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**PAPER**

# Conformational preferences of oxy-substituents in butenolide–tetrahydropyran spiroacetals and butenolide–piperidine spiro-*N*,*O*-acetals†

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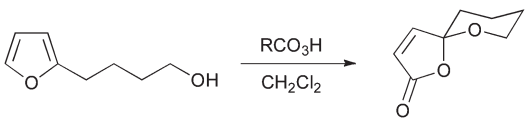
We describe the synthesis of a series of oxy-substituted butenolide spiroacetals and spiro-*N*,*O*-acetals by oxidative spirocyclisation of 2-[(4-hydroxy or 4-sulfonamido)butyl]furans. The axial–equatorial preference of each oxy-substituent is investigated (NMR) by an acid-catalysed thermodynamic relay of configuration between the spiro- and oxy-centres. The axial site is preferred for most oxy-substituents at synthetically useful levels. The potential origins of this preference are discussed in terms of a stabilising *gauche* effect combined with the influence of solvation. These results have relevance to the synthesis of bis(acetylenic)enol ether spiroacetals including AL-1 and related compounds.

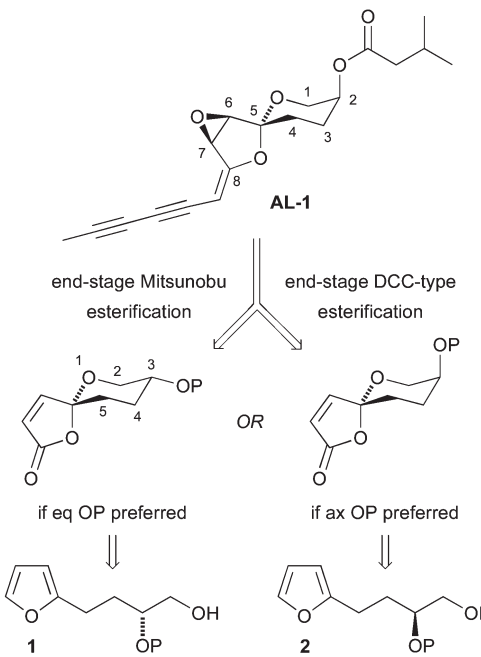
## Introduction

Oxidative spirocyclisation[1] of 2-(4-hydroxybutyl)furan derivatives under Lefebvre conditions[2] provides efficient access to 1,6-dioxaspiro[4.5]dec-3-en-2-one intermediates for the synthesis of natural products containing the 5,6-spiroacetal core (Scheme 1). Our group has employed this reaction in the context of the lituarines,[3] pyrenolide D,[4] and sawaranospirolides C and D.[5] We considered whether these spiroacetal butenolides could be elaborated by epoxidation and alkylidenation to AL-1, the most potent inhibitor of TPA-induced tumour promotion of a group of spiroacetal enol ethers from *Artemisia lactiflora*.[6,7] For this synthesis, selection of the correct enantiomer of a mono-protected diol spirocyclisation substrate (**1** or **2**, Scheme 2) requires knowledge of the conformational preferences of oxy-substituents at the 3-position of the tetrahydropyranyl ring in this system.

The conformational energy (*A*-value, $-\Delta G°$) for the acetoxy substituent in 3-acetoxytetrahydropyran is −0.71 kJ mol$^{-1}$, corresponding to a slight preference of the equatorial conformer (eq : ax ratio *ca.* 1.3 : 1).[8] However, in the majority of the reported structures containing the 5,6-spiroacetal motif bearing only a 3-acyloxy substituent in the THP ring—mainly natural products similar to AL-1[9]—the acyloxy substituent is axial and, on the basis that the structures are likely to be the thermodynamically preferred forms, it could be inferred that in these




**Scheme 1** Oxidative spirocyclisation of 2-(ω-hydroxyalkyl)furans provides butenolide spiroacetals.




**Scheme 2** The conformational preference of 3-oxy-substituents in THP–butenolide spiroacetals determines the choice of starting material and mode of final esterification. [AL-1 and THP numbering indicated].

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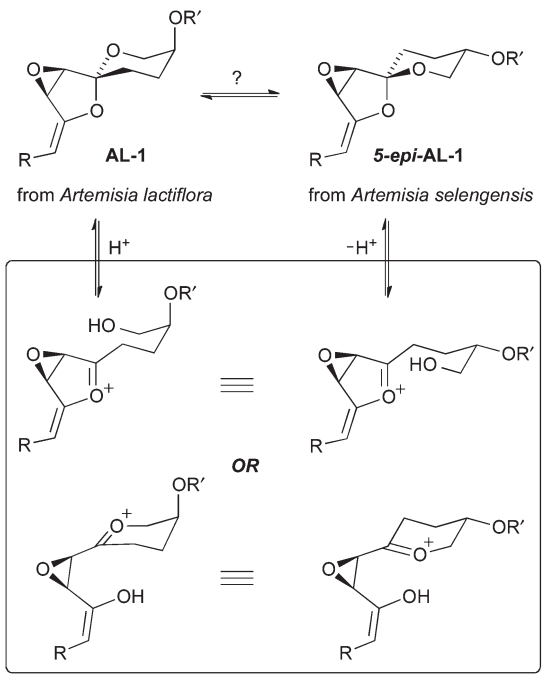
compounds the effective *A*-value is positive. Contrary to this, Hofer reported the isolation from *Artemisia selengensis* of an AL-1 isomer, in which the isovalerate substituent is equatorial;[10] however, the configuration of the spiro-centre is inverted in this compound (5-*epi*-AL-1) relative to that in AL-1 and the two natural products may therefore be viewed as 'anomers' related through open cationic intermediates as shown in Scheme 3.

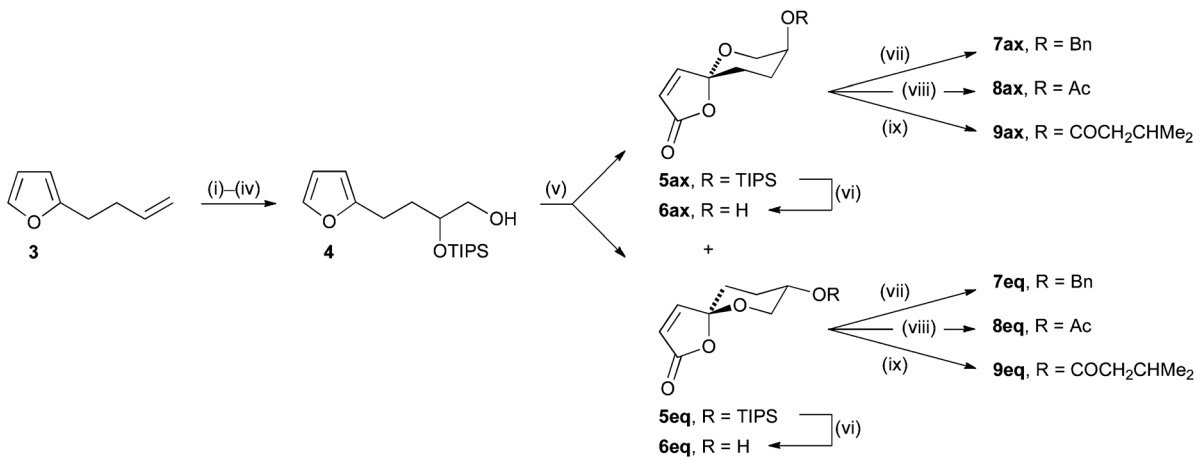
Within this context, we set out to explore whether a 3-oxy-substituent in the spiroacetal butenolide system exhibits a sufficient bias towards either an axial or equatorial site to set the absolute stereochemistry of the spiro-centre.[11] Such a relay of stereochemistry should be possible given our experience that the C(spiro)–O(butenolide) bond shows an essentially complete tendency to be axial; beyond anomeric stabilisation, this is likely aided by the expected equatorial preference for the –CH=CH– unit (the *A*-value of tetrahydropyranyl 2-OAc and 2-CH=$CH_2$ substituents are +2.5 and −9.5 kJ $mol^{-1}$, respectively).[8] In parallel, we also investigated analogous conformational biasing in butenolide *N*,*O*-spiroacetals with potential application to the synthesis of spirocyclic *Pandanus* alkaloids such as pandamarilactone-1.[12]




**Scheme 3** AL-1 and 5-*epi*-AL-1, isolated from separate *Artemisia* species, are in principle interconvertible by acid catalysis. [R = C≡CC≡CMe, R′ = $COCH_2CHMe_2$].

## Synthesis of substrates

Volatile alkene **3**[13] (Scheme 4) was dihydroxylated under standard Upjohn conditions[14] and the 2°-alcohol blocked as the TIPS ether to prevent competitive spirocyclisation by that hydroxyl group in the next step. Following oxidation, the TIPS-substituted spiroacetal **5** was obtained as a mixture of axial–equatorial diastereomers. The ratio of **5ax** : **5eq** present in the crude product directly after oxidation, and following chromatographic purification on silica, showed no trend, with significant variation between experiments. Attempted TIPS-deprotection of the separated isomers with aq. $H_2SiF_6$[15] gave a complex product mixture containing diastereomers of 5,5- and 5,6-spirocycles. Under mildly basic conditions, using TBAF, removal of the silyl group in both diastereomers was effective but in each case the isolated yield of the alcohols (**6**) was reduced slightly by the production of small amounts of the undesired diastereomers and 5,5-spirocycles during chromatography. The structures of **6ax** and **6eq** were confirmed by single crystal X-ray analysis (Fig. 1).[16] The appearance of the C*H*OH resonance in the $^1$H NMR spectra of **6ax** and **6eq** was not informative; in both isomers, the resonance appeared at *ca.* 3.9 ppm as a multiplet. However the C$H_2$O resonances showed that the dominant conformation in solution reflected that indicated in the crystal: for **6ax** these resonances appeared at $\delta_H$ 3.85 (dt, *J* 12.4, 1.9 Hz)




**Scheme 4** *Reagents and conditions*: (i) 1 mol% $OsO_4$, NMO, aq. acetone, 20 °C, 16 h (85%); (ii) TBSCl, imidazole, THF, 0 °C, 3 h (89%); (iii) TIPSOTf, pyridine, $CH_2Cl_2$, 0 °C, 0.5 h (99%); (iv) aq. $H_2SiF_6$, $CH_3CN$, 0 °C, 0.5 h (72%); (v) MCPBA, $CH_2Cl_2$, 0 °C, 2 h then 6.5 mol% TPAP, NMO, $CH_2Cl_2$, 20 °C, 18 h (**5ax** 29%, **5eq** 35%); (vi) TBAF, THF, 20 °C, 14 h (**6ax** 68%, **6eq** 69%); (vii) BnBr, $Ag_2O$, $CH_2Cl_2$, 20 °C, 20 h (**7ax** 59%, **7eq** 59%); (viii) AcOH, DCC, DMAP, $CH_2Cl_2$, 20 °C, 1 h (**8ax** 75%, **8eq** 80%); (ix) isovaleric acid, DCC, DMAP, $CH_2Cl_2$, 20 °C, 12 h (**9ax** 87%, **9eq** 92%).

and 4.09 (dd, *J* 12.4, 1.4 Hz) consistent with an equatorial C*H*OH; for **6eq** these resonances appeared at $\delta_H$ 3.70 (t, *J* 10.3 Hz) and 3.95 (ddd, *J* 10.3, 4.9, 2.1 Hz) consistent with an axial C*H*OH. Pure samples of each isomer were converted into three acid-stable derivatives **7–9** in both series for investigation of thermodynamic conformational–configurational preferences.

