Regiospecific Enolates from Tetrahydropyran-3-one. Synthetic Equivalents of a Thermodynamically and Kinetically Disfavoured Enolate Isomer

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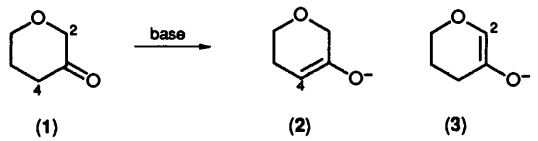
Two synthetic equivalents of the tetrahydropyran-3-one enolate **3** are described. Lithiation of the methoxy enol ether **8b** provides the β-lithiated enol ether **10** and although this species does serve as an equivalent of the enolate **3**, its use is limited by the observation that the mode of the acid-catalysed hydrolysis of the adducts **11** is controlled by the *'endo'* enol ether function. Using similar chemistry to that described for the synthesis of the methoxy derivative, the isomerically pure silyl enol ether **19** has also been prepared. This reagent represents a more general solution to the synthetic problems associated with access to the enolate **3** and reacts with a range of electrophiles in Lewis acid-mediated processes.

The manipulation of ketones *via* enolates represents one of the most important transformations in organic chemistry.[1] However, with unsymmetrically substituted ketones, difficulties may be encountered in controlling the distribution of possible enolate regioisomers. Often this problem of regiocontrol can be overcome by changes in reaction conditions used but this is not always possible. In the case of heterocyclic ketones, electronic factors exert a profound influence on the mode of enolization and sometime ago, Hirsch and Wang showed that tetrahydropyran-3-one underwent enolization, under both kinetically and thermodynamically controlled conditions, to give predominantly the C-4 enolate **2** rather than the isomeric C-2 enolate **3** (Scheme 1).[2] The preferred mode of enolization of the



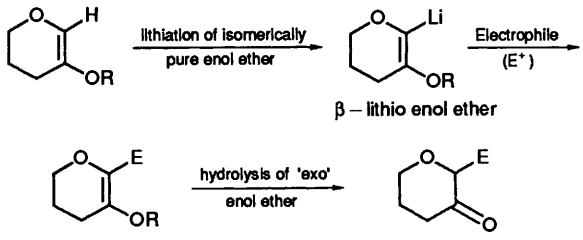
(1) (2) (3)

Scheme 1.

ketone **1** is, therefore, away from the ring-constrained heteroatom and similar observations have been reported for more highly substituted tetrahydropyran-3-one derivatives.[3] This preference is explained in stereoelectronic terms and is a consequence of the conformational constraints imposed on the ring-constrained oxygen lone pairs that result in a destabilizing interaction with an adjacent sp^2-hybridised anion, the enolate.[4] This situation is avoided in the case of enolate **2**.

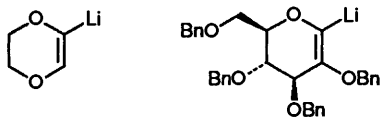
We are interested in developing the chemistry of enolates derived from heterocyclic-based ketones such as **1** for use as synthons in the construction of more complex heterocycles; however, the lack of an efficient route to the C-2 enolate **3** is obviously a problem that needs to be solved if the full potential of these ketones is to be realised. We have addressed this issue and in this paper we describe a solution to this problem.[5]

Our first efforts focused on the generation of a synthetic equivalent of the C-2 enolate **3**, based on the use of a β-lithiated enol ether and this basic strategy is outlined in Scheme 2. The use of a β-lithiated enol ether as an enolate equivalent has been described in acyclic systems[6] and more recently the heterocyclic derivatives **4**[7] and **5**[8] have also been described. However, the chemistry shown in Scheme 2 has several problems that must addressed if this approach is to be successfully



Scheme 2.

implemented. Firstly, synthetic access to an isomerically pure enol ether is required and clearly, in the case of systems related to compound **1**, the corresponding ketone does not represent



(4) (5)

satisfactory precursor. Secondly, the release of the ketone in the final step is complicated by the presence of *two* enol ether functions and, if this strategy is to be successful, there is a necessary requirement to control this cleavage step in favour of the *'exo'* over the *'endo'* enol ether.

Results and Discussion

The synthesis of the requisite alkyl enol ethers **8a** and **8b** is shown in Scheme 3 and the methodology used is based on the earlier work of Brown[9] and others[10a–c] on the oxidation of 3,4-dihydro-2*H*-pyran. Alkylation of the secondary hydroxy function of compound **6** was carried out using benzyl bromide or iodomethane and hydrolysis of the acetal moiety gave the ethers **7a** and **7b** in 76 and 65% overall yields, respectively. Elimination of water from **7a** and **7b** proceeded smoothly to give the corresponding *O*-benzyl and *O*-methyl enol ethers **8a** and **8b**; various conditions were examined, but methanesulphonyl chloride–triethylamine proved to be the method of choice for

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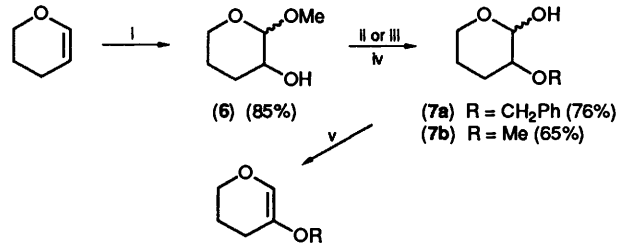
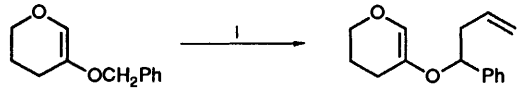


Scheme 3. *Reagents and conditions:* i, *m*-chloroperoxybenzoic acid (*m*CPBA), MeOH; ii, NaH, $PhCH_2Br$ (for **7a**); iii, NaH, MeI (for **7b**); iv, H^+, H_2O; iv, CH_3SO_2Cl, Et_3N.

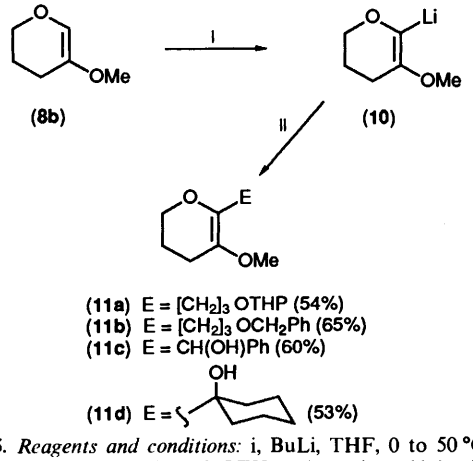
this transformation. Lithiation of the *O*-benzyl derivative **8a** was carried out using Bu^{t}Li at 0 °C and the resulting anion was quenched with allyl bromide to give an adduct in 50% yield. However, the presence of a vinylic proton [δ 6.10 (1 H, t, *J* 1.5 Hz)] showed that reaction had proceeded *via* lithiation at the benzylic centre, leading to the benzyl-substituted derivative **9** (Scheme 4). It is not clear whether this preference for



Scheme 4. *Reagents and conditions:* Bu^{t}Li, THF, −78 to 0 °C; allyl bromide, THF, −78 °C.

