oil

R_f = 0.15 (silica, hexanes/EtOAc 7:3)

$^1\text{H NMR}$ (400 MHz, CDCl_3) δ ppm 1.24 (t, J = 7.1 Hz, 3 H), 1.83 (s, 3 H), 2.98 (d, J = 7.7 Hz, 1 H), 3.21 (dd, J = 13.7, 7.7 Hz, 1 H), 4.13 (m, 2 H), 4.30 (d, J = 17.5 Hz, 1 H), 4.55 (d, J = 17.5 Hz, 1 H), 5.15 (m, 1 H), 5.78 (d, J = 15.8 Hz, 1 H), 6.38 (d, J = 15.5 Hz, 1 H), 7.01 (m, 1 H), 7.08 (d, J = 6.9 Hz, 2 H), 7.13 (d, J = 7.2 Hz, 2 H), 7.26 (m, 6 H), 7.47 (d, J = 15.5 Hz, 1 H), 9.60 (broad s, 1 H)

$^{13}\text{C NMR}$ (100.6 MHz, CDCl_3) δ ppm 9.9, 14.3, 38.1, 50.4, 59.1, 60.7, 122.1, 123.2, 126.6, 126.9, 127.9, 128.8, 129.1, 129.3, 137.1, 137.4, 141.3, 145.2, 155.1, 166.2, 167.2

MS (ES) m/z 421 ($\text{M}+\text{H}$) $^+$

Z-Oxime 4b:

Molecular formula $\text{C}_{25}\text{H}_{28}\text{N}_2\text{O}_4$

White foam

R_f = 0.10 (silica, hexanes/EtOAc 7:3)

IR (thin film, cm^{-1}) ν_{max} 3380, 2920, 1713, 1640, 1606, 1454, 1411, 1368, 1304, 1271, 1189, 1028

$[\alpha]_{\text{D}}^{20}$ -71 (c 1.0, CHCl_3)

$^1\text{H NMR}$ (400 MHz, CDCl_3) δ ppm 1.24 (t, J = 7.1 Hz, 3 H), 1.82 (s, 3 H), 2.99 (m, J = 13.7 Hz, 1 H), 3.22 (dd, J = 13.7, 7.9 Hz, 1 H), 4.14 (q, J = 7.1 Hz, 2 H), 4.29 (d, J = 17.5 Hz, 1 H), 4.52 (d, J = 17.5 Hz, 1 H), 5.13 (m, 1 H), 5.79 (d, J = 15.9 Hz, 1 H), 6.41 (d, J = 15.8 Hz, 1 H), 7.03 (m, 3 H), 7.14 (d, J = 6.9 Hz, 2 H), 7.26 (m, 6 H), 7.97 (d, J = 15.8 Hz, 1 H), 9.15 (broad s, 1 H)

$^{13}\text{C NMR}$ (100.6 MHz, CDCl_3) δ ppm 14.3, 16.9, 38.0, 50.5, 59.1, 60.7, 123.3, 126.6, 125.5, 126.9, 128.1, 128.8, 129.1, 129.3, 130.2, 137.0, 137.3, 145.1, 151.6, 166.1, 167.2

HRMS (FAB+) m/z calcd for $\text{C}_{25}\text{H}_{29}\text{N}_2\text{O}_4$ ($\text{M}+\text{H}$) $^+$ 421.2127, found 421.2129

E-Oxime 3a:

Due to its instability and in order to get some analytical data, this isomer has to be kept at -78 °C right after being chromatographed.

Molecular formula C₂₁H₂₈N₂O₄

Colorless oil

R_f = 0.15 (silica, hexanes/EtOAc 7:3)

¹H NMR (400 MHz, CDCl₃) δ ppm 0.92 (m, 6 H), 1.23 (t, *J* = 7.2 Hz, 3 H), 1.80 (s, 3 H), 2.16 (m, 1 H), 4.13 (q, *J* = 7.2 Hz, 2 H), 4.61 (m, 3 H), 5.90 (d, *J* = 15.6 Hz, 1 H), 6.42 (d, *J* = 15.5 Hz, 1 H), 6.83 (dd, *J* = 15.6, 9.1 Hz, 1 H), 7.17 (d, *J* = 7.3 Hz, 2 H), 7.29 (m, 3 H), 7.44 (d, *J* = 15.5 Hz, 1 H), 9.44 (broad s, 1 H)