For the corresponding *N*,*O*-spiroacetal series, oxidative spirocyclisation conditions had first to be established and to that end two model substrates **10** and **12** were prepared using the routes shown in Scheme 5. Sulfonamide protection for the nitrogen was selected because of its compatibility to the Lefebvre conditions used in the aza-Achmatowicz reaction[17,18] and in the hope that the spirocyclic products might be crystalline, allowing X-ray crystallographic analysis. Application of the MCPBA oxidation conditions that had proven reliable in the ω-hydroxyalkyl series (*cf.* Scheme 4) were not successful in delivering *N*,*O*-spiroacetals with sulfonamides **10** and **12**; these attempts merely generated small quantities of hydroxybutenolides. Initial success was achieved with peracetic acid, as in Lefebvre's original work,[2] and the novel *N*,*O*-spiroacetals **11** and **13** were produced in low yield. Later work showed that hydroxy- or methoxybutenolides produced from these substrates by a variety of oxidation methods (including MCPBA or $^1O_2$ *etc.*) could be cyclised effectively by stirring in aq. $H_2SO_4$.[19] This one-pot, two-step protocol worked well and, for example, spirocycle **13** was produced in up to 89% yield.[20]

Scheme 6 summarises the synthesis of two sulfonamide analogues of spirocyclisation substrates **7** and **9**. The routes began from the readily available, and cheap, food flavourant 3-(2-furyl) acrolein (**14**) that was hydrogenated selectively without competitive reduction of the furan ring with Ashfeld's recently described procedure.[21] This method gave essentially pure product direct from the reaction and, with dichloromethane as the solvent, the volatile aldehyde **15**[22] was isolated without significant loss during the work-up process. This aldehyde was then converted into the isovalerate substrate **17** using classical chemistry *via* the cyanohydrin. The benzyl substrate (**19**) proved rather more elusive and all attempts to effect *O*-benzylation of alcohol **16** failed. Based on Oriyama's two-step procedure for the preparation of *O*-alkylcyanohydrins from dialkyl acetals,[23] routes to dibenzyl acetal **18** were screened. Of these, Bentley's mild procedure[24] with NCS and thiourea produced the acetal without competitive decomposition of the furan ring, which had been a problem using standard acidic conditions. Conversion to the *O*-benzyl cyanohydrin could be achieved on a small scale with TCNE as the catalyst[25] but with quantities greater than *ca.* 200 mg the reaction was accompanied by significant decomposition. Finally, activation of the acetal *via* the *O*,*P*-acetal enabled

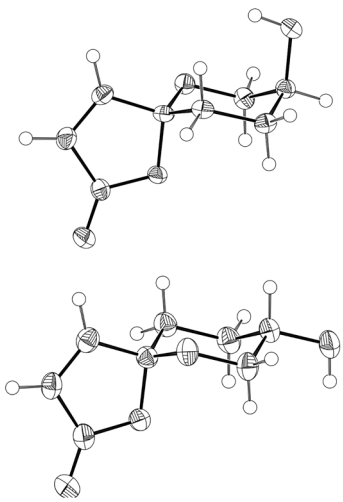
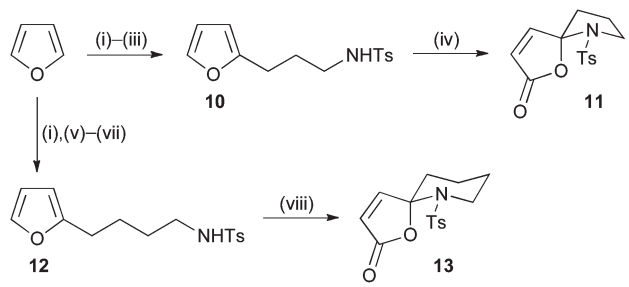
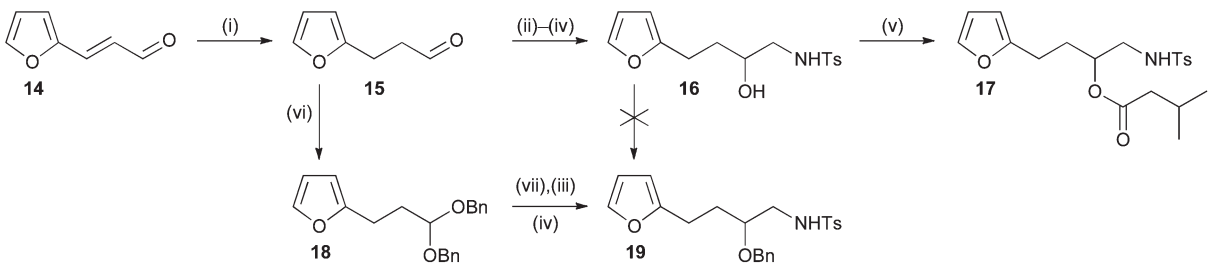


**Fig. 1** Molecular structures of **6ax** (upper) and **6eq** (lower) from single crystal X-ray analysis.[16]

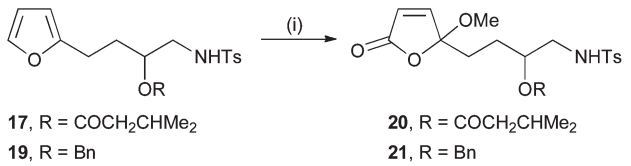



**Scheme 5** *Reagents and conditions*: (i) BuLi, THF, −78 °C, 1 h, 0 °C, 2 h then $Br(CH_2)_3Cl$, 20 °C, 16 h (92%); (ii) NaI, butan-2-one, reflux, 4 h (63%); (iii) $TsNH_2$, KOH, DMSO, 50 °C, 1.5 h (79%); (iv) AcOOH, AcOH, $CH_2Cl_2$, 0 °C → 20 °C, 16 h (23%) or MCPBA, $CH_2Cl_2$, 20 °C, 16 h then aq. $H_2SO_4$ (30%), 20 °C, 16 h (72%); (v) NaCN, DMSO, 80 °C, 5 h (95%); (vi) $LiAlH_4$, $Et_2O$, 20 °C, 0.25 h (97%); (vii) TsCl, aq. $Na_2CO_3$, THF, 20 °C, 6.5 h (86%); (viii) AcOOH, AcOH, $CH_2Cl_2$, 0 °C → 20 °C, 16 h (19%) or MCPBA, $CH_2Cl_2$, 20 °C, 16 h then aq. $H_2SO_4$ (30%), 20 °C, 16 h (89%).




**Scheme 6** *Reagents and conditions*: (i) $Cp_2TiCl_2$, Zn, $Et_3NH^+Cl^-$, $CH_2Cl_2$, 20 °C, 1 h (96%); (ii) TMSCN, $K_2CO_3$, DMF, 20 °C, 40 min (82%); (iii) $LiAlH_4$, $Et_2O$, 20 °C, 0.5 h (towards **16** 90%, towards **19** 85%); (iv) TsCl, $Et_3N$, DMAP, $CH_2Cl_2$ 0 °C, 1 h (**16** 94%, **19** 81%); (v) isovaleric anhydride, TMSOTf, $CH_2Cl_2$, −10 °C, 1 h (80%); (vi) BnOH, 2 mol% thiourea, 5 mol% NCS, 20 °C, 4 h (77%); (vii) TMSCN, TMSOTf, P(*o*-tolyl)$_3$, $CH_2Cl_2$, 20 °C, 1 h (73%).




**Scheme 7** *Reagents and conditions*: (i) $O_2$, rose bengal, MeOH, h$\nu$, 0 °C, 10 min then $Ac_2O$, pyridine, 20 °C, 15 min (**20** 99%, **21** 77%).

