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Michael and Substitution Reactions of Bicyclic Tetronic, Tetramic and Thiotetronic Esters.

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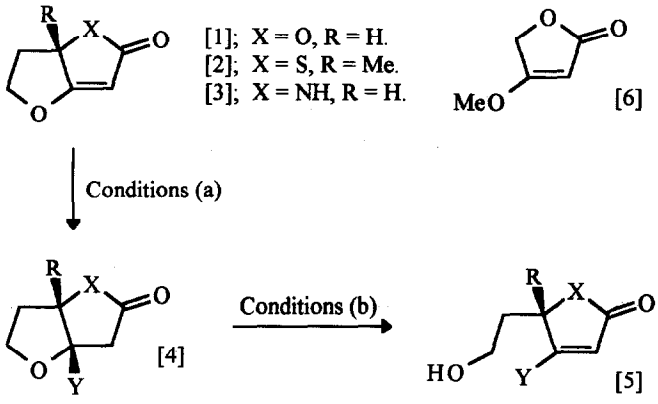
Abstract: The 1,4-addition of several hetero- and carbon nucleophiles to the bicyclic structures **1**, **2**, **3** and **17** are reported along with the conversion of the resultant adducts to substituted tetronic, tetramic, and thiotetronic acids as well as the formation of substituted butenolides; a novel reaction mechanism has been observed for the iodotrimethylsilane (TMSI) or acetic anhydride/magnesium bromide mediated furan ring opening reactions of the bicyclic tetronate **1**.

As part of an ongoing programme aimed towards development of the chemistry and applications in synthesis of tetronic, thiotetronic and tetramic acids, we have prepared a range of bicyclic derivatives[1] and are at present investigating their potential as synthetic intermediates.[2] Our original studies concentrated on the bicyclic derivatives **1**, **2** and **3** and are concerned with their conversion to the corresponding free acids such as **5** (X = NH, O, S; Y = OH; R = H, Me). During our investigation we found that we were able to effect this and other transformations under relatively mild conditions[3] and somewhat surprisingly we found that it was also possible in some cases to intercept the intermediate compounds **4** which occur in these processes. We now report in full[4] our findings on the range and limitations of the reaction. For comparison a series of control reactions were also performed using a model system, methyl tetronate **6**

One of our original goals was to develop a range of ring opening methods applicable to this system and initially we looked at transesterification reactions. We found that the reaction of heterocycles **1-3** with methanol under several conditions led to a mixture of two products, **4** and **5** **(table 1)**. The reaction of **1** with methanolic camphor sulphonic acid (CSA, catalytic) led to the formation of the substitution product **5** in 87% yield together with the formation of the Michael adduct **4** in 13% yield (entry 2). Surprisingly when the reaction was repeated in the absence of CSA (entry 1) we obtained a quantitative yield (by ^{1}H nmr) of the assumed intermediate from the previous reaction **4**; this result illustrates the reactivity of the system. This product could then be converted to the methyl tetronate **5** if required by further treatment with methanolic CSA. A similar result was obtained with the thiotetronate **2** leading to the methyl thiotetronate **5** in 76% yield together with the intermediate adduct **4** in 24% yield (entry 4).



(a), (b) see table 1. X = O, S, NH. R = H, Me. Y = OBn, STol, NHTol, OH, OMe, CF_3CO_2.

Table 1

Entry	X	R	Conditions A[a]	Yield			Conditions B[a]	Yield	
				Y	[4]	[5]		Y	[5]
1	O	H	MeOH/48hrs	OMe	72[b]	-			
2	O	H	MeOH/CSA/48hrs	OMe	13	87			
3	O	H	MeOH/CSA/Δ/18hrs	OMe	18	82			
4	S	Me	MeOH/CSA/48hrs	OMe	24	76			
5	S	Me	MeOH/CSA/Δ/18hrs	OMe	23	77			
6	NH	H	MeOH/CSA/48hrs	OMe	52	36			
7	NH	H	MeOH/CSA/Δ/48hrs	OMe	95	-[c]			
8	O	H	BnOH/CSA/48hrs	BnO	95[b]	-	silica gel	BnO	52
9	O	H	TolSH/2hrs	TolS	95	-			
10	S	Me	TolSH/DBU(cat)/24hrs	TolS	95	-			
11	O	H	$TolNH_2$/8hrs	TolNH	-[c]	88			
12	S	Me	$TolNH_2$/Δ/$CHCl_3$/72hrs	TolNH	-[c]	32[d]			
13	O	H	TFAH/neat/30min	TFA[e]	95	-	H_2O	OH	50[f]
14	S	Me	TFAH/neat/72hrs	TFA[e]	9	91	H_2O	OH	65[f]
15	NH	H	TFAH/neat/2hrs	TFA[e]	95	-	H_2O	OH	77[f]

a. All reactions in dichloromethane at R.T. unless otherwise stated, Tol = tolyl, Δ = reflux. b. >95% by proton nmr, ring opens on silica. c. Not observed by proton nmr. d. Accompanied by extensive decomposition. e. TFA = trifluroacetoxy-. f. In equilibrium with [4] (Y = OH).

Treatment of tetramate **3** (X = NH) under acidic conditions (entry 6) again led to a mixture of the two products, but this time favouring the Michael adduct, (52% yield) over the product of substitution, (36% yield). Interestingly, when the reaction was repeated at reflux (entry 7) the product composition changed fully

in favour of the bicyclic product **4** indicating that under these conditions an equilibrium exists between **4** and **5** which strongly favours the bicyclic product **4** over the methyl tetramate **5**. Treatment of **1** or **2** with methanolic CSA at reflux had little effect on the observed ratios (entries 3 and 5), however the existence of the equilibrium was confirmed by experiment, as isolated samples of **5** (X = NH, O or S) all rapidly convert to the previously observed mixtures when treated in refluxing methanolic CSA. The reason for this difference in reactivity and preference for the cyclised product in the reaction of **3** may be due to diminished resonance interactions between the amide and enolether function present in the disfavoured methyl tetramate product.[5]

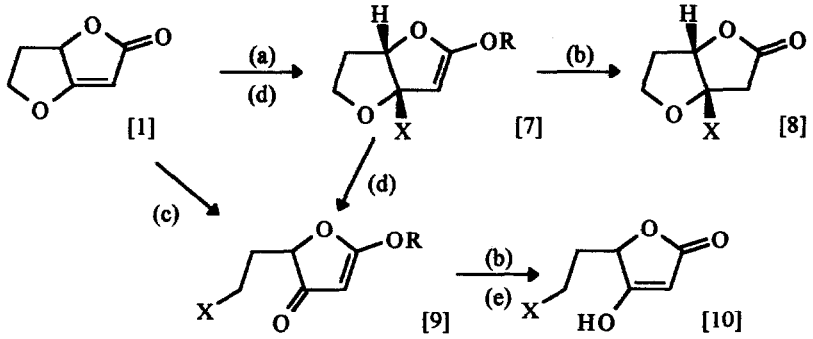
Heterocycles **1-3** were treated with further oxygen, sulphur and nitrogen nucleophiles again yielding either **4** or **5**. Tetronate **1** reacted smoothly with benzyl alcohol (entry 8) under acid catalysis to yield the Michael product **4** which was characterised by ^{1}H nmr but underwent rearrangement to the ring-opened product **5** on attempted chromatography. The reaction of **1** with *p*-thiocresol (entry 9) was rapid and required no acid catalysis yielding the Michael adduct **4** in 95% yield; attempted rearrangement of the adduct to the ring opened product under acid catalysis was unsuccessful and led only to decomposition. Thiotetronate **2** required base (DBU) catalysis to effect the same transformation however in 95% yield (entry 10). In the reaction of **1** with *p*-toluidine (entry 11) we were unable to observe the Michael product (^{1}H nmr) and obtained instead an 88% yield of the ring opened substitution product **5**. The reaction of thiotetronate **2** with *p*-toluidine was slow and required reflux in chloroform to effect the formation of the substitution product **5** in 32% yield; this was accompanied by considerable decomposition, probably due to thiolester cleavage (entry 12). The reaction of heterocycles **1** or **3** with trifluoroacetic acid (entry 13 and 15) was surprising in that the Michael adducts **4** were obtained in near quantitative yield indicating again the ease with which the system will react with even poor nucleophiles; on further reaction of these adducts with aqueous trifluoroacetic acid the free tetronic and tetramic acids were obtained in good yield. In contrast the reaction of thiotetronate **2** with trifluoroacetic acid (entry 14) was sluggish and over the 7 day reaction period it was possible to observe the slow formation of the intermediate adduct **4** and its subsequent rearrangement to the major substitution product **5**. The slow reaction of **2** and relative instability of the adduct **4** can be rationalised by the steric hindrance of the methyl group present in **2**. The mixture obtained was easily converted into the free thiotetronic acid on aqueous hydrolysis.

