A Diastereoselective Intermolecular Heck Reaction of 1,3-Diosepins

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Supporting Information

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**General Methods:** All reactions were performed under an inert atmosphere of argon in flame-dried glassware with magnetic stirring. Acetonitrile (ACS grade) was purchased from Fisher Scientific and distilled from CaH$_2$ before use. Column chromatography was performed on EM Science silica gel 60 (230-400 mesh). Thin layer chromatography was performed on EM Science 0.25 mm silica gel 60-F plates. Visualization was accomplished with UV light, KMnO$_4$, or aqueous ceric ammonium molybdate followed by heating.

Pd(OAc)$_2$ was purchased from Fluka. All other chemicals were purchased from Aldrich Chemical Co. and used without further purification.

$^1$H NMR spectra are reported as follows: chemical shift in parts per million (δ, ppm) from an internal standard [deuterated chloroform (CDCl$_3$)], multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), integration, and coupling constant (Hz). $^{13}$C NMR chemical shifts are reported in ppm from (CDCl$_3$) taken as 77.23 ppm. Mass spectra were obtained on Fisons VG Autospec. Gas chromatography was performed on a Varian Cp 3800 gas chromatograph equipped with a flame ionization detector using a Chromopack Cp-Sil 8 CB (15 M X 0.25 mm) capillary column. Microwave reactions were conducted in a CEM Discovery microwave reactor.

**General Procedure A for the preparation of symmetric 1,3-dioxepins.** Note: This procedure is used for low molecular weight and thermally unstable aldehydes. A round-bottom flask was charged with aldehyde (15 mmol, 1 eq.), cis-1,4-butenediol (1.8 eq.) and $p$-TsOH (0.1 eq.). The mixture was diluted with Et$_2$O (25 mL/ g of diol) and mixed...
at 25 °C for 15 min. or until the solution became cloudy. MgSO₄ was then added (1g/ g of aldehyde) and the mixture was monitored by TLC. Upon disappearance of the aldehyde more MgSO₄ was added (1g/ g of aldehyde). The solution was filtered through a pad of celite, the cake was washed with anhydrous Et₂O and the solvent was removed in vacuo. The residue was purified by silica gel column chromatography using 9:1 or 6:1 (Hex:EtOAc) as eluent.

General Procedure B for the preparation of symmetric 1,3-dioxepins. A round-bottom flask was charged with aldehyde (15 mmol, 1 eq.), cis-1,4-butenediol (1.8 eq.) and p-TsOH (0.1 eq.). The mixture was diluted with benzene (25 mL/ g of diol) and mixed at 25 °C for 15 min. or until the solution became cloudy. The solution was then heated under Dean-Stark conditions (bath temperature typically 90 °C). Upon disappearance of the aldehyde by TLC, the crude reaction mixture was cooled to ambient temperature and the solvent was removed in vacuo. The residue was purified by silica gel column chromatography using 9:1 or 6:1 (Hex:EtOAc) as eluent.

General Procedure A for the Heck Reaction of 1,3-Dioxepins. A round-bottom flask was charged with Pd(OAc)₂ (0.05 eq.), PPh₃ (0.10 eq.), K₂CO₃ (1.78 eq.), and n-Bu₄NCl (1 eq.). The flask was purged with argon and a 9:1 mixture of acetonitrile and deionized water were added (0.5M with respect to 1,3-dioxepin). After mixing for 0.25h at 50 °C 1,3-dioxepin (5 mmol, 1 eq.) and sp²-iodide (1.05 eq.) were added. The
reaction was allowed to stir for 12-36h. Standard work-up proceeded with the addition of MgSO$_4$ (1g/0.5 mL H$_2$O) and dilution with Et$_2$O (6 mL/1 mL of reaction mixture) and mixed for 15 min. This solution was flushed through a small pad of celite (1 cm) on top of a small pad of silica gel (1 cm) and eluted with Et$_2$O. To this solution was added MgSO$_4$ and activated charcoal, the mixture was allowed to stir at ambient temperature for 1h and then filtered through a pad of celite. The solvents were removed in vacuo and the residue was purified by column chromatography using 9:1 or 6:1 (Hex:EtOAc) as eluent.

General Procedure B for the Heck Reaction of 1,3-Dioxepins. A round-bottom flask was charged with Pd(OAc)$_2$ (0.08 eq.) and BnNEt$_3$ (2 eq.). The flask was purged with argon and DMF was added (0.4M with respect to 1,3-dioxepin). i-Pr$_2$NEt was added and the mixture was heated at 80 °C for 10 min. 1,3-dioxepin (8 mmol, 1 eq.) and sp$^2$-iodide (1 eq.) were added and the reaction was allowed to stir for 12h. The reaction was then cooled to ambient temperature and diluted with Et$_2$O. The organic layer was washed 4 x H$_2$O and 1 x brine. The organic layer was dried over MgSO$_4$ and filtered. The solvent was removed in vacuo and the residue was purified by column chromatography using 9:1 or 6:1 (Hex:EtOAc) as eluent.

