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Novel Reactions of 2-Carbomethoxymethyl-2-Thiophenyl-8-oxabicyclo[3.2.1]octan-3-one

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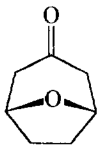
Abstract: The title compound rearranges to produce 1-carbomethoxymethyl-2-thiophenyl-8-oxabicyclo-[3.2.1]octan-7-one on treatment with $BF_3.Et_2O$. and undergoes an oxidation/rearrangement to form 2-carbomethoxymethyl-2-thiophenyl-3.9-dioxabicyclo[4.2.1]nonan-4-one on treatment with $NaIO_4$.

As part of our continuing efforts to use 8-oxabicyclo[3.2.1]octan-3-one (**1**) for the construction of pseudoguaianolide sesquiterpene lactones[1], we required access to gram quantities of the 2-carbomethoxymethyl derivative (**2**). The parent structure **1** was prepared on the 30 gram scale used well-tried methods[2], but attempts to convert this into the monosubstituted product **2** using a variety of bases in conjunction with methyl bromoethanoate provided at best 35-40% yield of the required product. This was always contaminated with up to 10% of the symmetrical disubstituted product **3** and this was difficult to remove. In contrast, reaction of **1** with LDA in a mixture of THF and DMPU[3] with subsequent addition of diphenyl disulphide, provided the expected thiophenyl derivative **4** as a mixture of isomers (67% isolated yield) with only a small quantity of the dithiophenyl derivatives **5**. There was no necessity to separate the isomers **4** since reaction with sodium hydride in THF and methyl bromoethanoate provided only one dialkylated product **6** (52% or 68% if recovered starting material was taken into account). The stereoselectivity of this alkylation was in accord with our previous results in this area[4] and was conclusively demonstrated through an X-ray crystallographic analysis of compound **6**[5].



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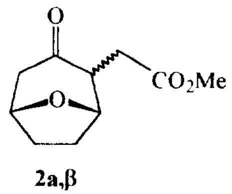
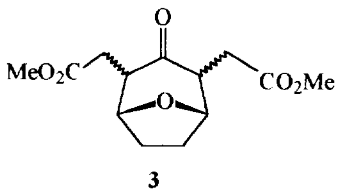


2a,β
2b, α



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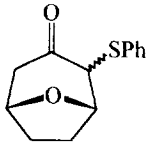
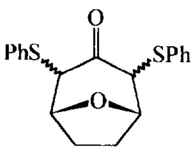
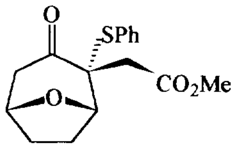


4a, α
4b, β

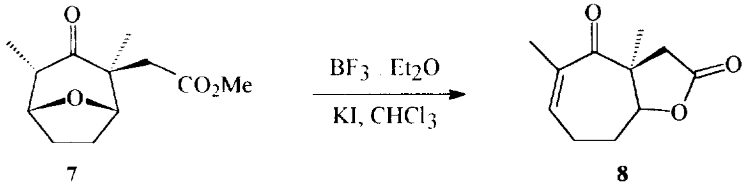


5a,αα
5b, αβ

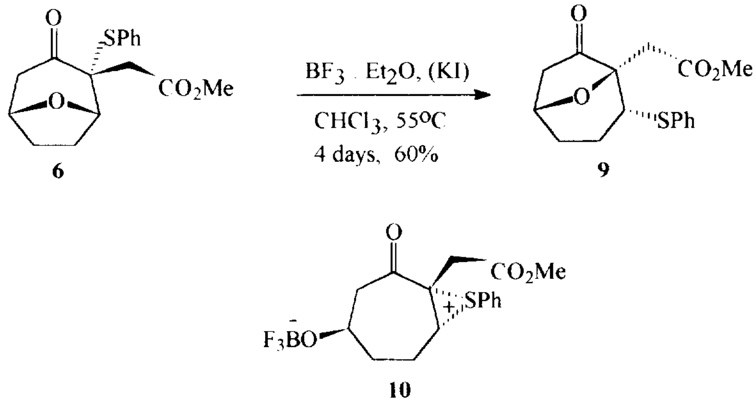


6

In our previous work (Scheme 1) we had used the carbomethoxy group to participate in the cleavage of the ether bridge of compound **7** using $BF_3.Et_2O$ in the presence of KI to produce **8**[1]. With quantities of compound **6** in hand we investigated the equivalent reaction with this substrate. To our surprise this compound reacted with this same reagent mixture to yield one product, the rearranged thiophenyl derivative **9**, in *ca.* 60% isolated yield (4 days at 55°C). This presumably arises *via* the episulphonium ion **10** (Scheme 2). The same result was observed in the absence of KI.