In contrast to these results a series of control experiments were performed on methyl tetronate [6], which proved to be totally inert to all of the reaction conditions described, even with prolonged reaction times. To the best of our knowledge mild transesterification/substitution reactions of this type have not been reported for tetronates or tetramates.[6]

We were also interested in the application of iodotrimethylsilane (TMSI) to these systems as it is a reagent that has previously been reported to effect the de-esterification of methyl[7] or benzyl tetronates[8] and the ring opening of tetrahydrofurans.[9] Indeed in our hands treatment of methyl tetronate **6** with a two fold excess of TMSI led to the slow formation of an intermediate silylenol ether (presumably at the 2 position); the reaction proceeded to 75% completion (^{1}H nmr) after 2 weeks[10] at room temperature and on hydrolysis this intermediate gave free tetronic acid. By contrast, on treatment of **1** with a slight excess of freshly prepared TMSI we observed the rapid (30 min) formation of the silyl enolate **7** (X = I, R = TMS) (by ^{1}H nmr) which on careful hydrolysis led to the iodonated lactone **8** (X = I) in good overall yield. The intermediate **7** has arisen from 1,4-addition of TMSI to tetronate **1** and its rapid formation presents a stark contrast to the previous result involving methyl tetronate. By careful observation (^{1}H nmr) it was shown that no stable

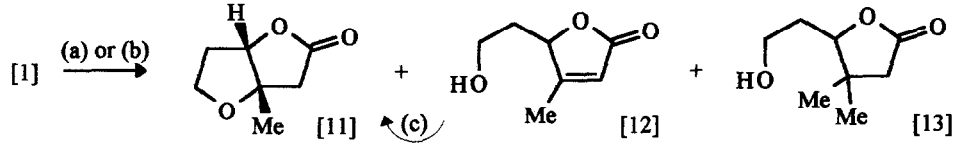
intermediates of this type were present in the reaction of TMSI with methyl tetronate **6**. Further reaction of **1** with an excess of TMSI for 14 hours led to the formation of the ring opened product **9** (X = I, R = TMS) (^{1}H nmr), the furan ring being cleaved in analogy with previous reports.[9] Hydrolysis of **9** gave the free tetronic acid **10** (X = I) in 59% overall yield.

A similar reaction is observed on treatment of **1** with acetic anhydride and magnesium bromide in acetonitrile; conditions previously used for the ring opening of tetrahydrofurans.[11] Under these conditions a ring opened enolacetate **9** (X = Br, R = Ac) was formed in 84% yield. The reaction is thought to proceed via the intermediate **7** (X = Br, R = Ac), in a parallel mechanism to that for TMSI; evidence for this is that small quantities (c.a. 5%) of the bicyclic product **8** (X = Br), which has arisen from hydrolysis of **7** are isolated. The initial step in the reaction is assumed to be the conjugate addition of a bromide ion to **1** under Lewis acidic conditions followed by trapping of the enolate as an acetate and subsequent ring opening by a further bromide ion. Acidic hydrolysis of **9** gave the free tetronic acid **10** (X = Br) in 70% yield.



(a) 1.1 eqv. TMSCl, NaI, MeCN, 30min; X = I, R = TMS. (b) NH_4Cl(aq); X = I. (c) 1.5 eqv. TMSI, MeCN, 14hrs; X = I, R = TMS. (d) Ac_2O, $MgBr_2$, MeCN, 24hrs; X = Br, R = Ac.(e) CF_3CO_2H(aq); X = Br.

Following these findings we then investigated the reaction of the bicyclic tetronate esters with carbon nucleophiles, particularly dialkylcuprates because of their well known preference to undergo 1,4-addition.[12] On treatment of **1** with a slight excess of dimethylcuprate we were pleased to find that the starting material was completely consumed after 15 min at -78°C, unfortunately a mixture of products was obtained, composed of the Michael adduct **11** and the substitution product **12**; trace amounts of the product of double addition **13** were also observed (^{1}H nmr).

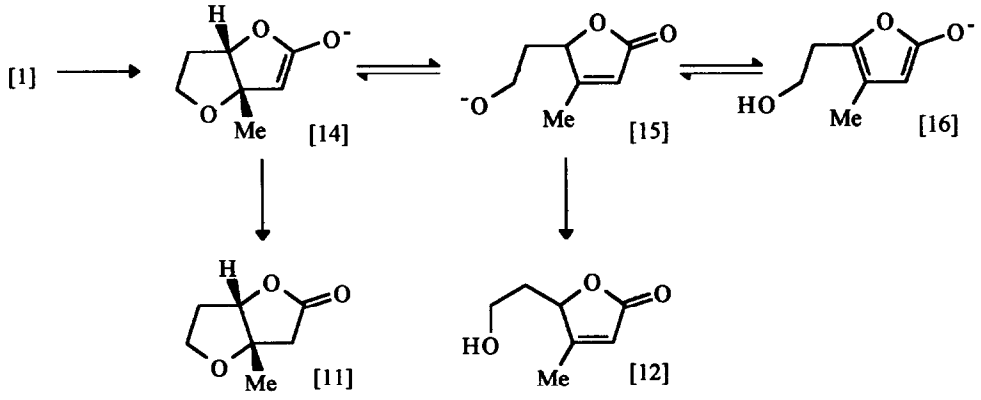


(a) 1.2 Eqv. Me_2CuLi_2I, THF, Et_2O, Hexane, see **Table 2**. (b) Me_2CuLi_2I (1.5 eq.), TMSCl (10 eq.), THF, hexane, -20°C, 5min, (c) DBU (0.2 eqv), $CHCl_3$.

Table 2

Entry	Time	Temp/°C	Yield/%		Overall/%
			11	**12**	
1	5 min	-100	20	20	40
2	10 min	-100	17	29	46
3	15 min	-80	10	32	42
4	45 min	-80	13	3	16

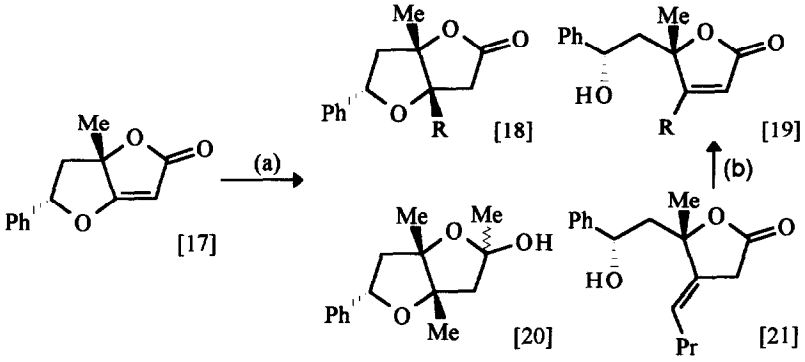
The overall yields of these products and their relative amounts is dependent on the exact conditions employed, as illustrated by a series of experiments (**Table 2**). The initial product formed in the reaction mixture must be the enolate **14**, which shows some stability at low temperatures as illustrated by the isolation of **11** from the reaction mixture (entry 1). However this intermediate undergoes rearrangement to form the alkoxide **15** on standing (entry 2) or warming to slightly higher temperature (entry 3). Unfortunately **15** appears to be unstable to the reaction conditions as illustrated by the dramatic drop in yield of **12** over prolonged reaction times (entry 4); all these reactions were accompanied by considerable decomposition. The fate of **15** is not a further addition of cuprate to give ultimately **13**, as only trace amounts of this product are isolated under any conditions (this was also observed when >2 fold excess of cuprate was employed in the reaction). A possibility is that **15** undergoes a proton transfer to give the enolate **16** and that either of these intermediates take part in further reactions leading to decomposition.



One further possibility is that a similar deprotonation may be occurring on the starting material itself as the deprotonation of tetronates and related systems is a well documented process.[13] Despite the low material yields obtained these results represent, to the best of our knowledge, the first report[14] of a conjugate addition of a carbanion to a tetronate, indeed our own model studies of dialkyl cuprate additions to methyl tetronate **6** showed its inertness all the reaction conditions we employed and again illustrates the reactive nature of the bicyclic tetronate **1**. With these preliminary results in hand we set about improving the yield and selectivity of the additions. Our initial attempts at modifying the reaction conditions by using higher order cuprates or by varying the solvent used were unsuccessful and we thus rationalised that two possibilities existed for improving the procedure, firstly trapping of the enolates **14** or **15** in the reaction mixture or secondly, by blocking the position of deprotonation and thus prevent the decomposition of the products and/or starting material.

