Supporting Information

Palladium-Catalyzed Sequential Alkylation-Alkenylation Reactions. Application to the Synthesis of 2-Substituted-4-Benzoxepines and 2,5-Disubtituted-4-Benzoxepines

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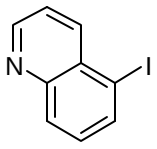
The following includes general experimental procedures, specific details for representative reactions, and isolation and spectroscopic information for the new compounds prepared. All ^{1}H and ^{13}C NMR spectra were recorded in deuterated chloroform using tetramethylsilane or residual chloroform as internal standard at ambient temperature unless noted. High resolution mass spectra were obtained at 70 eV. Aryl iodides were purchased from commercial sources (**4**, **7**, **10**, **17**, **19**, **25**), synthesized using literature procedures (**8**[1], **9**[2], **11**[1], **18**[2]), or prepared as described in this section (**20**, **28**). Bromoenoates (**5**, **26**) were prepared as described in this section.

Aryl iodides.

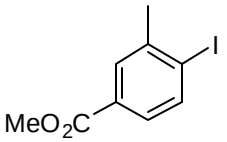


20

5-iodoquinoline (20). To a slurry of 5-aminoquinoline (348 mg, 2.4 mmol) in HCl (4 ml) at –10ºC was added dropwise a solution of $NaNO_2$ (200 mg, 2.9 mmol) in H_2O (4 mL). The resulting yellow mixture was stirred 30 min at –10ºC. A solution of KI (797 mg, 4.8 mmol) in

[1] Larock, R. C.; Harrison, W. L. *J. Am. Chem. Soc.* **1984**, *106*, 4218-4227.
[2] Lautens, M.; Paquin, J.-F.; Piguel, S.; Dahlmann, M. *J. Org. Chem.* **2001**, *66*, 8127-8134.

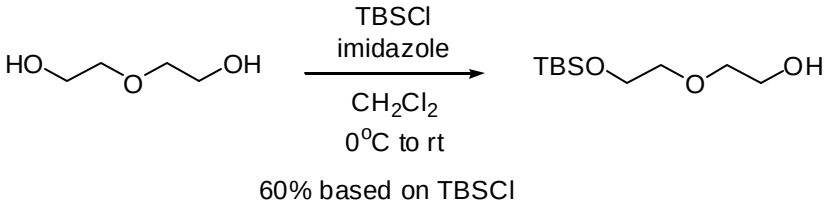
H_2O (4 mL) was then added slowly. The resulting brown mixture was stirred 30 min at –10ºC and warmed to rt and stirred for 2 hrs. The aqueous mixture was washed with Et_2O (2×) and then basified (pH ~ 10) using Na_2CO_3 and extracted with Et_2O (3×). The organic layers were combined, washed with 5% $NaHSO_3$ (3×), H_2O (2×), brine, and dried over $MgSO_4$. Activated charcoal was added and the resulting suspension was stirred 15 min, filtrated over Celite, and the solvent was evaporated to yield the desired product (114 mg, 19%) as a beige solid. IR (film) ν = 3068, 3027, 1555, 1488, 946 cm^{-1}; ^1H NMR δ 8.90 (dd, 1H, *J* = 4.2, 1.5 Hz), 8.40 (m, 1H), 8.12 (m, 2H), 7.47 (m, 2H); ^{13}C NMR δ 151.2, 148.7, 140.4, 137.7, 130.5, 130.4, 130.2, 122.7, 98.5; HRMS calcd for C_9H_6NI 254.9545, found 254.9552.



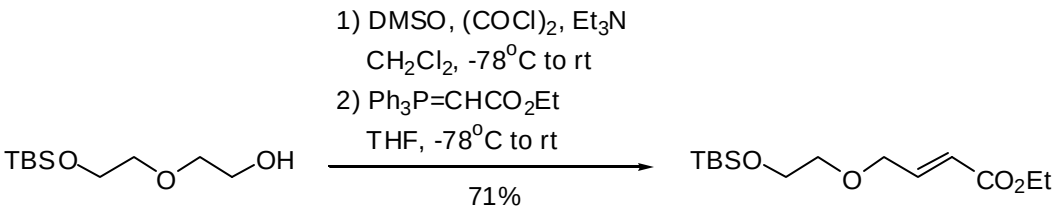
28

Methyl 4-iodo-3-methylbenzoate (28). A mixture of 4-iodo-3-methylbenzoic acid (1.0 g, 3.82 mmol) and H_2SO_4 (few drops) in MeOH (20 mL) was refluxed for 19 hrs. The mixture was cooled to rt and the solvent was evaporated. The residue was dissolved in Et_2O and washed with satd $NaHCO_3$ (3×), H_2O, brine, dried over $MgSO_4$, and the solvent was evaporated to yield **28** (704 mg, 70%) as a white solid. IR (film) ν = 3020, 2953, 1717, 1431, 1303, 1256, 1108, 757 cm^{-1}; ^1H NMR δ 7.89 (m, 2H), 7.50 (dd, 1H, *J* = 8.1, 2.1 Hz), 3.90 (s, 3H), 2.47 (s, 3H); ^{13}C NMR δ 166.7, 141.8, 139.1, 130.3, 128.0, 107.4, 52.2, 28.0; HRMS calcd for $C_9H_9O_2I$ 275.9647, found 275.9647.

Bromoenoates.

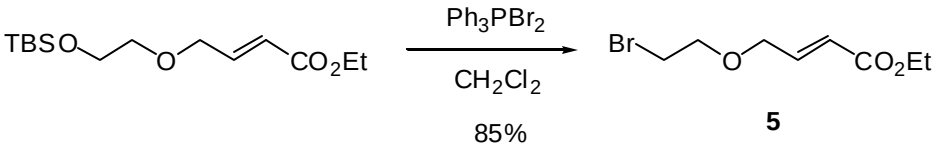


2-(2-*tert*-butyldimethylsiloxyethoxy)ethanol. To a 0°C solution of di(ethyleneglycol) (3.5 mL, 36.9 mmol) in CH_2Cl_2 (40 mL) was added imidazole (1.26 g, 18.5 mmol) and the resulting mixture was stirred 5 min and TBSCl (2.79g, 18.5 mmol) was added in one portion. The reaction mixture was stirred 1hr at 0°C and warmed to rt and stirred overnight. Water was added, the organic layer was washed with 10% HCl, satd $NaHCO_3$, brine, dried over $MgSO_4$, and the solvent was evaporated to give the crude product that was purified by flash chromatography using 30% EtOAc/hexane as eluant to give the desired product (2.40 g, 60% based on TBSCl) as a colourless liquid. IR (neat) ν = 3415, 2948, 2854, 1254, 1145 cm^{-1}; ^1H NMR δ 3.81-3.68 (m, 4H), 3.61 (m, 4H), 2.40 (t, 1H, *J* = 6.0 Hz), 0.91 (s, 9H), 0.08 (s, 6H); ^{13}C NMR δ 72.4, 72.3, 62.7, 61.7, 25.8, 18.3, -5.4; HRMS calcd for $C_6H_{15}O_3Si$ $[M - t\text{-Bu}]^+$ 163.0790, found 163.0786.