General procedure for the synthesis of 4-substituted dioxepins. To a round-bottom flask was added 37.82 mmol of propargyl alcohol and 40 mL of THF. The reaction was
cooled to -78 °C and 49.6 mL (79.42 mmol) of a 1.6 M n-BuLi solution in hexanes was added dropwise. After the addition, the reaction was left to stir for 1h and then 5.0 mL (37.82 mmol) of aldehyde was added in one portion. The reaction was allowed to warm to 0 °C over 3h and then was quenched by addition of 30 mL of sat. aq. NH₄Cl. The layers were separated and the aqueous layer was extracted with Et₂O (3 x 35 mL). The organic layers were combined and washed with 50 mL of H₂O then brine. The organic layer was dried over MgSO₄, filtered and concentrated to afford the desired bis-propargylic alcohol.

A round bottom flask was charged with 23.65 mmol of bis-propargylic alcohol, 0.45 g of Pd/CaCO₃ poisoned with Pb (Lindlar’s catalyst), 9.5 mL of pyridine, 18.4 mL of 1-octene, and 50 mL of THF. Argon was bubbled through the solution for 30 min., and then the reaction was purged with H₂ (from a balloon) for 5 minutes. The reaction was allowed to stir at ambient temperature under an atmosphere of H₂ (from a balloon) and was monitored by TLC. Upon consumption of the starting material the crude reaction was filtered through a pad of celite and washed with EtOAc. The filtrate was concentrated in vacuo (removing the majority of the remaining pyridine) and subsequently diluted with 100 mL of EtOAc. The solution was then washed 3 x with sat. aq. CuSO₄. The organic layer was dried over MgSO₄, filtered and concentrated to afford the desired cis-butene diol. Analytically pure material may be isolated after silica gel column chromatography with 3:7 (Hex:EtOAc) as eluent.

A round-bottom flask equipped with a Dean-Stark trap and reflux condenser was charged with 24.45 mmol of bis-allylic alcohol, 25.67 mmol of paraformaldehyde, 0.1 eq. of p-TsOH and 50 mL of benzene. The reaction was monitored by TLC and upon
disappearance of the starting material the reaction was concentrated and purified via Kugelrohr distillation (90 °C at 5 mm of Hg) afforded the desired 4-substituted dioxepin.

General procedure of acid-mediated acetal cleavage: A round bottom flask was charged with 0.10 mmol of dioxepin, 0.1 mL of AcOH, 0.11 mL of Ac₂O, 0.1 eq. of H₂SO₄ and 0.2 mL of MeOH at 0 °C. The reaction was stirred for 1h and then was diluted with 2 mL Et₂O and 2 mL of H₂O. The layers were separated and the aqueous layer was extracted with Et₂O (2 x 10 mL). The organic layers were combined, dried over MgSO₄, filtered and concentrated. The crude product was purified on silica gel (25 % EtOAc/Hexanes) to afford the desired tetrahydrofuran as a 1:1 mixture of anomeric isomers.

Synthesis of 2-(4-Nitro-phenyl)-4,4,7,7-tetradeuterio-4,7-dihydro-[1,3]dioxepine (23). Exo-3,6-epoxy-1,2,3,6-tetrahydrophthalic anhydride was reduced to 23-a in the presence of LiAlD₄ according to a literature procedure. The crude diol 23-a (12 mmol) was then condensed with p-nitrobenzaldehyde in the presence of 0.1 eq. p-TsOH under Dean-Stark conditions to provide 23-b. 23-b (8 mmol) was thermally decomposed by exposure to microwaves (250 W) in 10 mL of toluene at 170 °C for 3h to provide 23 in 73%.

Mass spectrometry was attempted under TOF+, FAB+ and ES- ionization for 1,3-dioxepins 5, 6, 7, 8, 9, 12, 13, 22, 24, and 26; however, mass spectra were not obtained due to decomposition.

\( \text{2-Phenethyl-6-phenyl-4,5-dihydro-[1,3]dioxepine (2).} \) \(^1\)H NMR (400 MHz CDCl\(_3\)) \( \delta \) 7.37-7.18 (10H, m), 6.43 (1H, dd, \( J = 7.5, 3.0 \) Hz), 4.89 (1H, d, \( J = 7.5 \) Hz), 4.59 (1H, dd, \( J = 5.3, 5.3 \) Hz), 4.09 (1H, dd, \( J = 11.5, 5.1 \) Hz), 3.89 (1H, dddd, \( J = 10.7, 7.7, 5.1, 2.6 \) Hz), 3.20 (1H, dd, \( J = 11.4, 11.4 \) Hz), 2.81 (2H, t, \( J = 2.8 \) Hz), 2.18-2.06 (2H, m); \(^{13}\)C NMR (100 MHz CDCl\(_3\)) \( \delta \) 145.3, 141.7, 140.9, 128.9, 128.7, 128.7, 128.1, 127.2, 126.1, 112.5, 106.9, 76.2, 48.4, 37.3, 30.8; IR (NaCl dep from CH\(_2\)Cl\(_2\)) 3027, 2867, 1647, 1453, 1145, 700 cm\(^{-1}\); HRMS (FAB+) calcd for C\(_{19}\)H\(_{20}\)O\(_2\), 280.1463. Found 280.1471.