The first of these involved the addition of an excess of trimethylsilyl chloride (TMSCl) to the reaction mixture to act as a trap for any enolate intermediates which may occur. After optimisation (above scheme, conditions (b)) this resulted in cleaner transformations to give the substitution product **12** in 50% yield together with the addition product **11** in 3% yield. If the reaction is performed at lower temperatures (-78°C) it is possible to obtain higher yields of **11** indicating that at these temperatures the trapping of the intermediate enolate **14** competes effectively with the ring opening step to give enolate **15**, however the best yields obtained were of the order of 30%. To circumvent this problem the product **12** (or mixtures of **11** and **12**) can be converted into **11** in 80% yield by treatment with a catalytic quantity of DBU.[15]

In order to test our second hypothesis involving blocking the acidic position present in the starting material and the product, dialkylcuprate additions were attempted using the bicyclic tetronate **17**. (prepared in analogy with previous work[1,16]) Treatment of **17** with either dimethyl or di-*n*-butylcuprate results in the formation of several products **18-21** which are similar in nature to those previously isolated from the reactions of **1** (**Table 3**).



(a) See **Table 3**, (b) DBU/$CHCl_3$, R = Me, nBu.

Table 3

Entry	R	Conditions[a]	Yield/%[b]			
			18	**19**	**20**	**21**
1	Me	1.3 Me_2CuLi_2I/-20°C/1hr	0	51[c]	0	-
2	Me	6.0 Me_2CuLi_2I/HMPA/-20°C/1hr	0	75	0	-
3	Me	6.0 Me_2CuLi_2I/25°C/14hrs	16	41	13	-
4	Me	6.0 Me_2CuLi_2I/HMPA/25°C/14hr	52	39	0	-
5	Bu	1.3 nBu_2CuLi_2I/-20°C/1hr	-	43	-	12
6	Bu	6.0 nBu_2CuLi_2I/HMPA/-20°C/1.5 hr	-	70	-	18

a. All reaction performed on 0.8 mmol scale in a THF/diethyl ether/hexane solvent mixture.

b. All yields refer to purified products.

c. Unreacted starting material (6%) recovered.

The major product in most reactions is the product of vinylic substitution **19** (entries 1,2,5 and 6), the best condition being those using HMPA as a co-solvent (entries 2 and 6). However some interesting side reactions are also occurring, for example the reaction of **17** with dimethylcuprate in the absence of HMPA was slow and had not gone to completion after 1 hour; **19** being the only product observed (entry 1). In contrast if the reaction was performed at a higher temperature (entry 3) three products were obtained, the previously observed **19**, the intermediate Michael adduct **18** and **20**, the product resulting from formal 1,2-addition to the lactone carbonyl of **18**. Repetition of this reaction using HMPA increased the yield of **18** and suppressed the formation of **20** (entry 5). The observation, that the Michael adduct **18** is not found at low temperatures but is at higher temperatures, would suggest that an equilibrium process is operating which favours the intermediate leading to **18** at elevated temperatures.

In the reactions involving di-n-butylcuprate (entries 5 and 6) a minor product **21** is formed, which contains a double bond exo to the lactone ring. This may have arisen from the deprotonation of the intermediate **19** (R = nBu) at the α-methylene position to generate an intermediate enolate which on quenching yields a mixture of **19** and **21**. This observation offers some support to our original proposition that a deprotonation process is responsible for the poor material yields obtained in similar reactions performed on **1**. The isomerisation of **21** to **19** is easily effected in quantitative yield by treatment with a catalytic amount of DBU in chloroform.[17] It is pleasing to note that in all the reactions of **17**, decomposition has been suppressed and high overall material yields (51-91%) are obtained.

In all these transformations, the ease of reactivity of substrates **1**, **2**, **3** and **17** towards addition and substitution compared with that of methyl tetronate **6**, can be rationalised by consideration of the strain imposed on the bicyclic systems by the double bond present at the ring junction. Relief of this strain is obviously a thermodynamically favourable process which consequently aids the addition of the incoming nucleophile. The development and further application of these reactions will be reported in due course.

Thanks are given to the ERASMUS scheme, to the University of Wales at Bangor for funding and to Dr J. A. Ballantine at the S.E.R.C. Mass Spectrometry Service at Swansea.

Experimental

Column chromatography was carried out on Kieselgel (230-400 mesh) with the eluant specified in each case. TLC was conducted on precoated Kieselgel 60 F254 (Art. 5554; Merck) glass plates. All non-aqueous reactions were conducted in oven-dried apparatus under a static atmosphere of argon. Light petroleum refers to the fraction boiling in the range 35-60°C. Dichloromethane, diethyl ether, and THF were dried and distiled before use using standard methods. Chemical shifts are reported as δ values relative to tetramethylsilane as an internal standard. ^{1}H nmr spectra were recorded in deuterochloroform (unless otherwise stated) on a Bruker AC250 spectrometer. IR were recorded as thin films (oils) or as a chloroform solution on a Perkin Elmer 1600 series instrument. Mass spectra were recorded on a VG Masslab Model 12/253 spectrometer using CI (with ammonia as the reagent gas) or EI. All compounds were oils unless otherwise stated and melting points were recorded with a Gallenkamp MF370 apparatus and are uncorrected.

General conditions for the addition and substitution reactions of heterocycles 1-3 with methanol.

The substrate **1**, **2**, or **3** was dissolved in methanol (2 ml per mmol) at room temperature and *d*-camphor-10-sulfonic acid (CSA, 0.1-0.2 mol equivalents) added. After the requisite time (see table 1) the

solvent was removed and the crude reaction products were chromatographed (Rf and solvent given) to give **4** and **5** (Y = OMe in all cases, yields as shown in table 1).

Data for 4

1,5-Dioxa-4-methoxy-2-oxobicyclo[3.3.0.^{4,8}]octane, 4 (X = O, R = H).

Reaction scale 1.11 mmol, column solvent 50% diethyl ether in petrol, Rf = 0.28. **^{1}H nmr**; δ = 2.22 (1H, m, CH), 2.36 (1H, m, CH), 2.78 (1H, d, J = 17.4 Hz, CH), 2.93 (1H, d, J = 17.4 Hz, CH), 3.33 (3H, s, OMe) 4.03 (1H, m, CH), 4.13 (1H, m, CH), 4.78 (1H, dd, J = 1.9, 6.2 Hz, CH). **^{13}C nmr**; δ = 30.70 (CH_2), 38.24 (CH_2), 51.30 (CH_3), 67.85 (CH_2), 86.03 (CH), 111.37 (C), 172.72, (C). **IR**; ν = 2942, 2838 (C-H), 1790 (C=O). **MS(EI)**; 158 (25%, M^+), 127 (5%, M^+-MeO).

1-Aza-4-methoxy-5-oxa-2-oxobicyclo[3.3.0.^{4,8}]octane, 4 (X = NH, R = H).

Reaction scale 2.40 mmol, column solvent ethyl acetate, Rf = 0.25, white crystalline solid; M. Pt = 125°C. **^{1}H nmr**; δ = 1.94 (1H, m, CH), 2.27 (1H, m, CH), 2.64 (1H, d, J = 17.0 Hz, CH), 2.72 (1H, d, J = 17.0 Hz, CH), 3.30 (3H, s, OMe), 4.03 (3H, m, CH and CH_2), 7.30 (1H, s, NH). **^{13}C nmr**; δ = 32.07 (CH_2), 40.09 (CH_2), 50.68 (CH_3), 62.84 (CH), 67.48 (CH_2), 112.40 (C), 174.11, (C). **IR**; ν = 3400 (br., N-H), 2954 (C-H), 1695 (C=O). **MS(EI)**; 157 (40%, M^+), 125 (100%, M^+-CH_4O), 57 (100%). **HRMS**; M^+, $C_7H_{11}O_3N$ requires 157.0739, found 157.0739. **Microanalysis**; Expected C = 53.59, H = 7.05, N = 8.91, Found; C = 53.82, H = 7.27, N = 8.78.

4-Methoxy-8-methyl-5-oxa-2-oxo-1-thiabicyclo[3.3.0.^{4,8}]octane, 4 (X = S, R = Me).