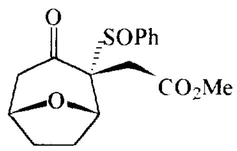


Scheme 1

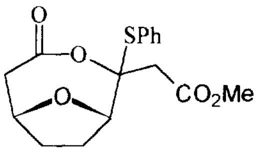


Scheme 2

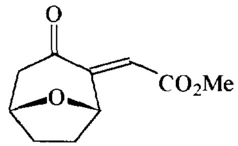
In an attempt to circumvent this problem we attempted to prepare the sulphoxide **11** by oxidation of **6** with sodium periodate in methanol at room temperature. Although the reaction failed to go to completion, two crystalline products were obtained. One was clearly the desired sulphoxide **11** (3% isolated yield or 11% if recovered starting material was taken into account), but the structure of the major product was not immediately obvious. Its molecular weight (323.095, $C_{16}H_{18}O_5S$) was identical to that of the sulphoxide and on this basis the isolated yield was 17% (70% if recovered starting material was taken in account). In the IR spectrum there were two carbonyl absorptions at 1735 and 1758 cm^{-1}, and the ^{13}C NMR spectrum clearly showed ten discrete signals in addition to those expected for the phenyl ring. DEPT studies confirmed the presence of one CH_3, four CH_2's, two CH's and three quaternary carbons. These latter signals were the most intriguing. One was clearly an ester carbonyl (168.85 δ) but the other signals at 122.20 δ and 153.53 δ were less easily assigned. Further NMR studies (HETCOR and 2D-COSY) were consistent with the structure **12**, and we propose the mechanism shown in Scheme 3 for the production of this novel compound.



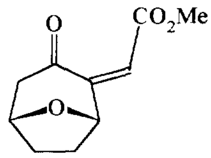
11



12



13



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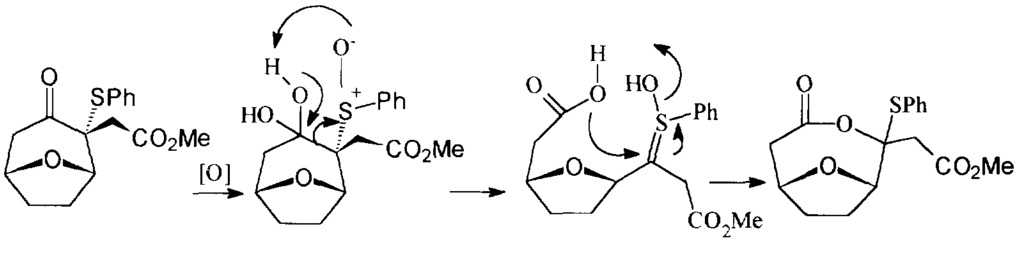

Scheme 3

Attempts to improve the yields of these products produced additional products rather than the desired improvements. At 40°C ($NaIO_4$ in methanol) very little of the novel product was obtained (3%, all the subsequent yields assume that recovered starting material has been taken into account), but an improved yield of the sulphoxide (34%) together with the elimination product **13** (11%). With peracetic acid the same products were obtained but in the yields of 10%, 30% and 17% respectively. Finally, reaction with H_2O_2 and SeO_2 (1 equivalent of each) provided the sulphoxide as the sole product (49%), the same reagent mixture but with two equivalents of H_2O_2 yielded sulphoxide and two isomeric products **13** and **14** in yields of 47%, 29% and 38% respectively. This dramatic variability in reaction pathway was unexpected and rendered the chemistry unusable. In consequence, the thiophenyl compound **6** was reduced to the bicyclic ester **2b** using Raney nickel, and the reaction not only proceeded in high yield but with complete stereoselectivity. Once again the structure was rigorously established through the use of X-ray crystallography[5]. A discussion of the chemistry of this key compound will be the subject of another paper.

EXPERIMENTAL

Routine Experimental Procedures and Instrumentation:

Reagents and solvents were purified when necessary according to the usual procedures described in the literature[6]. Flash chromatography[7] on silica gel (32-63μm) was used for the purification of the products of each reaction. Rfs were determined by Analytical Thin Layer Chromatography on a 0.25 mm film of silica gel containing fluorescent indicator UV_{254} supported on a plastic sheet (Camlab plc.).

The melting points were determined on a Electrothermal digital apparatus without correction. Infrared Spectra were recorded on a Perkin Elmer 881 grating spectrometer, scanning from 625 to 4000 cm^{-1}. The samples were diluted in chloroform or dichloromethane and run against a reference cell with the same solvent. Mass Spectra were recorded at the SERC Mass Spectrometry Centre at Swansea University. Alternatively some spectra were recorded on a MICROMASS 7070F at Reading University. ^{1}H and ^{13}C NMR spectra were recorded on a JEOL JNM-EX400 (400 and 100.53MHz). Alternatively they were recorded on a Bruker WM400 at the Chemistry Department at Warwick University. Samples were dissolved in $CDCl_3$ and tetramethylsilane was used as the internal standard ($\delta = 0$). All the NMR analysis was supported by NOE, DEPT, COSY and HETCOR spectral data. Elemental Analyses were performed by MEDAC LTD at the Chemistry department of Brunel University - London. The analyses were obtained in duplicate and the average values are quoted. X-Ray crystallography data were collected with MoKα radiation using the MARresearch Image Plate System. The crystals were positioned at 75mm from the Image Plate. 95 frames were measured at 2° intervals with a counting time of 2 minutes. Data analysis was carried out with the XDS program[8]. The structures were solved using direct methods with the Shelx86 program[9]. The non-hydrogen atoms were refined with anisotropic thermal parameters. The hydrogen atoms were included in geometric positions. The structure was then refined using Shelxl[10]. 8-Oxabicyclo[3.2.1]octan-3-one (**1**) was prepared according procedure described in the literature[2].

