Radical-Initiated, Skeletal Rearrangements of Bicyclo-[2.2.2] Lactones

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Supplementary Material

General Methods.

Nuclear magnetic resonance spectra were recorded on Varian Gemini 200 or VXR-200 (^{1}H 200MHz, ^{13}C 50 MHz) or on a Gemini-300 machine (^{1}H 300MHz, ^{13}C 75MHz). Chemical shifts are reported in ppm downfield from an internal tetramethylsilane standard for 1H spectra. ^{13}C spectra were calibrated using the solvent peak. (centre line of $CDCl_3$=77ppm). Standard pulse sequences were used to assist assignments. APT (J-modulated spin echo) sequences were used routinely for ^{13}C spectra and selective decoupling was used to assist ^{1}H nmr assignments. nOe difference spectra and COSY spectra were used using the manufacturers pulse sequences. ^{13}C-^{1}H correlation spectra used the HETCOR pulse sequence. IR spectra were recorded on Bio-Rad FTS135 spectrometer as thin films or KBr discs. Mass Spectra were recorded using VARIAN MAT -44 and FINNIGAN MAT TSQ 70 spectrometers. Elemental Analyses were performed at the university of Stuttgart, Germany.
Tlc was performed on Merck 0.2 mm aluminum backed plates and visulaised using UV light and developed using basic $KMnO_4$ solution. Column chromatography was performed using Merck silica gel 60 (230-400 mesh) under pressure.

THF and toluene were distilled from sodium before use. PA Dichloromethane was distilled from calcium hydride. PA benzene was used directly without further distillation , but was degassed prior to use by passing Ar through the solvent for 5 minutes under ultrasonication.

The following, less familiar, abbreviations are used in the nmr assignments.
br: broad. ap: apparent.

(1S*, 4S*, 8S*)-3-Oxo-8-phenylselenyl-2-oxa-bicyclo[2.2.2]oct-5-ene-4-carboxylic acid methyl ester. (11)

Copper (II) triflate (18 mg, 0.05 mmol) and (S)-diphenylbisoxazoline **10** (25 mg, 0.075 mmol) were dissolved in dry CH_2Cl_2 (4 ml) under argon and the mixture was stirred for 1 hour. The mixture was cooled to -78 °C and a solution of 3-Carbomethoxy-2-pyrone **1** (308 mg, 2.0 mmol) in CH_2Cl_2 (2 ml) was added followed immediately by phenylvinylselenide (550 mg, 3.0 mmol). The cooling bath was removed and the mixture was stirred at room temperature for 16 hours. The mixture was filtered through a plug of silica and the silica washed with dichloromethane. The combined filtrates were evaporated under reduced pressure and the residue purified by column chromatography (EtOAc:petrol 2:8) to give 610 mg of the bicyclic product **11** (90%).

δ_H (200 MHz; $CDCl_3$) 1. 95 (1 H, ddd, *J*=1.7, 3.4, 14.6, 7-H_{endo}), 2.91 (1 H, ddd, *J*=3.6, 9.1, 14.6, 7-H_{exo}), 3.56 (3 H, s, OMe), 3.95 (1 H, dd, *J*=3.4, 9.1, 8-H), 5.22-5.28 (1 H, m, 1-H), 6.56 (1 H, dd, *J*=5.1, 7.7, 6-H), 6.95 (1 H, d, *J*=7.7, 5-H), 7.26-7.32 (3 H, m, H-Ar), 7.53-7.58 (2 H, m, H-Ar); δ_C (50 MHz; $CDCl_3$) 36.04 (C8), 36.90 (C7), 52.44 (OMe), 59.52 (C4), 74.04 (C1), 128.37 (C5 or C6 or CAr_{para}), 128.53 (CAr_{ipso}), 129.10 (CAr_{ortho}), 131.28 (C5 or C6 or CAr_{para}), 131.56 (C5 or C6 or CAr_{para}), 135.12 (CAr_{meta}), 167.06 (CO_2Me), 168.91 (C3); ν_{max} (cm^{-1}, film) 3073, 2952, 1741(C=O), 1577, 1438, 1287, 1087, 736; *m/z*(CI +ve) 339 (24%, ^{80}SeM+H), 307 (30%, ^{80}SeM+H-MeOH), 279 (10%, 307-CO), 183 (30%, M+H-SePh), 155 (100%, M+H-CH_2CHSePh), 137 (62%, 155-H_20); *m/z*(CI -ve) 519 (10%, 2M-SePh), 181 (100%; M-H-SePh), 157 (20%, $PhSe^-$); (Found C, 53.51, H, 4.20. $C_{15}H_{14}O_4Se$ requires C, 53.43, H, 4.18%). Analysis of the selectivity using nmr in the presence of $Eu(hfc)_3$ showed the ee to be 56% in favour of the 1*S* isomer.