\( \text{Diphenyl-4,5-dihydro-[1,3]dioxepine (4).} \) \(^2\) \(^1\)H NMR (400 MHz CDCl\(_3\)) \( \delta \) 7.54-7.21 (10H, m), 6.53 (1H, dd, \( J = 7.5, 3.0 \) Hz), 5.57 (1H, s), 5.00 (1H, d, \( J = 7.3 \) Hz), 4.19 (1H, dd, \( J = 11.5, 5.1 \) Hz), 3.97 (1H, ddd, \( J = 7.9, 5.3, 2.8 \) Hz), 3.42 (1H, dd, \( J = 11.5, 11.5 \) Hz); \(^{13}\)C NMR (100 MHz CDCl\(_3\)) \( \delta \) 145.4, 140.7, 138.9, 129.1, 129.0, 128.6, 128.2, 127.3, 126.2, 113.3, 106.7, 76.3, 48.5; IR (NaCl dep from CH\(_2\)Cl\(_2\)) 3031, 2868, 1647, 1453, 1029, 699 cm\(^{-1}\); HRMS (FAB+) calcd for C\(_{17}\)H\(_{16}\)O\(_2\), 253.1229. Found 253.1222.

\( \text{5-Phenyl-2-(1-phenyl-cyclopropyl)-4,5-dihydro-[1,3]dioxepine (5).} \) \(^1\)H NMR (400 MHz CDCl\(_3\)) \( \delta \) 7.46-7.12 (10H, m), 6.34 (1H, dd, \( J = 7.7, 3.0 \) Hz), 4.79 (1H, d, \( J = 7.7, 3.0 \) Hz), 4.75 (1H, d, \( J = 10.7, 7.7 \) Hz), 3.92 (1H, ddd, \( J = 7.9, 5.3, 2.8 \) Hz), 3.43 (1H, dd, \( J = 11.5, 11.5 \) Hz); \(^{13}\)C NMR (100 MHz CDCl\(_3\)) \( \delta \) 145.4, 140.7, 138.9, 129.1, 129.0, 128.6, 128.2, 127.3, 126.2, 113.3, 106.7, 76.3, 48.5; IR (NaCl dep from CH\(_2\)Cl\(_2\)) 3031, 2868, 1647, 1453, 1029, 699 cm\(^{-1}\); HRMS (FAB+) calcd for C\(_{17}\)H\(_{16}\)O\(_2\), 253.1229. Found 253.1222.

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\(^2\) The starting material for 14, 4,7-dihydro-2-phenyl-1,3-dioxepin, may be purchased from Aldrich CAS# 2568-24-3.
d, $J = 7.5$ Hz), 4.61 (1H, s), 4.02 (1H, ddd, $J = 11.7$, 5.5, 1.3 Hz), 3.85-3.76 (1H, m), 3.13 (1H, dd, $J = 11.5$, 11.5 Hz), 1.17-1.07 (2H, m), 0.88-0.79 (2H, m); $^{13}$C NMR (100 MHz CDCl$_3$) δ 145.2, 141.9, 140.8, 130.7, 128.8, 128.5, 128.2, 128.1, 127.2, 126.9, 111.9, 109.8, 76.3, 48.3, 29.9, 10.2, 9.8; IR (NaCl dep from CH$_2$Cl$_2$) 3027, 2867, 1646, 1494, 1142, 700 cm$^{-1}$.

![5-Phenyl-2-[1-(4-trifluoromethyl-phenyl)-cyclobutyl]-4,5-dihydro-[1,3]dioxepine (6). $^1$H NMR (400 MHz CDCl$_3$) δ 7.59-7.13 (9H, m), 6.39 (1H, dd, $J = 7.5$, 3.0 Hz), 4.82 (1H, s), 4.79 (1H, s), 4.08 (1H, dd, $J = 11.7$, 5.5 Hz), 3.82-3.75 (1H, m), 3.19 (1H, dd, $J = 11.3$, 11.3 Hz), 2.71-2.49 (2H, m), 2.47-2.35 (2H, m), 2.20-2.06 (1H, m), 1.93-1.82 (1H, m); $^{13}$C NMR (100 MHz CDCl$_3$) δ 149.8, 145.5, 140.8, 128.9, 128.7, 128.3, 128.1, 127.2, 124.6, 111.8, 110.8, 76.7, 50.4, 48.2, 30.5, 30.2, 16.2; IR (NaCl dep from CH$_2$Cl$_2$) 2947, 2866, 1647, 1327, 1163, 700 cm$^{-1}$.]