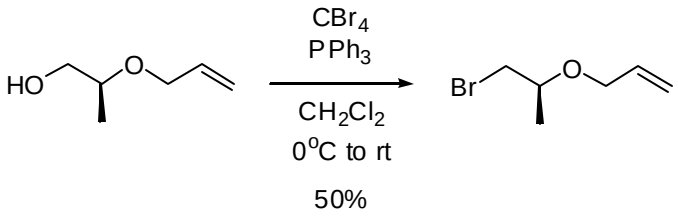


Ethyl (2*E*)-4-(2-*tert*-butyldimethylsiloxyethoxy)but-2-enoate. To a -78°C solution of DMSO (993 µL, 14.0 mmol) in CH_2Cl_2 (20 mL) was added dropwise $(COCl)_2$ (916 µL, 10.5 mmol). The mixture was stirred at -78°C for 30 min. A solution of 2-(2-*tert*-butyldimethylsiloxy-

ethoxy)ethanol (1.54 g, 6.99 mmol) in CH_2Cl_2 (5 mL) was added dropwise and the reaction mixture was stirred 45 min at -78°C. Et_3N (4.81 mL, 34.5 mmol) was added dropwise and the reaction mixture was stirred 15 min at -78°C and warmed to rt and stirred for 1 hr. The reaction mixture was cooled to -78°C and a solution of (carbethoxymetylene)triphenylphosphorane (2.92 g, 8.39 mmol) in THF (20 mL) was added dropwise. The mixture was stirred 15 min at -78°C and warmed to rt and stirred for 2 hrs. Satd NH_4Cl was added; the aqueous layer was extracted with CH_2Cl_2 (3×). The combined organic layers were washed with H_2O, brine, dried over $MgSO_4$, and the solvent was evaporated to yield the crude product that was purified by flash chromatography using Et_2O/hexane (10 → 15%) as eluant to yield the desired product (1.44 g, 71%) as a colourless liquid along with the cis isomer (179 mg, 9%). Trans isomer: IR (neat) ν = 2940, 2856, 1725, 1466, 1304 cm^{-1}; ^1H NMR δ 6.95 (dt, 1H, *J* = 15.9, 4.2 Hz), 6.10 (dt, 1H, *J* = 15.9, 2.1 Hz), 4.20 (m, 4H), 3.79 (t, 2H, *J* = 5.1 Hz), 3.56 (t, 2H, *J* = 5.1 Hz), 1.29 (t, 3H, *J* = 7.2 Hz), 0.91 (s, 9H), 0.08 (s, 6H); ^{13}C NMR δ 166.3, 144.4, 121.1, 72.3, 69.8, 62.7, 60.2, 25.8, 18.3, 14.2, -5.4; HRMS calcd for $C_{10}H_{19}O_4Si$ $[M - t\text{-Bu}]^+$ 231.1053, found 231.1055. Cis isomer: IR (neat) ν = 2939, 2857, 1724, 1465, 1412 cm^{-1}; ^1H NMR δ 6.39 (dt, 1H, *J* = 12.0, 4.8 Hz), 5.80 (dt, 1H, *J* = 12.0, 2.4 Hz), 4.62 (dd, 2H, *J* = 4.8, 2.4 Hz), 4.17 (q, 2H, *J* = 7.2 Hz), 3.78 (t, 2H, *J* = 5.1 Hz), 3.56 (t, 2H, *J* = 5.1 Hz), 1.29 (t, 3H, *J* = 7.2 Hz), 0.90 (s, 9H), 0.08 (s, 6H); ^{13}C NMR δ 166.0, 148.7, 119.3, 72.2, 69.3, 62.6, 60.1, 25.9, 18.3, 14.2, -5.3; HRMS calcd for $C_{14}H_{28}O_4Si$ 288.1757, found 288.1754.

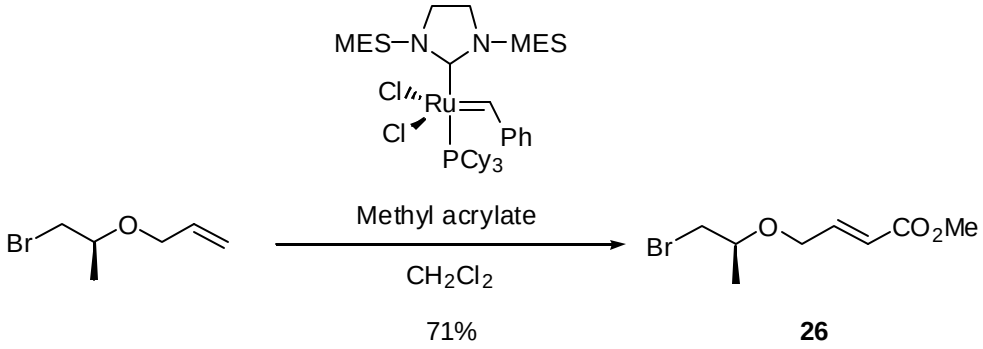


Ethyl (2*E*)-4-(2-bromoethyl)but-2-enoate (5). To a suspension of Ph_3PBr_2 in CH_2Cl_2 (8 mL) was added a solution of ethyl (2*E*)-4-(2-*tert*-butyldimethylsiloxyethoxy)but-2-enoate in CH_2Cl_2 (4 mL), the resulting suspension turned into a solution after 5 min and was stirred 2 hrs at rt. CH_2Cl_2 was added and the solution was washed with H_2O (2×), brine, dried over $MgSO_4$, and the solvent was evaporated to give the crude product that was purified by flash chromatography using CH_2Cl_2/toluene (10 → 15%) as eluant to yield the desired product (512 mg, 85%) as a slightly yellow liquid. IR (neat) ν = 2981, 2907, 2846, 1724, 1662, 1303, 1178 cm^{-1}; ^1H NMR δ 6.94 (dt, 1H, *J* = 15.6, 4.5 Hz), 6.11 (dt, 1H, *J* = 15.6, 2.1 Hz), 4.22 (m, 4H), 3.81 (t, 2H, *J* = 6.0 Hz), 3.49 (t, 2H, *J* = 6.0 Hz), 1.30 (t, 3H, *J* = 7.2 Hz); ^{13}C NMR δ 166.1, 143.5, 121.7, 70.6, 69.5, 60.4, 30.1, 14.2; HRMS calcd for $C_8H_{13}O_3Br$ 236.0048, found 236.0040.



3-{[(1*S*)-2-bromo-1-methylethyl]oxy}prop-1-ene. To a 0ºC solution of (2*S*)-2-(allyloxy)-propan-1-ol[3] (718 mg, 6.18 mmol) in CH_2Cl_2 (20 mL) was added CBr_4 (3.07 g, 9.27 mmol) and PPh_3 (2.43 g, 9.27 mmol). The mixture was stirred 10 min at 0ºC and then warmed to rt and

stirred overnight. The solvent was evaporated and the crude product was purified by flash chromatography using Et_2O/hexane (2 → 5%) as eluant gave the desired product (550 mg, 50%) as a volatile colourless liquid. $[\alpha]^{25}_D$ = +3.2 (c 1.25, $CHCl_3$); IR (neat) ν = 3081, 2978, 2865, 1138, 1084, 926 cm^{-1}; ^{1}H NMR δ 5.92 (ddt, 1H, *J* = 17.4, 10.2, 5.7 Hz), 5.30 (dq, 1H, *J* = 17.4, 1.5 Hz), 5.19 (dq, 1H, *J* = 10.2, 1.5 Hz), 4.05 (dt, 2H, *J* = 5.7, 1.5 Hz), 3.69 (m, 1H), 3.39 (m, 2H), 1.29 (d, 3H, *J* = 6.6 Hz); ^{13}C NMR δ 134.6, 117.1, 74.0, 70.0, 36.3, 18.8; MS (EI) : 85(100), 64(64), 121(22), 123(20).

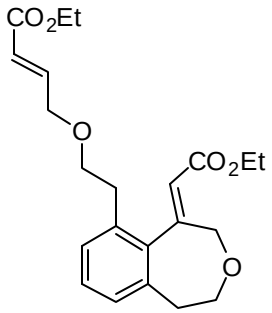


Methyl (2*E*)-4-{[(1*S*)-2-bromo-1-methylethyl]oxy}but-2-enoate (26). To a solution of 3-{[(1*S*)-2-bromo-1-methylethyl]oxy}prop-1-ene (200 mg, 1.12 mmol) and methyl acrylate (2.5 mL, 28.0 mmol) in CH_2Cl_2 (2.5 mL) was added Grubb's 2nd generation catalyst (48 mg, 5 mol%). The resulting mixture was stirred at rt for 4 hrs and DMSO[4] (200 μL, 50 equiv. relative to the catalyst) was added and the mixture stirred for 20 hrs. Evaporation of the volatiles gave a crude product that was purified by flash chromatography using Et_2O/hexane (1:9) as eluant to yield **26** (189 mg, 71%) as a colorless liquid. $[\alpha]^{25}_D$ = +16.8 (c 1.15, $CHCl_3$); IR (neat) ν = 2986, 2959, 2845, 1723, 1303 cm^{-1}; ^{1}H NMR δ 6.97 (dt, 1H, *J* = 15.6, 4.2 Hz), 6.13 (dt, 1H, *J* = 15.6, 2.1

[3] Obtained in 66% yield over 2 steps from ethyl (S)-(-)-lactate, for experimental details, see Broggini, G.; Molteni, G.; Pilati, T. *Tetrahedron: Asymmetry* **2000**, *11*, 1975-1984.
[4] Ahn, Y. M.; Yang, K. L.; Georg, G. I. *Org. Lett.* **2001**, *3*, 1411-1413.