Reaction scale 0.24 mmol, column solvent 15% diethyl ether in petrol, Rf = 0.26. **^{1}H nmr**; δ = 1.67 (3H, s, Me) 2.31 (2H, m, CH_2), 2.86 (1H, d, J = 16.8 Hz, CH), 3.12 (1H, d, J = 16.8 Hz, CH), 3.35 (3H, s, OMe) 4.12 (3H, m, CH_2). **^{13}C nmr**; δ = 24.51 (CH_3), 37.24 (CH_2), 46.92 (CH_2), 51.96 (CH_3), 65.28 (C), 66.85 (CH_2), 111.37 (C), 200.49(C). **IR**; ν = 1720 (C=O). **MS(CI)**; 189 (60%, M+H^+), 206 (55%, M+NH_4^+).

Data for 5.

5-(2-Hydroxyethyl)-4-methoxy-2(5*H*)-furanone, 5 (X = O, R = H).

Reaction scale 1.15 mmol, column solvent 20% ethyl acetate in diethyl ether, Rf = 0.20, white crystalline solid; M.Pt = 68-69°C. **^{1}H nmr**; δ = 1.71 (1H, m, CH), 2.10, (1H, br s, OH), 2.16 (1H, m, CH), 3.73 (2H, dd, J = 5.2, 6.9 Hz, CH_2), 3.84 (3H, s, OMe), 4.90 (1H, dd, J = 3.5, 9.0 Hz, CH), 5.01 (1H, s, CH). **^{13}C nmr**; δ = 34.75 (CH_2), 58.00 (CH_2), 59.48 (CH_3), 76.23 (CH), 88.20 (CH), 172.79 (C), 183.03, (C). **IR**; ν = 3470 (O-H), 1722 (C=O), 1626 (C=C). **MS(EI)**; 158 (45%, M^+). **UV**; λ_{max} = 220 nm (E = 11,000). **Microanalysis**; $C_7H_{10}O_3$ Expected: C = 53.16, H = 6.37; Found: C = 53.42, H = 6.81, .

5-(2-Hydroxyethyl)-4-methoxy-2(5*H*)-pyrrolidone, 5 (X = NH, R = H).

Reaction scale 2.40 mmol, column solvent 10% methanol in ethyl acetate, Rf = 0.22, white crystalline solid; M. Pt = 111°C. **^{1}H nmr**; ($CDCl_3$/D_6-DMSO); δ = 0.88 (1H, m, CH), 1.31, (1H, dtd, 3.4, 6.6, 13.8 Hz, CH), 2.98 (2H, dt, 5.2, 6.6 Hz, CH_2), 3.13 (3H, s, OMe), 3.44 (1H, dd, J = 3.4, 9.4 Hz, CH), 3.83, (1H, br t,

J = 5.0 Hz, OH), 4.29 (1H, s, CH), 6.60 (1H, s, NH). **^{13}C nmr**; δ = 34.61 (CH_2), 56.30 (CH_3), 58.32 (CH), 59.59 (CH_2) 93.12 (CH), 174.74 (C), 178.95, (C). **IR**; ν = 3343 (br., O-H, N-H), 2951 (C-H), 1664 (C=O), 1618 (C=C). **MS(EI)**; 157 (30%, M^+), 112 (100%, M^+-C_2H_5O). **HRMS**; $M+H^+$, $C_7H_{12}O_3N$ requires 158.0817, found 158.0827. **Microanalysis**; Expected; C = 53.49, H = 7.05, N = 8.91, Found; C = 53.44, H = 7.18, N = 8.63.

5-(2-Hydroxyethyl)-4-methoxy-5-methyl-2(5*H*)-thiopheneone, 5 (X = S, R = Me).

Reaction scale 0.24 mmol, column solvent 90% diethyl ether in petrol, Rf = 0.15. **^{1}H nmr**; δ = 1.68 (3H, s, Me), 1.95 (1H, br s, OH), 2.17 (2H, m, CH_2), 3.75 (2H, m, CH_2), 3.85 (3H, s, OMe), 5.34 (1H, s, CH). **^{13}C nmr**; δ = 26.99 (Me), 41.01 (CH_2), 57.38 (C), 59.59 (CH_3), 59.73 (CH_2), 101.22 (CH), 187.32 (C), 193.21 (C). **IR**; ν = 3406 (O-H), 1669 (C=O), 1600 (C=C). **MS(CI)**; 189 (100%, $M+H^+$), 157 (100%, $M-OMe^+$).

4-Benzyloxy-5-(2-hydroxyethyl)-2(5*H*)-furanone, 5 (X = O, R = H, Y = OBn).

D-camphor-10-sulfonic acid (23 mg, 0.1 mmol) was added to a solution of **1** (100.0 mg, 0.793 mmol) in dichloromethane (1 ml) and benzyl alcohol (257.0 mg, 2.38 mmol). The resulting solution was stirred for one day whereupon **1** had been consumed (tlc). Examination by ^{1}H nmr showed the presence of **4** (X = O, Y = OBn, R = H) as indicated by an AB pattern centred at d = 2.82 (J = 17.2 Hz). Attempted purification by chromatography led to conversion to the title compound. Alternately the crude reaction mixture is absorbed onto a silica gel column (10 g) from a diethyl ether solution and allowed to stand for 24hrs. Ellution of the column (diethyl ether) gave the crude product which after chromatography (60% diethyl ether in petrol, Rf = 0.26) gave **5** (96.0 mg, 0.410 mmol, 52%) as an oil. **^{1}H nmr**; δ = 1.84 (1H, m, CH), 2.19 (1H, br s, CH), 2.24 (1H, m, CH), 3.82 (2H, m, CH_2), 5.00 (1H, dd, J = 3.3, 9.0 Hz CH), 5.06 (1H, s, CH_2), 5.14 (1H, s, CH), 7.39, (5H, m, Ph). **^{13}C nmr**; δ = 31.23 (CH_2), 59.76 (CH_2), 74.51 (CH_2), 75.83 (CH), 89.60 (CH), 127.87 (CH), 128.82 (CH), 129.07 (CH), 133.66 (C), 172.05 (C), 180.54 (C). **IR**; ν = 3500 (O-H), 1748 (C=O), 1629 (C=C). **MS(CI)**; 215 (100%, $M-OH^+$).

1,5-Dioxa-2-oxo-4-thiatolylbicyclo[3.3.0.^{4,8}]octane, 4 (X = O, R = H, Y = STol).

Tetronate **1** (117.4 mg, 0.936 mmol) and *p*-thiocresol (143 mg, M.W.124, 1.153 mmol) were dissolved in dichloromethane (1 ml) and the resulting solution stirred for one hour, at which point thin layer chromatography indicated total consumption of starting material. Removal of solvent and chromatography (20% ether in petrol, Rf = 0.21) gave **4** (X = O, R = H, Y = STol, 218 mg, 95 % yield). **^{1}H nmr**; δ = 2.00 (1H, m, CH), 2.20 (1H, m, CH), 2.37 (3H, s, Me), 2.90 (1H, d, J = 18.2 Hz, CH), 3.00 (1H, d, J = 18.2 Hz, CH), 4.09 (2H, m, CH_2), 4.99 (1H, dd, J = 1.5, 5.7 Hz, CH), 7.31 (4H, AA'BB', Ph). **^{13}C nmr**; δ = 21.13 (Me), 31.55 (CH_2), 42.99 (CH_2), 68.05 (CH_2), 88.46 (CH), 95.64 (C), 126.36 (C), 129.90 (CH), 135.55 (CH), 139.74 (C), 173.19 (C). **IR**; ν = 1789 (C=O). **MS(CI)**; 268 (100%, $M+NH_4^+$), 251 (60%, $M+H^+$).

8-Methyl-5-oxa-2-oxo-1-thia-4-thiatolylbicyclo[3.3.0.^{4,8}]octane, 4 (X = S, R = Me, Y = STol).

p-Thiocresol (47 mg, 0.38 mmol) was added to a stirred solution of thiotetronate **2** (28.5 mg, 0.18 mmol) in chloroform (1 ml) containing a catalytic amount of DBU (c.a. 1 mg). After 48 hrs at room

temperature the solvent was removed and chromatography (7% diethyl ether in petrol, Rf = 0.20) gave **4** (X = S, R = Me, Y = STol, 48 mg, 0.17 mmol, 95%) as an oil. **^{1}H nmr**; δ = 1.87 (3H, s, Me), 2.40 (2H, m, CH_2), 2.38 (3H, s, Me), 2.95 (1H, d, J = 17.3 Hz, CH), 3.22 (1H, d, J = 17.3, CH), 4.20 (2H, m, CH_2) 7.17 (2H, d, J = 8.2 Hz, 2 x CH), 7.46 (2H, d, J = 8.2 Hz, 2 x CH). **^{13}C nmr**; δ = 21.24 (Me), 25.85 (Me), 38.77 (CH_2), 54.67 (CH_2), 66.82 (CH_2), 67.75 (C), 100.50 (C), 127.14 (C), 129.74 (CH), 136.30 (CH), 139.52 (C), 201.48 (C). **IR**; ν = 1712 (C=O). **MS(CI)**; 281 (100%, $M+H^+$), 298 (10%, $M+NH_4^+$), 157 (80%, M^+-STol).