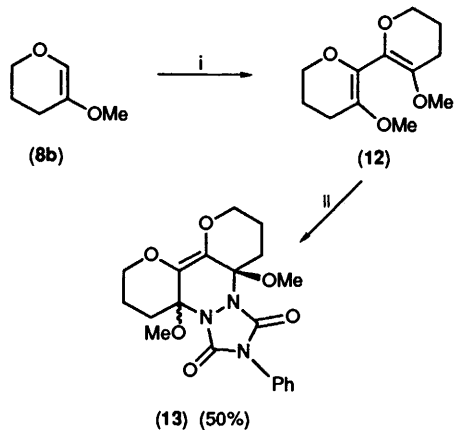
benzylic *vs.* vinylic deprotonation is kinetic in nature and, although this was not pursued, similar problems have been encountered with the more highly functionalized carbohydrate derivative **5**.[8]

The use of the *O*-methyl derivative **8b** proved to be more successful and the corresponding β-lithiated enol ether **10** was obtained using either Bu^{n}Li or Bu^{t}Li in a variety of solvents [tetrahydrofuran (THF), dimethoxyethane, diethyl ether, or hexane]; the best conditions involved Bu^{n}Li in THF at 0 °C, then warming to 50 °C for 1 h. Vinyl anion **10** was trapped by a series of simple electrophiles to give adducts **11a–d** in reasonable yield (Scheme 5). Attempts were also made to extend



Scheme 5. *Reagents and conditions:* i, BuLi, THF, 0 to 50 °C; ii, see Experimental section—$I[CH_2]_3OTHP$ (to give **11a**), $I(CH_2)_3OCH_2Ph$ (to give **11b**), PhCHO (to give **11c**), cyclohexanone (to give **11d**).

the scope of this methodology by generation of a homocuprate from compound **8b** but lithiation followed by treatment of vinyl-lithium **10** with CuI led only to dimer **12** which was most conveniently characterized as the Diels–Alder cycloadduct (**13**) (Scheme 6).

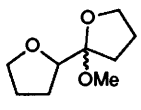


Scheme 6. *Reagents and conditions:* i, BuLi, THF, 0 to 50 °C, then Cu(I)I, −78 °C; ii, *N*-phenyltriazoline-2,5-dione.

The final step of the sequence outlined in Scheme 2 requires release of the masked ketone function at C-3 by hydrolysis of the *exo* enol ether. For this, attention was focused on the alkylated derivatives **11a** and **11b** which had originally been chosen as model substrates for a longer term programme, that is, the synthesis of the herbicidin class of nucleosides.[11] Acid-catalysed hydrolysis of compound **11a** was expected to give the bicyclic hemiketal **16**, a model for a structural subunit found in the herbicidins, but when this reaction was carried out, two products were obtained as a 1:1 mixture in 60% yield, that *retained* the methoxy residue and these products were assigned as the diastereoisomeric spiroketals **14a,b** (Scheme 7).* This conclusion was based on two observations. Firstly, prolonged reaction under these hydrolysis conditions served *only* to equilibrate the two diastereoisomers (**14a** ⇌ **14b**) (K_{eq} = 1) and no loss of methanol was observed. Secondly, the fully coupled ^{13}C NMR spectrum of both **14a** and **14b** showed OCH_3 as a doublet of quartets (^1J 140 and ^3J 4.5 Hz). The long range ^3J coupling is consistent[12] with the spiroketal structure and is due to coupling through oxygen, between $O^{13}CH_3$ and the adjacent methine at C-10. Literature precedent suggests that a ^4J coupling through oxygen, as would be the case with the alternative structure **17a,b**, would be ⩽ 1 Hz.[12]

The formation of the spiroketals **14a,b** is clearly due to participation of the *endo* enol ether and reactions that involve the intermediacy of an oxonium ion appear to be dictated by the ring oxygen atom. This may also be a reflection of the conformational constraints imposed on the ring-oxygen's lone pairs and, in that sense, be related to the regioselectivity observed in the enolisation of ketone **1**. To overcome this problem, we examined an alternative method of enol ether cleavage based on the use of iodotrimethylsilane (TMSI) which offers a mechanistic pathway that does not rely on oxygen-stabilized carbocation.[13] The *O*-THP residue of **11a** was labile

* The bis(tetrahydrofuran) (**A**) was also considered as a possibility but was excluded on the basis of the spectroscopic and chemical evidence available.



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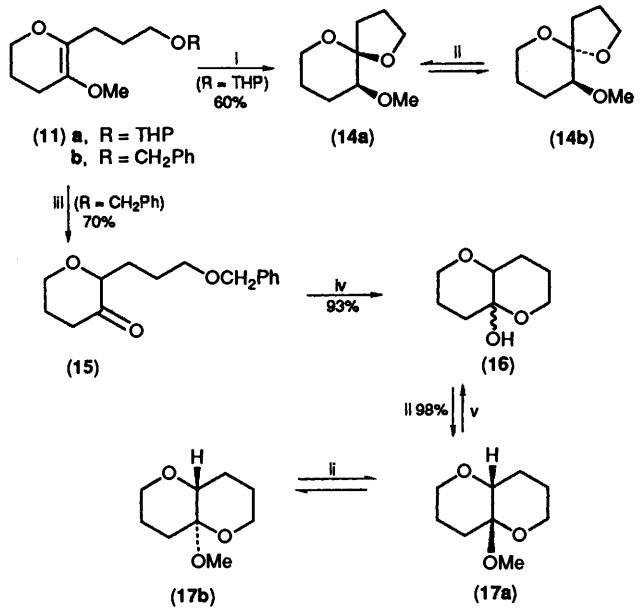
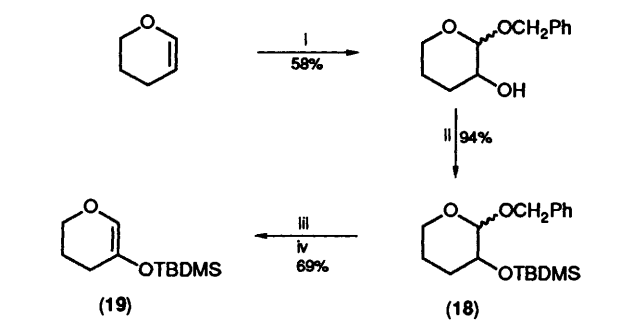
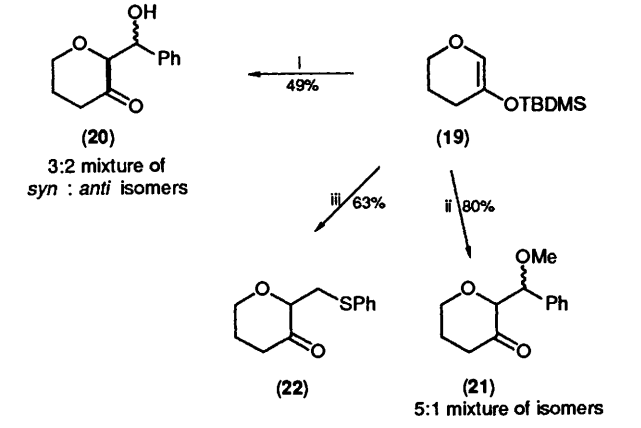


Scheme 7. *Reagents:* i, HCl, H_2O, THF; ii, H^+, MeOH; iii, Me_3SiCl, NaI, MeCN; iv, H_2, 10% Pd on C; v, H^+, H_2O.



Scheme 8. *Reagents:* i, *m*CPBA, $PhCH_2OH$; ii, TBDMSCl, 1,8-diazabicyclo[5.4.0]undec-7-ene, CH_2Cl_2; iii, H_2, 10% Pd on C, EtOH; iv, $MeSO_2Cl$, Et_3N.