Hz), 4.22 (dd, 2H, *J* = 4.2, 2.1 Hz), 3.71 (m, 4H), 3.40 (m, 2H), 1.30 (d, 3H, *J* = 6.0 Hz); ^{13}C NMR δ 166.5, 144.3, 120.8, 75.0, 67.5, 51.5, 36.0, 18.7; HRMS calcd for $C_8H_{13}O_3Br$ 237.0126, found 237.0130.

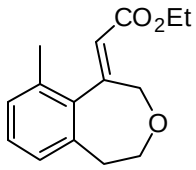
2-Substituted-4-benzoxepines and 2,5-disubstituted-4-benzoxepines.



6

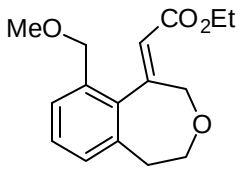
Cyclization using iodobenzene. General procedure. Ethyl (2*E*)-4-{2-[(5*Z*)-5-(2-ethoxy-2-oxoethylidene)-1,2,4,5-tetrahydro-3-benzoxepin-6-yl]ethoxy}but-2-enoate (6). Under argon, a flame-dried round-bottom flask equipped with a condenser was charged with iodobenzene (20 μL, 0.18 mmol), **5** (182 mg, 0.77 mmol), Cs_2CO_3 (118 mg, 0.36 mmol), norbornene (40.9 mg, 0.43 mmol), tri-2-furylphosphine (8.5 mg, 0.037 mmol), $Pd(OAc)_2$ (4.0 mg, 0.018 mg) and CH_3CN (5 mL). The reaction mixture was heated at 85ºC for 15 hrs. The reaction was quenched by the addition of satd NH_4Cl and the mixture was extracted with Et_2O (3×). The combined organic layers were washed with brine and dried over $MgSO_4$. Removal of the solvent gave the crude product that was purified by flash chromatography using Et_2O/hexane (10→20%) as eluant to give the desired product (36.7 mg, 53%) as a colourless oil. IR (neat) ν = 2978, 2929, 2859, 1718, 1704, 1658, 1623, 1177 cm^{-1}; ^{1}H NMR δ 7.25 (m, 2H), 7.03 (dd, 1H, *J* = 6.0, 2.4 Hz), 6.91 (dt, 1H, *J* = 15.6, 4.4 Hz), 6.02 (d, 1H, *J* = 15.6 Hz), 5.81 (t, 1H, *J* = 2.0 Hz), 4.86 (br m, 2H),

4.20 (m, 6H), 3.85-3.58 (m, 4H), 3.12 (br m, 2H), 2.94 (br m, 1H), 2.56 (br m, 1H), 1.22 (m, 6H); ^{13}C NMR δ 166.2, 165.8, 162.3, 144.1, 138.9, 136.7, 135.1, 128.8, 128.4, 125.7, 121.2, 118.2, 71.9, 69.5, 68.8, 67.7, 60.2, 53.3, 34.0, 33.1, 14.2, 14.1; HRMS calcd for $C_{22}H_{28}O_6$ 388.1886, found 388.1875.



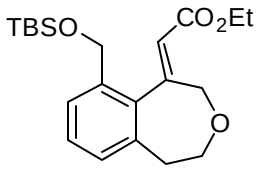
12

Cyclization using *ortho*-substituted aryl iodides. General procedure. Ethyl (2*Z*)-(9-methyl-4,5-dihydro-3-benzoxepin-1(2*H*)-ylidene)acetate (12). A round-bottom flask equipped with a condenser was charged with 2-iodotoluene (32 μL, 0.25 mmol), **5** (241 mg, 1.0 mmol), Cs_2CO_3, (164 mg, 0.50 mmol), norbornene (54 mg, 0.57 mmol), $Pd(OAc)_2$ (5.9 mg, 0.026 mmol), tri-2-furylphosphine (11.8 mg, 0.051 mmol) and CH_3CN (2.5 mL). The resulting solution was heated at 85ºC for 23 hrs. The reaction was quenched by the addition of satd NH_4Cl and the mixture was extracted with Et_2O (3×). The combined organic layers were washed with brine and dried over $MgSO_4$. Removal of the solvent gave the crude product that was purified by preparative TLC with CH_2Cl_2 as the eluant to afford **12** (53.2 mg, 85%) as a colourless oil. IR (neat) ν = 3063, 2978, 2950, 2850, 1708, 1623, 1169 cm^{-1}; ^{1}H NMR δ 7.19 (m, 2H), 6.99 (t, 1H, *J* = 4.0 Hz), 5.73 (t, 1H, *J* = 2.4 Hz), 4.88 (m, 2H), 4.21 (q, 2H, *J* = 7.2 Hz), 3.79 (m, 2H), 2.90 (br s, 2H), 2.37 (s, 3H), 1.31 (t, 3H, *J* = 7.2 Hz); ^{13}C NMR δ 165.9, 162.5, 138.3, 136.6, 134.4, 129.7, 128.3, 125.1, 118.2, 68.6, 67.8, 60.1, 33.8, 20.5, 14.2; HRMS calcd for $C_{15}H_{18}O_3$ 246.1255, found 246.1263.



13

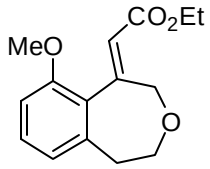
Ethyl (2*Z*)-[9-(methoxymethyl)-4,5-dihydro-3-benzoxepin-1(2*H*)-ylidene]acetate (13). Following the general procedure for *ortho*-substituted aryl iodides on a 0.27 mmol scale using **8** and **5**, **13** was isolated as a colourless oil (17.4 mg, 23%) by preparative TLC using 30% Et_2O/hexane. IR (neat) ν = 3064, 2978, 2928, 2863, 2822, 1708, 1622, 1448, 1177 cm^{-1}; ^1H NMR δ 7.41 (dd, 1H, *J* = 7.8, 0.9 Hz), 7.30 (t, 1H, *J* = 7.8 Hz), 7.11 (dd, 1H, *J* = 7.8, 0.9 Hz), 5.88 (t, 1H, *J* = 2.4 Hz), 4.88 (br s, 2H), 4.41 (s, 2H), 4.21 (q, 2H, *J* = 7.2 Hz), 3.80 (br s, 2H), 3.36 (s, 3H), 2.62 (br s, 2H), 1.31 (t, 3H, *J* = 7.2 Hz); ^{13}C NMR δ 165.9, 161.4, 138.9, 136.8, 134.9, 128.7, 128.5, 127.2, 118.1, 72.6, 68.7, 67.7, 60.1, 57.9, 33.8, 14.2; HRMS calcd for $C_{16}H_{20}O_4$ 276.1362, found 276.1372.