![1-(5-Phenyl-4,5-dihydro-[1,3]dioxepin-2-yl)-cyclobutanol (7). $^1$H NMR (400 MHz CDCl$_3$) δ 7.38-7.20 (5H, m), 6.45 (1H, dd, $J = 7.5$, 3.0 Hz), 4.90 (1H, ddd, $J = 7.3$, 1.1, 0.8 Hz), 4.54 (1H, s), 4.13 (1H, ddd, $J = 11.7$, 5.3, 1.1 Hz), 3.93-3.86 (1H, m), 3.27 (1H, dd, $J = 11.5$, 11.5 Hz), 2.51 (1H, s), 2.37-2.25 (2H, m), 2.11-2.01 (2H, m), 1.89-1.78 (1H, m), 1.72-1.58 (1H, m); $^{13}$C NMR (100 MHz CDCl$_3$) δ 145.1, 140.5, 129.0, 128.1, 127.4, 112.6, 108.8, 76.3, 75.8, 48.3, 31.2, 31.1, 12.5; IR (NaCl dep from CH$_2$Cl$_2$) 3419, 2948, 1646, 1453, 1139, 701 cm$^{-1}$.]
Supplementary Information

5-(4-Methoxy-phenyl)-2-(4-nitro-phenyl)-4,5-dihydro-[1,3]dioxepine (8). 8 Was recrystallized from EtOAc and Hexanes using vapor diffusion to yield white needles. $^1$H NMR (400 MHz CDCl$_3$) $\delta$ 8.23 (2H, d, $J$ = 9.0 Hz), 7.72 (2H, d, $J$ = 9.0 Hz), 7.18 (2H, d, $J$ = 8.7 Hz), 6.88 (2H, d, $J$ = 8.7 Hz), 6.53 (1H, dd, $J$ = 7.3, 2.6 Hz), 5.63 (1H, s), 5.04 (1H, d, $J$ = 7.2 Hz), 4.20 (1H, dd, $J$ = 11.7, 5.1 Hz), 3.97-3.89 (1H, m), 3.80 (3H, s), 3.42 (1H, dd, $J$ = 11.7, 11.7 Hz); $^{13}$C NMR (100 MHz CDCl$_3$) $\delta$ 159.0, 148.4, 145.3, 144.9, 132.3, 129.1, 127.5, 123.7, 114.4, 104.8, 76.5, 55.5, 47.5; IR (NaCl dep from CH$_2$Cl$_2$) 2958, 2866, 1645, 1516, 1028, 700 cm$^{-1}$.

2-(1-Phenyl-cyclobutyl)-5-styryl-4,5-dihydro-[1,3]dioxepine (9). $^1$H NMR (400 MHz CDCl$_3$) $\delta$ 7.39-7.20 (10H, m), 6.50 (1H, d, $J$ = 15.8 Hz), 6.37 (1H, d, ddd, $J$ = 7.3, 2.6, 2.6 Hz), 6.06 (1H, d, ddd, $J$ = 7.3, 2.6, 2.6 Hz), 6.06 (1H, d, ddd, $J$ = 15.8, 7.9, 1.7 Hz), 4.73 (1H, s), 4.71 (1H, s), 4.12 (1H, dd, $J$ = 11.5, 5.3 Hz), 3.46-3.36 (1H, m), 3.18 (1H, dd, $J$ = 11.5, 11.5 Hz), 2.68-2.54 (2H, m), 2.50-2.38 (2H, m), 2.19-2.06 (1H, m), 1.95-1.83 (1H, m); $^{13}$C NMR (100 MHz CDCl$_3$) $\delta$ 145.9, 145.3, 137.1, 131.8, 128.8, 128.3, 127.7, 127.6, 126.4, 126.3, 126.0, 111.1, 110.4, 74.3, 50.2, 44.8, 30.2, 30.0, 16.2; IR (NaCl dep from CH$_2$Cl$_2$) 2984, 2945, 1643, 1292, 699 cm$^{-1}$.

2-(3,4-Dimethoxy-phenyl)-5-[1-(3,4,5-trimethoxy-phenyl)-vinyl]-4,5-dihydro-[1,3]dioxepine (10). $^1$H NMR (400 MHz CDCl$_3$) $\delta$ 7.08-7.02 (2H, m), 6.84 (1H, d, $J$ = 8.3 Hz), 6.62 (2H, s), 6.53 (1H, dd, $J$ = 7.5, 3.0 Hz), 5.49 (1H, s), 5.38 (1H, s), 5.19 (1H, s), 5.01 (1H, d, $J$ = 7.3 Hz), 4.23 (1H, d, $J$ = 11.5, 4.5), 3.94-3.82
(16H, m), 3.38 (1H, dd, $J = 11.1, 11.1$ Hz); $^{13}$C NMR (100 MHz CDCl$_3$) $\delta$ 153.3, 149.6, 149.1, 148.4, 145.3, 138.2, 136.9, 131.6, 118.7, 114.2, 113.3, 110.9, 109.0, 106.4, 103.9, 74.4, 61.1, 56.4, 56.2, 56.1, 46.9; IR (NaCl dep from CH$_2$Cl$_2$) 2937, 2836, 1645, 1411, 1128, 732 cm$^{-1}$; HRMS (+TOF MS) calcd for C$_{24}$H$_{28}$O$_7$, 428.4700. Found 429.1893.