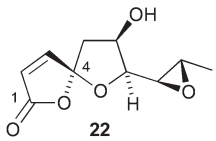
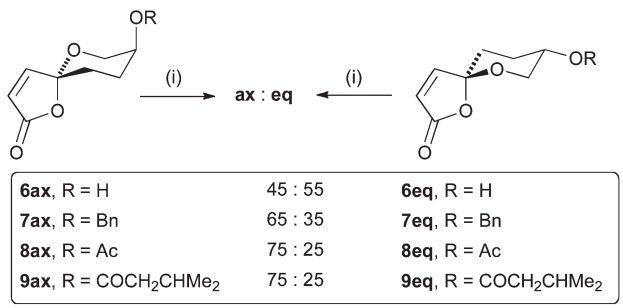



**Fig. 2** *O*-Cyclisation substrate for pyrenolide D isomers.

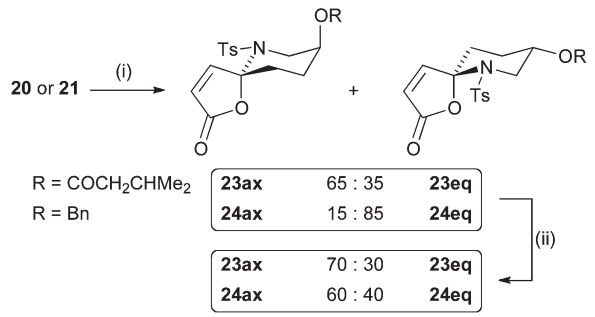



**Scheme 8** *Reagents and conditions*: (i) 1 mol% aq. HI, $CD_3CN$, 20 °C, 0.5–72 h (NMR). [isomer ratios to nearest 5%.]

the desired *O*-benzyl cyanohydrin to be obtained in good yield on multigram scale.[26] Completion of the route by reduction and sulfonylation proceeded without complication. The two substrates (**17** and **19**) were converted into methoxybutenolides **20** and **21**, respectively, by $^1O_2$ followed by dehydration of the intermediate hydroperoxides with $Ac_2O$ (Scheme 7).[27]

## Equilibration studies

In a separate project[28] we found that attempts to effect 5-*endo* cyclisation of epoxyalcohol **22** (Fig. 2)[29] with an excess of $I_2$ in acetonitrile, *en route* to pyrenolide D isomers, led to scrambling of the 4-spiro-centre. On this basis, we initially selected these mild conditions to effect equilibration of the **6ax** and **6eq** diastereomers. However, the results were not reproducible and, suspecting adventitious HI to be the active catalyst,[30] NMR-tube reactions were set up in $CD_3CN$ with the addition of 1 mol% HI (57% aq. solution). Under these conditions, interconversion occurred generally rapidly, with the thermodynamic ratio being fully attained within 2 h. For each substrate, both separated diastereomers converged to the same equilibrium ratio (Scheme 8) and the final NMR spectra were essentially identical. The NMR spectra of the OH and OBn substrates indicated the formation of by-products, including 5,5-spiroacetal isomers after prolonged reaction times (days). Attempts to effect isomerisation with HI in $CDCl_3$ were unsuccessful, presumably due to poor solubility and reduced dissociation of the acid in this solvent.




**Scheme 9** *Reagents and conditions*: (i) aq. $H_2SO_4$ (40%), 20 °C, 2–5 d (**23** 27%, **24** 79%); (ii) 1 mol% aq. HI, $CD_3CN$, 20 °C, 5 min–24 h (NMR). [isomer ratios to nearest 5%.]

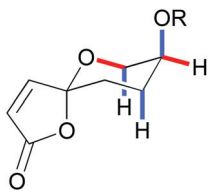



**Fig. 3** Additional (C–H)σ-(C–OR)σ* and (C–H)σ-(C–$O_{THP}$)σ* interactions in **6–9ax**.

Spirocyclisation of sulfonamide substrates **20** and **21** was achieved with $H_2SO_4$ as in the model studies (Scheme 9). Cleavage of the ester competed during cyclisation of isovalerate substrate (**20**), which required 5 days to reach completion even with a stronger acid solution. The benzyl substrate (**21**) converted much more rapidly and cleanly. Although it was expected that these strongly acidic conditions would lead to full equilibration of isomers, the product ratios were very different in the two series; this could, of course, be attributed to selective hydrolysis of the equatorial isovalerate **23eq**. In both cases, the axial–equatorial diastereomers were not separable therefore equilibrations were conducted on the mixtures in $CD_3CN$ as before. The product ratios fit the pattern established in the spiro-*O*,*O*-acetal series with a higher axial preference found for the isovalerate (*ca.* 2.5 : 1) than for the benzyl ether (*ca.* 1.5 : 1).

## Discussion

Although one can only speculate on the physical origins of the trends displayed by the equilibria in Schemes 8 and 9, it is clear that the axial *vs.* equatorial preferences of 3-oxy substituents in these spirocyclic systems do not follow from equilibrium free energies (*A*-values) in the cyclohexyl or tetrahydropyranyl parents. The preference could be a manifestation of the *gauche* effect[31] in which two additional (C–H)σ-(C–O)σ* interactions may operate in the axial isomer (Fig. 3); this effect should be more pronounced with the –OX substituents formally derived from the acids (HOX) with the lower p$K_a$.[32]

The interpretation of the *gauche* effect in terms of hyperconjugation implies lengthening of the interacting C–H and C–O bonds accompanied by shortening of the intervening C–C bonds. Comparison bond lengths taken from the crystal structures of **6ax** and **6eq** (Fig. 4) do indeed show that the two relevant

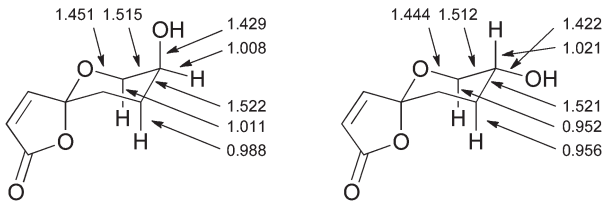



**Fig. 4** Comparison key bond lengths (Å) in **6ax** and **6eq** from X-ray data.



C–$H_{ax}$ bonds in **6ax** are longer than those in **6eq** ($\Delta_{ave}$ = +0.0455 Å); furthermore, both relevant C–O bonds in **6ax** are longer than their counterparts in **6eq** although the differences are small ($\Delta_{ave}$ = +0.007 Å); against this, there is no evidence of C–C bond contraction in **6ax** *vs.* **6eq** ($\Delta_{ave}$ = +0.002 Å) and the C(OH)–H bond in **6ax** is shorter than in **6eq** ($\Delta_{ave}$ = −0.013 Å). All of this has to be considered in view of differential crystal packing effects between the isomers *and* the solution-phase study which indicates very little difference between the axial and equatorial diastereomers in **6** (*i.e.* the *gauche* effect is the least significant in this compound).

For derivatives **7–9**, for which no crystal structure data were available, we turned to computation to offer some insight into our results. Thus, for each structure we performed a conformational search (Monte Carlo, MMFF);[33] for expediency, the twist-boat conformers and those having an equatorial C–OCO bond were discarded; the geometries of the remaining conformers were then individually optimised (B3LYP/6-31G*) and the relative Boltzmann-weighted energies obtained. These calculations, which neglect entropic contributions and solvation effects, showed qualitative agreement with the NMR-derived ratios, all derivatives (including **6**) showing a small favourable energy for the axial isomers [−(0.85–2.22 kJ $mol^{-1}$)] corresponding to equilibrium ratios of 1.41–2.45 : 1 in their favour. By examination of the computed bond lengths, the only consistent pattern is that the C–OR bond is longer in the axial isomers than the equatorial isomers ($\Delta_{ave}$ = +0.0068 Å).

Finally, any interpretation of configurational preferences based on intrinsic factors within each molecule, has to be tempered by a consideration of differential solvation effects. Acetonitrile ($\varepsilon_r$ = 37.5) should favour the more polar forms of molecules where these can interconvert (as in **6–9**, **23** and **24**) and the computed dipole moments for the lowest energy conformer are certainly larger for **8ax** and **9ax** than their equatorial isomers (4.86 D and 4.75 D, respectively *vs.* 2.50 D and 2.70 D, respectively). The computed dipole moments for the hydroxy compounds are 2.90 D for **6ax** and 3.17 D for **6eq**, in line with a slight preference for the equatorial isomer; the benzyl derivatives do not fit the pattern (**7ax**, $\mu_D$ = 4.25 D; **7eq**, $\mu_D$ = 5.10 D).

In summary, it appears that the results can be understood, at least qualitatively, on the basis of a stabilising *gauche* effect, originating in (C–H)σ-(C–O)σ* hyperconjugation, combined with favourable solvation of the more polar isomers.

## Conclusion

Butenolide–tetrahydropyran and butenolide–*N*-sulfonylpiperidine spiroacetals couple conformational biasing (*cf.* 4-*tert*-butylcyclohexyl)[34] with dynamic configurational interconversion by acid catalysis. This study has found a synthetically useful axial preference for 3-acyloxy substituents in these spirocycles, which provides confidence that the total synthesis of AL-1 and related molecules could be achieved from either enantiomer of 2-(3,4-dihydroxybutyl)furan following the general route implied in Scheme 2.

## Experimental

In the NMR listings, protons are assigned by number according to the compound systematic name, with assignments by substructure included only where appropriate for clarity.

### 4-(Furan-2-yl)butan-1,2-diol[35]

A mixture of alkene **3**[13] (3.00 g, 24.6 mmol), NMO (3.17 g, 26.6 mmol), $OsO_4$ (69 mg, 0.271 mmol), acetone (70 mL) and water (10 mL) was stirred at RT for 16 h and then poured onto hydrochloric acid (1.0 M, 100 mL). The mixture was extracted with ethyl acetate (5 × 100 mL) and the combined organic layers were washed with brine (100 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Column chromatography (petrol–ethyl acetate, 1 : 1) afforded the title diol as a colourless oil (3.27 g, 85%). $R_f$ 0.10 (petrol–ethyl acetate, 1 : 1); $\nu_{max}/cm^{-1}$ (thin film) 3384s br, 2933s, 1597m, 1509s, 1146m; $\delta_H$ ($CDCl_3$, 400 MHz) 1.75–1.82 (2 H, m, 2 × H-3), 1.97 (2 H, br s, 2 × OH), 2.71–2.88 (2 H, m, 2 × H-4), 3.48 (1 H, dd, *J* 11.0, 7.5 Hz) and 3.67 (1 H, dd, *J* 11.0, 3.0 Hz, 2 × H-1), 3.78 (1 H, dtd, *J* 7.5, 5.0, 3.0 Hz, H-2), 6.02 (1 H, dd, *J* 3.0, 1.0 Hz), 6.29 (1 H, dd, *J* 3.0, 1.5 Hz) and 7.31 (1 H, dd, *J* 1.5, 1.0 Hz, Fu); $\delta_C$ ($CDCl_3$, 100 MHz) 24.1 ($CH_2$), 31.4 ($CH_2$), 66.7 ($CH_2$), 71.4 (CH), 105.2 (CH), 110.2 (CH), 141.1 (CH), 155.3 (C); HRMS ($ESI^+$) found 179.0685; $C_8H_{12}NaO_3$ ($MNa^+$) requires 179.0679.