¹³C NMR (100.6 MHz, CDCl₃) δ ppm 9.9, 14.4, 17.3, 19.8, 29.6, 49.5, 60.6, 63.5, 122.4, 124.9, 126.7, 127.8, 129.0, 137.5, 141.1, 144.5, 155.1, 166.2, 167.2

MS (ES) *m/z* 373 (M+H)⁺

Z-Oxime 4a:

Molecular formula C₂₁H₂₈N₂O₄

White foam

R_f = 0.10 (silica, hexanes/EtOAc 7:3)

IR (thin film, cm⁻¹) ν_{max} 3278, 2967, 1715, 1641, 1602, 1464, 1419, 1369, 1299, 1250, 1190, 1031

[α]_D²⁰ -57 (*c* 1.0, CHCl₃)

¹H NMR (400 MHz, CDCl₃) δ ppm 0.9 (m, 6 H), 1.23 (t, *J* = 7.2 Hz, 3 H), 1.79 (s, 3 H), 2.17 (m, 1 H), 4.13 (q, *J* = 7.2 Hz, 2 H), 4.60 (m, 3 H), 5.91 (d, *J* = 15.6 Hz, 1 H), 6.45 (d, *J* = 15.8 Hz, 1 H), 6.83 (dd, *J* = 15.6, 9.1 Hz, 1 H), 7.16 (d, *J* = 7.3 Hz, 2 H), 7.31 (m, 3 H), 7.96 (d, *J* = 15.8 Hz, 1 H), 9.51 (broad s, 1 H)

¹³C NMR (100.6 MHz, CDCl₃) δ ppm 14.3, 16.9, 19.8, 20.2, 29.6, 49.5, 60.6, 63.5, 125.0, 125.8, 126.7, 127.9, 129.0, 130.0, 137.4, 144.3, 151.6, 166.1, 167.2

HRMS (FAB+) *m/z* calcd for C₂₁H₂₉N₂O₄ (M+H)⁺ 373.2127, found 373.2138

B – General procedure for nitrones preparation in CH₂Cl₂

1 – Preparation of nitrone **5**

After three days at r.t. in CH₂Cl₂ (4 mL), the *E*-oxime **3a** (260 mg, 0.7 mmol) gave rise to the quantitative formation of a single diastereomer as observed in the crude product ¹H NMR spectrum. The product was of adequate purity for use in the next reaction step. A pure sample of the nitrone **5** (79 mg, 30%) could be obtained as a colorless oil, by flash chromatography on silica gel using a gradient elution starting with CH₂Cl₂/MeOH (99:1) to CH₂Cl₂/MeOH (95:5). In order to establish the stereochemistry, NMR was carried out in benzene-*d*₆.

Molecular formula C₂₁H₂₈N₂O₄

Colorless oil

R_f = 0.18 (silica, CH₂Cl₂/MeOH 95:5)

IR (thin film, cm⁻¹) ν_{max} 2966, 2930, 1741, 1695, 1419, 1185, 1026

[α]_D²⁰ -84 (*c* 1.0, CHCl₃)

¹H NMR (600 MHz, C₆D₆) δ ppm 0.75 (d, *J* = 7.2 Hz, 3 H), 0.80 (d, *J* = 7.1 Hz, 3 H), 1.07 (t, *J* = 7.1 Hz, 3 H), 1.60 (m, 1 H), 1.91 (m, 1 H), 1.95 (s, 3 H), 2.06 (m, 1 H), 2.45 (m, 2 H), 3.08 (d, *J* = 9.4 Hz, 1 H), 3.70 (d, *J* = 15.4 Hz, 1 H), 4.07 (m, 1 H), 4.18 (m, 1 H), 4.38 (d, *J* = 10.9 Hz, 1 H), 5.23 (d, *J* = 15.4 Hz, 1 H), 7.16 (d, *J* = 7.8 Hz, 2 H), 7.19 (m, *J* = 7.4 Hz, 1 H), 7.26 (m, 2 H)

¹³C NMR (151 MHz, C₆D₆) δ ppm 13.8, 16.9, 17.0, 18.9, 26.9, 30.0, 39.3, 39.7, 44.4, 61.7, 64.2, 75.6, 127.7, 127.9, 128.1, 128.9, 137.2, 167.9, 172.4