14

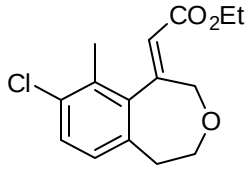
Ethyl (2*Z*)-[9-(*tert*-butyldimethylsiloxymethyl)-4,5-dihydro-3-benzoxepin-1(2*H*)-ylidene]acetate (14). Following the general procedure for *ortho*-substituted aryl iodides on a 0.17 mmol scale using **9** and **5**, **14** was isolated as a colourless oil (34.1 mg, 23%) by preparative TLC using 40% Et_2O/hexane. IR (neat) ν = 2950, 2929, 2852, 1708, 1662, 1620, 1461 cm^{-1}; ^1H NMR δ 7.33 (d, 1H, *J* = 8.0 Hz), 7.20 (t, 1H, *J* = 8.0 Hz), 7.00 (d, 1H, *J* = 8.0 Hz), 5.85 (t, 1H, *J* = 2.4 Hz), 4.79 (br s, 2H), 4.56 (s, 2H), 4.20 (m, 2H), 3.70 (br s, 2H), 2.60 (br s, 2H), 1.21 (t, 3H,

J = 7.2 Hz), 0.82 (s, 9H), 0.0 (s, 6H); ^{13}C NMR δ 165.9, 161.5, 138.1, 137.7, 136.5, 128.5, 128.2, 126.7, 118.2, 68.6, 67.8, 63.3, 60.0, 33.8, 25.8, 18.2, 14.2, -5.3; HRMS calcd for $C_{17}H_{23}O_4Si$ [M - *t*-Bu]$^+$ 319.1366, found 319.1371.



15

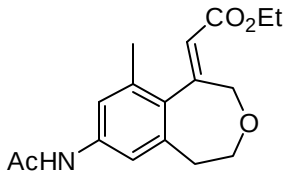
Ethyl (2*Z*)-(9-methoxy-4,5-dihydro-3-benzoxepin-1(2*H*)-ylidene)acetate (15). Following the general procedure for *ortho*-substituted aryl iodides on a 0.15 mmol scale using **9** and **5**, **14** was isolated as a colourless oil (30 mg, 75%) by flash chromatography using 5% Et_2O/hexane. IR (neat) ν = 3063, 2957, 2929, 282, 1704, 1620, 1268, 1468 cm^{-1}; ^{1}H NMR δ 7.24 (t, 1H, *J* = 8.0 Hz), 6.89 (d, 1H, *J* = 8.0 Hz), 6.78 (d, 1H, *J* = 8.0 Hz), 5.97 (t, 1H, *J* = 2.4 Hz), 4.88 (d, 2H, *J* = 7.2 Hz), 4.20 (q, 2H, *J* = 7.2 Hz), 3.79 (m, 5H), 2.84 (t, 2H, *J* = 6.4 Hz), 1.32 (t, 3H, *J* = 7.2 Hz); ^{13}C NMR δ 166.3, 157.9, 156.1, 138.3, 129.5, 127.1, 120.2, 1191, 110.3, 68.7, 67.7, 59.9, 55.7, 33.7, 14.3; HRMS calcd for $C_{15}H_{18}O_4$ 262.1205, found 262.1201.



21

Cyclization using polysubstituted aryl iodides. General procedure. Ethyl (2*Z*)-(8-chloro-9-methyl-4,5-dihydro-3-benzoxepin-1(2*H*)-ylidene)acetate (21). A round-bottom flask equipped with a condenser was charged with Cs_2CO_3 (130 mg, 0.40 mmol), norbornene (38 mg, 0.40

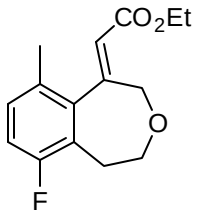
mmol), $Pd(OAc)_2$ (4.5 mg, 0.020 mmol), tri-2-furylphosphine (9.2 mg, 0.040 mmol). A solution of **5** and 2-chloro-6-iodotoluene (50.6 mg, 0.20 mmol) in CH_3CN (2 mL) was added. The resulting mixture was heated at 85ºC for 19 hrs and then quenched by addition of H_2O. The aqueous solution was extracted with Et_2O (3×). The organic layers were combined, washed with brine, and dried over $MgSO_4$. Removal of the solvent gave a crude oil that was purified by flash chromatography using 10% acetone/hexane to give **21** as a colorless solid (47.2 mg, 85%). IR (neat) ν = 3060, 2929, 2867, 1695, 1174 cm^{-1}; ^1H NMR δ 7.30 (d, 1H, *J* = 8.1 Hz), 6.95 (d, 1H, *J* = 8.1 Hz), 5.69 (t, 1H, *J* = 2.4 Hz), 4.87 (m, 2H), 4.22 (q, 2H, *J* = 7.2 Hz), 3.77 (br m, 2H), 3.07 (br m, 1H), 2.59 (br m, 1H), 2.40 (s, 3H), 1.32 (t, 3H, *J* = 7.2 Hz); ^{13}C NMR δ 165.8, 162.1, 140.3, 135.1, 134.4, 132.8, 129.1, 126.0, 119.1, 68.5, 67.6, 60.3, 33.6, 18.3, 14.2; HRMS calcd for $C_{15}H_{17}O_3Cl$ 280.0866, found 280.0874.



22

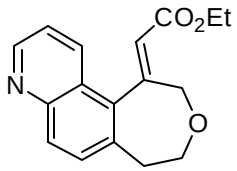
Ethyl (2*Z*)-[7-(acetylamino)-9-methyl-4,5-dihydro-3-benzoxepin-1(2*H*)-ylidene]acetate (22). Following the general procedure for polysubstituted aryl iodides on a 0.200 mmol scale using **18** and **5**, **22** was isolated as a slightly yellow solid (48.5 mg, 80%) by flash chromatography using EtOAc/hexane (50 → 60%) as eluant. IR (neat) ν = 3728, 2924, 2851, 1700, 1516 cm^{-1}; ^1H NMR δ 7.58 (br s, 1H), 7.31 (s, 1H), 7.22 (s, 1H), 5.68 (t, 1H, *J* = 2.4 Hz), 4.86 (d, 2H, *J* = 2.4 Hz), 4.21 (q, 2H, *J* = 7.2 Hz), 3.77 (br m, 2H), 2.80 (br m, 2H), 2.32 (s, 3H), 2.15 (s, 3H), 1.31 (t, 3H,

J = 7.2 Hz); ^{13}C NMR δ 168.5, 166.0, 162.1, 137.8, 137.7, 135.6, 134.4, 120.4, 118.2, 116.8, 68.7, 67.7, 60.2, 33.9, 24.6, 20.7, 14.2; HRMS calcd for $C_{17}H_{21}NO_4$ 303.1471, found 303.1478.



23

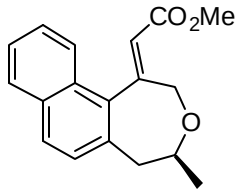
Ethyl (2*Z*)-(6-fluoro-9-methyl-4,5-dihydro-3-benzoxepin-1(2*H*)-ylidene)acetate (23). Following the general procedure for polysubstituted aryl iodides on a 0.200 mmol scale using **19** and **5**, **23** was isolated as a colourless oil (41.2 mg, 78%) by flash chromatography using acetone/hexane (3 → 5%) as eluant. IR (neat) ν = 2977, 2860, 1709, 1628, 1482, 1238, 1181 cm^{-1}; ^{1}H NMR δ 7.12 (m, 1H), 6.96 (t, 1H, *J* = 8.4 Hz), 5.72 (t, 1H, *J* = 2.4 Hz), 4.87 (d, 2H, *J* = 2.4 Hz), 4.22 (q, 2H, *J* = 7.2 Hz), 3.78 (br s, 2H), 2.94 (br s, 2H), 2.32 (s, 3H), 1.32 (t, 3H, *J* = 7.2 Hz); ^{13}C NMR δ 165.8, 161.6, 161.5, 159.1, 155.9, 140.4, 140.3, 130.5, 130.4, 130.0, 129.9, 1229, 122.7, 118.7, 115.1, 114.8, 110.7, 68.5, 67.1, 64.5, 60.3, 25.0, 24.9, 20.0, 14.2; HRMS calcd for $C_{15}H_{17}O_3F$ 264.1162, found 264.1154.