### 1-(*tert*-Butyldimethylsilyloxy)-4-(furan-2-yl)butan-2-ol

A solution of 4-(furan-2-yl)butan-1,2-diol (3.06 g, 19.6 mmol), imidazole (1.72 g, 25.3 mmol) and *tert*-butyldimethylsilyl chloride (2.92 g, 19.4 mmol) in THF (50 mL) was stirred for 3 h at 0 °C. The mixture was diluted with ether (100 mL), poured onto water (100 mL), and the separated aqueous layer was extracted with ether (2 × 50 mL). The combined organic layers were washed sequentially with $NaHCO_3$ solution (sat. aq., 50 mL) and brine (50 mL), then dried over $MgSO_4$ and concentrated *in vacuo*. Column chromatography (petrol–ether, 10 : 1) afforded the *title alcohol* as a colourless oil (4.70 g, 89%). $R_f$ 0.55 (petrol–ether, 1 : 1); $\nu_{max}/cm^{-1}$ (thin film) 3444s br, 2930s, 1598m, 1508m, 1256s; $\delta_H$ ($CDCl_3$, 400 MHz) 0.09 and 0.10 (2 × 3 H, 2 × s, $Si(CH_3)_2$), 0.92 (9 H, s, $SiC(CH_3)_3$), 1.72–1.77 (2 H, m, 2 × H-3), 2.45 (1 H, br s, OH), 2.68–2.76 (2 H, m, 2 × H-4), 3.43 (1 H, dd, *J* 10.0, 7.0 Hz) and 3.63 (1 H, dd, *J* 10.0, 3.5 Hz, 2 × H-1), 3.64–3.70 (1 H, m, H-2), 5.99 (1 H, d, *J* 3.0 Hz), 6.27 (1 H, dd, *J* 3.0, 2.0 Hz) and 7.31 (1 H, d, *J* 2.0 Hz, Fu); $\delta_C$ ($CDCl_3$, 100 MHz) −5.4 ($CH_3$), −5.4 ($CH_3$), 18.3 (C), 24.2 ($CH_2$), 25.9 ($CH_3$), 31.2 ($CH_2$), 67.1 ($CH_2$), 71.0 (CH), 104.9 (CH), 110.1 (CH), 140.9 (CH), 155.7 (C); HRMS ($ESI^+$) found 271.1732; $C_{14}H_{27}O_3Si$ ($MH^+$) requires 271.1724.

**1-(*tert*-Butyldimethylsilyloxy)-4-(furan-2-yl)-2-(triisopropylsilyloxy)butane**

To a stirred solution of 1-(*tert*-butyldimethylsilyloxy)-4-(furan-2-yl)butan-2-ol (90 mg, 0.333 mmol) in dichloromethane (1 mL) at 0 °C was added triisopropylsilyl trifluoromethanesulfonate (0.15 mL, 0.56 mmol) and pyridine (0.30 mL, 3.72 mmol). The mixture was stirred for 30 min then poured onto $NH_4Cl$ solution (sat. aq., 10 mL) and extracted with ether (3 × 10 mL). The combined organic layers were washed sequentially with $NaHCO_3$ solution (sat. aq., 10 mL) and brine (10 mL), then dried over $MgSO_4$ and concentrated *in vacuo*. Column chromatography (petrol–dichloromethane, 50 : 1) afforded the *title compound* as a colourless oil (140 mg, 99%). $R_f$ 0.42 (petrol–dichloromethane, 20 : 1); $\nu_{max}/cm^{-1}$ (thin film) 2946s, 1597s, 1508m, 1012s; $\delta_H$ ($CDCl_3$, 400 MHz) 0.09 (6 H, s, $Si(CH_3)_2$), 0.92 (9 H, s, $SiC(CH_3)_3$), 1.08 (21 H, app. s, $Si(i\text{-}Pr)_3$), 1.83–2.04 (2 H, m, 2 × H-3), 2.71–2.78 (2 H, m, 2 × H-4), 3.48 (1 H, dd, *J* 10.0, 7.5 Hz) and 3.62 (1 H, dd, *J* 10.0, 5.0 Hz, 2 × H-1), 3.88–3.92 (1 H, m, H-2), 5.59 (1 H, dd, *J* 3.5, 1.0 Hz), 6.28 (1 H, dd, *J* 2.0, 1.0 Hz) and 7.30 (1 H, dd, *J* 3.5, 2.0 Hz, Fu); $\delta_C$ ($CDCl_3$, 100 MHz) −5.4 (two peaks, 2 × $CH_3$), 12.6 (CH), 18.1 ($CH_3$), 18.3 (C), 22.9 ($CH_2$), 25.9 ($CH_3$), 32.6 ($CH_2$), 66.5 ($CH_2$), 72.1 (CH), 104.4 (CH), 110.0 (CH), 140.7 (CH), 156.6 (C); HRMS ($ESI^+$) found 427.3056; $C_{23}H_{47}O_3Si_2$ ($MH^+$) requires 427.3058.

**4-(Furan-2-yl)-2-(triisopropylsilyloxy)butan-1-ol (4)**

$H_2SiF_6$ (0.13 mL, 25% by weight solution in water, 0.23 mmol) was added to a solution of 1-(*tert*-butyldimethylsilyloxy)-4-(furan-2-yl)-2-(triisopropylsilyloxy)butane (500 mg, 1.17 mmol) in acetonitrile (10 mL) at 0 °C. The mixture was stirred at 0 °C for 30 min, diluted with ether (30 mL) and poured onto $NaHCO_3$ solution (sat. aq., 30 mL). The separated aqueous layer was extracted with ether (2 × 30 mL) and the combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. Column chromatography (petrol–ether, 2 : 1) afforded *alcohol* **4** as a colourless oil (262 mg, 72%). [Further elution yielded the diol, 4-(furan-2-yl)butan-1,2-diol, as a colourless oil (40 mg, 22%)]. $R_f$ 0.16 (petrol–ether, 9 : 1); $\nu_{max}/cm^{-1}$ (thin film) 2944s, 2867s, 1600m, 1510m, 1260m, 1113m; $\delta_H$ ($CDCl_3$, 400 MHz) 1.02–1.10 (21 H, m, $Si(i\text{-}Pr)_3$), 1.88–2.05 (2 H, m, 2 × H-3), 2.60–2.76 (2 H, m, 2 × H-4), 3.56 (1 H, dd, *J* 10.0, 3.5 Hz) and 3.67 (1 H, dd, *J* 10.0, 7.0 Hz, 2 × H-1), 3.86–4.01 (1 H, m, H-2), 5.99 (1 H, dd, *J* 3.0, 1.0 Hz), 6.27 (1 H, dd, *J* 3.0, 2.0 Hz) and 7.30 (1 H, dd, *J* 2.0, 1.0 Hz, Fu); $\delta_C$ ($CDCl_3$, 100 MHz) 12.5 (CH), 18.1 ($CH_3$), 23.7 ($CH_2$), 32.1 ($CH_2$), 65.4 ($CH_2$), 72.0 (CH), 104.9 (CH), 110.1 (CH), 140.9 (CH), 155.4 (C); HRMS ($ESI^+$) found 335.2010; $C_{17}H_{32}NaO_3Si$ ($MNa^+$) requires 335.2013.

**(5*R**,8*S**)-8-Triisopropylsilyloxy-1,6-dioxaspiro[4.5]dec-3-en-2-one (5ax) and (5*S**,8*S**)-8-triisopropylsilyloxy-1,6-dioxaspiro[4.5]dec-3-en-2-one (5eq)**

MCPBA (5.04 g, 70% by weight, 20.4 mmol) was added to a stirred solution of alcohol **4** (5.81 g, 18.6 mmol) in dichloromethane (95 mL) at 0 °C. After 1 h, a further portion of MCPBA (642 mg, 70% by weight, 3.72 mmol) was added to complete the oxidation. After a further 1 h, $Na_2S_2O_3$ solution (1.0 M, 50 mL) was added and the mixture was stirred vigorously for 5 min. The separated organic layer was washed with $NaHCO_3$ solution (sat. aq., 50 mL) and the combined aqueous layers back-extracted with dichloromethane (2 × 30 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. The crude residue was immediately taken up in dichloromethane (95 mL), and NMO (2.40 g, 20.5 mmol) and TPAP (230 mg, 0.654 mmol) were added. The mixture was stirred for 14 h then further portions of NMO (2.40 g, 20.5 mmol) and TPAP (195 mg, 0.555 mmol) were added. After 4 h, the reaction showed no further progression (TLC) therefore solid $Na_2SO_4$ (5.0 g, 35 mmol) was added, the mixture was stirred for 1 h, then diluted with ether (200 mL), filtered through a pad of Celite, and concentrated *in vacuo*. The residue was purified by column chromatography (petrol–ether, 19 : 1 → 9 : 1) to yield the *title spirocycles* **5ax** (1.75 g, 29%) and **5eq** (2.11 g, 35%) as colourless oils. Data for **5ax**: $R_f$ 0.58 (petrol–ether, 1 : 1); $\nu_{max}/cm^{-1}$ (thin film) 2942s, 1774s, 1464m, 1093s; $\delta_H$ ($CDCl_3$, 400 MHz) 1.06–1.13 (21 H, m, $Si(i\text{-}Pr)_3$), 1.57 (1 H, ddd, *J* 13.5, 4.0, 2.5 Hz, H-10), 1.88–1.95 (1 H, m) and 2.14 (1 H, tdd, *J* 13.5, 4.5, 2.5 Hz, 2 × H-9), 2.41 (1 H, td, *J* 13.5, 4.5 Hz, H-10), 3.82 (1 H, dt, *J* 12.0, 2.0 Hz, H-7), 4.01 (1 H, app. br s, H-8), 4.07 (1 H, dd, *J* 12.0, 1.5 Hz, H-7), 6.11 (1 H, d, *J* 5.5 Hz, H-3), 7.18 (1 H, d, *J* 5.5 Hz, H-4); $\delta_C$ ($CDCl_3$, 100 MHz) 12.2 (CH), 18.1 ($CH_3$), 26.4 ($CH_2$), 26.8 ($CH_2$), 63.7 ($CH_2$), 69.7 (CH), 106.9 (C), 122.3 (CH), 154.3 (CH), 170.6 (C); HRMS ($ESI^+$) found 349.1806; $C_{17}H_{30}NaO_4Si$ ($MNa^+$) requires 349.1806. Data for **5eq**: $R_f$ 0.41 (petrol–ether, 1 : 1); $\nu_{max}/cm^{-1}$ (thin film) 2945s, 2867s, 1775s, 1463m, 1101m; $\delta_H$ ($CDCl_3$, 400 MHz) 1.02–1.08 (21 H, m, $Si(i\text{-}Pr)_3$), 1.87–2.10 (4 H, m, 2 × H-9 and 2 × H-10), 3.74 (1 H, t, *J* 10.0 Hz, H-7), 3.86 (1 H, ddd, *J* 10.0, 5.0, 2.0 Hz, H-8), 3.91 (1 H, dd, *J* 10.0, 5.0 Hz, H-7), 6.12 (1 H, d, *J* 5.5 Hz, H-3), 7.11 (1 H, d, *J* 5.5 Hz, H-4); $\delta_C$ ($CDCl_3$, 100 MHz) 12.2 (CH), 18.0 ($CH_3$), 29.4 ($CH_2$), 31.5 ($CH_2$), 65.4 ($CH_2$), 69.1 (CH), 105.5 (C), 123.4 (CH), 153.7 (CH), 170.2 (C); HRMS ($ESI^+$) found 349.1807; $C_{17}H_{30}NaO_4Si$ ($MNa^+$) requires 349.1806.