2-(1-Phenyl-cyclobutyl)-5-(2-phenyl-propenyl)-4,5-dihydro-[1,3]dioxepine (11). $^1$H NMR (400 MHz CDCl$_3$) $\delta$ 7.36-7.15 (10H, m), 6.30 (1H, dd, $J = 7.2, 3.0$ Hz), 5.48 (1H, dd, $J = 9.6, 1.1$ Hz), 4.62 (1H, s), 4.58 (1H, dd, $J = 7.5, 1.1$ Hz), 3.98 (1H, dd, $J = 11.7, 6.4$ Hz), 3.65-3.55 (1H, m), 3.06 (1H, dd, $J = 11.3, 11.3$), 2.63-2.49 (2H, m), 2.44-2.32 (2H, m), 2.14-2.00 (4H, m), 1.89-1.77 (1H, m); $^{13}$C NMR (100 MHz CDCl$_3$) $\delta$ 146.0, 145.1, 143.4, 137.5, 128.4, 127.8, 127.7, 127.3, 126.2, 136.0, 125.9, 111.8, 111.3, 73.5, 50.2, 41.4, 30.2, 30.0, 16.3, 16.2; IR (NaCl dep from CH$_2$Cl$_2$) 2945, 2861, 1645, 1494, 1139, 699 cm$^{-1}$; HRMS (FAB+) calcd for C$_{19}$H$_{20}$O$_2$S, 313.1262. Found 313.1270.

5-Phenyl-2-styryl-4,5-dihydro-[1,3]dioxepine (12). $^1$H NMR (400 MHz CDCl$_3$) $\delta$ 7.44-7.16 (10H, m), 6.83 (1H, d, $J = 16.2$ Hz), 6.49 (1H, dd, $J = 6.8, 3.2$ Hz), 6.30 (1H, dd, $J = 16.0, 3.4$ Hz), 5.22 (1H, s), 4.97 (1H, d, $J = 7.2$ Hz), 4.18-4.11 (1H, m), 3.94-3.91 (1H, m), 3.35 (1H, dd, $J = 11.5, 11.5$ Hz); $^{13}$C NMR (100 MHz CDCl$_3$) $\delta$ 145.2, 140.7, 133.2, 129.2, 129.0, 128.8, 128.4, 128.1, 127.3, 127.1, 125.9, 113.2, 105.9, 76.1, 48.5; IR (NaCl dep from CH$_2$Cl$_2$) 3028, 2867, 1645, 1492, 1146, 700 cm$^{-1}$.

3-(5-Phenyl-4,5-dihydro-[1,3]dioxepin-2-yl)-acrylic acid ethyl ester (13). $^1$H NMR (400 MHz CDCl$_3$) $\delta$ 7.36-7.19 (5H, m), 6.87 (1H, dd, $J = 16.0, 3.8$ Hz),
6.44 (1H, dd, J = 7.2, 2.8 Hz), 6.22 (1H, d, J = 15.8 Hz), 5.16 (1H, d, J = 3.6 Hz), 4.97 (1H, dd, J = 7.5, 1.1 Hz), 4.21 (2H, q, J = 7.1 Hz), 4.11 (1H, dd, J = 11.5, 5.1 Hz), 3.93-3.85 (1H, m), 3.29 (1H, dd, J = 11.7, 11.7 Hz), 1.28 (3H, t, J = 7.03); ^13C NMR (100 MHz CDCl3) δ 166.1, 145.0, 142.0, 140.4, 129.0, 128.1, 127.4, 124.3, 113.6, 103.5, 76.0, 60.9, 48.4, 14.4; IR (NaCl dep from CH2Cl2) 2981, 2870, 1724, 1647, 1146, 702 cm^{-1}.

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\text{4-Pentyl-4,7-dihydro-[1,3]-dioxepine (14a).} \] ^1H NMR (400 MHz, CDCl3) δ 5.60-5.68 (1H, m), 5.54-5.59 (1H, m), 4.91 (1H, d, J = 5.2 Hz), 4.86 (1H, d, J = 4.8 Hz), 4.17-4.32 (3H, m), 1.20-1.68 (8H, m), 0.86 (3H, t, J = 6.8 Hz); ^13C NMR (100 MHz, CDCl3) δ 134.7, 129.9, 95.7, 76.8, 66.9, 35.6, 31.9, 25.4, 22.8, 14.3; IR (NaCl dep from CH2Cl2) 2927, 2855, 1123, 1085 cm^{-1}; HRMS (ESI) m/e calcd for C10H18O2 170.1307. Found 170.1306.