2α-Thiophenyl-8-oxabicyclo[3.2.1]octan-3-one (4a), 2β-thiophenyl-8-oxabicyclo-[3.2.1]octan-3-one (4b), 2α,4α-dithiophenyl-8-oxabicyclo[3.2.1]octan-3-one (5a) and 2α,4β-dithiophenyl-8-oxabicyclo[3.2.1]-octan-3-one (5b):

To a diisopropylamine solution (19.92g, 0.2mol) in dry THF (40ml) was added n-butyllithium (80ml, 0.2mol, 2.5M in hexane) under a nitrogen atmosphere at -78°C. This mixture was stirred for 1 hour and then a solution of 8-oxabicyclo-[3.2.1]octan-3-one (**1**) (24.29g, 0.2mmol; 180ml dry THF) was added via syringe. After 2 hours stirring at -78°C, DMPU (100ml) and a solution of diphenyl disulphide (42.52g, 0.2mol; 140ml dry THF) were added. The temperature was allowed to rise to room temperature and the mixture was stirred overnight. The mixture was concentrated and diethyl ether (700ml) was added, then hydrochloric acid solution (100ml, 2M) and the organic phase was washed with a saturated solution of sodium bicarbonate (200ml), and dried over magnesium sulphate. After filtration, it was concentrated and the products separated and purified by flash chromatography on silica gel with a mixture of petroleum spirit and ethyl acetate (4:1) as eluants. The products **4a** and **4b** (24.34g, 0.1mol, 54% yield) and **5a** and **5b** (3.30g, 0.01mol, 5% yield) were obtained and some starting material (4.71g, 0.04mol, 19%) was also recovered.

Compound 4a ($C_{13}H_{14}O_2S$, white solid): *m.p.* 53-54°C; *Rf:* 0.28 (petroleum spirit/ethyl acetate 3:1); *IR* $\nu_{max.}$ *(cm^{-1}):* 3060 (W); 3005, 2971 (S); 2920, 2882 (W); 1714 (VS); 1583 (M); 1480, 1470, 1439 (S); 1412 (M); 1349, 1286 (S), 1271 (M); 1233 (S); 1179 (M); 1121 (VS); 1089 (M); 1052 (S); 1025 (M); 969 (S); 957 (M); 920 (W); 885 (S); 835 (M); 689 (S); 637 (W); *^{1}H NMR (400MHz, $CDCl_3$) δ:* 1.70-1.77 (m, 1H, H7), 1.91-2.15 (m, 3H, H6,H6' and H7'), 2.41-2.46 (dd, 1H, J=1.1 and 14.8Hz, H4), 2.79-2.84 (dd, 1H, J=5.4 and 14.8Hz, H4'), 4.25-4.26 (d, 1H, J=4.7, H2), 4.51-4.54 (dd, 1H, J=4.8 and 7.0Hz, H1), 4.74-4.77 (dd, 1H, J *ca.* 6Hz, H5), 7.24-7.32 (m, 3H, Ph), 7.41-7.44 (m, 2H, Ph); *^{13}C NMR (100MHz, $CDCl_3$) δ (DEPT):* 25.43 (CH_2, C6), 29.32 (CH_2, C7), 49.75 (CH_2, C4), 63.01 (CH, C2), 76.05 (CH, C5), 78.52 (CH, C1), 127.55 (CH, Ph), 129.14 (CH, Ph), 132.25 (CH, Ph), 132.54 (C, Ph), 202.90 (C, C=O). *Accurate Mass Peak Match:* 234.0714 ($C_{13}H_{14}SO_2$ requires 234.07145).

Compound 4b ($C_{13}H_{14}O_2S$, white solid): *m.p.* 79-80°C; *Rf:* 0.28 (petroleum spirit/ethyl acetate 3:1); *IR* $\nu_{max.}$ *(cm^{-1}):* 3060 (W); 3005, 2966 (S); 1710 (VS); 1583 (M); 1482, 1469 (S); 1450 (W); 1440, 1409, 1345 (S); 1317, 1301 (W); 1282 (M); 1198, 1169, 1130 (S); 1072 (VS); 1025 (W); 1001, 980 (M); 955 (W); 909 (M); 887 (W); 854 (M); 829 (W); 688 (M); *^{1}H NMR (400MHz, $CDCl_3$) δ:* 1.72-1.81 (m, 2H, H6 and H7), 1.99-2.07 (m, 1H, H6'), 2.07-2.21 (m/d, 2H, J=15.4Hz, H7' and H4), 3.32-3.37 (ddd, 1H, J=1.8, 5.1 and 15.3Hz, H4'), 3.44 (s, 1H, H2), 4.74-4.77 (t, 1H, J ca.6Hz, H5), 4.78-4.80 (d, 1H, J=7.7Hz, H1), 7.23-7.38 (m, 3H, Ph), 7.41-7.44 (m, 2H, Ph); *^{13}C NMR (100MHz, $CDCl_3$) δ (DEPT):* 28.55 (CH_2, C6), 28.80 (CH_2, C7), 45.56 (CH_2, C4), 61.34 (CH, C2), 75.79 (CH, C5), 79.02 (CH, C1), 127.67 (CH, Ph), 129.10 (CH, Ph), 131.58 (CH, Ph), 133.85 (C, Ph), 203.60 (C, C=O); *Accurate Mass Peak Match:* 234.0714 ($C_{13}H_{14}SO_2$ requires 234.07145).