Scheme 9. *Reagents and conditions:* i, PhCHO, $SnCl_4$, CH_2Cl_2, −78 °C; ii, $PhCH(OMe)_2$, $Me_3SiOSO_2CF_3$, CH_2Cl_2, −78 °C; iii, $PhSCH_2Cl$, $ZnBr_2$, CH_2Cl_2, room temperature.

in the presence of TMSI, but the *O*-benzyl derivative **11b** underwent smooth cleavage to give the desired 2-substituted tetrahydropyran-3-one **15** in 70% yield. Hydrogenolysis of compound **15** gave the bicyclic hemiketal **16** as a 2:1 mixture of *cis* and *trans* isomers (in solution); a structural assignment that was confirmed by X-ray crystallographic analysis.* Exposure of compound **16** to acidic methanol gave a separable mixture of the methoxy ketals **17a** and **17b** in 98% yield and this reaction was readily reversed using aqueous acid. In addition, although **17a** and **17b** equilibrated readily (K_{eq} = 1) using an acid catalyst, we observed no other skeletal rearrangements.

Although the ketone functionality of adduct **11b** could be exposed using TMSI, the use of β-lithiated enol ether **10** as a synthetic equivalent of the C-2 enolate **3** does not represent a good and general solution to the problem as outlined in the introduction to this paper. The value of vinyl anions of this type is frequently limited by their high basicity, and difficulties were also encountered in the cleavage of the aldehyde and ketone adducts **11c** and **11d**, which have the additional complication of a labile allylic hydroxyl residue.

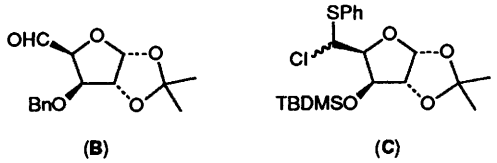
The chemistry shown in Scheme 3 is, however, an efficient way to prepare 5-alkoxy-3,4-dihydro-2*H*-pyrans, but given the limitations associated with the use of the vinyl-lithium **10** as a synthetic equivalent of enolate **3** we required a more readily cleaved enol ether. The obvious extension was to incorporate silyl, rather than alkyl group into this scheme to afford, in a sequence that did not involve the intermediacy of an enolate, a synthetically flexible silyl enol ether.[14] Some minor alterations of the earlier chemistry were required but the *O*-(t-butyldimethyl)-silyl derivative **19** was prepared in good yield as shown in Scheme 8. The only significant modification involved the use of benzyl alcohol rather than methanol during the initial oxidation step, which allowed conversion of acetal **18** into the corresponding hemiacetal to be achieved under nonacidic conditions. Conventional acid hydrolysis of silyl ether **18** using the conditions shown in Scheme 3, resulted in significant loss of the silyl residue which is presumed to arise by migration between adjacent oxygen atoms.

The reactivity of silyl enol ether **19** did not appear to be adversely influenced by the ring-constrained oxygen atom and a series of straightforward and representative transformations were carried out under standard conditions as shown in Scheme 9. Most attention focused on the use of processes involving the Lewis acid-mediated generation of 'S_N1'-type electrophiles[15] from aldehydes,[16] acetals,[17] and α-chloro sulphides.[18] In the case of the aldol reactions involving the silyl ether **19** and benzaldehyde, and the corresponding dimethylacetal, the diastereoselectivities observed with the adducts **20** and **21** were comparable to that previously observed for 1-(trimethylsilyloxy)cyclohexene,[16,17] although we did not establish the configuration of the major isomer of **21**.

The principle advantage of the methodology shown in Scheme 9 over that based on a β-lithiated enol ether such as **10** is that the ketone function is released *directly* under the reaction conditions used to introduce the electrophile.† This allows direct isolation of *e.g.*, aldol products that are not

* Although the crystal examined in this X-ray crystallographic study corresponded to the *cis* isomer, it cannot be concluded that **16** exists exclusively in this configuration in the solid state.

† The more highly substituted carbohydrate-derived aldehyde (**B**) and the α-chloro sulphide (**C**) both reacted efficiently with silyl enol ether **19**. These studies relate directly to the synthesis of the herbicidins and will be reported at a later date.



accessible *via* the vinyl-lithium **10** but also avoids the complications of using very basic organolithium reagents.

In conclusion, we have examined various reagents as synthetic equivalents of the C-2 enolate **3** of tetrahydropyran-3-one **1**. Although under certain conditions the novel β-lithiated enol ether **10** did fulfil this function, this reagent was not a general solution to this synthetic problem. Nevertheless, this early study did establish a basis for the synthesis of the corresponding silyl enol ether **19** which is not only a readily available reagent but provides, for the first time, access to this otherwise inaccessible heterocyclic enolate. This methodology should also be applicable to more highly substituted heterocyclic ketones and this aspect is currently under investigation with an emphasis on developing a synthetic entry into the herbicidin class of nucleosides.

Experimental

General experimental protocols have been described previously.[19] Assignment of ^1H and ^{13}C NMR spectral data described below was carried out using a combination of homo- and hetero-nuclear 2D correlation and NOE experiments.

3-Benzyloxytetrahydropyran-2-ol **7a**.—2-Methoxytetrahydropyran-3-ol **6**[9] (10.0 g, 75 mmol) in dimethylformamide (DMF) (80 ml) was added to an ice-cold suspension of NaH (4.0 g, 170 mmol) in DMF (200 ml). The mixture was stirred for 20 min after which benzyl bromide (14.4 g, 84 mmol) was added to it. The reaction mixture was then allowed slowly to warm to room temperature after which it was stirred for 3 h. Methanol (20 ml) was added and after 1 h the solution was diluted with CH_2Cl_2 (500 ml), washed with saturated aqueous sodium hydrogen carbonate (2 × 200 ml), and dried ($MgSO_4$). Removal of solvent gave 2-methoxy-3-benzyloxytetrahydropyran as a colourless oil which was used without further purification. This compound was dissolved in 2M hydrochloric acid (100 ml), heated at 60 °C for 3 h, and then stirred at room temperature for 15 h. The mixture was extracted with CH_2Cl_2 (5 × 50 ml) and the extracts were dried (Na_2SO_4). After removal of solvent, the residue was purified by flash chromatography to give **7a**[10a,b] (11.8 g, 76% overall yield) as a colourless oil and as a mixture of diastereoisomers: δ_H (270 MHz; $CDCl_3$) 1.35–2.20 (4 H, overlapping multiplets), 2.79–3.99 (3 H, overlapping multiplets), 4.51–4.95 (4 H, overlapping multiplets), and 7.20–7.45 (5 H, m).

3-Methoxytetrahydropyran-2-ol **7b**.—This material was prepared from 2-methoxytetrahydropyran-3-ol **6**[9] using the method described by Hurd and Richardson.[10c]

5-Benzyloxy-3,4-dihydro-2H-pyran **8a**.—Methanesulphonyl chloride (0.35 g, 3.1 mmol) was added dropwise to a solution of 3-benzyloxytetrahydropyran-2-ol **7a** (508 mg, 2.4 mmol) and triethylamine (2.5 g, 25 mmol) in dry chloroform (20 ml) cooled to 0 °C under nitrogen. The mixture was allowed to warm to room temperature and after 45 min complete conversion into the mesylate was observed by TLC; the reaction was conveniently followed using a methanol quench. The mixture was heated under reflux for 5 h and the resulting brown solution was cooled to room temperature, washed successively with water (2 × 10 ml) and saturated aqueous copper sulphate (10 ml), dried (Na_2SO_4), and evaporated to give a brown oil. This was purified by flash chromatography to give the enol ether **8a** as a colourless oil (306 mg, 66%), b.p. 110–115 °C (0.7 mmHg; Kugelrohr) (Found: M^+, 190.0988. $C_{12}H_{14}O_2$ requires M, 190.0993); ν_{max}(film) 1660w, 1440 and 1360 cm^{-1}; δ_H(270 MHz; $CDCl_3$) 1.85–1.94 (2 H, m), 2.30 (2 H, td, J 6.5 and 1.5 Hz), 3.85 (2 H, dd, J 6 and 4.5 Hz), 4.63 (2 H, s), 6.30 (1 H, t, J 1.5 Hz) and 6.29–7.35 (5 H, m); m/z 190 (M^+, 13%) and 91 (100).