4-Azatolyl-5-(2-hydroxyethyl)-2(5*H*)-furanone, 5 (X = O, R = H, Y = NHTol).

Tetronate **1** (100 mg, 0.793 mmol) and *p*-toluidine (229 mg, 2.14 mmol) were dissolved in dichloromethane (1 ml) and the resulting solution stirred for 24 hrs. Removal of solvent and chromatography (15 % ethyl acetate in diethyl ether Rf = 0.26) gave **5** (X = O, R = H, Y = NHTol, 163 mg, 88%) as a cream solid. M. Pt = 147-148 °C. **^{1}H nmr**; ($CDCl_3/CD_3OD$), δ = 1.98 (1H, m, CH), 2.20 (1H, m, CH), 2.32 (3H, s, Me), 3.40 (1H, br s, OH), 3.86 (2H, dd, J = 3.7, 7.4 Hz, CH_2), 5.07 (1H, dd, J = 4.4, 7.4 Hz, CH), 5.16 (1H, s, CH), 7.10 (4H, AA'BB', J = 8.4 Hz, Ph), 8.94 (1H, s, NH). **^{13}C nmr**; ($CDCl_3/CD_3OD$) δ = 20.29 (Me), 35.96 (CH_2), 57.77 (CH_2), 77.51 (CH), 82.46 (CH), 119.82 (CH), 119.86 (CH), 129.70 (CH), 134.02 (C), 137.01 (C), 167.40 (C), 176.84 (C). **IR**; ν = 3230 (O-H), 1700 (C=O), 1594 (C=C). **MS(CI)**; 234 (100%, $M+H^+$).

4-Azatolyl-5-(2-Hydroxyethyl)-5-methyl-2(5*H*)-thiopheneone, 5 (X = S, R = Me, Y = NHTol).

Thiotetronate **2** (21.8 mg, 0.138 mmol) was dissolved in chloroform (1 ml) and *p*-toluidine (60 mg, 0.56 mmol) was added; the reaction was heated at reflux for 72 hours to effect complete conversion. After evaporation, chromatography (diethyl ether Rf = 0.24) gave **5** (X = S, R = Me, Y = NHTol; 12 mg, 0.046 mmol, 32%) as a glass. **^{1}H nmr**; δ = 1.82 (3H, s, Me), 2.26 (2H, m, CH_2), 2.34 (3H, s, Me), 3.85(2H, m, CH_2), 5.43 (1H, s, C-3, CH), 7.04 (2H, d, J = 8.3 Hz, 2 x CH), 7.15 (2H, d, J = 8.3 Hz, 2 x CH), 7.39 (1H, s, broad, NH). **^{13}C nmr**; δ = 20.90 (CH_3), 28.03 (CH_3), 41.66 (CH_2), 59.55 (CH_2) 77.19 (C), 99.90 (CH), 122.44 (CH), 130.05 (CH), 135.54 (C), 136.97 (C), 172.67 (C), 192.84 (C). **IR**; ν = 3250 (br, N-H and O-H), 1630 (C=O), 1572 (C=C). **MS(CI)**; 264 (100%, $M+H^+$).

1,5-Dioxa-4-trifluoroacetoxy-2-oxobicyclo[3.3.0.^{4,8}]octane, 4 (X = O, R = H, Y = CF_3COO).

Tetronate **1** (55.0 mg, 0.440 mmol) was dissolved in trifluoroacetic acid (1 ml) at room temperature; after 30 min. the solvent was removed to give **4** (113mg, 95%) as an oil. Attempted purification (distillation or chromatography) led to decomposition. **^{1}H nmr**; δ = 2.38 (1H, m, CH), 2.61 (1H, m, CH), 3.19 (1H, d, J = 18.0 Hz, CH) 3.48 (1H, δ, J = 18.0 Hz, CH), 4.32 (2H, m, CH_2), 5.20 (1H, dd, J = 2.0, 8.0 Hz CH). **^{13}C nmr**; δ = 30.18 (CH_2), 39.61 (CH_2), 71.10 (CH_2), 86.14 (CH), 113.93 (CF_3), 155.38 ($\underline{C}OCF_3$), 164.67 (C), 181.92 (C). **IR**; ν = 3006, 2961, 2915 (C-H), 1789 (C=O), 1658 (C=O).

4-Hydroxy-5-(2-hydroxyethyl)-2(5*H*)-furanone, 5 (X = O, R = H, Y = OH).

Tetronate **1** (104.8 mg, 0.830 mmol) was dissolved in trifluoroacetic acid (2 ml) and stirred until complete consumption of starting material (tlc); water (10ml) and THF (10 ml) were added and the solution

was stirred for a further 3 hrs. At this point the solvent was evaporation and the product purified by column chromatography (ethyl acetate, Rf = 0.35) to give **5** (X = O, R = H, Y = OH; 59.3 mg, 0.418 mmol, 50%). **^{1}H nmr**; mixture of cyclic **4**, open chain enol **5** and open chain keto forms; ratio 5 : 5 : 1. δ = 2.10-2.5 (2H, m, 3 x CH_2, **4**, **5** and keto), 2.92 (1H, d, J = 17.7, CH, **4**), 3.00 (1H, d, J = 17.7, CH, **4**), 3.22 (1H, d, J = 22.5 Hz, CH, keto), 3.32 (1H, d, J = 22.5 Hz, CH, keto), 3.9 (br s, OH's for **4**, **5** and keto) 4.16 (2H, m, CH_2, **4** and keto), 4.55 (2H, m, CH_2, **5**), 4.85 (1H, dd, J = 1.7, 4.6 Hz, CH, **4**), 4.95 (1H, dd, J = 4.2, 7.7 Hz, CH, **5**), 5.12 (1H, s, CH, **5**). **^{13}C nmr**; δ = 29.39 (CH_2, keto), 30.27 (CH_2, **5**), 30.36 (CH_2, **4**), 37.00 (CH_2, keto), 41.22 (CH_2, **4**), 62.82 (CH_2, keto), 63.33 (CH_2, **5**), 68.17 (CH_2, **4**), 76.29 (CH, **5**), 79.35 (CH, keto), 79.35 (C, **4**), 87.01 (CH, **4**), 89.39 (CH, **5**), 108.43 (C, **5**), 173.87 (C, **5**), 175.88 (C, keto), 181.75 (C, **5**), 204.11 (C, keto). **IR**; ν = 3398 (O-H), 1732 (br, C=O), 1652 (C=C). **UV**; λ/nm (E) = 315 (930), 245 (2,160), 220 (3,030), 205 (3,400), on addition of excess aqueous NaOH; 310 (1,400), 245 (3,740), 210 (15,350). **MS(CI)**; 162 (100%, M+NH_4^+), 144 (10%, M^+).

4-Hydroxy-5-(2-hydroxyethyl)-5-methyl-2(5*H*)-thiopheneone, 5 (X = S, R = Me, Y = OH) via 5-(2-hydroxyethyl)-5-methyl-4-trifluoroacetoxy-2(5*H*)-thiopheneone, 5 (X = S, R = Me, Y = CF_3COO) and 8-Methyl-5-oxa-2-oxo-1-thia-4-trifluoroacetoxy[3.3.0.^{4,8}]octane, 4 (X = S, R = Me, Y = CF_3COO).