Compound 5a ($C_{19}H_{18}O_2S_2$, yellow solid): *Rf:* 0.24 (petroleum spirit/diethyl ether 4:1); *^{1}H NMR (220MHz, $CDCl_3$) δ:* 1.75-2.11 (m, 2H, H6 and H7), 2.12-2.30 (m, 2H, H6' and H7'), 4.36-4.42 (d, 2H, J=4.4Hz, H2 and H4), 4.40-4.49 (m, 2H, H1 and H5), 7.30-7.42 (m, 6H, Ph), 7.43-7.58 (m, 4H, Ph).

Compound 5b ($C_{19}H_{18}O_2S_2$, yellow solid): *Rf:* 0.23 (petroleum spirit/diethyl ether 4:1); *IR* $\nu_{max.}$ *(cm^{-1}):* 3056, 2957, 2922, 2850 (M); 1711 (S); 1678, 1669, 1651, 1624 (W); 1583,1482 (M); 1439 (S); 1344 (M); 1302, 1273 (W); 1245, 1230, 1206, 1147, 1115, 1089 (M); 1062 (S); 1026 (M); 1002, 969, 950 (W); 909 (M); 884 (W); 862 (M); 781 (W); 744, 691 (S); 656 (W); *^{1}H NMR (220MHz, $CDCl_3$) δ:* 1.70-2.10 (m, 2H, H6 and H7), 2.10-2.30 (m, 2H, H6' and H7'), 3.62 (s, 1H, H2), 4.55-4.70 (bt, 1H, J=4.4Hz, H5), 4.83-4.92 (bd, 1H, J=6.6, H1), 4.93-5.10 (bd, 1H, J=4.4Hz, H4'), 7.25-7.40 (m, 6H, Ph), 7.40-7.56 (m, 4H, Ph); *^{13}C NMR (100MHz, $CDCl_3$) δ (DEPT):* 24.73 (CH_2, C7), 24.25 (CH_2, C6), 59.35 (CH, C4), 62.17 (CH, C2), 79.78 (CH, C5), 80.40 (CH, C1), 127.74 (CH, Ph), 127.93 (CH, Ph), 129.51 (CH, Ph), 131.90 (CH, Ph), 132.47 (CH, Ph), 132.94 (C, Ph), 133.66 (C, Ph), 200.28 (C, C3 (C=O)); *MS (mixture of* 5a *and* 5b *1:1) m/z (%):* 342 (20), 233 (100), 218 (4), 205 (6), 187 (19), 165 (13), 149 (18), 136 (13), 123 (44), 122 (21), 109 (48), 95 (25), 77 (24), 69 (17), 67 (24), 65 (27), 51 (17), 46 (25), 39 (30).

2α-Thiophenyl,2β-methoxycarbonylmethyl-8-oxabicyclo[3.2.1]octan-3-one (6):

To a suspension of sodium hydride (2.43g, 60.4mmol, 60%) in dry THF (35ml) was added a solution of 2-thiophenyl-8-oxabicyclo[3.2.1]octan-3-one (14.00g, 60.0mmol, mixture of compounds **5a** and **5b**) in dry THF (75ml), at room temperature, under nitrogen. The reaction mixture was stirred at 80°C for 3 hours. Then methyl bromoacetate (6.3ml, 63mmol) was added via syringe and the reaction mixture was stirred at the same temperature for 4 hours and then left to cool to room temperature, stirring overnight. The reaction was quenched with a saturated aqueous solution of ammonium chloride (400ml) and the products were extracted with diethyl ether (4 x 200ml). The combined organic extracts were dried over magnesium sulphate and concentrated. The product was purified by flash chromatography on a silica gel column with a mixture of petroleum spirit and diethyl ether (2:1) as eluants. The alkylation product **6** (9.53g, 31.11mmol, 52% yield) was obtained and some starting material was also recovered (3.36g, 14.34mmol, 24%). The product was recrystallized for X-Ray crystallography using n-hexane/diethyl ether.

Compound 6 ($C_{16}H_{18}SO_4$, white crystals): *m.p.* 89-90^oC; *Rf:* 0.30 (petroleum spirit/ diethyl ether 1:1); *IR* $\nu_{max.}$ *(cm^{-1}):* 3080-2840 (M); 1735, 1709 (S); ; 1438 (MS), 1281, 1229, 1202, 1180 (M); 1159, 1133, 1102 (S); 1024, 997 (M); 663, 623 (M); *^1H NMR (400MHz, $CDCl_3$) δ:* 1.62-1.78 (m, 1H, H6), 1.93-2.01 (m, 2H, H6' and H7), 2.35-2.40 (dd, 1H, J=1.29 and 14.33Hz, H4), 2.59-2.66 (d/m, 2H, J=15.36, H8 and H7'), 3.08-3.13 (dd, 1H, J=5.35 and 14.33Hz, H4'), 3.50-3.55 (d, 1H, J=15.33Hz, H8'), 3.70 (s, 3H, OMe), 3.91-3.93 (bd, 1H, J=6.51, H1), 4.70-4.74 (bt, 1H, J ca. 6Hz, H5), 7.24-7.41 (m, 3H, Ph), 7.52-7.56 (m, 2H, Ph); *^{13}C NMR (25MHz, $CDCl_3$) δ (DEPT):* 25.17 (CH_2, C7), 29.12(CH_2, C6), 40.44 (CH_2, C8), 47.50 (CH_2, C4), 51.88 (CH_3, OMe), 67.25 (C, C2), 76.99 (CH, C5), 81.86 (CH, C1), 128.31 (C, Ph-S), 128.98 (CH, Ph-o), 129.52 (CH, Ph-p), 138.09 (CH, Ph-m), 170.42 (C, C9 (C=O)), 203.87 (C, C3 (C=O)); *MS m/z (%):* 306 (100), 289 (3), 275 (36), 257 (3), 247 (2), 234 (3), 222 (13), 197 (19), 165 (9), 135 (24), 109 (12), 91 (9), 77 (4), 65 (8), 59 (5), 55 (5), 41 (6), 39 (8); *Elemental Analysis:* C 62.73%, H 5.92%, S 10.47% (calc. C 62.82%, H 5.92%, S 10.47%).