5-(Methoxy)-3,4-dihydro-2H-pyran **8b**.—Methanesulphonyl chloride (1.12 g, 9.8 mmol) was added dropwise to a solution of 3-methoxytetrahydropyran-2-ol **7b** (990 mg, 7.5 mmol) and triethylamine (2.9 g, 28.7 mmol) in dry chloroform (40 ml) cooled to 0 °C under nitrogen. The mixture was allowed to warm to room temperature and stirred for 15 min. The solution was heated under reflux for 3 h and the resulting brown solution was then cooled to room temperature. The reaction mixture was diluted with diethyl ether (100 ml), washed with water (100 ml) followed by saturated aqueous copper sulphate (100 ml), and dried (Na_2SO_4). Following the careful removal of solvent using a Vigreux column, the residue was purified by passage down an alumina (neutral) column [light petroleum (b.p. 30–40 °C)–diethyl ether (9:1)] to give the enol ether **8b** as a colourless oil (638 mg, 75%), b.p. 110–115 °C (760 mmHg; Kugelrohr) (Found: M^+, 114.066. $C_6H_{10}O_2$ requires M, 114.068); ν_{max}(film) 1440, 1368 and 1125 cm^{-1}; δ_H(270 MHz; $CDCl_3$) 1.89 (2 H, m), 2.17 (2 H, t, J 6.5 Hz), 3.47 (3 H, s), 3.82 (2 H, t, J 4 Hz) and 6.18 (1 H, s); m/z 114 (M^+, 64%), 99 ($M^+ - CH_3$, 8), 86 ($M^+ - C_2H_4$, 38), 85 (21), 57 (64) and 56 (100).

5-(1-Phenylbut-3-enyloxy)-3,4-dihydro-2H-pyran **9**.—t-Butyl-lithium (1.7M in pentane; 0.35 ml, 0.6 mmol) was added dropwise to a solution of 5-benzyloxy-3,4-dihydro-2*H*-pyran **8a** (100 mg, 0.53 mmol) in dry tetrahydrofuran (THF) (2 ml) at −78 °C under nitrogen. The resulting clear yellow solution was then allowed to warm to 0 °C for 30 min and then cooled to −78 °C. Allyl bromide (129 mg, 1.1 mmol) was then added and the resulting clear colourless solution was stirred for 15 min before being quenched with saturated aqueous ammonium chloride (2 ml). The reaction mixture was extracted with ethyl acetate (3 × 2 ml) and the extracts were dried (Na_2SO_4). Evaporation of the solvents gave a clear colourless oil which was purified by radial chromatography ('Chromatotron') [ethyl acetate–light petroleum (5:95)] to give the enol ether **9** as a colourless oil (60 mg, 50%) (Found: M^+, 230.1341. $C_{15}H_{18}O_2$ requires M, 230.1305); ν_{max}(film) 1625, 1480 and 1435 cm^{-1}; δ_H(270 MHz; $CDCl_3$) 1.78–1.86 (2 H, m), 2.05–2.18 (2 H, m), 2.44 (1 H, quin, J 7 Hz), 2.63 (1 H, quin, J 7 Hz), 3.68–3.73 (2 H, m), 4.62 (1 H, dd, J 7.5 and 5.5 Hz), 5.02–5.09 (2 H, m), 5.78 (1 H, ddt, J 17, 10 and 7 Hz), 6.10 (1 H, t, J 1.5 Hz) and 7.22–7.36 (5 H, m); m/z 230 (M^+, 2%), 189 ($M^+ - C_3H_5$), 131 (72) and 100 (100).

General Procedure for the Metallation of 5-Methoxy-3,4-dihydro-2H-pyran **8b** *and Reaction of Organolithium* **10** *with Electrophiles*.—To a stirred solution of 5-methoxy-3,4-dihydro-2*H*-pyran **8b** (0.5 mmol, 1 equiv.) in dry THF (*ca.* 1 ml/0.5 mmol) at 0 °C under nitrogen was added butyl-lithium (1.2 equiv.). The resulting clear orange solution was warmed at 50 °C for 1 h and then cooled to either −78 °C or 0 °C (see below) and a solution of the appropriate electrophile in THF was added. When reaction was complete as judged by TLC the reaction mixture was quenched with saturated aqueous ammonium chloride and the product was extracted with diethyl ether. The extracts were dried (Na_2SO_4) and following removal of solvents, the product was purified by flash chromatography using ethyl acetate–petroleum mixtures.

5-Methoxy-6-(3-tetrahydropyran-2-yloxypropyl)-3,4-dihydro-2H-pyran **11a**. Addition of 1-iodo-3-(tetrahydropyranyl-2-yloxy)propane[20] (0.50 equiv.) to the anion **10** was carried out at 0 °C and the reaction mixture was then heated at 50 °C for 1 h to give compound **11a** as a colourless oil in 54% yield based on 1-iodo-3-(tetrahydropyranyl-2-yloxy)propane (Found: M^+, 256.1672. $C_{14}H_{24}O_4$ requires M, 256.1674); ν_{max}(film) 1730w, 1430w, 1345w, 1250w and 1025 cm^{-1}; δ_H(270 MHz; $CDCl_3$) 1.56–1.93 (10 H, m), 2.19–2.37 (4 H, m), 3.41–3.58 (5 H, m), 3.77 (1 H, dt, J 9.5 and 7 Hz), 3.86 (2 H, t, J 5.5 Hz), 3.77 (1 H, m)

and 4.60 (1 H, dd, *J* 4.5 and 2.5 Hz); *m/z* 256 (M^+, 16%), 172 ($M^+ - C_5H_8O$, 26), 171 ($M^+ - C_5H_9O$, 25) and 85 (100).

6-(3-*Benzyloxypropyl*)-5-*methoxy*-3,4-*dihydro*-2H-*pyran* **11b**. Addition of 3-benzyloxypropyl iodide[21] (0.50 equiv.) to the anion **10** was carried out at 0 °C and the reaction mixture was then heated at 50 °C for 1 h to give compound **11b** as a colourless oil in 65% yield based on 3-benzyloxypropyl iodide (Found: M^+, 262.1569. $C_{16}H_{22}O_3$ requires *M*, 262.1569); ν_{max}(film) 1497, 1360, 1275 and 1090 cm^{-1}; δ_H(270 MHz; $CDCl_3$) 1.78 (2 H, quin, *J* 7 Hz), 1.82–1.91 (2 H, m), 2.17 (2 H, t, *J* 6.5 Hz), 2.28 (2 H, t, *J* 7.5 Hz), 3.45 (3 H, s), 3.49 (2 H, t, *J* 6.5 Hz), 3.81 (2 H, t, *J* 5 Hz), 4.51 (2 H, s) and 7.23–7.44 (5 H, m); *m/z* (CI; NH_3) 280 ($M^+ + NH_3$, 3%), 263 ($M^+ + 1$, 61) and 262 (M^+, 21).

α-(5-*Methoxy*-3,4-*dihydro*-2H-*pyran*-6-*yl*)*benzyl alcohol* **11c**. This reaction was carried out at −78 °C using benzaldehyde (2 equiv.) to give **11c** as a colourless oil in 60% yield (Found: M^+, 220.1091. $C_{13}H_{16}O_3$ requires *M*, 220.1091); ν_{max}(film) 3430 (OH), 1655w, 1590w, 1480w and 1440w cm^{-1}; δ_H(270 MHz; $CDCl_3$) 1.85–1.96 (2 H, m), 2.22–2.38 (2 H, m), 3.00 (1 H, br s, OH), 3.51 (3 H, s), 3.80–3.92 (2 H, m), 5.68 (1 H, s) and 7.21–7.46 (5 H, m); *m/z* 220 (M^+, 100%), 203 ($M^+ - OH$, 15), 202 ($M^+ - H_2O$, 20) and 188 (34).