**(5*R**,8*S**)-8-Hydroxy-1,6-dioxaspiro[4.5]dec-3-en-2-one (6ax)**

To a stirred solution of silyl ether **5ax** (1.47 g, 4.50 mmol) in THF (35 mL) at 0 °C was added dropwise TBAF (5.0 mL, 1.0 M in THF, 5.0 mmol). The solution was allowed to warm to RT, stirred for 14 h, and then concentrated *in vacuo*. Purification by column chromatography (petrol–ethyl acetate, 3 : 2) afforded *alcohol* **6ax** (519 mg, 68%) as a white solid. $R_f$ 0.10 (petrol–ethyl acetate, 1 : 1); m.p. 54 °C; $\nu_{max}/cm^{-1}$ (thin film) 3444m br, 2939m, 1767s, 1247s, 1108s, 1000s, 917s, 818s, 701s; $\delta_H$ (400 MHz, $CDCl_3$) 1.56 (1 H, ddd, *J* 13.5, 4.5, 2.5 Hz, H-10), 1.89–1.95 (1 H, m) and 2.12 (1 H, tdd, *J* 13.5, 4.5, 2.5 Hz, 2 × H-9), 2.33 (1 H, td, *J* 13.5, 4.5 Hz, H-10), 2.69 (1 H, br s, OH), 3.85 (1 H, dt, *J* 12.5, 2.0 Hz, H-7), 3.94 (1 H, app. s, H-8), 4.09 (1 H, dd, *J* 12.5, 1.5 Hz, H-7), 6.09 (1 H, d, *J* 5.5 Hz, H-3), 7.20 (1 H, d, *J* 5.5 Hz, H-4); $\delta_C$ (100 MHz, $CDCl_3$) 25.6 ($CH_2$), 26.1 ($CH_2$), 62.8 (CH), 69.0 ($CH_2$), 106.7 (C), 123.0 (CH), 154.2 (CH), 170.6 (C); HRMS ($ESI^-$) found 169.0505; $C_8H_9O_4$ [(M – $H^+$)$^-$] requires 169.0506.

**(5*S**,8*S**)-8-Hydroxy-1,6-dioxaspiro[4.5]dec-3-en-2-one (6eq)**

To a stirred solution of silyl ether **5eq** (2.11 g, 6.46 mmol) in THF (50 mL) at 0 °C was added dropwise TBAF (7.1 mL, 1.0 M in THF, 7.1 mmol). The solution was allowed to warm to RT, stirred for 14 h, and then concentrated *in vacuo*. Purification by column chromatography (petrol–ethyl acetate, 3 : 2) afforded *alcohol* **6eq** (759 mg, 69%) as a pale yellow solid. $R_f$ 0.15 (petrol–ethyl acetate, 1 : 1); m.p. 48 °C; $\nu_{max}/cm^{-1}$ (thin film) 3418m br, 2951m, 1768s, 1233m, 1101m, 1021s, 918s, 815m, 714m; $\delta_H$ (400 MHz, $CDCl_3$) 1.85–2.00 (3 H, m, H-9 and 2 × H-10), 2.00–2.08 (1 H, br s, OH), 2.13–2.19 (1 H, m, H-9), 3.70 (1 H, t, *J* 10.5 Hz, H-7), 3.82–3.90 (1 H, m, H-8), 3.93–3.97 (1 H, ddd, *J* 10.5, 5.0, 2.0 Hz, H-7), 6.14 (1 H, d, *J* 5.5 Hz, H-3), 7.15 (1 H, d, *J* 5.5 Hz, H-4); $\delta_C$ (100 MHz, $CDCl_3$) 28.4 ($CH_2$), 31.3 ($CH_2$), 64.4 (CH), 68.6 ($CH_2$), 105.8 (C), 123.2 (CH), 154.1 (CH), 170.7 (C); HRMS ($ESI^+$) found 193.0472; $C_8H_{10}NaO_4$ ($MNa^+$) requires 193.0471.

**(5*R**,8*S**)-8-Benzyloxy-1,6-dioxaspiro[4.5]dec-3-en-2-one (7ax)**

Benzyl bromide (39 μL, 0.323 mmol) and $Ag_2O$ (204 mg, 0.880 mmol) were added to a stirred solution of alcohol **6ax** (50 mg, 0.294 mmol) in dichloromethane (500 μL). The reaction mixture was stirred for 20 h and then concentrated *in vacuo*. Purification by column chromatography (petrol–ether, 3 : 1) afforded *benzyl ether* **7ax** (45 mg, 59%) as a white solid. $R_f$ 0.20 (petrol–ether, 7 : 3); $\nu_{max}/cm^{-1}$ (thin film) 3090m, 3031m, 2936s, 1768s, 1454s, 1369s, 1246s, 909s, 815s, 697s; $\delta_H$ (400 MHz, $CDCl_3$) 1.59 (1 H, dt, *J* 13.5, 3.5 Hz, H-10), 2.08–2.14 (2 H, m, H-9 and H-10), 2.32–2.40 (1 H, m, H-9), 3.59 (1 H, m, H-8), 4.06 (2 H, app. s, 2 × H-7), 4.61 (2 H, s, C$H_2$Ph), 6.12 (1 H, d, *J* 5.5 Hz, H-3), 7.22 (1 H, d, *J* 5.5 Hz, H-4), 7.28–7.40 (5 H, m, Ph); $\delta_C$ (100 MHz, $CDCl_3$) 22.8 ($CH_2$), 26.7 ($CH_2$), 66.3 ($CH_2$), 69.1 (CH), 70.3 ($CH_2$), 106.7 (C), 123.1 (CH), 127.6 (CH), 127.8 (CH), 128.5 (CH), 138.1 (C), 154.2 (CH), 170.5 (C); HRMS (EI) found 260.1052; $C_{15}H_{16}O_4$ ($M^+$) requires 260.1043.

**(5*S**,8*S**)-8-Benzyloxy-1,6-dioxaspiro[4.5]dec-3-en-2-one (7eq)**

Repetition of the procedure for benzyl ether **7ax**, starting instead with alcohol **6eq**, afforded *benzyl ether* **7eq** as a white solid (45 mg, 59%). $R_f$ 0.14 (petrol–ether, 7 : 3); m.p. 42 °C; $\nu_{max}/cm^{-1}$ (thin film) 2949s, 1768s, 1454m, 1372m, 1238s, 1097s, 915s, 814m, 699m; $\delta_H$ (400 MHz, $CDCl_3$) 1.87–2.01 (3 H, m, H-9 and 2 × H-10), 2.18–2.24 (1 H, m, H-9), 3.58–3.65 (1 H, m, H-8), 3.80 (1 H, t, *J* 10.5 Hz) and 4.00 (1 H, ddd, *J* 10.5, 5.0, 2.0 Hz, 2 × H-7), 4.57 and 4.64 (2 × 1 H, 2 × d, *J* 12.0 Hz, C$H_2$Ph), 6.12 (1 H, d, *J* 5.5 Hz, H-3), 7.12 (1 H, d, *J* 5.5 Hz, H-4), 7.27–7.39 (5 H, m, Ph); $\delta_C$ (100 MHz, $CDCl_3$) 25.9 ($CH_2$), 31.3 ($CH_2$), 66.8 ($CH_2$), 70.8 ($CH_2$), 71.1 (CH), 105.7 (C), 123.4 (CH), 127.6 (CH), 127.8 (CH), 128.5 (CH), 138.2 (C), 153.7 (CH), 170.2 (C); HRMS (EI) found 260.1048; $C_{15}H_{16}O_4$ ($M^+$) requires 260.1043.

**(5*R**,8*S**)-8-Acetoxy-1,6-dioxaspiro[4.5]dec-3-en-2-one (8ax)**

Acetic acid (17 μL, 0.294 mmol), DCC (61 mg, 0.296 mmol) and one crystal of DMAP were added to a stirred solution of alcohol **6ax** (50 mg, 0.294 mmol) in dichloromethane (750 μL). The reaction mixture was stirred for 1 h and then concentrated *in vacuo*. Purification by column chromatography (petrol–ether, 3 : 2) afforded *ester* **8ax** (47 mg, 75%) as a white solid. $R_f$ 0.18 (petrol–ether, 3 : 2); m.p. 108 °C; $\nu_{max}/cm^{-1}$ (thin film) 3098w, 2940m, 1769s, 1732s, 1442m, 1372s, 1232s, 911s, 822s, 696s; $\delta_H$ (400 MHz, $CDCl_3$) 1.59–1.67 (1 H, m, H-10), 1.99–2.05 (1 H, m, H-9), 2.11 (3 H, s, $CH_3$), 2.16–2.27 (2 H, m, H-9 and H-10), 3.95 (1 H, dt, *J* 13.0, 2.0 Hz) and 4.13 (1 H, dd, *J* 13.0, 1.5 Hz, 2 × H-7), 4.91–4.93 (1 H, m, H-8), 6.13 (1 H, d, *J* 5.5 Hz, H-3), 7.20 (1 H, d, *J* 5.5 Hz, H-4); $\delta_C$ (100 MHz, $CDCl_3$) 21.2 ($CH_3$), 23.1 ($CH_2$), 26.7 ($CH_2$), 65.6 (CH), 66.3 ($CH_2$), 106.1 (C), 123.3 (CH), 153.7 (CH), 170.1 (C), 170.5 (C); HRMS (EI) found 212.0676; $C_{10}H_{12}O_5$ ($M^+$) requires 212.0679.