1α-Methoxycarbonylmethyl-2α-thiophenyl-8-oxabicyclo[3.2.1]octan-7-one (9):

To a solution of 2α-thiophenyl,2β-methoxycarbonylmethyl-8-oxabicyclo[3.2.1]-octan-3-one (**6**) (0.50g, 1.63mmol; 10ml $CHCl_3$) was added boron trifluoride etherate (1ml, ca. 8mmol) at room temperature, under a nitrogen atmosphere. The mixture was stirred at 55 ^oC for 4 days. Then a saturated aqueous solution of sodium bicarbonate (10ml) was added and the products extracted with DCM (4 x 20ml). The organic phase was washed with saturated sodium thiosulphate aqueous solution (20ml), dried over magnesium sulphate and concentrated. The product was purified by flash chromatography on a silica gel column with a mixture of petroleum spirit and ethyl acetate (1:1) as eluants, yielding 0.29g (0.95mmol, 58%) of **9**. The product was recrystallized for X-ray crystallography from a mixture of n-hexane and diethyl ether. Addition of dry potassium iodide (4.89mmol) to the initial solution of **6** did not change the results of this experiment.

Compound 9 ($C_{16}H_{18}SO_4$, white crystals): *m.p.* 88-89 ^oC; **Rf:** 0.37 (petroleum spirit / ethyl acetate 2:1); *IR* ν_{max} *(cm^{-1}):* 3080-2840 (M); 1759, 1736 (S); 1462 (M); 1439 (S); 1361, 1342 (M); 1240-1080 (bM); 1086 (S); 1063, 1026, 996, 962 (M); 800-680 (bW); 690 (M); 622 (W); *^1H NMR (400 MHz, $CDCl_3$) δ:* 1.59-1.74 (m, 2H, H3 and H4), 2.05-2.13 (m, 2H, H3' and H4'), 2.25-2.30 (d, 1H, J=17.77Hz, H6), 2.65-2.70 (d, 1H, J=16.53Hz, H8), 2.83-2.90 (dd, 1H, J=17.76 and 8.05Hz, H6'), 3.25-3.29 (d, 1H, J=16.53Hz, H8'), 3.34-3.39 (dd, 1H, J=4.99 and 6.38Hz, H2), 3.59 (s, 3H, OMe), 4.69-4.72 (dd, 1H, J= 3.00 and 8.03 Hz, H5), 7.21-7.29 (m, 3H, Ph), 7.38-7.42 (m, 2H, Ph); *^{13}C NMR (62.89 MHz, $CDCl_3$) δ (DEPT):* 26.45 (CH_2, C4), 30.16 (CH_2, C3), 37.69 (CH_2, C8), 41.11 (CH_2, C6), 50.79 (CH, C2), 51.59 (CH_3, OMe), 72.35 (CH, C5), 81.88 (C, C1), 127.38 (CH, Ph-p), 128.97 (CH, Ph-o), 132.15 (CH, Ph-m), 133.86 (C, Ph-S), 169.68 (C, C9 (C=O)), 212.39 (C, C7 (C=O)); *MS (EI^+, I 2.24v) m/z (%):* 306 (11), 275 (66), 257 (4), 224 (27), 197 (83), 177 (31), 165 (45), 149 (10), 136 (50), 135 (60), 123 (39), 109 (27), 95 (26), 91 (26), 81 (8), 77 (8), 67 (35), 65 (18), 59 (17), 55 (15), 43 (11), 41 (23), 39 (22); *Elemental Analysis:* Calculated C 62.73%, H 5.92%, S 10.47%; Observed C 62.68%, H 5.90%, S 10.33%.

Oxidation of 2α-thiophenyl,2β-methoxycarbonylmethyl-8-oxabicyclo[3.2.1]octan-3-one (6):

a ($NaIO_4$): To a solution of **6** (600 mg, 1.96 mmol) in methanol (6 ml) was added an aqueous solution of sodium metaperiodate (420 mg, 1.96 mmol; 3 ml H_2O) dropwise at 0°C. The mixture was stirred at this temperature for 4 hours, then at RT overnight. The white precipitate formed over the reaction time was separated by filtration. The filtrate was concentrated and taken up into DCM (10 ml). Distilled water was added (10 ml) and extractions with DCM (3 x 20 ml) were performed. The combined organic extracts were dried over magnesium sulphate, filtered and concentrated to a yellow oil (630 mg). The mixture was submitted to flash column chromatography on silica gel with a mixture of petroleum spirit and ethyl acetate as eluants (from 50% to 100% ethyl acetate). 71% of the starting material (425 mg) was recovered and two products were obtained: **11** (18mg, 3% yield) and **12** (110 mg, 17% yield).