Thiotetronate **2** (28.5 mg, 0.180 mmol) was dissolved in deuterochloroform (0.4 ml) and trifluoroacetic acid (1.0 ml), the course of the reaction being followed by proton nmr. After 7 days less than 2 % of starting material was present and the relative amounts of **4** (X = S, R = Me, Y = CF_3COO; partial **^{1}H nmr**; δ = 3.50 (1H, d, J = 19.4 Hz, CH), 3.80 (1H, d, J = 19.4 Hz, CH)) and **5** (X = S, R = Me, Y = CF_3COO; partial **^{1}H nmr**; δ = 6.00 (1H, s, CH) were 9:91 respectively. The solvents were removed under reduced pressure and the residue dissolved in water (1 ml) and TFA (0.2 ml) to effect hydrolysis. After 3 days the solvent was again removed, the residue dissolved in dichloromethane (20 ml) and extracted with aqueous sodium hydroxide 1M (20 ml) This aqueous layer was extracted again with dichloromethane (20 ml), acidified to pH = 1 with hydrochloric acid (1M) and extracted with dichloromethane (2 x 20 ml). These final extracts were dried (magnesium sulphate), evaporated and after chromatography (75% diethyl ether in petrol, Rf = 0.1-0.3) gave **5** (X = S, R = Me, Y = OH; 21 mg, 0.121 mmol, 65%). **^{1}H nmr**; δ = 1.74 (3H, s, Me), 2.35 (2H, m, CH_2), 2.74 (1H, br s, OH), 3.01 (1H, d, J = 17.1, CH), 3.10 (1H, d, J = 17.1, CH), 4.13 (2H, m, CH_2). **^{13}C nmr**; δ = 20.29 (CH_2), 24.55 (CH_3), 50.20 (CH_2), 64.85 (C), 67.30 (CH_2), 105.19 (C), 199.93(C). **IR**; ν = 3419 (br, O-H), 2968, 2924, 2856 (C-H), 1699 (C=O). **MS(CI)**; 192 (100%, M+NH_4^+), 174 (75%, M^+),157 (45%, M-OH^+).

1-Aza-5-oxa-2-oxo-4-trifluoroacetoxybicyclo[3.3.0.^{4,8}]octane, 4 (X = NH, R = H, Y = $COCF_3$).

Tetramate **3** (105 mg, 0.840 mmol) was dissolved in trifluoroacetic acid (2 ml) and allowed to stand for 1 hr at which point tlc (ethyl acetate) indicated the complete consumption of starting material. Evaporation of the solvent (high vacuum) gave **4** (X = NH, R = H, Y = $COCF_3$; 191 mg, 0.798 mmol, 95 %) as a viscous oil. **^{1}H nmr**; δ = 2.13 (1H, m, CH), 2.55 (1H, m, CH), 3.25 (1H, d, J = 18.7 Hz, CH), 3.46 (1H, d, J = 18.7 Hz, CH), 4.31 (2H, m, CH_2), 4.85 (1H, dd, J = 4.0, 9.2 Hz, CH), 8.12, (1H, s, NH). **^{13}C nmr**; δ = 30.80 (CH_2), 41.37 (CH_2), 64.62 (CH), 70.69 (CH_2), 114.27, (CH), 115.01 (CF_3), 159.60 ($\underline{C}OCF_3$), 164.67 (C), 175.25 (C). **IR**; ν = 1792 (C=O), 1696 (C=O).

5*H*-4-Hydroxy-5-(2-hydroxyethyl)pyrrol-2(1*H*)-one, 5 (X = NH, R = H, Y = OH).

Tetramate **3** (300mg, 2.4 mmol) was dissolved in trifluoroacetic acid (5 ml) and allowed to stand for 16 hrs at which point tlc indicated the complete consumption of starting material. Water (5 ml) was added and the solution stirred for a further 48 hours. Evaporation of the solvent, followed by drying (Phosphorus pentoxide) and trituration of the residual oil with diethyl ether gave **5** (X = NH, R = H, Y = OH, 264 mg, 1.85 mmol, 77%) as an off-white solid. M. Pt = 145-147 °C. **^{1}H nmr**; (($CD_3)_2C$=O, compound is predominantly in bicyclic form **4**, Y = OH), δ = 1.75 (1H, m, CH), 2.12 (1H, m, CH), 2.37 (1H, d, J = 17.0 Hz, CH), 2.47 (1H, d, J = 17.0 Hz, CH), 3.77 (1H, m, CH), 3.83 (1H, app t, J = 7.2 Hz, CH), 3.93 (1H, m, CH), 6.14 (1H, broad s, OH), 7.75 (1H, s, NH). **^{13}C nmr**; (($CD_3)_2C$=O), δ = 31.24 (CH_2), 43.52 (CH_2), 63.08 (CH), 66.29 (CH_2), 108.60 (C), 172.75 (C). **^{1}H nmr**; (($CDCl_3/CF_3COOH$; compound is predominantly in keto form of **5**), δ = 2.17 (1H, m, CH), 2.50 (2H, m, CH, OH), 3.15 (2H, s, CH_2), 4.25 (2H, m, 2 x CH), 4.42 (1H, dd, J = 3.6, 7.1 Hz, CH), 8.10 (1H, broad s, NH). **^{13}C nmr**; ($CDCl_3/CF_3COOH$), δ = 29.43 (CH_2), 40.14 (CH_2), 62.24 (CH), 63.63 (CH_2), 175.86 (C), 206.16 (C). **IR**; ν = 3250 (N-H), 3100 (Broad O-H), 1667 (C=O). **MS(CI)**; 161 ($M+NH_4^+$,100%), 144 (75%, $M+H^+$, 90%). **HRMS**; $C_6H_9NO_3$ Expected; 143.0582, Found; 143.0582.

1,5-Dioxa-4-iodo-2-oxobicyclo[3.3.0.^{4,8}]octane, 8 (X = I).

Trimethylsilyl chloride (18.4 mg, 0.169 mmol) and sodium iodide (25.4 mg, 0.169 mmol) were added sequentially to a solution of tetronate **1** (19.4 mg, 0.154 mmol) in acetonitrile (1ml). After 30 min, water (5 ml) and saturated ammonium chloride solution (5 ml) were added, the solution extracted (chloroform, 3 x 10 ml), these extracts dried (magnesium sulphate) and evaporated to give **8** (X = I; 37.5 mg, 0.148 mmol, 96%) as an oil. **^{1}H nmr**; δ = 2.32 (1H, m, CH), 2.55 (1H, m, CH), 3.36 (1H, d, J = 19.5 Hz, CH), 3.54 (1H, d, J = 19.5 Hz, CH), 4.10 (2H, m, CH_2), 5.54 (1H, d, J = 6.0 Hz, CH). **^{13}C nmr**; δ = 29.32 (CH_2), 48.50 (CH_2), 70.10 (CH_2), 94.49 (CH), 95.41 (C), 171.48 (C). **IR**; ν = 2980 (C-H), 1790 (C=O). **MS(EI)**; 254, (100%, M^+), 127 (67%, $M\text{-}I^+$).

4-Hydroxy-5-(2-iodoethyl)-2(5*H*)-furanone, 10 (X = I) via 5-(2-iodoethyl)-2-trimethylsilyloxy-4(5*H*)-furanone, 9 (X = I, R = TMS).

Iodotrimethylsilane (118.8 mg, 0.594 mmol) was added to a solution of **1** (50 mg, 0.396 mmol) in deuterated acetonitrile (1 ml). After for 16 hrs, analysis of the reaction mixture by proton nmr showed the presence of **9** (X = I, R = TMS); **^{1}H nmr**; (CD_3CN) δ = 0.10 (9H, s, TMS), 2.13 (1H, m, CH), 2.45 (1H, m, CH), 3.39 (2H, m, CH_2), 4.90 (1H, dd, J = 3.6, 10.7 Hz, CH), 5.22 (1H, s, CH). At this point saturated ammonium chloride solution (0.5 ml) and water (0.5 ml) were added to the reaction which was then stirred for 16 hrs. The reaction mixture was then diluted with dichloromethane (10 ml) and washed successively with sodium thiosulphate solution (10 ml, 5% w/v solution) and brine, re-extracting with ethyl acetate (10 ml) each time. Drying (magnesium sulphate) and evaporation of these extracts gave after chromatography (ethyl acetate/petrol, gradient ellution, Rf = 0.1-0.4 in ethyl acetate) **9** (X = I, 58.8 mg, 0.233 mmol, 59%) as an oil (rapidly deteriorates). **^{1}H nmr**; (CD_3CN) δ = 2.00 (1H, m, CH), 2.21 (1H, m, CH), 3.27 (2H, m, CH_2), 4.89 (1H, m, CH), 5.08 (1H, s, CH, D_2O exchangeable), 10.2 (1H, br s, OH, D_2O exchangeable). **IR**; ν = 3750-2750 (br, OH), 2982 (C-H), 1707 (C=O), 1619 (C=C).

2-Acetoxy-5-(2-bromoethyl)-4(5*H*)-furanone, 9 (X = Br, R = OAc) and 4-bromo-1,5-dioxa-2-oxobicyclo[3.3.0.^{4,8}]octane, 8 (X = Br).