**(5*S**,8*S**)-8-Acetoxy-1,6-dioxaspiro[4.5]dec-3-en-2-one (8eq)**

Repetition of the procedure for acetate **8ax**, starting instead with alcohol **6eq**, afforded *ester* **8eq** as a white solid (50 mg, 80%). $R_f$ 0.21 (petrol–ether, 3 : 2); m.p. 68 °C; $\nu_{max}/cm^{-1}$ (thin film) 3100w, 2962m, 1771s, 1738s, 1371s, 1233s, 1107s, 1035s, 1001s, 918s, 816m, 721m; $\delta_H$ (400 MHz, $CDCl_3$) 1.86–2.05 (3 H, m, H-9 and 2 × H-10), 2.04 (3 H, s, $CH_3$), 2.12–2.16 (1 H, m, H-9), 3.77 (1 H, t, *J* 10.5 Hz) and 3.94 (1 H, ddd, *J* 10.5, 5.0, 2.0 Hz, 2 × H-7), 4.84–4.91 (1 H, m, H-8), 6.12 (1 H, d, *J* 5.5 Hz, H-3), 7.15 (1 H, d, *J* 5.5 Hz, H-4); $\delta_C$ (100 MHz, $CDCl_3$) 21.0 ($CH_3$), 25.0 ($CH_2$), 31.0 ($CH_2$), 65.2 ($CH_2$), 66.3 (CH), 105.3 (C), 123.4 (CH), 153.4 (CH), 170.0 (C), 170.2 (C); HRMS ($ESI^+$) found 235.0579; $C_{10}H_{12}NaO_5$ ($MNa^+$) requires 235.0577.

**(5*R**,8*S**)-8-Isovaleryloxy-1,6-dioxaspiro[4.5]dec-3-en-2-one (9ax)**

Isovaleric acid (32 μL, 0.294 mmol), DCC (61 mg, 0.296 mmol) and one crystal of DMAP were added to a stirred solution of alcohol **6ax** (50 mg, 0.294 mmol) in dichloromethane (750 μL). The reaction mixture was stirred for 12 h and then concentrated *in vacuo*. Purification by column chromatography (petrol–ether, 3 : 2) afforded *ester* **9ax** (65 mg, 87%) as a colourless oil. $R_f$ 0.47 (petrol–ether, 3 : 2); $\nu_{max}/cm^{-1}$ (thin film) 3098w, 2960s, 2873m, 1771s, 1732s, 1371s, 911s, 822s, 698s; $\delta_H$ (400 MHz, $CDCl_3$) 0.95 (6 H, d, *J* 6.6 Hz, CH(C$H_3$)$_2$), 1.62–1.64 (1 H, m, H-10), 1.98–2.03 (1 H, m, H-9), 2.05–2.17 (1 H, m, C$H$(CH$_3$)$_2$), 2.18–2.26 (2 H, m, H-9 and H-10), 2.24 (2 H, d, *J* 7.5 Hz, $CH_2CO$), 3.94 (1 H, dt, *J* 13.0, 2.0 Hz) and 4.13 (1 H, dd, *J* 13.0, 1.5 Hz, 2 × H-7), 4.94 (1 H, app. s, H-8), 6.12 (1 H, d, *J* 5.5 Hz, H-3), 7.18 (1 H, d, *J* 5.5 Hz, H-4); $\delta_C$ (100 MHz, $CDCl_3$) 22.3 ($CH_3$), 23.1 ($CH_2$), 25.8 (CH), 26.8 ($CH_2$), 43.5 ($CH_2$), 65.2 (CH), 66.3 ($CH_2$), 106.1 (C), 123.3 (CH), 153.8 (CH), 170.1 (C), 172.5 (C); HRMS ($ESI^+$) found 277.1041; $C_{13}H_{18}NaO_5$ ($MNa^+$) requires 277.1046.

**(5*S**,8*S**)-8-Isovaleryloxy-1,6-dioxaspiro[4.5]dec-3-en-2-one (9eq)**

Repetition of the procedure for isovalerate **9ax**, starting instead with alcohol **6eq**, afforded *ester* **9eq** as a colourless oil (69 mg, 92%). $R_f$ 0.32 (petrol–ether, 3 : 2); $\nu_{max}/cm^{-1}$ (thin film) 3099w, 2961s, 2874m, 1772s, 1733s, 1371m, 1240s, 1103s, 1022s,

919s, 815m, 720m; $\delta_H$ (400 MHz, $CDCl_3$) 0.92 (6 H, d, *J* 6.6 Hz, $CH(CH_3)_2$), 1.86–1.90 (1 H, m, H-10), 1.98–2.18 (4 H, m, 2 × H-9, H-10 and $CH(CH_3)_2$), 2.16 (2 H, d, *J* 6.5 Hz, $CH_2CO$), 3.78 (1 H, t, *J* 10.5 Hz) and 3.94 (1 H, ddd, *J* 10.5, 5.0, 2.0 Hz, 2 × H-7), 4.86–4.93 (1 H, m, H-8), 6.12 (1 H, d, *J* 5.5 Hz, H-3), 7.15 (1 H, d, *J* 5.5 Hz, H-4); $\delta_C$ (100 MHz, $CDCl_3$) 22.3 ($CH_3$), 25.1 ($CH_2$), 25.8 (CH), 31.0 ($CH_2$), 48.3 ($CH_2$), 65.2 ($CH_2$), 66.0 (CH), 105.3 (C), 123.4 (CH), 153.5 (CH), 170.0 (C), 172.3 (C); HRMS ($ESI^+$) found 277.1060; $C_{13}H_{18}NaO_5$ ($MNa^+$) requires 277.1046.

### 2-[3-*N*-(4-Methylbenzenesulfonamido)propyl]furan (10)[36]

To a solution of *p*-toluenesulfonamide (6.74 g, 39.4 mmol) in dry DMSO (20 mL) was added KOH (1.25 g, 22.3 mmol). The reaction mixture was stirred at 50 °C for 2 h, then 2-(3-iodopropyl)furan[37] (4.04 g, 17.1 mmol) added and stirring continued for 1.5 h at 50 °C. After cooling to RT, the mixture was diluted with water (100 mL), extracted with dichloromethane (3 × 100 mL); the combined organics were then washed with water (2 × 150 mL), brine (50 mL), and dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (petrol–ethyl acetate, 3 : 1 → 1 : 1) gave the title compound (**10**) as a white crystalline solid (3.74 g, 79%). Data as reported.[36]

### 6-(4-Methylbenzenesulfonyl)-1-oxa-6-azaspiro[4.4]non-3-en-2-one (11)

*Method A*. To a stirred solution of sulfonamide **10** (0.10 g, 0.36 mmol) in anhydrous dichloromethane (25 mL) at 0 °C was added peracetic acid (0.23 mL, 32% by weight in acetic acid, 1.10 mmol). The reaction mixture was stirred for 16 h and then concentrated *in vacuo*. Purification by column chromatography (petrol–ethyl acetate, 2 : 1) gave the *spirocycle* (**11**) as an orange oil (24 mg, 23%).

*Method B*. To a solution of sulfonamide **10** (400 mg, 1.43 mmol) in dichloromethane (30 mL) at 0 °C was added MCPBA (950 mg, 65% by weight, 3.58 mmol). The solution was allowed to warm to RT, stirred for 16 h then quenched with $Na_2S_2O_3$ solution (sat. aq., 100 mL). The aqueous layer was extracted with ethyl acetate (3 × 100 mL), the combined extracts concentrated *in vacuo*, then $H_2SO_4$ (30% aq., 5.0 mL) added. The mixture was stirred at RT for 16 h, neutralised with $NaHCO_3$ solution (sat. aq., 100 mL) and extracted with ethyl acetate (3 × 100 mL). The combined organic layers were dried over $MgSO_4$, concentrated *in vacuo*, and the residue purified by column chromatography (petrol–ethyl acetate, 3 : 1 → 1 : 1) to give the *title compound* (**11**) as a pale brown oil (302 mg, 72%). $R_f$ 0.20 (petrol–ethyl acetate, 2 : 1); $\nu_{max}/cm^{-1}$ (thin film) 2960m, 1767s, 1598w, 1452w, 1353s, 1239m, 1163s, 912m, 665m; $\delta_H$ (400 MHz, $CDCl_3$) 1.94–2.01 (1 H, m, H-9), 2.02–2.10 (2 H, m, 2 × H-8), 2.29–2.38 (1 H, m, H-9), 2.42 (3 H, s, $CH_3$), 3.53 (1 H, td, *J* 8.5, 4.5 Hz) and 3.72 (1 H, app. q, *J* 8.5 Hz, 2 × H-7), 6.16 (1 H, d, *J* 5.5 Hz, H-3), 7.31 (2 H, d, *J* 8.5 Hz, Ar), 7.44 (1 H, d, *J* 5.5 Hz, H-4), 7.64 (2 H, d, *J* 8.5 Hz, Ar); $\delta_C$ (100 MHz, $CDCl_3$) 21.6 ($CH_2$), 21.7 ($CH_3$), 39.2 ($CH_2$), 49.5 ($CH_2$), 101.2 (C), 121.8 (CH), 127.6 (CH), 129.7 (CH), 135.3 (C), 144.3 (C), 154.8 (CH), 170.0 (C); HRMS ($ESI^+$) found 316.0611; $C_{14}H_{15}NNaO_4S$ ($MNa^+$) requires 316.0614.