HRMS (FAB+) *m/z* calcd for C₂₁H₂₉N₂O₄ (M+H)⁺ 373.2127, found 373.2129

2 – Preparation of nitrones 7 and 8

The above treatment was applied to the *E*-oxime **3b** (510 mg, 1.21 mmol). After three days, the *E*-oxime disappeared to give rise to the formation of two diastereomers as observed in the crude product ^1H NMR spectrum. This mixture was used directly in the next step without any further purification. However, purification of the crude material by flash chromatography on silica gel using a gradient elution starting with $\text{CH}_2\text{Cl}_2/\text{MeOH}$ (99:1) to $\text{CH}_2\text{Cl}_2/\text{MeOH}$ (97:3) gave an analytically pure sample of nitrones **7** and **8** (159 mg, 31%) as white crystals, which degraded with time. The ^1H NMR spectrum, recorded after purification, showed a 1:0.4 mixture of diastereomers. The ratio was determined by integration of proton 4 in each diastereomer. Since the nitrones were obtained as an inseparable mixture, we give only characteristic data.

Molecular formula $\text{C}_{25}\text{H}_{28}\text{N}_2\text{O}_4$

White crystals

R_f = 0.20 (silica, $\text{CH}_2\text{Cl}_2/\text{MeOH}$ 95:5)

MS (ES) m/z 421 ($\text{M}+\text{H}$)⁺

Major nitrone 7 (The only discernible peaks from the mixture **7** and **8** are reported):

^1H NMR (300 MHz, CDCl_3) δ ppm 1.23 (t, J = 7.2 Hz, 3 H), 2.19 (s, 3 H), 2.92 (m, 1 H), 3.06 (m, 1 H), 3.83 (m, 1 H), 3.99 (d, J = 15.3 Hz, 1 H), 4.24 (m, 2 H), 4.64 (m, 1 H), 5.04 (d, J = 15.3 Hz, 1 H) 6.80 (m, 2 H) 7.06 (m, 2 H)

Minor nitrone 8 (The only discernible peaks from the mixture **7** and **8** are reported):

¹H NMR (300 MHz, CDCl₃) δ ppm 1.26 (t, *J* = 7.2 Hz, 3 H), 2.17 (s, 3 H), 3.14 (d, *J* = 15.1 Hz, 1 H), 3.65 (m, 1 H), 4.24 (m, 2 H), 4.82 (m, 1 H), 5.01 (d, *J* = 15.1 Hz, 1 H), 6.88 (m, 2 H), 7.15 (m, 2 H)

Note: There is a group of overlapping multiples from 2.35 – 2.87 ppm. Another group of overlapping peaks from 7.17 – 7.39 ppm.

¹³C NMR for mixture (151 MHz, CDCl₃) δ ppm 13.9, 14.1, 19.2, 19.3, 30.6, 31.1, 34.6, 35.9, 36.9, 39.7, 43.2, 43.8, 44.4, 45.2, 56.7, 58.9, 62.4, 62.5, 71.6, 74.4, 127.1, 127.6, 127.6, 128.6, 128.8, 129.0, 135.7, 136.1, 136.4, 136.5, 146.6, 166.8, 167.1, 171.8, 171.9

C – Procedure for preparation of nitrone **11** in acetic acid

Z-oxime **4a** (323 mg, 0.9 mmol) was dissolved in glacial acetic acid (3 mL) and the solution was heated at 100 °C for 4 h. The reaction mixture was then cooled to r.t., neutralized with a saturated aqueous NaHCO₃ solution and the resulting aqueous layer was extracted with CH₂Cl₂ (3 times). The combined organic layers were washed with saturated aqueous NaCl solution, dried over Na₂SO₄ and concentrated *in vacuo* to afford cycloadduct **11** (315 mg, 98%) as a light brown foam and as the only diastereomer as observed in the crude product ¹H NMR spectrum. This crude was then used directly for dipolar cycloaddition without further purification. A pure sample of nitrone **11** (248 mg, 77%) could be obtained as a beige foam after purification of the crude product by flash chromatography on silica gel using a gradient elution starting with CH₂Cl₂/MeOH (99:1) to CH₂Cl₂/MeOH (98:2).