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\text{4-Pentyl-5-phenyl-4,5-dihydro-[1,3]-dioxepine (14).} \] ^1H NMR (400 MHz, CDCl3) δ 7.13-7.32 (5H, m), 5.42 (1H, dd, J = 6.8, 1.6 Hz), 4.70 (1H, dd, J = 6.8, 1.2 Hz), 4.58 (1H, ddd, J = 7.6, 1.6, 1.6 Hz), 3.49 (1H, m), 3.27 (1H, m), 1.02-1.50 (8H, m), 0.79 (3H, t, J = 7.2 Hz); ^13C NMR (100 MHz, CDCl3) δ 144.2, 128.8, 128.6, 127.0, 111.9, 97.4, 86.9, 54.1, 33.7, 31.8, 25.6, 22.7, 14.2; IR (NaCl dep from CH2Cl2) 3062, 3028, 2926, 2870, 2800, 1647, 1492 cm^{-1}; HRMS (ESI) m/e calcd for C16H22O2 246.1620. Found 246.1616.
5-(4-Methoxy-phenyl)-4-pentyl-4,5-dihydro-[1,3]-dioxepine (15): \(^1^H\)

NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.08 (2H, d, \(J = 8.4\) Hz), 6.84 (2H, d, \(J = 8.4\) Hz), 6.30 (1H, dd, \(J = 7.8, 3.0\) Hz), 5.43 (1H, d, \(J = 6.9\) Hz), 4.77 (1H, d, \(J = 6.9\) Hz), 4.58 (1H, dd, \(J = 8.1, 2.7\) Hz), 3.80 (3H, s), 3.46 (1H, ddd, \(J = 10.2, 2.7, 2.7\) Hz), 3.23 (1H ddd, \(J = 8.4, 8.4, 2.4\) Hz), 1.09-1.54 (8H, m), 0.82 (3H, t, \(J = 6.6\) Hz); \(^{13}C\) NMR (100 MHz, CDCl\(_3\)) \(\delta\) 158.6, 144.0, 134.8, 129.5, 114.2, 112.2, 97.4, 87.1, 55.5, 53.3, 33.7, 31.8, 25.6, 22.8, 14.2; IR (NaCl dep from CH\(_2\)Cl\(_2\) 2953, 2928, 2870, 1650, 1512 cm\(^{-1}\); HRMS (ESI) m/e calcd for C\(_{17}\)H\(_{24}\)O\(_3\) 276.1726. Found 276.1721.

5-(3-nitro-phenyl)-4-pentyl-4,5-dihydro-[1,3]-dioxepine (16). \(^1^H\)

NMR (300 MHz, CDCl\(_3\)) \(\delta\) 8.13 (1H, m), 8.07 (1H, m), 7.50-7.57 (2H, m), 6.37 (1H, dd, \(J = 8.1, 3.0\) Hz), 5.45 (1H, d, \(J = 6.9\) Hz), 4.82 (1H, d, \(J = 7.0\) Hz), 4.53 (1H, dd, \(J = 8.1, 2.4\) Hz), 3.51 (1H, ddd, \(J = 9.9, 2.7, 2.7\) Hz), 3.32 (1H ddd, \(J = 9.6, 9.6, 2.4\) Hz) 1.06-1.52 (8H, m), 0.81 (3H, t, \(J = 6.9\) Hz); \(^{13}C\) NMR (75 MHz, CDCl\(_3\)) \(\delta\) 145.3, 144.9, 135.0, 129.9, 123.4, 122.4, 110.0, 97.4, 86.4, 53.8, 33.7, 31.7, 25.5, 22.7, 14.2; IR (NaCl dep from CH\(_2\)Cl\(_2\) 2930, 2871, 1651, 1530, 1352 cm\(^{-1}\); HRMS (ESI) m/e calcd for C\(_{16}\)H\(_{21}\)NO\(_4\) 291.1471. Found 291.1476.

4-Cyclohexyl-4,7-dihydro-[1,3]-dioxepine (17a). \(^1^H\) NMR (400 MHz, CDCl\(_3\)) \(\delta\) 5.63-5.72 (2H, m), 4.91 (1H, d, \(J = 4.8\) Hz), 4.76 (1H, d, \(J = 4.8\) Hz), 4.15-4.31
(2H, m), 4.05 (1H, m), 1.6-1.8 (4H, m), 1.44-1.54 (1H, m), 1.00-1.30 (4H, m); \( ^{13} \)C NMR (100 MHz, CDCl\(_3\)) \( \delta \) 133.9, 130.5, 95.9, 80.7, 66.9, 42.8, 29.3, 28.0, 26.6, 26.4; IR (NaCl dep from CH\(_2\)Cl\(_2\)) 2925, 2852, 1449, 1122, 1072 cm\(^{-1}\); HRMS (ESI) \( m/e \) calcd for C\(_{11}\)H\(_{18}\)O\(_2\) 182.1306. Found 182.1303.