The same method described above was followed, the mixture being stirred at 40°C for 7 hours and then at RT overnight. Three products were obtained: **11** (13% yield), **12** (1% yield) and **13** (4% yield) and 61% of the starting material was recovered.

b (HOOAc): To a solution of **6** (500 mg, mmol) in acetone (16 ml) was added hydrogen peroxide 30% w/v (0.72 ml, mmol) and glacial acetic acid (0.1 ml) at room temperature. The mixture was stirred for 5 days. Then the solvent was evaporated, ethyl acetate (20 ml) was added and the mixture was washed with sodium bicarbonate aqueous saturated solution (20 ml). The organic phase was dried over magnesium sulphate, filtered and concentrated to a yellow oil (600 mg). This mixture was submitted to a flash chromatography on silica gel with a mixture of petroleum spirit and ethyl acetate (2:1 to neat ethyl acetate) as eluants. 6% of the starting material was recovered (30 mg) and three products were obtained: **11** (148 mg, 28% yield), **12** (49 mg, 9% yield) and **13** (52 mg, 16% yield).

c (H_2O_2/SeO_2): To a solution of **6** (175 mg, 0.57 mmol) in methanol (2 ml) was added dropwise a solution of hydrogen peroxide 30% w/v (ca. 0.067 ml, 4 drops; ca. 0.6 mmol) and selenium dioxide (0.063 g, 0.57 mmol) in water (0.25 ml) at 0°C. The reaction mixture was stirred at room temperature for 20 min and 10 ml of a saturated aqueous solution of sodium chloride was added. Extractions with DCM (5 x 10 ml) were performed. The combined organic extracts were dried over magnesium sulphate, filtered and concentrated to a yellow oil (200 mg). This mixture was submitted to flash column chromatography on silica gel with a mixture of petroleum spirit and ethyl acetate (1:3) as eluants. 43% of the starting material was recovered (77 mg) and **11** (50 mg, 27% yield) was obtained.

The same method described above was followed, with the addition of another equivalent of hydrogen peroxide. No starting material was recovered and three products were obtained: **11** (88 mg, 47%), **13** (33 mg, 29%) and **14** (43 mg, 38%).

Compound 11 ($C_{16}H_{18}SO_5$, white crystals): *m.p.* 110.7-110.9 °C; *IR* $\nu_{max.}$ *in DCM* (cm^{-1}): 3061, 2955, 2927, 2854 (M); 1739, 1709 (S); 1682-1536 (various signals W); 1471, 1445, 1439, 1418 (M); 1363 (MS); 1335, 1320, 1305, 1258 (M); 1236, 1209, 1195, 1181, 1172, 1132 (MS); 1097 (M); 1078 (MS); 1066 (M); 1042 (MS); 1023, 1000, 980, 966, 937, 910, 883, 828 (M); 801, 771 (W); 717, 710 (M); 704, 700, 696 (W); 689 (M); 666, 623 (W); ^1H *NMR* ($CDCl_3$, *400 MHz*) δ: 1.86.93 (m, 1H, H6); 2.05-2.15 (m, 1H, H6'); 2.15-2.25 (m, 1H, H7); 2.38-2.42 (dd, 1H, J=1.53 and 13.74 Hz, H4); 2.50-2.56 (m, 1H, H7'); 2.89-2.94 (ddd, 1H, J=1.5, 5.2 and 13.9 Hz, H4'); 3.06 (s, 3H, OMe); 3.08-3.13 (d, 1H,H8); 3.41-3.45 (d, 1H, J=18.3 Hz, H8'), 4.58-4.60 (d, 1H, J=7.6 Hz, H1); 4.77-4.80 (bt, 1H, J=6Hz, H5); 7.36-7.40 (m, 3H, Ph); 7.86-7.90 (m, 2H, Ph); *^{13}C NMR ($CDCl_3$, 100.4 MHz) δ (DEPT):* 24.95 (CH_2, C7); 28.87 (CH_2, C6); 32.25 (CH_2, C8); 49.44 (CH_2, C4); 51.43 (CH_3, OMe); 77.22 (CH, C5); 80.27 (CH, C1); 127.22 (CH, Ph-m);127.37 (C, C2);128.36 (CH, Ph); 131.15 (CH, Ph); 138.56 (C, Ph (C-S)); 170.09 (C, C=O); 204.85 (C, C=O); *MS m/z (mH^+):* 323.0953 ($C_{16}H_{19}SO_5$ requires 323.09537).