(1S*, 5S*, 4R*)-3-Oxo-2-oxa-bicyclo[3.3.0]oct-7-ene-4-carboxylic acid methyl ester 4

Method 1

Selenide **11** (500 mg, 1.48 mmol) was dissolved in 75 ml of benzene and heated to reflux. A solution of triphenyltinhydride (655 mg, 1.86 mmol) and AIBN (35 mg, 0.23 mmol) in benzene (25 ml) was added via syringe pump over 1.5 hours. The mixture was heated for a further 45 minutes before being cooled to room temperature. The solvent was removed under reduced pressure and the residue was further purified by flash column chromatography (gradient elution EtOAc : Petrol 2:8 to 3:7) to give the bicyclic lactone **4** (208 mg, 77%) as a 15:1 mixture of endo exo isomers.

δ_H (300 MHz; $CDCl_3$) 2.37 (1 H, ap dquin, *J*= 17.6, 2.3, 6-H_{endo}), 2.80 (1 H, ddm, *J*=17.6, 8.0, 6-H_{exo}), 3.36 (1 H, d, *J*=6.6, 4-H), 3.48 (1 H, ap qd, *J*=8.0, 2.5, 5-H), 3.79 (3 H, s, OMe), 5.57 (1 H, dm, *J*=7.7, 1-H), 5.88 (1 H, ap dq, *J*=5.7, 2.2, 8-H), 6.09 (1 H, ap dt, *J*=5.7, 2.1, 7-H); δ_C (75 MHz; $CDCl_3$) 38.38 (C6), 40.11 (C5), 53.07 (OMe), 53.84 (C4), 88.57 (C1), 128.90 (C8), 136.78 (C7), 168.27 (CO_2Me), 171.60 (C3); ν_{max} (cm^{-1}, film) 2956, 1773 (lactone C=O), 1735 (ester C=O), 1437, 1271, 1148, 1024, 989; *m/z*(CI +ve) 183 (100%, M+H), 139 (20%, M+H-CO_2), 137 (50%, M-CO_2H); *m/z*(CI -ve) 181 (100%, M-H), 164 (20%, M-H_2O), 153 (18%, M-H-CO), 137 (20%, M-H-CO_2); (Found C, 59.69., H, 5.54. $C_9H_{10}O_4$ requires C, 59.34, H, 5.53%). (1*S*, 4*R*, 5*S*) is the major isomer starting from selenide **11**.

(1R*, 5S*, 4R*)-3-Oxo-2-oxa-bicyclo[3.2.1]oct-6-ene-4-carboxylic acid methyl ester (8a) (major) and

(1R*, 5S*, 4S*) 3-Oxo-2-oxa-bicyclo[3.2.1]oct-6-ene-4-carboxylic acid methyl ester (8b) (minor)

Method 2

Selenide **11** (250 mg, 0.75 mmol), tristrimethylsilylsilane (277 mg, 1.11 mmol) and AIBN (18 mg, 0.11 mmol) were dissolved in 60 ml of benzene and heated to reflux for about 45 minutes. The mixture was cooled to room temperature and the solvent was removed under reduced pressure. The mixture was applied to a short (4 cm) column of flash silica and the column eluted with a mixture of petrol, EtOAc and NEt_3 (90:10:10) until the silicon and selenium residues had eluted (about 10 fractions) The solvent was then changed to a mixture of petrol, EtOAc and NEt_3 (50:50:10) and elution continued. The lactones **8a** and **8b** were obtained as an inseparable 60:40 mixture (117 mg, 87%). It is important that following evaporation of the benzene the column is completed as rapidly as possible in order to prevent allylic rearrangement.

Data for the inseparable 60:40 mixture of epimers at C4. Signals from minor isomer have ‘ marking.