**4-Cyclohexyl-5-phenyl-4,5-dihydro-[1,3]-dioxepine (17).** \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 7.14-7.32 (5H, m), 6.27 (1H, dd, \( J = 8.0, 3.2 \) Hz), 5.41 (1H, d, \( J = 6.8 \) Hz), 4.72 (1H, d, \( J = 6.8 \) Hz), 4.57 (1H, dd, \( J = 7.6, 2.4 \) Hz), 3.76 (1H, ddd, \( J = 10.4, 2.8, 2.8 \) Hz), 3.16 (1H, d, \( J = 10.4 \) Hz), 1.75 (2H, m), 1.57 (2H, m), 1.39 (1H, m), 1.17-1.31 (2H, m), 0.92-1.13 (4H, m); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \( \delta \) 143.6, 128.9, 128.3, 127.4, 126.9, 112.1, 97.6, 91.3, 50.0, 39.0, 31.4, 26.6, 26.6, 26.4, 26.4, 25.7; IR (NaCl dep from CH\(_2\)Cl\(_2\)) 3061, 3027, 2926, 2853, 1647, 1493 cm\(^{-1}\); HRMS (ESI) \( m/e \) calcd for C\(_{17}\)H\(_{22}\)O\(_2\) 258.1620. Found 258.1624.

**7-Cyclohexyl-5-phenyl-4,5-dihydro-[1,3]-dioxepine (18).** \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 7.20-7.32 (5H, m), 5.17 (1H, d, \( J = 6.8 \) Hz), 4.89 (1H, d, \( J = 4.0 \) Hz), 4.73 (1H, d, \( J = 6.8 \) Hz), 3.86 (1H, dd, \( J = 11.2, 3.6 \) Hz), 3.75 (1H, ddd, \( J = 8.4, 4.0, 4.0 \) Hz), 3.43 (1H, dd, \( J = 11.2, 8.8 \) Hz), 1.96 (1H, m), 1.70-1.85 (4H, m), 1.63 (1H, m), 1.10-1.30 (5H, m); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \( \delta \) 164.2, 142.2, 128.8, 128.1, 127.0, 107.8, 97.5, 76.0, 47.5, 44.1, 31.2, 31.1, 26.5, 26.4, 26.4; IR (NaCl dep from CH\(_2\)Cl\(_2\)) 3061, 3027, 2926, 2853, 2802, 1664, 1451 cm\(^{-1}\); HRMS (ESI) \( m/e \) calcd for C\(_{17}\)H\(_{22}\)O\(_2\) 258.1620. Found 258.1623.
4-Cyclohexyl-5-(4-methoxy-phenyl)-4,5-dihydro-[1,3]-dioxepine (19). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.08 (2H, d, $J = 8.7$ Hz), 6.84 (2H, d, $J = 8.7$ Hz), 6.27 (1H, dd, $J = 8.1$, 3.0 Hz), 5.42 (1H, d, $J = 6.6$ Hz), 4.73 (1H, d, $J = 6.9$ Hz), 4.57 (1H, dd, $J = 8.1$, 2.7 Hz), 3.80 (3H, s), 3.73 (1H, ddd, $J = 10.2$, 2.7, 2.7 Hz), 3.12 (1H, d, $J = 9.6$ Hz), 1.00-1.82 (11H, m); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 158.5, 143.5, 134.8, 129.3, 114.2, 112.4, 97.6, 91.4, 55.5, 49.2, 38.9, 31.4, 26.6, 25.7; IR (NaCl dep from CH$_2$Cl$_2$) 2928, 2853, 1647, 1512, 1173 cm$^{-1}$; HRMS (ESI) m/e calcd for C$_{18}$H$_{24}$O$_3$ 288.1726. Found 288.1721.

4-tert-Butyl-4,7-dihydro-[1,3]-dioxepine (21a). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 5.76 (1H, m), 5.70 (1H, m), 4.90 (1H, d, $J = 4.8$ Hz), 4.75 (1H, d, $J = 4.8$ Hz), 4.25 (2H, m), 3.87 (1H, m), 0.96 (9H, s); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 131.5, 131.2, 96.2, 83.8, 66.7, 34.5, 26.0; IR (NaCl dep from CH$_2$Cl$_2$) 3036, 2957, 2909, 2872, 2781, 1479 cm$^{-1}$; HRMS (ESI) m/e calcd for C$_9$H$_{16}$O$_2$ 126.1956. Found 126.1950.