Molecular formula C₂₁H₂₈N₂O₄

Beige foam

R_f = 0.18 (silica, CH₂Cl₂/MeOH 95:5)

IR (thin film, cm⁻¹) $\nu_{\max}$ 2970, 2937, 1740, 1696, 1421, 1205, 1020

$[\alpha]_D^{20}$ -151 (c 1.0, CHCl₃)

¹H NMR (600 MHz, CDCl₃) δ ppm 0.84 (d, J = 6.9 Hz, 3 H), 1.00 (d, J = 7.1 Hz, 3 H), 1.11 (t, J = 7.1 Hz, 3 H), 2.20 (m, 1 H), 2.23 (s, 3 H), 2.33 (m, 1 H), 2.59 (m, J = 19.1, 11.3 Hz, 1 H), 2.90 (m, 1 H), 3.00 (dd, J = 19.1, 5.3 Hz, 1 H), 3.23 (dd, J = 9.7, 3.4 Hz, 1 H), 3.76 (d, J = 15.2 Hz, 1 H), 4.19 (m, 2 H), 4.88 (d, J = 5.7 Hz, 1 H), 5.17 (d, J = 15.2 Hz, 1 H), 7.12 (d, J = 7.1 Hz, 2 H), 7.27 (m, 1 H), 7.31 (m, 2 H)

¹³C NMR (151 MHz, CDCl₃) δ ppm 14.0, 15.1, 19.2, 26.7, 30.7, 35.9, 37.5, 44.0, 60.7, 62.4, 73.3, 127.7, 128.8, 135.7, 146.7, 166.7, 172.4

HRMS (FAB+) m/z calcd for C₂₁H₂₉N₂O₄ (M+H)⁺ 373.2127, found 373.2126

D – Procedure for [3+2] cycloaddition reactions

1 – [3+2] cycloaddition between nitron 5 and DMAD

A mixture of nitron **5** (168 mg, 0.45 mmol) and dimethyl acetylenedicarboxylate (83 mg, 72 μ L, 0.59 mmol) in anhydrous toluene (2 mL) was stirred at r.t. for 30 min. The resulting mixture was then concentrated *in vacuo*. Flash chromatography on silica gel of the crude product eluting with CH₂Cl₂/MeOH (99:1) afforded the cycloadduct **6** (121 mg, 52%) as a pale yellow oil.

Molecular formula C₂₇H₃₄N₂O₈

Pale yellow oil

R_f = 0.47 (silica, CH₂Cl₂/MeOH 95:5)

IR (thin film, cm⁻¹) $\nu_{\max}$ 2973, 2959, 2929, 1748, 1701, 1646, 1435, 1333, 1285, 1203, 1190, 1163, 1129, 1082, 1028

$[\alpha]_D^{20}$ -128 (c 1.0, CHCl₃)

¹H NMR (600 MHz, CDCl₃) δ ppm 0.85 (d, J = 7.1 Hz, 3 H), 0.95 (d, J = 7.4 Hz, 3 H), 1.26 (t, J = 7.1 Hz, 3 H), 1.54 (s, 3 H), 1.75 (m, 2 H), 1.87 (m, 1 H), 2.08 (m, 1 H), 3.11 (dd, J = 14.5, 3.4 Hz, 1 H), 3.43 (d, J = 9.4 Hz, 1 H), 3.50 (d, J = 10.9 Hz, 1 H), 3.83 (s, 3 H), 3.87 (d, J = 15.5 Hz, 1 H), 3.87 (s, 3 H), 4.09 (m, 1 H), 4.30 (m, 1 H), 5.25 (d, J = 15.5 Hz, 1 H), 7.10 (d, J = 7.4 Hz, 2 H), 7.27 (m, 1 H), 7.33 (m, 2 H)

HRMS (FAB+) m/z calcd for C₂₇H₃₅N₂O₈ (M+H)⁺ 515.2393, found 515.2380

2 – [3+2] cycloaddition between nitrone **11** and DMAD

A mixture of nitrone **11** (350 mg, 0.94 mmol) and dimethyl acetylenedicarboxylate (170 mg, 150 μ L, 1.2 mmol) in anhydrous toluene (3 mL) was stirred at 65 °C for 2 h. The solvent was removed at reduced pressure to give the crude product containing two diastereomers as observed by ¹H NMR in a 1:0.28 ratio. The ratio was determined by integration of the methyl group of the ester in each diastereomer. Flash chromatography on silica gel of the crude material using hexanes/EtOAc (75:25) furnished the two diastereomers **12** and **13** (367 mg, 76%). A small amount of pure major cycloadduct **12** (69 mg) was recovered followed by an inseparable mixture (298 mg) of the two components as the most polar fraction, both as clear oils. Attempts to obtain the minor

cycloadduct pure **13** by chromatography failed, and only enriched fractions were obtained.