24

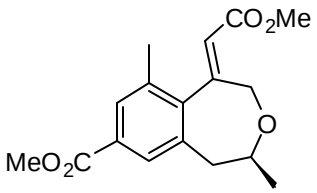
Ethyl (2*Z*)-4,5-dihydrooxepino[4,5-*f*]quinolin-1(2*H*)-ylideneacetate (24). Following the general procedure for polysubstituted aryl iodides on a 0.200 mmol scale using **20** and **5**, **24** was isolated as yellow oil (40.8 mg, 72%) by flash chromatography using 70% Et_2O/hexane as

eluant. IR (neat) ν = 3075, 2957, 2860, 1710, 1502, 1200, 1164, 1105 cm^{-1}; ^1H NMR δ 8.89 (d, 1H, *J* = 4.2 Hz), 8.44 (d, 1H, *J* = 8.7 Hz), 8.10 (d, 1H, *J* = 8.7 Hz), 7.56 (d, 1H, *J* = 8.7 Hz), 7.41 (dd, 1H, *J* = 8.7, 4.2 Hz), 5.86 (t, 1H, *J* = 2.1 Hz), 5.01 (d, 2H, *J* = 2.1 Hz), 4.26 (q, 2H, *J* = 7.2 Hz), 3.95 (br m, 1H), 3.79 (br m, 1H), 3.34 (br m, 1H), 2.80 (br m, 1H), 1.34 (t, 3H, *J* = 7.2 Hz); ^{13}C NMR δ 165.7, 160.4, 149.7, 147.9, 135.3, 134.3, 133.3, 130.3, 129.8, 125.8, 121.4, 120.3, 68.6, 66.8, 60.4, 33.9, 14.2; HRMS calcd for $C_{17}H_{17}NO_3$ 283.1208, found 283.1205.



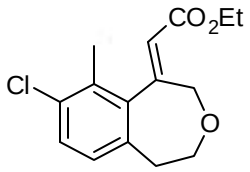
27

Methyl (2*Z*)-[(4*S*)-4-methyl-4,5-dihydronaphtho[1,2-*d*]oxepin-1-(2*H*)-ylidene]acetate (27). Following the general procedure for polysubstituted aryl iodides on a 0.200 mmol scale using **25** and **26**, **27** was isolated as 1.2:1 mixture of **27** and unreacted **26** (82 mg, 72% yield of **27**) by flash chromatography using 15% Et_2O/hexane. Analytically pure material could be obtained by further purification by flash chromatography using 5% acetone/hexane as eluant to obtained **27** as a white solid. $[\alpha]^{25}_D$: +20.2 (c 1.0, $CHCl_3$); IR (film) ν = 2932, 2865, 1707, 1212, 1175, 1101 cm^{-1}; ^1H NMR δ 8.11 (d, 1H, *J* = 7.5 Hz), 7.82 (m, 2H), 7.45 (m, 2H), 7.28 (d, 1H, *J* = 7.5 Hz), 5.96 (t, 1H, *J* = 2.4 Hz), 5.06 (m, 2H), 4.42 (m, 1H), 3.79 (s, 3H), 3.40 (m, 1H), 2.57 (d, 1H, *J* = 14.4 Hz), 1.08 (d, 3H, *J* = 6.3 Hz); ^{13}C NMR δ 166.4, 162.5, 134.8, 133.2, 131.9, 130.7, 128.5, 128.3, 127.6, 126.5, 125.1, 125.0, 118.1, 72.0, 69.2, 51.4, 38.8, 20.4; HRMS calcd for $C_{18}H_{18}O_3$ 282.1256, found 282.1249.



29

Methyl (1*Z*,4*R*)-1-(2-methoxy-2-oxoethylidene)-4,9-dimethyl-1,2,4,5-tetrahydro-3-benzoxepine-7-carboxylate (29). Following the general procedure for polysubstituted aryl iodides on a 0.200 mmol scale using **28** and **26**, **29** was isolated as slightly yellow oil (35.5 mg, 55%, 71% based on recovered **28**) by flash chromatography using Et_2O/hexane (10→20%) as eluant. $[\alpha]^{25}_D$: +116.5 (c 0.97, $CHCl_3$); IR (neat) ν = 2952, 1725, 1710, 1630, 1434, 1218, 1102, 913 cm^{-1}; ^1H NMR (-20ºC) δ 7.90 (s, 1H), 7.64 (s, 1H), 5.77 (t, 1H, *J* = 2.5 Hz), 4.97 (s, 2H), 4.02 (m, 1H), 3.94 (s, 3H), 3.78 (s, 3H), 3.23 (dd, 1H, *J* = 14.0, 7.0 Hz), 2.49 (d, 1H, *J* = 14.0 Hz), 2.42 (s, 3H), 1.08 (d, 3H, *J* = 6.5 Hz); ^{13}C NMR δ 166.9, 166.1, 162.2, 142.6, 135.0, 130.9, 128.9, 127.3, 117.9, 72.3, 68.9, 52.3, 51.6, 38.2, 20.8, 20.0; HRMS calcd for $C_{17}H_{20}O_5$ 304.1311, found 304.1318.


CO2Et
Cl
O

21

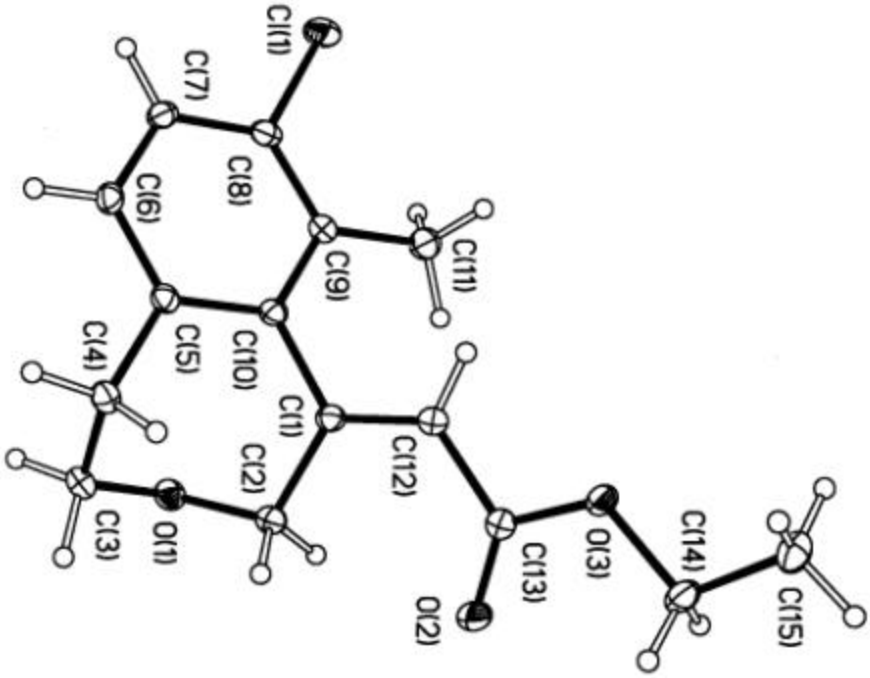

Cl(1)
C(7)
C(8)
C(6)
C(9)
C(11)
C(4)
C(5)
C(10)
C(1)
C(12)
C(2)
C(3)
O(1)
O(2)
C(13)
O(3)
C(14)
C(15)

Table 1. Crystal data and structure refinement for k01311.