1-(5-*Methoxy*-3,4-*dihydro*-2H-*pyran*-6-*yl*)*cyclohexanol* **11d**. This reaction was carried out at −78 °C using cyclohexanone (2 equiv.) to give **11d** as a colourless oil in 53% yield (Found: M^+, 212.1400. $C_{12}H_{20}O_3$ requires *M*, 212.1411); ν_{max}(film) 3490 (OH), 1440w, 1385w, 1205, 1140 and 1060 cm^{-1}; δ_H(270 MHz; $CDCl_3$) 1.56–1.72 (10 H, m), 1.86 (2 H, quin, *J* 6.5 Hz), 2.20 (2 H, t, *J* 6.5 Hz), 3.51 (3 H, s), 3.78 (2 H, t, *J* 5 Hz) and 4.37 (1 H, br s, OH); *m/z* 212 (M^+, 70%) and 169 ($M^+ - C_2H_5O$, 100).

6,6′-*Bis*(5-*methoxy*-3,4-*dihydro*-2H-*pyran*) **12**.—5-Methoxy-3,4-dihydro-2*H*-pyran **8b** (47 mg, 0.42 mmol) was metallated as described above. The resulting solution was cooled to −78 °C, and then transferred *via* a cannula to a stirred suspension of copper(I) iodide (21 mg, 0.11 mmol) in dry THF (1 ml) also at −78 °C under nitrogen. The resulting dark green–black suspension was stirred at −78 °C for 0.75 h after which the solution was allowed to warm slowly to room temperature overnight. It was then quenched with saturated aqueous ammonium chloride (5 ml), and the mixture was extracted with dichloromethane (4 × 5 ml). The extracts were dried (Na_2SO_4) and removal of solvent gave the dimer **12** as a yellow oil; δ_H(60 MHz; $CDCl_3$) 1.75–2.45 (8 H, m), 3.55 (6 H, s) and 3.95 (4 H, t, *J* 5 Hz).

The dimer **12** was dissolved in dry dichloromethane (5 ml), cooled to 0 °C under nitrogen, and treated with *N*-phenyltriazolinedione in dichloromethane until the red colour of the dienophile persisted. The mixture was then stirred at 0 °C for 1 h, the solvent was evaporated, and the resulting red solid was purified by flash chromatography to give the triazolinedione adduct **13** as colourless rhombohedral crystals (21 mg, 50% based on CuI), m.p. 173–174.5 °C (ethanol) (Found: C, 59.7; H, 5.9; N, 10.45. $C_{20}H_{23}N_3O_6$ requires C, 59.84; H, 5.77; N, 10.47%); ν_{max}($CHCl_3$) 1775, 1710, 1600w and 935 cm^{-1}; δ_H(270 MHz; $CDCl_3$) 1.73 (2 H, br d, *J* 14 Hz), 1.97 (2 H, td, *J* 13 and 4.5 Hz), 2.27 (2 H, qt, *J* 13 and 4.5 Hz), 3.17 (2 H, br d, *J* 13.5 Hz), 3.46 (6 H, s), 3.76 (2 H, ddd, *J* 13.5, 11, and 3 Hz), 4.33 (2 H, ddt, *J* 11, 5, and 1.5 Hz), 7.35–7.50 (5 H, m); *m/z* (CI) 402 ($M^+ + H$, 4%), 401 (M^+, 31), and 370 ($M^+ - C_2H_6$, 100).

Adduct **13** was a single compound but no attempt was made to establish the stereochemistry of this material.

10-*Methoxy*-1,6-*dioxaspiro*[4,5]*decanes* **14**.—The tetrahydropyranol enol ether **11a** (93 mg, 0.36 mmol) was set aside at room temperature for 12 h in concentrated hydrochloric acid–H_2O–THF (1:5:20) (2 ml). Following neutralization with saturated aqueous sodium hydrogen carbonate, the solution was concentrated, the aqueous residue was extracted with dichloromethane (3 × 3 ml), and the combined extracts were dried (Na_2SO_4) and evaporated. The products were separated using radial chromatography ('Chromatotron') [ethyl acetate–light petroleum (1:9)] to give the two diastereoisomeric *spiroketals* **14a,b** as colourless oils (35 mg, 60% combined yield). (*a*) R_f 0.51 [ethyl acetate–light petroleum (3:7)] (Found: $M^+ - C_2H_4$, 144.0787. $C_7H_{12}O_3$ requires *M*, 144.0786); ν_{max}($CHCl_3$) 1715w, 1590w and 920 cm^{-1}; δ_H(400 MHz; $CDCl_3$) 1.31 (1 H, m, 8-H), 1.80–1.91 (5 H, m, 8-H, 9-H_{ax}, 9-H_{eq}, 3-H and 4-H), 1.97–2.05 (2 H, m, 3-H, 4-H), 3.10 (1 H, m, 10-H), 3.38 (3 H, s, OCH_3), 3.57 (1 H, m, 7-H_{eq}), 3.83 (1 H, td, *J* 11.5 and 3 Hz, 7-H_{ax}) and 3.88–3.99 (2 H, m, 2-H_{ax} and 2-H_{eq}); δ_C(H-coupled) C_6D_6) 20.8 (t, *J* 128.5 Hz), 23.8 (t, *J* 128 Hz), 24.7 (t, *J* 130 Hz), 35.5 (t, *J* 132 Hz), 56.9 (qd, *J* 140 and 4.5 Hz, OCH_3), 61.9 (t, *J* 145 Hz), 68.1 (t, *J* 145.5 Hz), and 79.2 (d, *J* 143 Hz); *m/z* 144 ($M^+ - C_2H_4$, 12%) and 141 ($M^+ - OCH_3$, 100).

(*b*) R_f 0.46 [ethyl acetate–petrol (3:7)] (Found: fragment $M^+ - C_2H_4$, 144.0794. $C_7H_{12}O_3$ requires *M*, 144.0786); ν_{max}($CHCl_3$) 1715 cm^{-1}; δ_H(400 MHz; $CDCl_3$) 1.64–1.68 (3 H, m, 8-H_{ax}, 8-H_{eq} and 9-H_{ax}), 1.73 (1 H, ddd, *J* 12.5, 8.5 and 4.5 Hz, 4-H), 1.87 (1 H, m, 3-H), 1.96–2.07 (2 H, m, 3-H and 9-H_{eq}), 2.17 (1 H, ddd, *J* 12.5, 10 and 7.5 Hz, 4-H), 3.21 (1 H, dd, *J* 11 and 4.5 Hz, 10-H_{ax}), 3.37 (3 H, s, OCH_3), 3.49 (1 H, m, 7-H_{eq}), 3.75 (1 H, m, 7-H_{ax}), 3.91 (1 H, td, *J* 8 and 7 Hz, 2-H), and 3.99 (1 H, td, *J* 8 and 5.5 Hz, 2-H); δ_C(H-coupled; C_6D_6) 24.9 (t, *J* 128 Hz), 25.2 (t, *J* 132 Hz), 26.2 (t, *J* 126 Hz), 34.6 (t, *J* 133 Hz), 56.4 (qd, *J* 140 and 5.5 Hz), 61.1 (t, *J* 145 Hz), 68.7 (t, *J* 146.5 Hz) and 79.8 (d, *J* 141 Hz); *m/z* 144 ($M^+ - C_2H_4$, 18%) and 141 ($M^+ - OCH_3$, 100).