Major cycloadduct 12:

Molecular formula $C_{27}H_{34}N_2O_8$

$R_f = 0.14$ (silica, hexanes/EtOAc 7:3)

IR (thin film, cm^{-1}) ν_{max} 2964, 2932, 1743, 1697, 1650, 1438, 1417, 1344, 1317, 1208, 1161, 1138, 1088, 1018

$[\alpha]_D^{20} +35$ (c 1.0, $CHCl_3$)

1H NMR (600 MHz, $CDCl_3$) δ ppm 0.83 (d, $J = 6.7$ Hz, 3 H), 0.90 (d, $J = 7.1$ Hz, 3 H), 1.18 (t, $J = 7.1$ Hz, 3 H), 1.61 (s, 3 H), 1.76 (unresolved dd, $J = 13.3$ Hz, 1 H), 2.17 (m, 2 H), 2.66 (dd, $J = 13.3, 3.0$ Hz, 1 H), 2.90 (m, 1 H), 3.57 (m, 1 H), 3.77 (s, 3 H), 3.84 (d, $J = 15.4$ Hz, 1 H), 3.87 (s, 3 H), 4.13 (m, 2 H), 4.59 (d, $J = 4.9$ Hz, 1 H), 5.15 (d, $J = 15.4$ Hz, 1 H), 7.18 (d, $J = 7.2$ Hz, 2 H), 7.25 (m, 1 H), 7.32 (m, 2 H)

^{13}C NMR (151 MHz, $CDCl_3$) δ ppm 14.0, 15.1, 19.3, 22.5, 26.7, 35.1, 35.9, 36.9, 43.9, 51.9, 53.1, 61.5, 61.7, 63.5, 70.1, 118.9, 127.5, 127.7, 128.7, 136.4, 148.7, 158.9, 162.6, 167.8, 174.6

HRMS (FAB+) m/z calcd for $C_{27}H_{35}N_2O_8$ (M+H) $^+$ 515.2393, found 515.2391

Minor cycloadduct 13 (NMR data deduced from the mixture of **12** and **13**):

Molecular formula $C_{27}H_{34}N_2O_8$

$R_f = 0.14$ (silica, hexanes/EtOAc 7:3)

1H NMR (The only discernible signals are reported) (600 MHz, $CDCl_3$) δ ppm 1.10 (t, 3 H), 1.51 (s, 3 H), 1.66 (unresolved dd, $J = 13.3$ Hz, 1 H), 1.99 (m, 1 H), 2.11 (m, 1 H), 3.05 (m, 1 H), 3.28 (m, 2 H), 3.73 (d, $J = 15.4$ Hz, 1 H), 4.07 (m, 2 H), 4.76 (d, $J = 4.8$ Hz, 1 H), 5.19 (m, 1 H), 7.10 (d, $J = 7.4$ Hz, 2 H), 7.24 (m, 3 H)

^{13}C NMR (The only discernible signals are reported) (151 MHz, $CDCl_3$) δ ppm 13.9, 15.0, 19.1, 35.9, 37.2, 52.2, 52.9, 60.4, 60.7, 61.4, 67.9, 69.9, 115.2, 127.5, 127.6, 135.9, 152.3, 158.9, 162.4, 168.9, 174.1

3 – [3+2] cycloaddition between the mixture of nitrones 7/8 and DMAD

A mixture of nitrones **7** and **8** (162 mg, 0.39 mmol) and dimethyl acetylenedicarboxylate (71 mg, 62 μ L, 0.5 mmol) in anhydrous toluene (2 mL) was stirred at 65 °C for 2 h. The solvent was removed at reduced pressure to give the crude product containing two diastereomers as observed by ^1H NMR in a 1:0.4 ratio. The ratio was determined by integration of the two methyl groups in each cycloadduct. Flash chromatography on silica gel of the crude material using hexanes/EtOAc (77:23) furnished the two cycloadducts **9** and **10** (152 mg, 70%). The following fractions by order of increasing polarity were obtained: the minor diastereomer **10** (23 mg, 15%) as clear oil, a mixture of minor and major diastereomers (30 mg, 20%) and the major diastereomer **9** (99 mg, 65%) as clear oil.