Identification code	k01311	
Empirical formula	C15 H17 Cl O3	
Formula weight	280.74	
Temperature	150(1) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)/c	
Unit cell dimensions	a = 8.8182(2) Å	α= 90°.
	b = 10.7490(2) Å	β= 103.1660(10)°.
	c = 15.0338(3) Å	γ = 90°.
Volume	1387.55(5) Å^3	
Z	4	
Density (calculated)	1.344 Mg/m^3	
Absorption coefficient	0.276 mm^{-1}	
F(000)	592	
Crystal size	0.30 x 0.26 x 0.20 mm^3	
Theta range for data collection	2.78 to 27.47°.	
Index ranges	0<=h<=11, 0<=k<=13, -19<=l<=19	
Reflections collected	14760	
Independent reflections	3163 [R(int) = 0.032]	
Completeness to theta = 27.47°	99.7 %	
Absorption correction	Semi-empirical from eqeuivalents	
Max. and min. transmission	0.9468 and 0.9217	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3163 / 0 / 175	
Goodness-of-fit on F^2	1.045	
Final R indices [I>2sigma(I)]	R1 = 0.0347, wR2 = 0.0843	
R indices (all data)	R1 = 0.0439, wR2 = 0.0898	
Extinction coefficient	0.013(3)	
Largest diff. peak and hole	0.292 and -0.272 e.Å^{-3}	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for k01311. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
Cl(1)	5276(1)	2805(1)	6322(1)	35(1)
O(1)	710(1)	6594(1)	7519(1)	25(1)
O(2)	1850(1)	9590(1)	5961(1)	36(1)
O(3)	2823(1)	9206(1)	4727(1)	27(1)
C(1)	1893(1)	6855(1)	6210(1)	21(1)
C(2)	1138(2)	7467(1)	6916(1)	24(1)
C(3)	-745(2)	6003(1)	7147(1)	27(1)
C(4)	-801(1)	5412(1)	6213(1)	25(1)
C(5)	710(1)	4757(1)	6211(1)	21(1)
C(6)	799(2)	3471(1)	6210(1)	23(1)
C(7)	2205(2)	2872(1)	6235(1)	24(1)
C(8)	3522(2)	3593(1)	6282(1)	24(1)
C(9)	3514(1)	4894(1)	6306(1)	22(1)
C(10)	2059(1)	5472(1)	6247(1)	20(1)
C(11)	5023(2)	5612(1)	6447(1)	32(1)
C(12)	2396(2)	7500(1)	5570(1)	24(1)
C(13)	2303(2)	8863(1)	5464(1)	25(1)
C(14)	2820(2)	10530(1)	4540(1)	31(1)
C(15)	3357(2)	10692(1)	3669(1)	33(1)

Table 3. Bond lengths [Å] and angles [°] for k01311.

Cl(1)-C(8)	1.7525(13)
O(1)-C(2)	1.4145(16)
O(1)-C(3)	1.4265(16)
O(2)-C(13)	1.2104(16)
O(3)-C(13)	1.3437(15)
O(3)-C(14)	1.4509(16)
C(1)-C(12)	1.3414(18)
C(1)-C(10)	1.4927(17)
C(1)-C(2)	1.5253(17)
C(3)-C(4)	1.5313(18)
C(4)-C(5)	1.5079(17)
C(5)-C(6)	1.3845(18)
C(5)-C(10)	1.4079(17)
C(6)-C(7)	1.3898(18)
C(7)-C(8)	1.3846(19)
C(8)-C(9)	1.3992(19)
C(9)-C(10)	1.4095(17)
C(9)-C(11)	1.5107(18)
C(12)-C(13)	1.4731(18)
C(14)-C(15)	1.501(2)
C(2)-O(1)-C(3)	113.05(10)
C(13)-O(3)-C(14)	116.31(10)
C(12)-C(1)-C(10)	119.71(11)
C(12)-C(1)-C(2)	122.97(12)
C(10)-C(1)-C(2)	117.32(11)
O(1)-C(2)-C(1)	112.46(11)
O(1)-C(3)-C(4)	112.53(10)
C(5)-C(4)-C(3)	110.59(10)
C(6)-C(5)-C(10)	119.86(11)
C(6)-C(5)-C(4)	121.12(11)
C(10)-C(5)-C(4)	118.96(11)
C(5)-C(6)-C(7)	120.85(12)
C(8)-C(7)-C(6)	118.36(12)

C(7)-C(8)-C(9)	123.47(12)
C(7)-C(8)-Cl(1)	117.04(10)
C(9)-C(8)-Cl(1)	119.49(10)
C(8)-C(9)-C(10)	116.69(11)
C(8)-C(9)-C(11)	120.26(11)
C(10)-C(9)-C(11)	122.94(12)
C(5)-C(10)-C(9)	120.70(12)
C(5)-C(10)-C(1)	117.85(11)
C(9)-C(10)-C(1)	121.45(11)
C(1)-C(12)-C(13)	124.92(12)
O(2)-C(13)-O(3)	123.62(12)
O(2)-C(13)-C(12)	126.42(12)
O(3)-C(13)-C(12)	109.95(11)
O(3)-C(14)-C(15)	107.18(11)

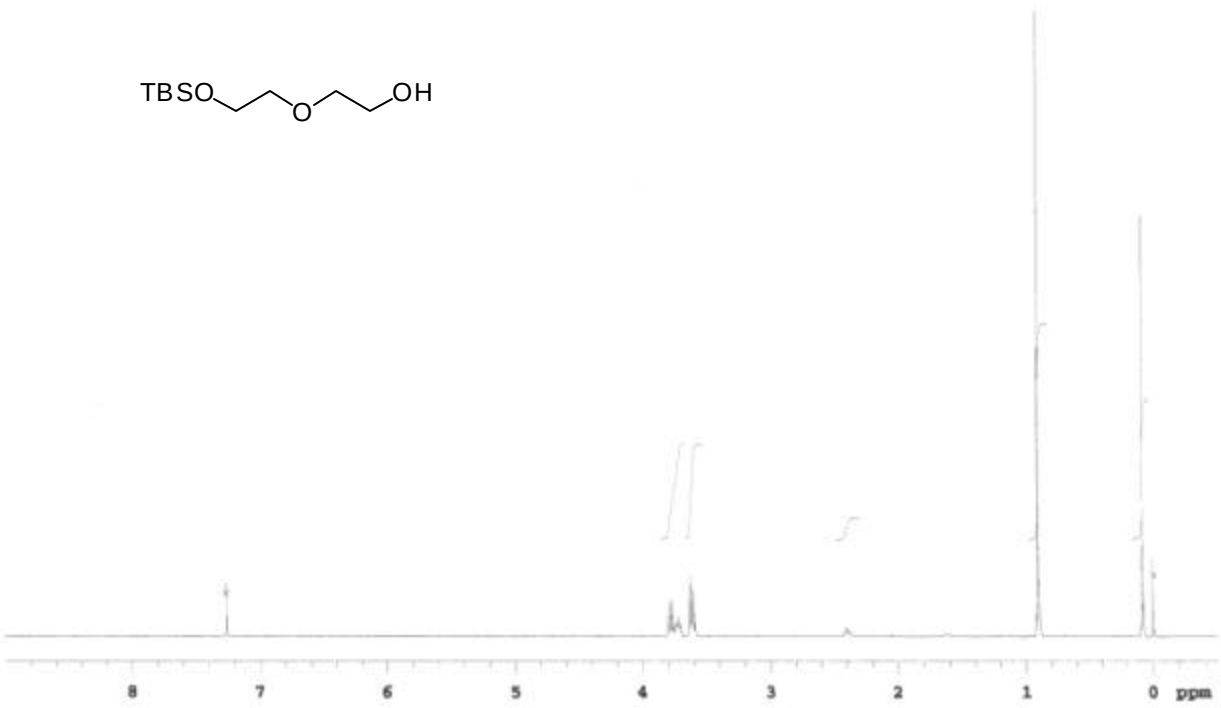
Symmetry transformations used to generate equivalent atoms:

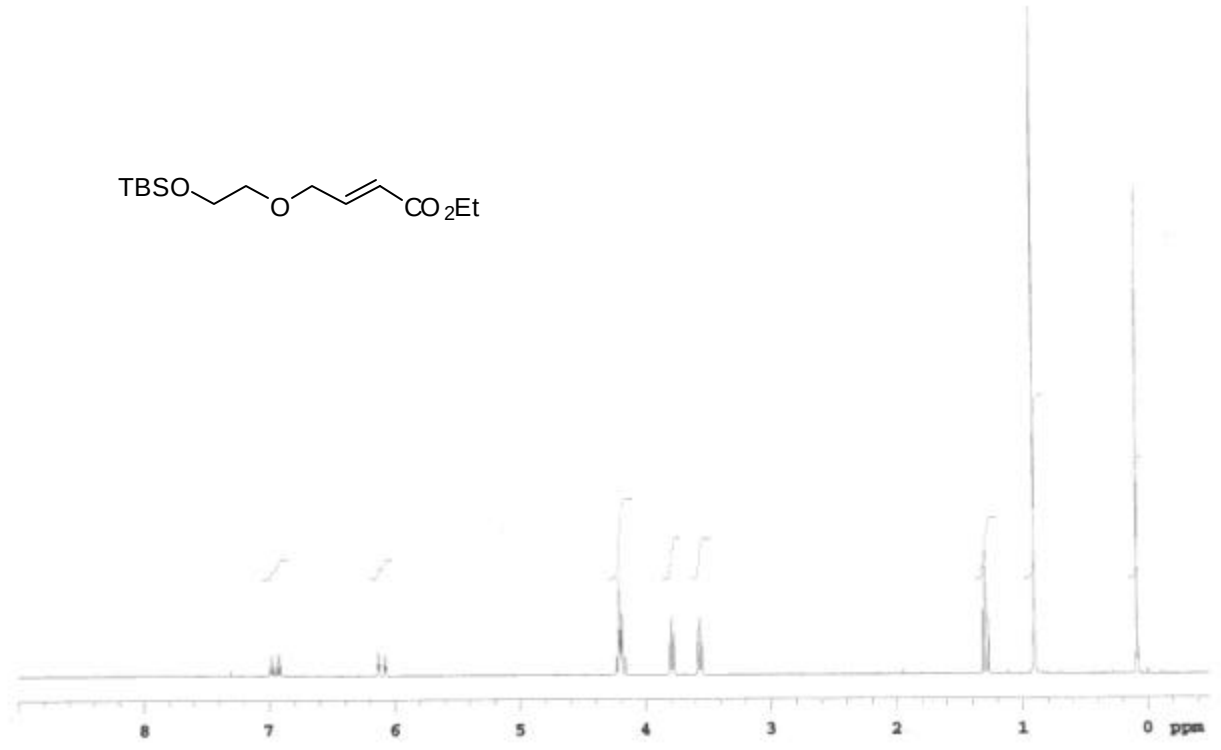
Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for k01311. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + \ldots + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

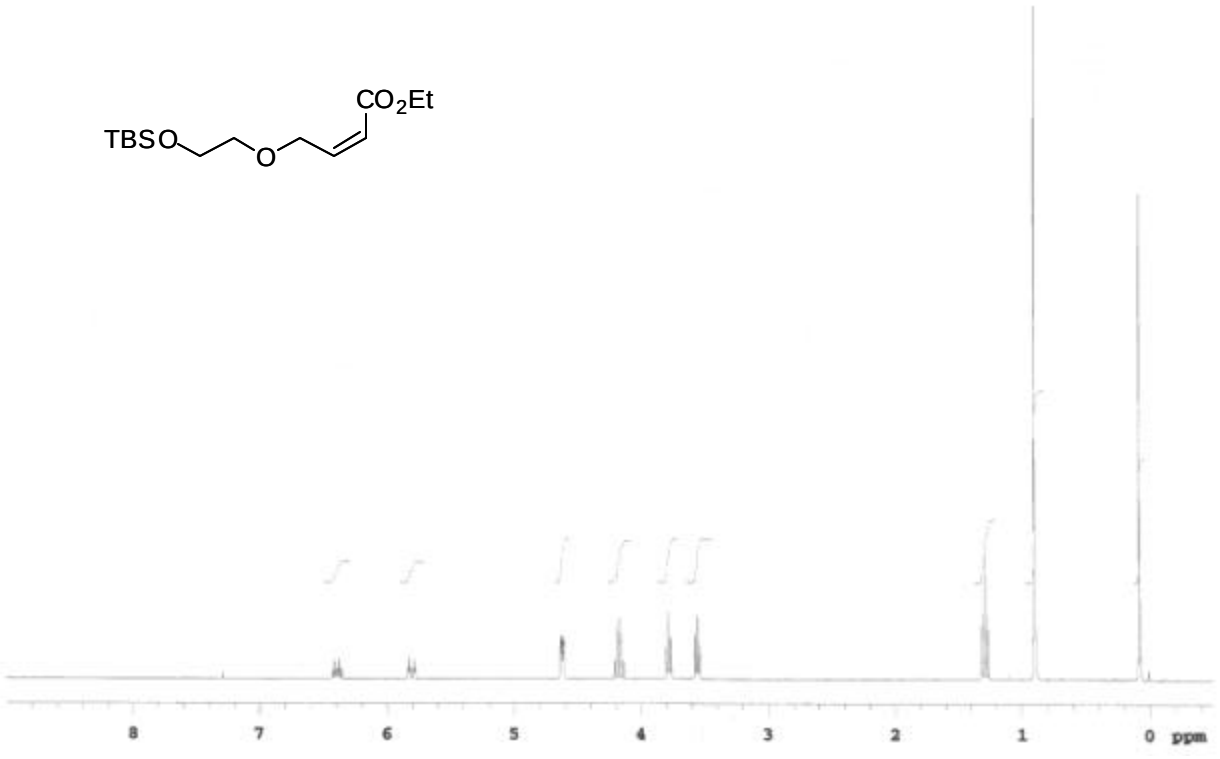
	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
Cl(1)	30(1)	29(1)	46(1)	-2(1)	12(1)	10(1)
O(1)	29(1)	27(1)	21(1)	0(1)	9(1)	2(1)
O(2)	55(1)	22(1)	40(1)	-1(1)	26(1)	3(1)
O(3)	38(1)	18(1)	26(1)	2(1)	13(1)	1(1)
C(1)	19(1)	19(1)	24(1)	-2(1)	5(1)	1(1)
C(2)	26(1)	23(1)	25(1)	-1(1)	9(1)	2(1)
C(3)	25(1)	29(1)	32(1)	0(1)	15(1)	1(1)
C(4)	20(1)	27(1)	28(1)	-1(1)	8(1)	-1(1)
C(5)	22(1)	23(1)	18(1)	0(1)	7(1)	0(1)
C(6)	27(1)	24(1)	21(1)	-1(1)	9(1)	-4(1)
C(7)	34(1)	18(1)	23(1)	0(1)	10(1)	0(1)
C(8)	26(1)	24(1)	23(1)	-1(1)	9(1)	5(1)
C(9)	22(1)	23(1)	23(1)	-1(1)	8(1)	1(1)
C(10)	23(1)	20(1)	18(1)	-1(1)	7(1)	1(1)
C(11)	21(1)	28(1)	48(1)	-2(1)	10(1)	-1(1)
C(12)	27(1)	21(1)	26(1)	-2(1)	10(1)	0(1)
C(13)	27(1)	22(1)	26(1)	0(1)	9(1)	0(1)
C(14)	43(1)	19(1)	33(1)	5(1)	11(1)	3(1)
C(15)	41(1)	29(1)	29(1)	6(1)	7(1)	-4(1)

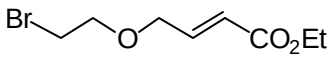
Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for k01311.

	x	y	z	U(eq)
H(2A)	1875	8075	7275	29
H(2B)	199	7928	6597	29
H(3A)	-1591	6624	7085	33
H(3B)	-930	5351	7575	33
H(4A)	-1671	4809	6069	30
H(4B)	-992	6065	5736	30
H(6A)	-113	2991	6192	28
H(7A)	2261	1990	6220	29
H(11A)	5827	5186	6903	48
H(11B)	4869	6453	6660	48
H(11C)	5352	5660	5867	48
H(12A)	2847	7045	5154	29
H(14A)	3532	10970	5048	38
H(14B)	1759	10875	4474	38
H(15A)	3389	11580	3527	50
H(15B)	2632	10267	3171	50
H(15C)	4399	10333	3741	50