2-(3-*Benzyloxypropyl*)*tetrahydropyran*-3-*one* **15**.—To a stirred solution of the enol ether **11b** (300 mg, 1.15 mmol) and anhydrous sodium iodide (170 mg, 1.13 mmol) in dry acetonitrile (1.5 ml) at 0 °C under nitrogen, was added chlorotrimethylsilane (124 mg, 1.15 mmol). The resulting deep-orange solution was stirred at 0 °C for 5 min, after which it was partitioned between aqueous sodium thiosulphate solution (1.5 ml; 0.25M) and dichloromethane (2 ml). The aqueous phase was further extracted with dichloromethane (3 × 2 ml) before the combined organic extracts were dried (Na_2SO_4) and evaporated to give an orange oil which was purified by flash chromatography to give the pyranone **15** as a colourless oil (196 mg, 70%) (Found: M^+, 248.1412. $C_{15}H_{20}O_3$ requires *M*, 248.1412); ν_{max}(liq. film) 1724 cm^{-1}; δ_H(270 MHz; $CDCl_3$) 1.67–1.99 (4 H, m, 1-H and 2-H), 1.99–2.19 (2 H, m, ring 5-H), 2.37–2.60 (2 H, m, ring 4-H), 3.50 (2 H, t, *J* 6.5 Hz, 3-H), 3.70 (1 H, td, *J* 11 and 4.5 Hz, 6-H_{ax}), 3.81 (1 H, m, ring 2-H), 4.05 (1 H, dt, *J* 11 and 4.5 Hz, 6-H_{eq}), 4.50 (2 H, s, OCH_2Ph) and 7.32 (5 H, m); *m/z* 248 (M^+, 1%), 157 ($M^+ - CH_2Ph$, 5), 129 (92), 107 (47) and 91 (100).

The 2,4-dinitrophenylhydrazone of **15** was prepared by standard means and isolated as yellow needles in 87% yield, m.p. 103–104 °C (ethanol) (Found: C, 58.5; H, 5.51; N, 12.88. $C_{21}H_{24}N_4O_6$ requires C, 58.87; H, 5.65; N, 13.08%); ν_{max}(KBr) 1615, 1587 and 1330 cm^{-1}; δ_H(400 MHz; C_6D_6), 1.19 (1 H, m, 5-H_{ax}), 1.35 (1 H, m, 5-H_{eq}), 1.57 (1 H, ddd, *J* 16, 11 and 6.5 Hz, ring 4-H_{ax}), 1.84–2.10 (2 H, m, 2-H), 2.08 (1 H, m, 1-H), 2.19 (1 H, m, ring 4-H_{eq}), 2.24 (1 H, m, 1-H), 3.17 (1 H, ddd, *J* 12, 11 and 3.5 Hz, ring 6-H_{ax}), 3.52 (2 H, t, *J* 5.5 Hz, 3-H), 3.67 (1 H, dt, *J* 11 and 4 Hz, ring 6-H_{eq}), 3.84 (1 H, dd, *J* 6.5 and 4.5 Hz, ring 2-H), 4.42 (2 H, s, OCH_2Ph), 7.16–7.38 (5 H, m), 7.53 (1 H, d, *J* 10 Hz), 7.72 (1 H, dd, *J* 10 and 3 Hz), 8.89 (1 H, d, *J* 3 Hz), and 10.69 (1 H, s, NH); *m/z* (FAB) 429 ($M^+ + H$, 10%).

Octahydropyrano[3,2-*b*]*pyran*-4a-*ol* **16**, cis–trans *Mixture*.—To a solution of the pyranone **15** (200 mg, 0.8 mmol) in absolute ethanol (2 ml) was added 10% palladium on charcoal

(*ca.* 25 mg). The resulting suspension was stirred vigorously under an atmosphere of hydrogen for 1 h and then the catalyst was removed by filtration through Celite. Evaporation of solvent and purification by chromatography gave **16** as a colourless oil (100 mg, 93%) which crystallised when set aside. Sublimation or recrystallisation from light petroleum–diethyl ether gave rhombohedral crystals, m.p. 78–80 °C (Found: C, 60.8; H, 9.1%; M^+, 158.0943 $C_8H_{14}O_3$ requires C, 60.7; H, 8.9%; *M*, 158.0943); ν_{max}(KBr disc) 3400 (OH) and 1735w cm^{-1} (CO); δ_H(400 MHz; C_6D_6, signals for the *cis* and *trans* isomers are indicated) 1.08 (0.67 H, br d, *J* 10 Hz, *cis* 7-H), 1.21 (1 H, br m, *J* 14 Hz, *cis* 3-H and *trans* 3-H), 1.30–1.35 (0.33 H, m, *trans* 7-H), 1.44–1.69 (1.67 H, m, *cis* 4-H, *trans* 4-H, 7-H and 8-H), 1.82–2.01 (2.33 H, m, *cis* 4-H and 8-H, *trans* 3-H, 4-H and 8-H), 2.03–3.30 (2 H, m, *cis* 3-H, 7-H and 8-H), 3.06–3.23 (2.33 H, m, *cis* + *trans* OH, *cis* 2-H_{ax}, *trans* 2-H_{ax} and 8a-H), 3.36 (0.67 H, t, *J* 3 Hz, *cis* 8a-H), 3.47 (0.33 H, dd, *J* 12 and 6 Hz, *trans* 6-H_{eq}), 3.68 (0.67 H, br d, *J* 13 Hz, *cis* 6-H_{eq}), 3.81 (0.33 H, dd, *J* 12 and 6 Hz, *trans* 2-H_{eq}) and 3.89–4.08 (1.67 H, m, *cis* 2-H_{eq}, 6-H_{ax} and *trans* 6-H_{ax}); δ_C(C_6D_6) 20.06 (*cis* C-7), 24.41 (*cis* C-3), 24.46 (*trans* C-8), 24.55 (*trans* C-3), 24.96 (*cis* C-8), 25.77 (*trans* C-7), 35.94 (*trans* C-4), 37.73 (*cis* C-4), 60.12 (*trans* C-6), 60.95 (*cis* C-6), 67.54 (*cis* C-2), 68.27 (*trans* C-2), 74.61 (*cis* C-8a), 79.72 (*trans* C-8a), 91.86 (*cis* C-4a) and 93.13 (*trans* C-4a); *m/z* 158 (M^+, 3%).

cis *and* trans-4a-(*Methoxy*)*octahydropyrano*[3,2-*b*]*pyran* **17a,b**.—To a stirred solution of the pyranopyranol **16** (60 mg, 0.38 mmol) in dry methanol (2 ml) at room temperature under nitrogen was added toluene-*p*-sulphonic acid (3 mg). The resulting clear solution was stirred for 2 h after which time the solvent was removed by evaporation. The residue was taken up in dichloromethane (10 ml) and washed with water (2 × 10 ml), dried (Na_2SO_4), and evaporated to give a mixture of the *cis* and *trans* pyranopyrans **17a,b** (64 mg, 98%) as a colourless oil which were separated by flash chromatography over silica.