Major cycloadduct 9:

Molecular formula $\text{C}_{31}\text{H}_{34}\text{N}_2\text{O}_8$

clear oil

R_f = 0.07 (silica, hexanes/EtOAc 7:3)

IR (thin film, cm^{-1}) ν_{max} 2931, 2853, 1751, 1704, 1647, 1454, 1437, 1411, 1332, 1290, 1189, 1158, 1127, 1084, 1029

$[\alpha]_{\text{D}}^{20}$ –81 (c 1.0, CHCl_3)

¹H NMR (600 MHz, CDCl₃) δ ppm 1.24 (t, *J* = 7.2 Hz, 3 H), 1.52 (s, 3 H), 1.69 (m, 1 H), 1.86 (m, 1 H), 2.08 (m, 1 H), 2.54 (dd, *J* = 15.7, 7.1 Hz, 1 H), 3.00 (d, *J* = 15.7 Hz, 1 H), 3.08 (dd, *J* = 14.3, 3.0 Hz, 1 H), 3.58 (d, *J* = 11.1 Hz, 1 H), 3.82 (s, 3 H), 3.84 (m, 1 H), 3.86 (s, 3 H), 3.90 (m, 1 H), 4.09 (m, 1 H), 4.32 (m, 1 H), 5.02 (d, *J* = 15.2 Hz, 1 H), 6.70 (d, *J* = 7.2 Hz, 2 H), 7.04 (d, *J* = 6.4 Hz, 2 H), 7.17 (m, 3 H), 7.25 (m, 3 H)

¹³C NMR (151 MHz, CDCl₃) δ ppm 14.0, 28.4, 31.4, 37.2, 42.6, 43.2, 44.2, 52.4, 53.2, 57.6, 61.9, 69.2, 71.9, 114.9, 126.9, 127.3, 127.5, 128.5, 128.8, 129.1, 135.9, 136.5, 152.2, 159.2, 162.4, 169.6, 172.6

HRMS (FAB+) *m/z* calcd for C₃₁H₃₅N₂O₈ (M+H)⁺ 563.2393, found 563.2392

Minor cycloadduct 10:

Molecular formula C₃₁H₃₄N₂O₈

clear oil

R_f = 0.10 (silica, hexanes/EtOAc 7:3)

IR (thin film, cm⁻¹) ν_{max} 2925, 2852, 1749, 1703, 1648, 1454, 1438, 1420, 1333, 1289, 1192, 1161, 1133, 1082, 1030

[α]_D²⁰ +40 (*c* 0.5, CHCl₃)

¹H NMR (600 MHz, CDCl₃) δ ppm 1.24 (t, *J* = 7.2 Hz, 3 H), 1.50 (s, 3 H), 1.67 (unresolved dd, 1 H), 2.08 (m, 1 H), 2.19 (m, 1 H), 2.74 (m, 1 H), 2.93 (d, *J* = 15.0 Hz, 1 H), 3.05 (m, 2 H), 3.57 (m, 1 H), 3.66 (d, *J* = 11.7, 1 H), 3.81 (s, 3 H), 3.88 (s, 3 H), 4.23 (m, 2 H), 4.94 (d, *J* = 15.0 Hz, 1 H), 6.79 (m, 2 H), 7.12 (d, *J* = 6.9 Hz, 2 H), 7.21 (m, 2 H), 7.32 (m, 4 H)

¹³C NMR (151 MHz, CDCl₃) δ ppm 14.2, 28.5, 31.5, 34.9, 38.3, 43.8, 45.3, 52.4, 53.2, 57.4, 61.8, 66.5, 72.1, 127.1, 127.9, 128.6, 128.9, 129.3, 136.1, 137.5, 152.2, 159.2, 162.4, 169.4, 172.6 (note: one of the aromatic carbons is overlapped with residual benzene-*d*₆)

HRMS (FAB+) *m/z* calcd for C₃₁H₃₅N₂O₈ (M+H)⁺ 563.2393, found 563.2413

barrier to rotation for protonated ester (carbonyl oxygen) = 18.1 kcal/mol

cis less stable than trans by 6.1 kcal/mol

observed cycloadduct is more stable than the expected one by 0.4 kcal/mol

Calculations are at the B3LYP/6-31G(d)//B3LYP/6-31G(d)
using the program, Jaguar, Schrodinger, Inc. Portland, OR.