### 2-[4-*N*-(4-Methylbenzenesulfonamido)butyl]furan (12)

To a solution of $Na_2CO_3$ (1.78 g, 16.7 mmol) in water (10 mL) was added 2-(4-aminobutyl)furan[38] (0.78 g, 5.60 mmol) in THF (10 mL). The reaction mixture was stirred until a homogeneous solution was achieved then *p*-toluenesulfonyl chloride (3.19 g, 16.7 mmol) was added. The reaction mixture was stirred for 6.5 h and then diluted with water (100 mL) and ethyl acetate (100 mL). The aqueous layer was extracted with ethyl acetate (3 × 75 mL) and the combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography (petrol–ether, 4 : 1 → 1 : 1) gave the *title compound* (**12**) as a white solid (1.41 g, 86%). $R_f$ 0.30 (petrol–ether, 1 : 1); m.p. 46–48 °C; $\nu_{max}/cm^{-1}$ (thin film) 3284s br, 2942m, 2867m, 1598m, 1428m, 1325s, 1159s, 1094s, 815m, 732m, 664s; $\delta_H$ (400 MHz, $CDCl_3$) 1.45–1.55 (2 H, m, 2 × H-3), 1.56–1.66 (2 H, m, 2 × H-2), 2.43 (3 H, s, $CH_3$), 2.56 (2 H, t, *J* 7.5 Hz, 2 × H-1), 2.94 (2 H, q, *J* 6.5 Hz, 2 × H-4), 4.78 (1 H, t, *J* 6.5 Hz, NH), 5.93 (1 H, d, *J* 3.0 Hz), 6.25 (1 H, dd, *J* 3.0, 2.0 Hz) and 7.27 (1 H, d, *J* 2.0 Hz, Fu), 7.30 and 7.75 (2 × 2 H, 2 × d, *J* 8.0 Hz, Ar); $\delta_C$ (100 MHz, $CDCl_3$) 21.5 ($CH_3$), 25.0 ($CH_2$), 27.1 ($CH_2$), 29.0 ($CH_2$), 42.9 ($CH_2$), 105.0 (CH), 110.1 (CH), 127.1 (CH), 129.7 (CH), 136.9 (C), 141.0 (CH), 143.4 (C), 155.5 (C); HRMS ($ESI^+$) found 316.0977; $C_{15}H_{19}NNaO_3S$ ($MNa^+$) requires 316.0978.

### 6-(4-Methylbenzenesulfonyl)-1-oxa-6-azaspiro[4,5]dec-3-en-2-one (13)

*Method A*. To a stirred solution of sulfonamide **12** (110 mg, 0.37 mmol) in anhydrous dichloromethane (25 mL) at 0 °C was added peracetic acid (0.23 mL, 32% by weight in acetic acid, 1.10 mmol). The reaction mixture was stirred for 16 h and then concentrated *in vacuo*. Purification by column chromatography (petrol–ethyl acetate, 2 : 1) gave the *spirocycle* (**13**) as a colourless oil that solidified on standing (22 mg, 19%).

*Method B*. MCPBA (184 mg, 70% by weight, 0.745 mmol) was added to a stirred solution of sulfonamide **12** (100 mg, 0.341 mmol) in dichloromethane (5 mL) at 0 °C. The reaction mixture was allowed to warm to RT, stirred for 16 h then quenched with $Na_2S_2O_3$ solution (sat. aq., 20 mL). The separated aqueous layer was extracted with ethyl acetate (3 × 20 mL), the combined extracts concentrated *in vacuo*, then $H_2SO_4$ (30% aq., 3.0 mL) was added. The mixture was stirred at RT for 16 h, then neutralised with $NaHCO_3$ solution (sat. aq., 20 mL) and extracted with ethyl acetate (3 × 20 mL). The combined organic layers were dried over $MgSO_4$, concentrated *in vacuo*, and purified by column chromatography (petrol : ethyl acetate, 3 : 1) to afford the *title compound* (**13**) as a white solid (93 mg, 89%). $R_f$ 0.61 (petrol–ethyl acetate, 1 : 1); m.p. 118–120 °C; $\nu_{max}/cm^{-1}$ (thin film) 2950m, 1770s, 1598m, 1446m, 1346s, 1248m, 1164s, 913m, 707m; $\delta_H$ (400 MHz, $CDCl_3$) 1.52–1.58 (1 H, m, H-10), 1.74–1.84 (3 H, m, H-8 and 2 × H-9), 1.87–1.99 (1 H, m, H-8), 1.95–2.05 (1 H, m, H-10), 2.41 (3 H, s, $CH_3$), 3.08 (1 H, td, *J* 11.5, 3.0 Hz) and 4.10 (1 H, ddd, *J* 11.5, 4.0, 3.0 Hz, 2 × H-7), 5.97 (1 H, d, *J* 5.5 Hz, H-3), 7.29 and 7.49 (2 × 2 H, 2 × d, *J* 8.0 Hz, Ar), 7.79 (1 H, d, *J* 5.5 Hz, H-4); $\delta_C$ (100 MHz, $CDCl_3$) 20.1 ($CH_2$), 21.6 ($CH_3$), 24.5 ($CH_2$), 37.6 ($CH_2$), 45.7 ($CH_2$), 95.5 (C), 118.2 (CH), 127.3 (CH), 129.9 (CH), 135.3 (C), 144.4

(C), 157.9 (CH), 169.9 (C); HRMS ($ESI^+$) found 330.0767; $C_{15}H_{17}NNaO_4S$ ($MNa^+$) requires 330.0770.

### 3-(Furan-2-yl)propanal[22] (15)

Zinc dust (1.00 g, 15.3 mmol) was added to a stirred solution of bis(cyclopentadienyl)titanium(IV) dichloride (76 mg, 0.305 mmol) and triethylamine hydrochloride (4.23 g, 30.7 mmol) in degassed dichloromethane (120 mL) at RT. When the reaction mixture changed from a dark red to yellow colour (typically 2 min), 3-(2-furyl)acrolein (**14**, 750 mg, 6.14 mmol) was added and stirring continued for 1 h. The reaction was then quenched with $NH_4Cl$ solution (sat. aq., 100 mL), filtered through a Celite pad, the aqueous layer extracted with dichloromethane (3 × 100 mL) and the combined organic layers dried over $MgSO_4$. After removal of the solvent *in vacuo*, the title compound (**15**) was obtained as a colourless oil (732 mg, 96%) that was sufficiently pure to use in the next reaction without further purification. $R_f$ 0.30 (petrol–ether, 8 : 1); $\delta_H$ (400 MHz, $CDCl_3$) 2.80 (2 H, t, *J* 7.5, 2 × H-2), 2.99 (2 H, t, *J* 7.5, 2 × H-3), 6.03 (1 H, d, *J* 2.5 Hz), 6.28 (1 H, dd, *J* 2.5, 1.5 Hz) and 7.31 (1 H, d, *J* 1.5 Hz, Fu), 9.83 (1 H, s, H-1); $\delta_C$ (100 MHz, $CDCl_3$) 20.7 ($CH_2$), 41.9 ($CH_2$), 105.5 (CH), 110.2 (CH), 141.3 (CH), 153.8 (C), 201.0 (CH).

### 4-(Furan-2-yl)-2-hydroxybutanenitrile

$K_2CO_3$ (92 mg, 0.67 mmol) and trimethylsilyl cyanide (2.33 mL, 18.5 mmol) were added to a solution of aldehyde **15** (1.65 g, 13.3 mmol) in dry DMF (37 mL) at 0 °C. The reaction mixture was warmed to RT and stirred for 40 min then water (150 mL) and ether (150 mL) were added. The separated organic layer was washed with water (2 × 100 mL), the aqueous layers back-extracted with ether (100 mL), and the combined organic layers dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography (methanol–dichloromethane, 0 → 2%) afforded the *title compound* as a colourless oil (1.65 g, 82%). $R_f$ 0.15 (dichloromethane); $\nu_{max}/cm^{-1}$ (thin film) 3441s br, 2959s, 2230w, 1718m, 1508m, 1255s, 1112s, 1009s; $\delta_H$ (400 MHz, $CDCl_3$) 2.19 (2 H, app. q, *J* 7.0 Hz, 2 × H-3), 2.84–2.91 (2 H, m, 2 × H-4), 3.24 (1 H, br s, OH), 4.49 (1 H, td, *J* 7.0, 2.0 Hz, H-2), 6.08 (1 H, d, *J* 3.0 Hz), 6.29–6.31 (1 H, m) and 7.73 (1 H, s, Fu); $\delta_C$ (100 MHz, $CDCl_3$) 23.1 ($CH_2$), 33.5 ($CH_2$), 60.2 (CH), 106.2 (CH), 110.3 (CH), 119.8 (C), 141.6 (CH), 153.2 (C); HRMS (FI) found 151.0629; $C_8H_9NO_2$ ($M^+$) requires 151.0628.

### 1-Amino-4-(furan-2-yl)butan-2-ol

$LiAlH_4$ (638 mg, 97% by weight, 16.3 mmol) was added to a solution of 4-(furan-2-yl)-2-hydroxybutanenitrile (1.65 g, 10.9 mmol) in ether (20 mL) at 0 °C and the reaction mixture was stirred at RT for 30 min. The solution was re–cooled to 0 °C, then water (0.6 mL), NaOH solution (20% aq., 0.6 mL), and a further portion of water (2 mL) were added in sequence. The suspension was stirred at RT for 10 min, filtered through a Celite plug, and the solvent removed *in vacuo* to afford the *title compound* as a yellow oil that was used without further purification (1.52 g, 90%). $R_f$ 0.14 [chloroform–methanol–$NH_3$ solution (conc. aq.), 10 : 1 : 0.1]; $\nu_{max}/cm^{-1}$ (thin film) 3297s br, 3116m, 2926s, 2857m, 1655s, 1508s, 1145s, 1074s; $\delta_H$ (400 MHz, $CD_3OD$) 1.69 (1 H, dtd, *J* 14.0, 9.0, 5.5 Hz) and 1.75–1.86 (1 H, m, 2 × H-3), 2.56 (1 H, dd, *J* 13.0, 8.0 Hz, H-1) and 2.64–2.75 (2 H, m, H-1 and H-4), 2.80 (1 H, ddd, *J* 15.0, 9.0, 5.5 Hz, H-4), 3.55 (1 H, tt, *J* 8.0, 4.5 Hz, H-2), 6.05 (1 H, dd, *J* 3.0, 1.0 Hz), 6.29 (1 H, dd, *J* 3.0, 2.0 Hz) and 7.34 (1 H, dd, *J* 2.0, 1.0 Hz, Fu); $\delta_C$ (100 MHz, $CD_3OD$) 24.1 ($CH_2$), 33.3 ($CH_2$), 47.3 ($CH_2$), 71.7 (CH), 104.9 (CH), 110.1 (CH), 141.1 (CH), 156.0 (C); HRMS ($ESI^+$) found 178.0841; $C_8H_{13}NNaO_2$ ($MNa^+$) requires 178.0838.