(*a*) *cis*-4a-Methoxyoctahydropyrano[3,2-*b*]pyran **17a** (26 mg, 39%), R_f 0.50 [ethyl acetate–light petroleum (3:7)] (Found: M^+, 172.1090. $C_9H_{16}O_3$ requires *M*, 172.1098); ν_{max}(film) 1457, 1430, 1319, 1289, 1262 and 1218 cm^{-1}; δ_H(400 MHz; $CDCl_3$) 1.24 (1 H, m, 7-H_{eq}), 1.38 (1 H, td, *J* 13 and 5 Hz, 4-H_{ax}), 1.53 (1 H, m, 3-H_{eq}), 1.65 (1 H, m, 8-H_{eq}), 1.80–2.00 (2 H, m, 7-H_{ax} and 3-H_{ax}), 2.02 (1 H, m, 8-H_{ax}), 2.10 (1 H, m, 4-H_{eq}), 3.21 (3 H, s, OCH_3), 3.22 (1 H, t, *J* 2.5 Hz, 8a-H), 3.37 (1 H, ddd, *J* 12.5, 11.5 and 2 Hz, 2-H_{ax}), 3.61–3.72 (2 H, m, 6-H_{ax} and 6-H_{eq}) and 3.96 (1 H, ddt, *J* 11.5, 4.5 and 1.5 Hz, 2-H_{eq}); δ_C(C_6D_6, H-coupled) 20.3 (t, *J* 127 Hz), 24.4 (t, *J* 128 Hz), 25.5 (t, *J* 129 Hz), 32.5 (t, *J* 127 Hz), 46.9 (q, *J* 141 Hz), 61.5 (t, *J* 144 Hz), 68.0 (t, *J* 141 Hz), 75.0 (d, *J* 144 Hz) and 94.8 (s); *m/z* 172 (M^+, 67%), 1410 (M^+ – CH_3O, 33) and 101 (100).

(*b*) *trans*-4a-Methoxyoctahydropyrano[3,2-*b*]pyran **17b** (23 mg, 34%), R_f 0.3 [ethyl acetate–light petroleum (3:7)] (Found: M^+, 172.1100. $C_9H_{16}O_3$ requires *M*, 172.1098); ν_{max}(film) 1458, 1438, 1283, 1262 and 1210 cm^{-1}; δ_H(400 MHz; $CDCl_3$) 1.37 (1 H, td, *J* 13.5 and 4.5 Hz, 4-H_{ax}), 1.53 (1 H, m, 3-H_{eq}), 1.62–1.90 (5 H, m, 8-H_{ax}, 8-H_{eq}, 7-H_{ax}, 7-H_{eq} and 3-H_{ax}), 2.12 (1 H, m, 4-H_{eq}), 3.22 (1 H, dd, *J* 11.5 and 4 Hz, 8a-H), 3.23 (3 H, s, OCH_3), 3.44–3.54 (2 H, m, 2-H_{ax}, 6-H_{eq}), 3.62 (1 H, ddd, *J* 12, 11 and 3 Hz, 6-H_{ax}) and 3.98 (1 H, ddt, *J* 11.5, 5 and 1.5 Hz, 2-H_{eq}); δ_C(H-coupled; C_6D_6) 24.5 (t, *J* 127 Hz), 24.7 (t, *J* 127 Hz), 26.4 (t, *J* 127 Hz), 29.8 (t, *J* 127 Hz), 46.9 (q, *J* 141 Hz), 60.6 (t, *J* 143 Hz), 68.5 (t, *J* 142 Hz), 80.8 (d, *J* 139 Hz) and 95.9 (s); *m/z* 172 (M^+, 62%), 141 (M^+ – OCH_3, 38) and 101 (100).

2-*Benzyloxy*-3-(t-*butyldimethylsilyloxy*)*tetrahydropyran* **18**.—To a cold (−10 to −5 °C) solution of 3,4-dihydro-2*H*-pyran (30 g, 357 mmol) in distilled benzyl alcohol (350 ml), was added *m*-chloroperoxybenzoic acid (80%; 53 g, 250 mmol) during *ca.* 25 min. The resulting suspension was allowed to warm slowly to room temperature and then stirred for 12 h. Following distillation to remove the excess of dihydropyran and benzyl alcohol, the reaction mixture was treated with 2M aqueous sodium hydroxide (200 ml) and stirred vigorously for 0.5 h. The mixture was extracted with dichloromethane (4 × 200 ml), dried (Na_2SO_4), and evaporated. Gravity chromatography on silica gave 2-benzyloxytetrahydropyran-3-ol as a colourless oil (30 g, 58%), b.p. 125–120 °C (0.06 mmHg) (Found: C, 69.4; H, 8.05. $C_{12}H_{16}O_3$ requires C, 69.25; H, 7.69%); ν_{max}(film) 3420br cm^{-1} (OH); δ_H(270 MHz; $CDCl_3$) 1.45–1.62 (2 H, m, 5-H), 1.74 (1 H, m, 4-H), 1.02 (1 H, m, 4-H), 2.59 (1 H, d, *J* 4.5 Hz, OH), 3.44–3.56 (2 H, m, 6-H), 3.93 (1 H, m, 3-H), 4.37 (1 H, d, *J* 5.5 Hz, 2-H), 4.52 (1 H, d, part of AB, *J* 11.5 Hz, $-OCH_2Ph$), 4.85 (1 H, d, part of AB, *J* 11.5 Hz, $-OCH_2Ph$) and 7.25–7.37 (5 H, m); *m/z* (CI; NH_3) 266 (M^+ + NH_3, 51%), 209 (M^+ + H, 5) and 191 (M^+ − OH, 38).

To a solution of t-butyldimethylsilyl chloride (4.5 g, 30 mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (4.5 g, 30 mmol) in dry dichloromethane (40 ml) at room temperature was added 2-benzyloxytetrahydropyran-3-ol (5.2 g, 25 mmol). The resulting clear solution was stirred at room temperature for 12 h, and then diluted with dichloromethane (40 ml), and washed successively with water (50 ml), 2M hydrochloric acid (50 ml), and saturated aqueous sodium hydrogen carbonate (50 ml). The solution was dried (Na_2SO_4) and removal of solvent gave the tetrahydropyran **18** as a colourless oil (7.5 g, 94%), b.p. 151–153 °C (0.05 mmHg) (Found: C, 67.0; H, 9.7. $C_{18}H_{30}O_3Si$ requires C, 67.08; H, 9.32%); δ_H(400 MHz; $CDCl_3$) 0.00 (3 H, s, $SiCH_3$), 0.02 (3 H, s, $SiCH_3$), 0.85 (9 H, s, Bu^t), 1.43 (1 H, m, 5-H), 1.52 (1 H, m, 5-H), 1.84 (1 H, m, 4-H), 1.94 (1 H, m, 4-H), 3.48 (1 H, ddd, *J* 11, 6.5 and 3.5 Hz, 6-H), 3.57 (1 H, dt, *J* 6.5 and 4 Hz, 3-H), 3.84 (1 H, ddd, *J* 11, 8 and 3.5 Hz, 6-H), 4.38 (1 H, d, *J* 4.5 Hz, 2-H), 4.51 (1 H, d, part of AB, *J* 12 Hz, OCH_2Ph), 4.80 (1 H, d part of AB, *J* 12 Hz, OCH_2Ph) and 7.22–7.36 (5 H, m); *m/z* (CI) 321 (M^+ + H, 1%), 265 (M^+ − Bu^t, 7) and 215 (*M* − OBn, 100).

5-(*t-Butyldimethylsilyloxy*)-3,4-*dihydro*-2H-*pyran* **19**.—To a solution of the tetrahydropyran **18** (1.27 g, 3.95 mmol) in absolute ethanol (5 ml) was added 10% palladium on charcoal (100 mg). The resulting suspension was stirred vigorously under an atmosphere of hydrogen for 6 h. The catalyst was then removed by filtration through Celite, and evaporation of the filtrate furnished a colourless oil which was purified by flash chromatography on silica to give 3-(t-butyldimethylsilyloxy)-tetrahydropyran-2-ol as a mixture of diastereoisomers (784 mg, 86%), b.p. 125 °C (0.09 mmHg; Kugelrohr) (Found: C, 56.6; H, 10.5. $C_{11}H_{24}O_3Si$ requires C, 56.85; H, 10.41%); ν_{max}(film) 3390 cm^{-1} (OH); δ_H(270 MHz; $CDCl_3$) 0.09 and 0.10 (6 H, s, 2 × $SiCH_3$), 0.90 and 0.92 (9 H, s, Bu^t), 1.44–2.01 (4 H, m, 4-H, 5-H), 3.26 (1 H, br s, OH), 3.42–3.55 and 3.70–3.75 (2 H, m, 6-H), 3.88–3.97 (1 H, m, 3-H) and 4.57 and 4.81 (1 H, br s, 2-H); *m/z* 215 (M^+ − OH, 1%), 129 (30), 101 (34), 83 (80) and 75 (100).