δ_H (300 MHz; $CDCl_3$) 1.95 (0.6 H, dddd, *J*=2.0, 3.0, 4.3, 12.2, 8-H_{eq}), 2.05 (0.4 H, d, *J*=12.2, 8’-H_{ax}), 2.12 (0.4 H, ddd, *J*=3.1, 4.4, 12.2, 8’-H_{eq}), 2.42 (0.6 H, d, *J*=12.2, 8-H_{ax}), 3.20-3.24 (0.6 H, m, 5-H), 3.24-3.29 (0.4 H, m, 5’-H), 3.59 (0.6 H, ap t, *J*=1.6, 4-H), 3.76 (1.2 H, s, 4’-CO_2*Me*), 3.79 (1.8 H, s, 4-CO_2*Me*), 3.87 (0.4 H, d, *J*= 4.1, 4’-H), 5.12-5.15 (1 H, m, 1-H and 1’-H), 6.43 (1 H, ap dd, *J*=2.0, 5.3, 7-H and 7’-H), 6.52 (0.6 H, dd, *J*=2.9, 5.7, 6-H), 6.55 (0.4 H, dd, *J*=2.9, 5.7, 6’-H); δ_C (75 MHz; $CDCl_3$) 38.2 (C8), 40.1 (C5’), 40.6 (C5), 41.1 (C8’), 52.3 (4’-CO_2*Me*), 52.7 (4-CO_2*Me*), 54.4 (C4), 56.1 (C4’), 81.6 (C1), 81.9 (C1’), 134.1 (C7’), 135.0 (C7), 141.1 (C6’), 141.5 (C6), 165.3 (C3), 165.5 (C3’), 168.3 (4’-*C*O_2Me), 168.7 (4-*C*O_2Me); ν_{max} (cm^{-1}, film) 2956, 1725 (C=0), 1436, 1362, 1168, 952, 737; *m/z*(CI +ve) 183 (100%, M+H), 139 (50%, M+H-CO_2), 137 (60%, M-CO_2H); *m/z*(CI -ve) 181 (100%, M-H), 153 (50%, M-H-CO), 137 (40%, M-H-CO_2); (Found C, 59.22., H, 5.62. $C_9H_{10}O_4$ requires C, 59.34, H, 5.53%).

Determination of the rate constant for cyclisation

Selenide **11** (50 mg, 0.15 mmol), triphenyltin hydride (218 mg, 0.62 mmol) and AIBN (7 mg, 0.044 mmol) were dissolved in 40 ml of benzene and heated to reflux for about 45 min. The mixture was cooled to room temperature and the solvent was removed under reduced pressure and the crude mixture analysed by nmr. The contaminating tin residues were then removed by column chromatography. The crude material was placed on a column which was eluted with a mixture of Petrol: EtOAc 9:1 until the tin residues had eluted (about 10 fractions) The solvent was then changed to Petrol: EtOAc 7:3 and elution continued. All fractions containing reaction products were combined and the ratios determined by nmr. The ratio of reduced material **3** to rearranged material **4** was 18:82 (0.0155 M) and 40:60 (0.0310 M).

(1R*, 4S*)-3-Oxo-2-oxa-bicyclo[2.2.2]oct-5-ene-4-carboxylic acid methyl ester (3).

δ_H (300 MHz; $CDCl_3$) 1.60-1.73 (2 H, m, 7-H_{endo}, 8-H_{endo}), 2.23-2.39 (2 H, m, 7-H_{exo}, 8-H_{exo}), 3.88 (3 H, s, OMe), 5.24-5.28 (1 H, m, 1-H), 6.52(1 H, dd, *J*=5.2, 7.8, 6-H), 6.77 (1 H, dd, *J*=1.7, 7.8, 5-H); δ_C (50 MHz; $CDCl_3$) 22.82 and 25.58 (C7 and C8), 52.85 (OMe), 54.68 (C4), 74.76 (C1), 131.23 and 132.44 (C5 and C6), 168.81 (CO_2Me), 170.28 (C3); ν_{max} (cm^{-1}, KBr) 1956, 1733 (C=O), 1439, 1365, 1284, 930, 736, 703; *m/z*(CI +ve) 183 (80%, M+H), 139 (60%, M+H-CO_2), 137 (100%, M-CO_2H); *m/z*(CI -ve) 181 (100%, M-H), 167 (38%, M-Me), 137 (90%, M-H-CO_2); (Found C, 59.31, H, 5.54. $C_9H_{10}O_4$ requires C, 59.34, H, 5.53%).