A mixture of magnesium powder (29 mg, 1.19 mmol) and 1,2-dibromoethane (373 mg, 1.99 mmol) in diethyl ether (2ml) was sonicated at room temperature under an argon atmosphere for 1.5 hours; removal of solvent under high vacuum gave magnesium bromide as a white solid. This reagent was suspended in dry acetonitrile (3 ml) and tetronate **1** (100 mg, 0.794 mmol) was added in one portion, followed by acetic anhydride (243 mg, 2.38 mmol). The solution was stirred for 20 hours at room temperature, during which time the magnesium bromide was seen to dissolve leaving a clear solution which was then followed by the production of a milky white precipitate. Dichloromethane (10 ml) and water (8 ml) were added to the suspension which was then separated and the aqueous layer further extracted with dichloromethane (2 x 20 ml). Drying (magnesium sulphate), filtration, evaporation and chromatography (50% diethyl ether in petrol, Rf = 0.26) gave **9** (X = Br, R = OAc; 165.0 mg, 0.663 mmol, 84%) as an oil. **^{1}H nmr**; δ = 2.14 (1H, m, CH), 2.35 (3H, s, CH_3), 2.45 (1H, m, CH), 3.57 (2H, dd, J = 7.9, 5.3, CH_2), 5.06 (1H, ddd, J = 4.4, 3.1, 1.3 Hz, CH), 6.12 (1H, d, J = 1.3 Hz, CH). **^{13}C nmr**; δ = 21.16 (CH_3), 27.36 (CH_2), 35.40 (CH_2), 76.91 (CH), 101.51 (CH), 165.40, (C), 169.40 (C), 171.4 (C). **IR**; ν = 1798 (C=O), 1762 (C=O), 1631 (C=C). **MS(CI)**; 249, (16%, M+H$^+$), 251 (15%, M+H$^+$), 43 (100%, CH_3CO^+). Re-chromatography of the residual column material (acetone/petrol gradient ellution, Rf = 0.64 in 50:50) gave **8** (7 mg, 0.034 mmol, 4%). **^{1}H nmr**; δ = 2.34 (1H, m, CH), 2.60 (1H, m, CH), 3.32 (1H, d, J = 18.0 Hz, CH), 3.48 (1H, d, J = 18.0 Hz, CH), 4.25 (2H, m, CH_2), 5.32 (1H, dd, J = 2.0, 6.0 Hz, CH).

5-(2-Bromoethyl)-4-hydroxy-2(5*H*)-furanone, 10 (X= Br)

2-Acetoxy-5-(2-bromoethyl)-4(5H)-furanone, **9** (X = Br, R = OAc; 82.0 mg, 0.329 mmol) was dissolved in trifluoroacetic acid (1 ml), chloroform (0.5 ml) and water (0.2 ml) and stirred until tlc indicated complete consumption of starting material (5 days). After evaporation of solvents, the residue was dissolved in dichloromethane (10 ml) and extracted with aqueous sodium hydroxide (20 ml, 1 M) The aqueous layer was washed again with dichloromethane (20 ml), acidified (pH = 1) with hydrochloric acid (1 M) and extracted with dichloromethane (2 x 20 ml). These final extracts were dried (magnesium sulphate), evaporated and dissolved in diethyl ether (5 ml) which was elluted through silica gel (3g) with further ether (15 ml) to give, after removal of solvent, **10** (48.0 mg, 0.232 mmol, 70%) as a light yellow solid. M. Pt = 48-50 ^{o}C (diethyl ether). **^{1}H nmr**; δ = 2.19 (1H, m, CH), 2.47 (1H, m, CH), 3.56 (2H, m,, CH_2), 5.05-5.12 (2H, m obscured by s, 2 x CH's) 9.0-11.5 (1H, br s, OH). **^{13}C nmr**; δ = 27.36 (CH_2), 34.72 (CH_2), 78.45 (CH), 88.99 (CH), 177.49 (C), 183.06 (C). Signals were also observed for the keto form; δ = 27.17 (CH_2), 33.47 (CH_2), 37.47 (CH_2), 83.64 (CH), 169.85 (C), 204.29 (C). **IR**; ν = 3400 (br O-H), 1721 (C=O), 1620 (C=C). **MS(EI)**; 206, 208 (4%, M$^+$), 178, 180 (5%, M-CO$^+$). **Microanalysis**; $C_6H_7BrO_3$ Expected; C = 34.81, H = 3.41; Found; C = 35.01, H = 3.32, .

General Conditions for Organocuprate Reactions

Preparation of dimethyl cuprate; Copper(I) iodide was suspended in dry ether (1-2 ml per mmol of copper iodide), cooled (0°C) and treated with methyllithium (2 equivalents of a 1.4 M solution in diethyl ether) to produce a clear solution of the reagent under argon which was freely transferable by syringe.

Preparation of di-n-butyl cuprate; Copper(I) iodide was suspended in dry ether (1-2 ml per mmol), cooled (0°C) and treated with butyllithium (1.5M in hexane, 2 eqvs) to produce a solution of the reagent under argon which was freely transferable by syringe

General Conditions; All reactions were performed in THF (10 ml per mmol of substrate) under the conditions shown in tables **2** and **3**. Reactions involving 1.2 or 1.3 equivalents of cuprate were performed under standard addition methods (table **2**, entries 1-4, and table **3**, entries 1 and 5). Reactions involving 6 equivalents used reverse addition (table **3** entries 2, 3, 4 and 6). All reactions performed at room temperature were initially started at -20°C with immediate warming. HMPA if used was added to the substrate at 0°C and sufficient THF added to keep the solution mobile at -20°C. TMSCl was pre-mixed with **1** at the specified temperature before addition of cuprate. Products were separated by chromatography (gradient ellution in ethyl acetate/diethyl ether/petrol mixtures).

5-(2-Hydroxyethyl)-4-methyl-2(5*H*)-furanone 11, 1,5-dioxa-4-methyl-2-oxobicyclo [3.3.0.^{4,8}]octane 12 and 5-(2-Hydroxyethyl)-4,4-dimethyl-4,5-dihydrofuran-2(3*H*)-one 13.

Trimethylsilyl chloride (1.63g 15.1 mmol) was added to a cooled (-20°C) stirred solution of tetronate **1** (94.9 mg, 0.750 mmol) in THF (7.5 ml). After 5 minutes dimethyl cuprate (6.5 ml of a 0.173 M solution) was added and the solution stirred for a further 5 minutes; saturated ammonium chloride solution (10 ml) was then added and the solution stirred to room temperature overnight. Extraction of the solution with ethyl acetate (3 x 20 ml), drying of the extracts, evaporation and chromatography (diethyl ether/ethyl acetate) gave **11** (45.6 mg, 0.321 mmol, 43%; 50% based on recovered **1** (12.7 mg) as an oil and **12** (3% based on proton nmr) as an oil.

Data for 11; Rf = 0.10 (diethyl ether). **^{1}H nmr**; δ = 1.66 (1H, m, CH), 2.09 (3H, d, J = 1.5 Hz, CH_3), 2.14 (2H, m, CH and OH), 3.86 (2H, m, CH_2), 5.03 (1H, br d, J = 9.6 Hz, CH), 5.82 (1H, q, J = 1.5 Hz, CH). **^{13}C nmr**; δ = 13.80 (CH_2), 34.89 (Me), 58.18 (CH_2), 82.11 (CH), 116.29 (CH), 169.74 (C), 173.42 (C). **IR**; ν = 3420 (O-H), 2920 (C-H), 1738 (C=O), 1641 (C=C). **MS(EI)**; 142 (28%, M^+), 124 (30%, M^+-H_2O), 98 (100%, M^+ - CO_2).

Data for 12; Rf = 0.42 (diethyl ether). **^{1}H nmr**; δ = 1.45 (3H, s, CH_3), 2.27 (2H, m, CH_2), 2.66 (1H, d, J = 18.4 Hz, CH), 2.85 (1H, d, J = 18.4 Hz, CH), 3.94 (1H, m, CH), 4.07 (1H, m, CH), 4.77 (1H, d, J = 4.5 Hz, CH). **^{13}C nmr**; δ = 22.88 (CH_2), 32.04 (Me), 41.62 (CH_2), 66.62 (CH_2), 85.35 (C), 87.99 (CH), 175.25 (C). **IR**; ν = 2981, 2940, 2880 (C-H), 1779 (C=O). **MS(EI)**; 142, (13%, M^+), 100 (18%, M^+-$COCH_2$), 43 (100%, $C_2H_3O^+$).