Compound 12 ($C_{16}H_{18}SO_5$, white crystals): *m.p.* 127.6-127.8 ^oC, *IR $\nu_{max.}$ in DCM (cm^{-1}):* 3055, 2984, 2957 (M); 1758 (S); 1735 (MS); 1691, 1680, 1645 (M); 1610-1510 (various W); 1478 (M); 1443 (MS); 1421, 1402, 1379, 1367, 1344, 1304, 1292 (M); 1278 (MS); 1253, 1248 (M); 1212 (MS); 1179, 1130 (S); 1082 (MS); 1038 (S); 998 (M); 938 (W); 898, 881 (M); 851 (W); 782 (M); 765 (W); 694, 690, 665, 666, 636 (M); *^1H NMR ($CDCl_3$, 400 MHz)δ:* 1.72-1.79 (m, 1H, H8); 2.01-2.07 (m/d, 2H, J=16.8 Hz, H5, H8'); 2.10-2.18 (m, 1H, H7); 2.25-2.31 (dt, 1H, J=2.1 and 10.3 Hz, H7'); 2.77-2.82 (dd, 1H, J=4.9 and 16.8, H5'); 3.81 (s, 3H, OMe); 4.53-4.56 (d/s, 3H, J=5.8, H1, CH_2ester), 4.60-4.63 (bt, 1H, J=6.0, H6); 7.41-7.52 (m, 3H, Ph); 7.69-7.71(m, 2H, Ph); *^{13}C NMR ($CDCl_3$, 100.4 MHz)δ (DEPT):* 29.52 (CH_2, C8); 34.71(CH_2, C5); 37.36 (CH_2, C7), 52.45(CH_3, OMe) 64.05(CH_2ester); 70.67(CH, C1); 73.13(CH, C6); 122.20(C, C3); 124.40(CH, Ph-m); 129.04(CH, Ph-o); 130.19(CH, Ph-p); 143.71 (C, Ph (Ph-S)); 153.53(C3=O); 168.85(C9=O); *MS m/z (mH^+):* 323.0953 ($C_{16}H_{19}SO_5$ requires 323.09537)

Compound 13 ($C_{10}H_{12}O_4$, yellow oil): *^1H NMR ($CDCl_3$, 400 MHz) δ:* 1.75-1.81 (m, 1H, H7); 1.85-1.92 (m, 1H, H6); 2.17-2.25 (m, 2H, H7', H6'); 2.43-2.47 (d, 1H, J=16.5Hz, H4); 2.86-2.90 (dd, 1H, J=6.1 and 16.6Hz, H4'); 3.76 (s, 3H, OMe); 4.76-4.79 (t, 1H, J=6.4Hz, H5); 4.88-4.89 (d, 1H, J=7.0Hz, H1); 5.79 (s, 1H, H8); NOE between protons H8 and OCH_3 is observed; *^{13}C NMR ($CDCl_3$, 100 MHz) δ (DEPT):* 29.11 (CH_2, C7), 30.52 (CH_2, C6), 49.93 (CH_2, C4), 52.23 (CH_3, OMe), 74.87 (CH, C5), 79.39 (CH, C1), 121.45 (CH, C8), 146.27 (C, C2), 166.51 (C, C9 (C=O)), 197.11 (C, C3 (C=O)); *MS m/z (%):* 197 (45), 165 (27), 152 (11), 140 (13), 136 (63), 126 (17), 123 (18), 108 (53), 91 (20), 85 (14), 79 (32), 66 (33), 59 (16), 53 (82), 39 (100); *Accurate Mass Peak Match:* 196.0738 ($C_{10}H_{12}O_4$ requires 196.0732)

Compound 14 ($C_{10}H_{12}O_4$, yellow solid): *^1H NMR ($CDCl_3$, 400 MHz) δ:* 1.71-1.79 (m, 1H, H7); 1.89-1.95 (m, 1H, H6); 2.21-2.30 (m, 1H, H7'); 2.30-2.41 (m, 1H, H6'); 2.45-2.50 (d, 1H, J=18.3Hz, H4); 2.86-2.93 (dd, 1H, J=6.6 and 18.3Hz, H4'); 3.78 (s, 3H, OMe); 4.74-4.78 (bt, 1H, J ca.7Hz, H5); 5.95-5.97 (d, 1H, J=7.7Hz, H1); 6.51 (s, 1H, H8); *NOE* between protons H8 and H1 and protons H8 and OCH_3 are observed; *^{13}C NMR ($CDCl_3$, 100 MHz) δ (DEPT):* 29.20 (CH_2, C7), 31.61 (CH_2, C6), 47.76 (CH_2, C4), 51.98 (CH_3, OMe), 73.34 (CH, C5), 74.75 (CH, C1), 119.72 (CH, C8), 151.29 (C, C2), 165.86 (C, C9 (C=O)), 196.70 (C, C3 (C=O)); **MS m/z (%):** 197 (36), 179 (22), 168 (22), 147 (11), 140 (23), 136 (50), 126 (23), 112 (30), 108(100), 91 (17), 80 (28), 65 (27), 59(10), 53 (39), 40 (84); *Accurate Mass Peak Match:* 196.0738 ($C_{10}H_{12}O_4$ requires 196.0732).

2α-methoxycarbonylmethyl-8-oxabicyclo[3.2.1]octan-3-one (2b):

To a suspension of Raney-nickel in THF was added a solution of **6** in THF and the reaction mixture was stirred at room temperature under a nitrogen atmosphere. The progress of the reaction was followed by TLC and more Raney-nickel was added as necessary until consumption of the starting material. (The reaction goes to completion in an average of 2 hours). The Raney-nickel was decanted and the solvent evaporated. The mixture was purified by flash column chromatography on silica gel with a mixture of petroleum spirit and ethyl acetate (3:2) as eluants. The ester **2b** was then obtained as a white crystalline solid (80% yield).