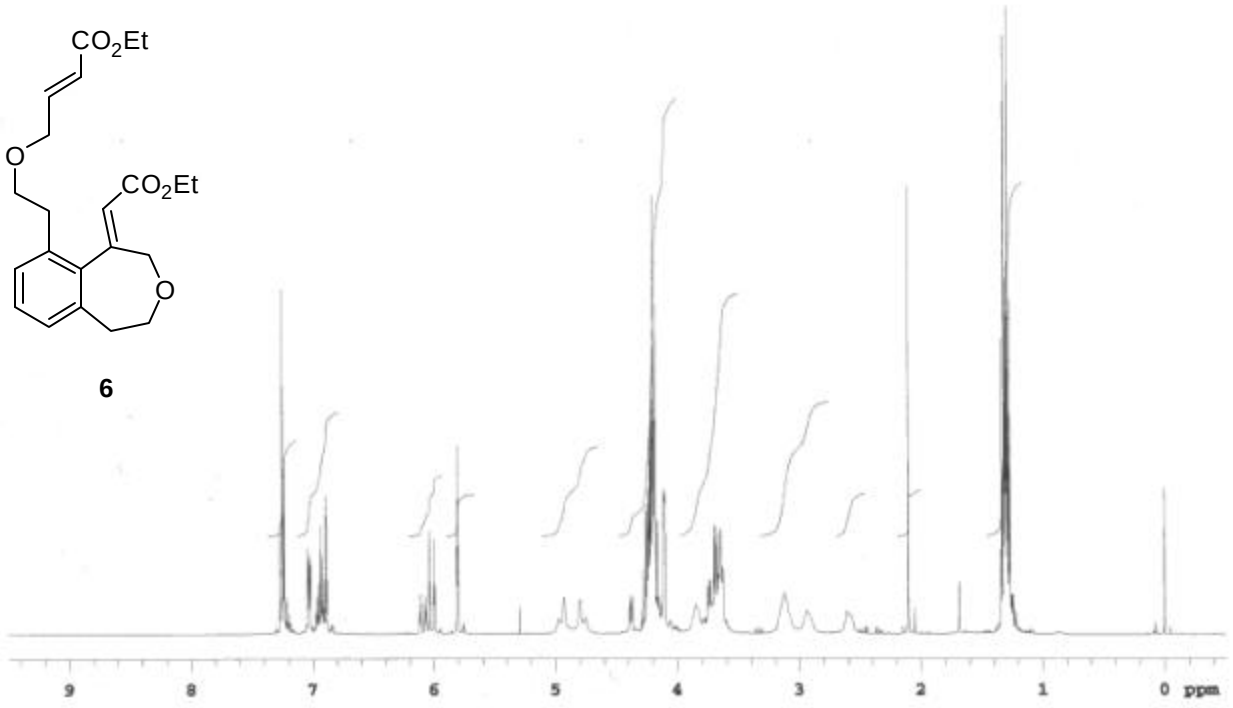

TBSO
O
OH
8
7
6
5
4
3
2
1
0
ppm


TBSO
O
CO2Et
8
7
6
5
4
3
2
1
0
ppm



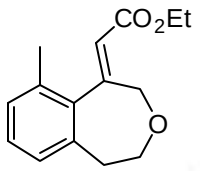


5



6

INDEX	FREQUENCY	PPM	HEIGHT
1	2871.653	7.192	52.4
2	2866.707	7.179	73.4
3	2796.569	7.004	18.7
4	2792.540	6.994	26.0
5	2787.963	6.983	15.2
6	2290.582	5.737	22.2
7	2288.201	5.731	37.9
8	2285.821	5.725	18.9
9	1948.863	4.881	52.5
10	1692.482	4.239	20.3
11	1685.156	4.220	59.7
12	1683.142	4.215	30.0
13	1678.014	4.202	62.9
14	1676.183	4.198	17.7
15	1671.055	4.185	23.1
16	1523.087	3.814	10.8
17	1517.044	3.799	21.3
18	1510.817	3.784	21.5
19	1493.989	3.742	9.4
20	945.680	2.368	200.0
21	926.085	2.319	14.4
22	532.540	1.334	97.0
23	525.398	1.316	114.7
24	518.073	1.297	63.4
25	516.608	1.294	36.4
26	513.128	1.285	10.7
27	509.466	1.276	13.9
28	505.803	1.267	11.8
29	0.000	0.000	12.2



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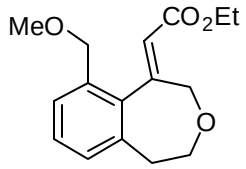

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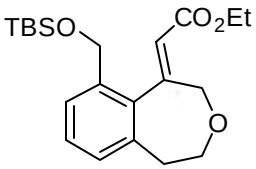

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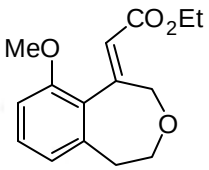

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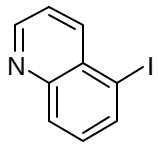

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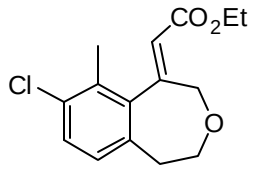

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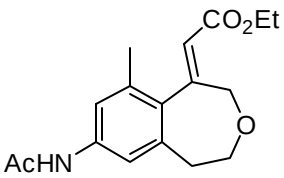

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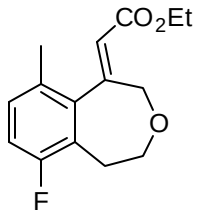

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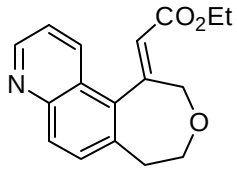

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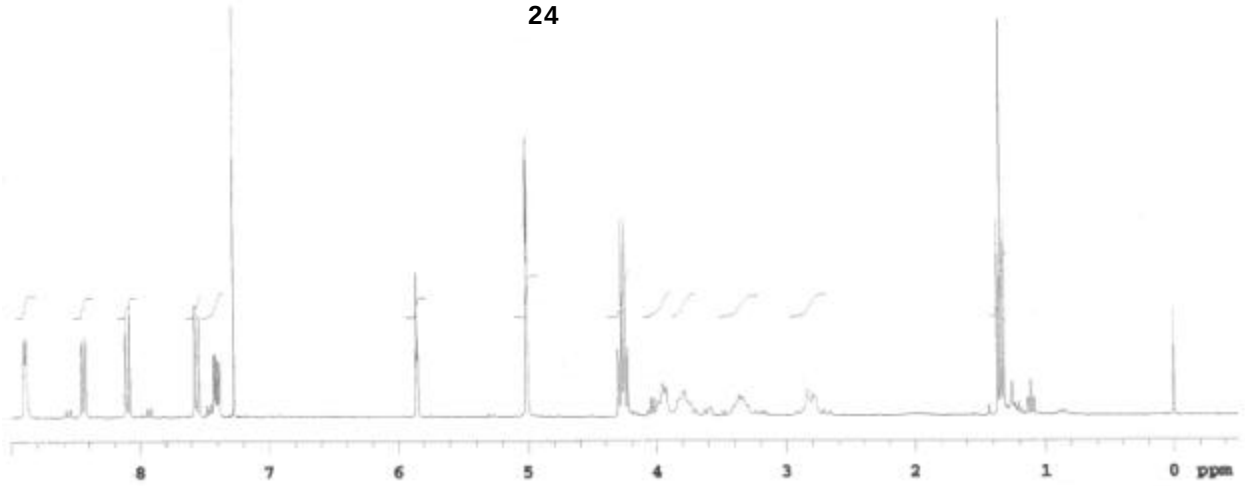

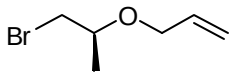

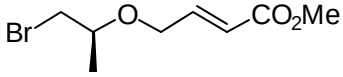

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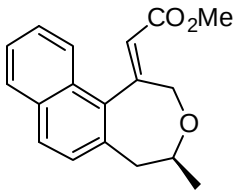

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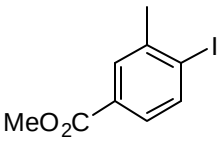

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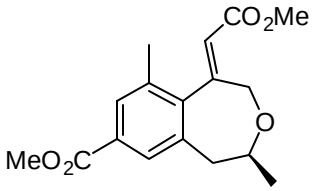

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