***(5S7S/5R7R)*-4,5-Dimethyl-5-(2-hydroxy-2-phenylethyl)-2(5*H*)-furanone 19 (R = Me), *(4S6S8S/4R6R8R)*-4,8-dimethyl-1,5-dioxa-2-oxo-6-phenylbicyclo[3.3.0.^{4,8}]octane 18 (R = Me) and *(4S6S8S/4R6R8R)*-1,5-dioxa-2-hydroxy-6-phenyl-2,4,8-trimethylbicyclo[3.3.0.^{4,8}]octane 20 (R =Me).**

Copper(I) iodide (788 mg, 4.14 mmol) was suspended in dry diethyl ether (5 ml) and cooled (0°C), whereupon methyl lithium (8.28 mmol, 5.52 ml of a 1.5 M solution) was added dropwise to produce a clear solution. HMPA (2 ml) and THF (2 ml) were then added and the solution cooled further (-20°C); at this point a solution of **17** (150 mg, 0.694 mmol) in THF (2 ml) was added and stirring continued for one hour at this temperature. Saturated ammonium chloride (10 ml) was added and the solution extracted with ethyl acetate (3 x 20 ml); these extracts were washed with water (2 x 20 ml), brine (2 x 20 ml), dried (magnesium sulphate), evaporated and on chromatography (70% diethyl ether in petrol, Rf = 0.23) gave **19** (R = Me; 120.0 mg, 0.516 mmol, 75%).

Data for 19 (R = Me); **^{1}H nmr**; δ = 1.52 (3H, s, Me), 1.87 (3H, s, Me), 1.92 (1H, dd, J = 15.0, 3.5 Hz, CH), 2.34 (1H, dd, J = 15.0, 8.3 Hz, CH), 2.82 (1H, s, OH), 4.77 (1H, dd, J = 8.3, 3.5 Hz, CH) 5.67 (1H, s, CH), 7.22-7.38 (5 H, m, Ph). **^{13}C nmr**; δ = 12.94 (Me), 24.00 (Me), 45.62 (CH_2), 70.49 (CH), 88.89 (C), 116.40 (CH), 125.76 (CH), 127.67 (CH), 128.42 (CH), 144.26 (C), 172.05 (C), 172.27(C). **IR**; ν = 3422 (O-H), 1738 (C=C) 1642 (C=C). **MS(CI)**; 250 (38%, M+NH_4^+), 232 (100%, M^+).

Two other compounds **18** and **19** were also isolated (see text): **Data for 18** (R = Me); Rf = 0.33 (70% diethyl ether in petrol) **^{1}H nmr**; δ = 1.48 (3H, s, CH_3), 1.54 (3H, s, CH_3), 2.61 (2H, d, J = 8.6 Hz, CH_2), 2.68 (1H, d, J = 17.8 Hz CH), 2.97 (1H, d, J = 17.8 Hz CH), 5.16 (1H, t, J = 8.6 Hz, CH), 7.31-7.39 (5H, m, Ph). **^{13}C nmr**; δ = 18.26 (Me), 21.15 (Me), 41.80 (CH_2), 45.75 (CH_2), 78.21 (CH), 87.76 (C), 94.92 (C), 126.06 (CH), 127.83 (CH), 128.50 (CH) 141.18 (C), 173.95 (C). **IR**; ν = 1772 (C=O). **MS(CI)**; 250 (100%, M+NH_4^+).

Data for 20; Rf = 0.39 (70% diethyl ether in petrol) **^{1}H nmr**; δ = 1.34 (3H, s, Me), 1.39 (3H, s, Me), 1.49 (3H, s, Me), 2.03 (1H, d, J = 14.0 Hz, CH), 2.42 (1H, d, J = 14.0 Hz, CH) 2.47 (1H, dd, J = 14.0, 8.2 Hz, CH), 2.97 (1H, dd, J = 14.0, 8.6 Hz, CH), 4.45 (1H, br s, OH), 5.08 (1H, t, J = 8.4 Hz, CH), 7.27-7.49 (5H, m, Ph). **^{13}C nmr**; δ = 17.85 (Me), 23.14 (Me), 26.81 (Me), 47.81 (CH_2), 49.29 (CH_3), 78.57 (CH), 92.74 (C), 92.92 (C), 104.11 (C), 126.93 (CH), 128.01 (CH), 128.61 (CH), 140.21 (C). **IR**; ν = 3495 (O-H), 2976 (C-H), 1750 (C=O [keto form]). **MS(CI)**; 231 (100%, M-OH^+).

***(5S,7S/5R,7R)*-4-*n*-Butyl-5-methyl-5-(2-hydroxy-2-phenylethyl)-2(5*H*)-furanone 19 (R = *n*-Bu), *(5S,7S/5R,7R)*-4,4-di-*n*-butyl-5-(2-hydroxy-2-phenylethyl)-5-methyl-4,5-dihydrofuran-2(3*H*)-one 20 (R = *n*-Bu) and *E*-*(5S,7S/5R,7R)*-5-(2-hydroxy-2-phenylethyl)-5-methyl-4-(*n*-propylmethylene)-4,5-dihydrofuran-2(3*H*)-one 21 (R = *n*-Pr).**

Copper(I) iodide (788 mg, 4.14 mmol) was suspended in dry diethyl ether (5 ml) and cooled (0°C), whereupon butyllithium (8.28 mmol, 5.7 ml of a 1.45 M solution) was added dropwise, followed by the addition of HMPA (2 ml) and THF (2 ml). The solution was cooled further (-20°C) and a solution of **17** (143 mg, 0.661 mmol) in THF (2 ml) was added. After one hour at this temperature, saturated ammonium chloride (10 ml) was added and the solution extracted with ethyl acetate (3 x 20 ml); these extracts were washed successively with water (2 x 20 ml), brine (2 x 20ml), dried (magnesium sulphate), evaporated and subject to chromatography (diethyl ether/petrol, gradient ellution), which gave **19** (R = *n*-Bu; 126.5 mg, 0.463 mmol, 70%) and **21** (R = *n*-Pr; 32.5 mg, 0.119 mmol, 18%).

Data for 19 (R = *n*-Bu); Rf = 0.14 (50% diethyl ether in petrol). **^{1}H nmr**; δ = 0.91 (3H, t, J = 7.1 Hz, Me), 1.36 (4H, m, 2 x CH_2), 1.53 (3H, s, Me), 1.95 (1H, dd, J = 15.0, 3.7, CH), 2.10 (2H, m, CH_2), 2.35 (1H, dd, J = 15.0, 8.0 Hz, CH), 2.68 (1H, s, OH), 4.77 (1H, dd, J = 8.0, 3.7 Hz, CH), 5.67 (1H, s, CH), 7.25-7.35 (5H, m, Ph). **^{13}C nmr**; δ = 13.54 (Me), 22.12 (CH_2), 26.85 (Me), 26.70 (CH_2), 29.44 (CH_2), 45.79, (CH_2), 70.21 (CH), 88.82 (C), 114.36 (CH), 125.81 (2 x CH), 127.42 (CH), 128.23 (2 x CH), 144.34 (C), 172.31 (C), 177.23(C). **IR**; ν = 3431 (C-H), 1750 (C=O), 1634 (C=C). **MS(CI)**; 292 (60%, $M+NH_4^+$), 274 (100%, $M+NH_4-OH_2^+$).

Data for 21 (R = *n*-Pr); Rf = 0.50 (50% diethyl ether in petrol). **^{1}H nmr**; δ = 1.20 (3H, t, J = 7.1 Hz, Me), 1.55 (2H, m, CH_2) 1.70 (3H, s, Me), 2.10 (4H, m, CH, CH_2 and OH), 2.50 (1H, dd, J = 14.3, 9.3 Hz, CH), 3..35 (2H, s, CH_2), 4.98 (1H, dd, J = 9.3, 3.0 Hz, CH), 5.48 (1H, m, CH), 7.25-7.55 (5H, m, Ph). **^{13}C nmr**; δ = 13.70 (Me), 22.17 (CH_2), 28.46 (Me), 31.69 (CH_2), 32.77 (CH_2), 49.61 (CH_2), 71.46 (CH), 89.07 (C), 123.88 (CH), 125.59 (CH), 127.70 (CH), 128.58 (CH), 137.20 (C), 144.52 (C), 174.49 (C). **IR**; ν = 3419 (O-H), 1756 (C=O). **MS(CI)**; 292 (100%, $M+NH_4^+$), 275 (15%, $M+H^+$).

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