Methanesulphonyl chloride (1.1 g, 9.6 mmol) was added dropwise to a solution of 3-(t-butyldimethylsilyloxy)tetrahydropyran-2-ol (1.1 g, 4.7 mmol) and triethylamine (2.2 g, 21.5 mmol) in dry chloroform (10 ml), cooled to 0 °C under nitrogen. The solution was allowed to warm to room temperature during 20 min after which it was heated under reflux for 3 h. The resulting brown solution was cooled to room temperature, washed successively with water (20 ml) and 2M hydrochloric acid (10 ml), and dried (Na_2SO_4). Evaporation gave a brown oil which was purified by flash chromatography on silica to give the silyl enol ether **19** as a colourless oil (805 mg, 80%), b.p. 120 °C (13 mmHg; Kugelrohr) (Found: C, 61.6; H, 10.6. $C_{11}H_{22}O_2Si$ requires C, 61.62; H, 10.35%); δ_H(270 MHz; $CDCl_3$) 0.00 [6 H, s, $Si(CH_3)_2$], 0.80 (9 H, s, $SiBu^t$), 1.70–1.78 (2 H, m, 3-H), 1.98 (2 H, td, *J* 6 and 1.5 Hz, 4-H), 3.66 (2 H,

dd, *J* 6 and 4.5 Hz, 2-H) and 6.17 (1 H, t, *J* 1.5 Hz, 6-H); *m/z* 214 (M^+, 100%), 129 (69), 127 ($M^+ - C_6H_{15}$, 80) and 101 (30).

α-(3-*Oxotetrahydropyran*-2-*yl*)*benzyl Alcohols* **20**.—To a stirred solution of benzaldehyde (42 mg, 0.4 mmol) in dichloromethane (2 ml) at −78 °C under nitrogen, was added distilled tin(IV) tetrachloride (104 mg, 0.4 mmol). The resulting colourless complex was stirred for 15 min, after which time silyl enol ether **19** (103 mg, 0.48 mmol) in dichloromethane (2 ml) was added dropwise over 5 min. The mixture was stirred at −78 °C for a further 2 h after which the reaction was quenched by rapidly injecting saturated aqueous sodium hydrogen carbonate (2 ml); the mixture was then allowed to warm to room temperature. The mixture was extracted with diethyl ether (2 × 30 ml) and the extracts were dried (Na_2SO_4) and concentrated. Purification by flash chromatography gave the tetrahydropyran-3-ones **20** (40 mg, 49%) as a 3:2 mixture of *syn* and *anti* diastereoisomers as a colourless oil; ν_{max}(film) 3430br (OH) and 1710 cm^{-1}; δ_H(270 MHz; $CDCl_3$) 1.97–2.29 (2 H, m, both isomers, 5-H), 2.41–2.67 (2 H, m, both isomers, 4-H), 2.82 (1 H, br s, both isomers, OH), 3.62 (1 H, ddd, *J* 11.5, 10 and 3.5 Hz, 6-H_{ax}, *anti* adduct), 3.70 (1 H, ddd, *J* 11.5, 10 and 3.5 Hz, 6-H_{ax}, *syn* adduct), 3.93 (1 H, d, *J* 7.5 Hz, 2-H, *anti* adduct), 4.00 (1 H, dddd, *J* 10, 6.4, 3.0 and 1.5 Hz, 6-H_{eq}, *anti* adduct), 4.04 (1 H, d, *J* 3.5 Hz, 2-H, *syn* adduct), 4.14 (1 H, dddd, *J* 11.5, 5.5, 3.5 and 1.5 Hz, 6-H_{eq}, *syn* adduct), 4.92 (1 H, d, *J* 7.5 Hz, C*H*(OH)Ph, *anti* adduct), 5.22 (1 H, d, *J* 3.5 Hz, C*H*(OH)Ph, *syn* adduct) and 7.25–7.43 (5 H, m, both isomers); *m/z* (CI) 207 (M^+ + H, 1%), 206 (M^+, 1.5) and 1.89 (M^+ −OH, 100).

α-(3-*Oxotetrahydropyran*-2-*yl*)*benzyl Methyl Ethers* **21**.—To a solution of the enol ether **19** (103 mg, 0.48 mmol) and benzaldehyde dimethyl acetal (84 mg, 0.55 mmol) in CH_2Cl_2 (5 ml) at −78 °C was added trimethylsilyl trifluoromethanesulphonate (5 μl). The mixture was stirred at −78 °C for 10 min and then quenched with water (5 ml). The organic layer was separated, dried (Na_2SO_4), and, after removal of solvent, the residue was purified by flash chromatography to give the adducts **21** (88 mg, 80%) as a 5:1 mixture of diastereoisomers (Found: C, 71.0; H, 7.4. $C_{13}H_{10}O_2$ requires C, 70.88: H, 7.33%) ν_{max} 1715 cm^{-1}; δ_H(270 MHz; $CDCl_3$) 1.91–2.00 (1 H, m, both isomers), 2.15–2.35 (1 H, m, both isomers), 2.41–2.52 (1 H, m, both isomers), 2.63–2.97 (1 H, m, both isomers), 3.23 (3 H, s, OMe, minor isomer), 3.27 (3 H, s, OMe, major isomer), 3.49–3.69 (1 H, m, both isomers), 3.91 (1 H, d, *J* 2.5 Hz, minor isomer), 4.05 (1 H, dt, *J* 12 and 5 Hz, major isomer), 4.20 (1 H, dt, *J* 12 and 5 Hz, minor isomer), 4.24 (1 H, d, *J* 4 Hz, major isomer), 4.66 (1 H, d, *J* 4 Hz, major isomer), 4.73 (1 H, d, *J* 2.5 Hz, minor isomer) and 7.20–7.44 (5 H, m); *m/z* (CI) 221 (M + 1, 5%), 189 (M − MeO, 40) and 121 (100).

2-(*Phenylthiomethyl*)*tetrahydropyran*-3-*one* **22**.—To a stirred solution of the silyl enol ether **19** (90 mg, 0.4 mmol) and chloromethyl phenyl sulphide (81 mg, 0.51 mmol) in dichloromethane (1 ml) at room temperature under nitrogen, was added anhydrous zinc bromide (10 mg). The resulting colourless suspension was stirred at room temperature for 0.5 h, and then diluted with dichloromethane (5 ml) and washed with water (5 ml). The organic layer was dried (Na_2SO_4) and evaporated and the residue was purified by flash chromatography on silica to give the phenylthiomethylpyranone **22** as a colourless oil (56 mg, 63%) (Found: M^+, 222.0712. $C_{12}H_{14}O_2S$ requires M, 222.0712); ν_{max}(film) 1710 and 1580 cm^{-1}; δ_H(270 MHz; $CDCl_3$) 2.01–2.29 (2 H, m), 2.41–2.68 (2 H, m), 3.11 (1 H, dd, *J* 13.5 and 8 Hz), 3.49 (1 H, dd, *J* 13.5 and 4 Hz), 3.77 (1 H, ddd, *J* 12, 10.5 and 3.5 Hz), 4.01 (1 H, dd, *J* 8 and 4 Hz), 4.13 (1 H, ddd, *J* 12.5, 3 and 1.5 Hz) and 7.16–7.42 (5 H, m); *m/z* 222 (M^+ 36%), 123 (100) and 71 (27).

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