7-tert-Butyl-5-phenyl-4,5-dihydro-[1,3]-dioxepine (22). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.22-7.36 (5H, m), 5.22 (1H, d, $J = 6.9$ Hz), 5.06 (1H, d, $J = 3.9$ Hz), 4.71 (1H, d, $J = 6.9$ Hz), 3.86 (1H, dd, $J = 10.8$, 3.0 Hz), 3.80 (1H, dd, $J = 8.4$, 3.6 Hz), 3.46 (1H, dd, $J = 10.8$, 8.7 Hz), 1.10 (9H, s); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 142.4, 128.9, 128.8, 128.1, 128.0, 127.0, 107.6, 97.5, 75.5, 47.3, 28.2; IR (NaCl dep from CH$_2$Cl$_2$) 2958, 1654, 1464, 1363, 1176, 700 cm$^{-1}$.
2-(4-Nitro-phenyl)-4,4,7,7-tetradeuterio-4,7-dihydro-[1,3]dioxepine (23). \(^1\)H NMR (400 MHz CDCl\(_3\)) \(\delta\) 8.23 (2H, d, \(J = 8.4\) Hz), 7.72 (2H, d, \(J = 8.4\) Hz), 5.88 (1H, s), 5.78 (2H, s); \(^{13}\)C NMR (100 MHz CDCl\(_3\)) \(\delta\) 146.0, 129.9, 127.9, 123.6, 101.1; IR (NaCl dep from CH\(_2\)Cl\(_2\)) 2875, 2213, 2099, 1513, 1348, 702 cm\(^{-1}\); HRMS (FAB+) calcd for C\(_{11}\)H\(_7\)D\(_4\)NO\(_4\), 226.1017. Found 226.1011.

2-(4-Nitro-phenyl)-5-phenyl-4,4,5-trideuterio-4,5-dihydro-[1,3]dioxepine (24). \(^1\)H NMR (400 MHz CDCl\(_3\)) \(\delta\) 8.23 (2H, dd, \(J = 8.7, 2.4\) Hz), 7.71 (2H, dd, \(J = 8.7, 2.1\) Hz), 5.63 (1H, d, \(J = 2.1\) Hz), 5.06 (1H, s), 3.97 (1H, s); \(^{13}\)C NMR (100 MHz CDCl\(_3\)) \(\delta\) 148.4, 145.2, 140.3, 129.1, 128.1, 127.5, 123.7, 113.8, 104.7, 48.2; IR (NaCl dep from CH\(_2\)Cl\(_2\)) 3081, 2873, 1635, 1345, 1128, 697 cm\(^{-1}\).

4-Phenethyl-2,5-diphenyl-4,5-dihydro-[1,3]dioxepine (26). \(^1\)H NMR (400 MHz CDCl\(_3\)) \(\delta\) 7.62-6.92 (15H, m), 6.41 (1H, dd, \(J = 7.9, 3.0\) Hz), 5.66 (1H, s), 4.76 (1H, dd, \(J = 7.7, 2.1\) Hz), 3.65 (1H, dd, \(J = 10, 2.7\) Hz), 3.57 (1H, ddd, \(J = 9.7, 9.7, 1.8\) Hz), 2.92-2.82 (1H, m), 2.60-2.50 (1H, m), 1.89-1.78 (1H, m), 1.74-1.63 (1H, m); \(^{13}\)C NMR (100 MHz CDCl\(_3\)) \(\delta\) 171.0, 143.96, 142.3, 141.8, 139.1, 129.0, 128.8, 128.6, 128.5, 128.4, 127.2, 126.2, 125.9, 112.1, 105.6, 85.1, 53.9, 35.3, 32.3; IR (NaCl dep from CH\(_2\)Cl\(_2\)) 3061, 2920, 1647, 1453, 1140, 698 cm\(^{-1}\).
2-Cyclohexyl-5-methoxy-3-phenyl-tetrahydro-furan (27): $^1$H NMR (400 MHz, CDCl$_3$) δ 7.14-7.33 (10H, m), 5.05 (1H, dd, $J = 4.2$, 1.5 Hz), 5.02 (1H, d, $J = 3.6$ Hz), 3.86 (2H, dd, $J = 8.8$, 6.0 Hz), 3.40 (3H, s), 3.36 (3H, s), 3.35 (1H, m), 3.02 (1H, dd, $J = 17.6$, 9.2 Hz), 2.59 (1H, ddd, $J = 13.6$, 10.8, 5.6 Hz), 2.29 (1H, dd, $J = 12.8$, 7.2 Hz), 2.08 (1H, ddd, $J = 12.0$, 12.0, 4.8 Hz), 1.86-2.00 (2H, m), 1.82 (1H, m), 1.64-1.74 (2H, m), 1.38-1.64 (8H, m), 0.80-1.22 (10H, m); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 143.5, 142.7, 128.8, 128.7, 128.4, 128.0, 126.7, 126.5, 104.7, 104.4, 91.4, 88.6, 54.8, 54.6, 47.3, 46.6, 44.2, 43.8, 43.6, 41.4, 30.0, 29.5, 28.7, 26.7, 26.4, 26.3, 26.2; IR (NaCl dep from CH$_2$Cl$_2$) 2924, 2852, 1449, 1099 cm$^{-1}$; HRMS (FAB+) m/e calcd for (M$^+$ - OMe)C$_{16}$H$_{21}$O 229.1592. Found 229.1588.

Stereochemical Assignment (nOe Experiments):

![Stereochemical Assignment Diagram]
Supplementary Information
Supplementary Information

![Chemical Structure](image1)

**Formula:** Ph-CO$_2$Et

**(13)**

![NMR Spectrum](image2)

**ppm**

![NMR Spectrum](image3)

**ppm**

S-27
(26)