Compound 2b ($C_{10}H_{14}O_4$, white crystals): *m.p.* 58.9-60.0°C; *IR* $\nu_{max.}$ *(paraffin liquid film; cm^{-1})*: 1736, 1709 (S); 1440, 1419, 1364 (S); 1339 (M); 1285, 1273, 1250, 1238, 1199, 1173, 1135 (S); 1100, 1074, 1056, 1037, 1001 (M); 992 (S); 975, 956, 934 (M); 893 (S); 869, 841, 826, 793, 772, 739, 700, 647, 609 (M); *^{1}H NMR (400MHz,$CDCl_3$) δ:* 161-171 (m, 2H, H7 and H6), 1.86-1.98 (m, 1H, H7'), 2.00-2.14 (m/dd, 2H, J_{H8-H2}= 6.60Hz and $J_{H8-H8'}$= 16.86Hz, H6' and H8), 2.26-2.30 (dd, 1H, J_{H4-H5}= 1.10Hz and $J_{H4-H4'}$= 15.01Hz, H4), 2.74-2.86 (dd/dd, 2H, $J_{H8'-H2}$= 7.33Hz, $J_{H8-H8'}$= 16.85Hz, $J_{H4'-H5}$= 5.1Hz and $J_{H4'-H4}$= 14.9Hz, H8' and H4'), 3.23-3.28 (dd, 1H, J_{H2-H8}= 6.60Hz, J_{H2-H1}= 11.50Hz, H2), 3.70 (s, 3H, OMe), 4.52-4.63 (m, 1H, H1), 4.75-4.78 (m (bt), 1H, (J ca. 6Hz), H5); *^{13}C NMR (100MHz, $CDCl_3$) δ (DEPT):* 25.56 (CH_2, C7), 29.39 (CH_2, C6), 29.96 (CH_2, C8), 49.03 (CH_2, C4), 51.94 (CH_3, OMe), 53.11 (CH, C2), 76.01 (CH, C5), 78.47 (CH, C1), 172.22 (C, C9 (C=O)), 206.86 (C, C3 (C=O)); *MS m z (%):* 199 (M^{+}+H, 78), 181 (12), 167 (51), 149 (22), 139 (19), 130 (37), 115 (13), 114 (13), 98 (20), 93 (15), 81 (11), 68 (17), 67 (17), 55 (87), 53 (33), 40 (100).

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References and Notes

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5. The atomic co-ordinates for this work are available on request from the Director of the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW. Any request should be accompanied by the full literature citation for this communication.

   Crystals of **6** are triclinic, spacegroup **P**-1, z=2 with a=8.919(8) Å, b=9.009(7) Å, c=10.301(9) Å, α=81.77(1)°, β=66.40(1)°, γ=88.36(1)°, U=750.3 Å^3. 22251 Independent reflections have been measured on a Marresearch Image Plate, the structure was solved by direct methods and refined to F^2, all non-hydrogen atoms anisotropically, hydrogens in geometric positions and refined on F^2 to R==0.0487.

   Crystals of **2b** are monoclinic, spacegroup $p2_1/c$, z=4 with a=5.659|(6) Å, b=9.601(7) Å, c=18..451(12) Å, β=95.52(1)°, U=997.8Å^3. 1573 Independent reflections have been measured (as above), the structure was solved by direct methods and refined on F^2, all non-hydrogens anisotropically, hydrogens in geometric positions, to R 0.0797.

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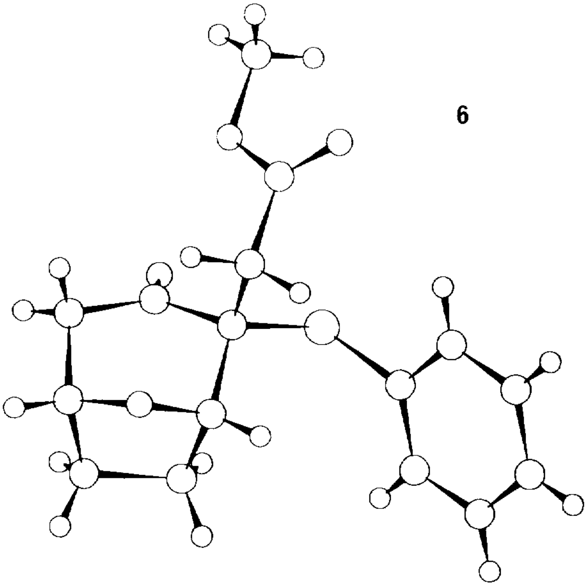
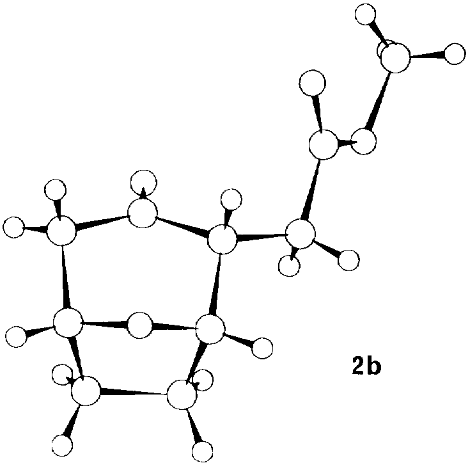
X-ray structures of 6 and 2b



6



2b

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