### *N*-[4-(Furan-2-yl)-2-hydroxybutyl]-4-methylbenzenesulfonamide (16)

*p*-Toluenesulfonyl chloride (418 mg, 2.19 mmol) was added to a stirred solution of 1-amino-4-(furan-2-yl)butan-2-ol (328 mg, 2.11 mmol), triethylamine (588 μL, 4.22 mmol) and DMAP (13 mg, 0.106 mmol) in dichloromethane (13 mL) at 0 °C. After stirring for 1 h at 0 °C, the reaction mixture was diluted with water (50 mL) and dichloromethane (50 mL). The separated aqueous layer was extracted with dichloromethane (2 × 50 mL), the combined organic layers were washed successively with hydrochloric acid (2.0 M, 100 mL), $NaHCO_3$ solution (sat. aq., 100 mL), brine (100 mL), then dried over $MgSO_4$, and concentrated *in vacuo*. Purification by column chromatography (methanol–dichloromethane, 0.5 → 4%) afforded the *title compound* (**16**) as a beige solid (614 mg, 94%). $R_f$ 0.13 (methanol–dichloromethane, 2%); m.p. 70–72 °C; $\nu_{max}/cm^{-1}$ (thin film) 3520s br, 3284s, 2925s, 1598s, 1508s, 1326s, 1160s, 1091m; $\delta_H$ (400 MHz, $CDCl_3$) 1.76 (2 H, m, 2 × H-3), 2.42 (3 H, s, $CH_3$), 2.60–2.86 (4 H, m, H-1, 2 × H-4 and OH), 3.04 (1 H, ddd, *J* 13.0, 7.0, 3.0 Hz, H-1), 3.71 (1 H, br s, H-2), 5.44 (1 H, d, *J* 5.5, NH), 5.96 (1 H, d, *J* 2.0 Hz, Fu), 6.25 (1 H, dd, *J* 3.0, 2.0 Hz, Fu), 7.25–7.31 (3 H, m, Ar and Fu), 7.74 (2 H, d, *J* 8.5 Hz, Ar); $\delta_C$ (100 MHz, $CDCl_3$) 21.5 ($CH_3$), 23.9 ($CH_2$), 32.7 ($CH_2$), 48.6 ($CH_2$), 69.6 (CH), 105.2 (CH), 110.2 (CH), 127.1 (CH), 129.8 (CH), 136.6 (C), 141.0 (CH), 143.6 (C), 155.0 (C); HRMS ($ESI^+$) found 332.0926; $C_{15}H_{19}NNaO_4S$ ($MNa^+$) requires 332.0927.

### *N*-[4-(Furan-2-yl)-2-(isovaleryloxy)butyl]-4-methylbenzenesulfonamide (17)

Trimethylsilyl trifluoromethanesulfonate (20 μL, 0.74 M in dichloromethane, 14.8 μmol) was added to a solution of sulfonamide **16** (200 mg, 0.646 mmol) and isovaleric anhydride (193 μL, 0.966 mmol) in dichloromethane (3 mL) at −10 °C. After stirring at this temperature for 1 h, the reaction was quenched with $NaHCO_3$ solution (sat. aq., 10 mL) then the separated aqueous layer was extracted with dichloromethane (3 × 10 mL), and the combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (petrol–ether, 2 : 1) afforded the *title compound* (**17**) as a pale yellow oil (203 mg, 80%). $R_f$ 0.10 (petrol–ether, 4 : 1); $\nu_{max}/cm^{-1}$ (thin film) 3284s, 2960s, 2872m, 1735s, 1598m, 1449s, 1333s, 1253m, 1162s, 1094s; $\delta_H$ (400 MHz,

$CDCl_3$) 0.94 (6 H, d, *J* 6.5 Hz, $CH(CH_3)_2$), 1.84–1.98 (2 H, m, 2 × H-3), 2.01–2.10 (1 H, m, $CH(CH_3)_2$), 2.13 (2 H, d, *J* 7.0 Hz, $CH_2CO$), 2.42 (3 H, s, $ArCH_3$), 2.62 (2 H, app. q, *J* 7.5 Hz, 2 × H-4), 3.08–3.13 (2 H, m, 2 × H-1), 4.83–4.90 (1 H, m, H-2), 4.92 (1 H, t, *J* 6.5 Hz, NH), 5.96 (1 H, d, *J* 3.0 Hz), 6.26 (1 H, dd, *J* 3.0, 2.0 Hz) and 7.27–7.29 (1 H, m, Fu), 7.31 and 7.73 (2 × 2 H, 2 × d, *J* 8.0 Hz, Ar); $\delta_C$ (100 MHz, $CDCl_3$) 21.5 ($CH_3$), 22.3 ($CH_3$), 23.7 ($CH_2$), 25.6 (CH), 29.9 ($CH_2$), 43.0 ($CH_2$), 46.1 ($CH_2$), 71.4 (CH), 105.4 (CH), 110.2 (CH), 127.0 (CH), 129.8 (CH), 136.8 (C), 141.1 (CH), 143.6 (C), 154.2 (C), 172.9 (C); HRMS ($ESI^+$) found 416.1500; $C_{20}H_{27}NNaO_5S$ ($MNa^+$) requires 416.1502.

### 2-[3,3-Bis(benzyloxy)propyl]furan (18)

Aldehyde **15** (200 mg, 1.61 mmol) was added to a solution of *N*-chlorosuccinimide (11 mg, 0.082 mmol) and thiourea (3.0 mg, 0.039 mmol) in anhydrous benzyl alcohol (2.0 mL) at RT. After stirring for 4 h, the reaction mixture was poured onto a short column of silica and eluted with petrol–ether (30 : 1). Evaporation of the solvent *in vacuo* afforded the *title compound* (**18**) as a colourless oil (400 mg, 77%). $R_f$ 0.51 (petrol–ether, 7 : 1); $\nu_{max}/cm^{-1}$ (thin film) 3031s, 2933s, 2872s, 1598m, 1497m, 1454s, 1354s, 1124s 1047s; $\delta_H$ (400 MHz, $CDCl_3$) 2.11–2.17 (2 H, m, 2 × H-2), 2.78 (2 H, t, *J* 7.5 Hz, 2 × H-1), 4.60 and 4.71 (2 × 2 H, 2 × d, *J* 11.5 Hz, 2 × $CH_2Ph$), 4.81 (1 H, t, *J* 6.0 Hz, H-3), 5.97 (1 H, dd, *J* 3.0, 1.0 Hz, Fu), 6.29 (1 H, dd, *J* 3.0, 2.0 Hz, Fu), 7.30–7.41 (11 H, m, Fu and 2 × Ph); $\delta_C$ (100 MHz, $CDCl_3$) 23.4 ($CH_2$), 31.7 ($CH_2$), 67.5 ($CH_2$), 101.4 (CH), 105.0 (CH), 110.1 (CH), 127.7 (CH), 127.8 (CH), 128.5 (CH), 138.1 (C), 141.0 (CH), 155.2 (C); HRMS ($ESI^+$) found 345.1461; $C_{21}H_{22}NaO_3$ ($MNa^+$) requires 345.1461.

### 2-Benzyloxy-4-(furan-2-yl)butanenitrile

Trimethylsilyl trifluoromethanesulfonate (673 μL, 3.72 mmol) was added dropwise to a solution of tri(*o*-tolyl)phosphine (1.27 g, 4.17 mmol) and acetal **18** (600 mg, 1.86 mmol) in dichloromethane (15 mL) at −10 °C. The solution was allowed to warm to RT, stirred until TLC analysis indicated complete consumption of starting material (typically 1 h), then cooled to 0 °C and trimethylsilyl cyanide (699 μL, 5.58 mmol) added. After stirring at RT for 6 h, the reaction was quenched with $NaHCO_3$ solution (sat. aq., 20 mL), the aqueous layer extracted with dichloromethane (3 × 20 mL), and the combined organic layers dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (petrol–ether, 100 : 1 → 40 : 1) afforded the *title compound* as a colourless oil (328 mg, 73%). $R_f$ 0.24 (petrol–ether, 10 : 1); $\nu_{max}/cm^{-1}$ (thin film) 3033m, 2932s, 2871s, 2239w, 1599m, 1508s, 1455s, 1336s, 1145s, 1099s; $\delta_H$ (400 MHz, $CDCl_3$) 2.15–2.30 (2 H, m, 2 × H-3), 2.86 (2 H, t, *J* 7.5 Hz, 2 × H-4), 4.17 (1 H, dd, *J* 7.5, 6.0 Hz, H-2), 4.53 and 4.87 (2 × 1 H, 2 × d, *J* 11.5 Hz, $CH_2Ph$), 5.98 (1 H, dd, *J* 3.0, 0.5 Hz), 6.28 (1 H, dd, *J* 3.0, 2.0 Hz) and 7.31 (1 H, dd, *J* 2.0, 0.5 Hz, Fu), 7.33–7.43 (5 H, m, Ph); $\delta_C$ (100 MHz, $CDCl_3$) 23.2 ($CH_2$), 32.0 ($CH_2$), 66.5 (CH), 72.4 ($CH_2$), 106.0 (CH), 110.2 (CH), 118.0 (C), 128.3 (CH), 128.5 (CH), 128.7 (CH), 135.8 (C), 141.5 (CH), 153.3 (C); HRMS (FI) found 241.1102; $C_{15}H_{15}NO_2$ ($M^+$) requires 241.1097.

### 2-Benzyloxy-4-(furan-2-yl)butan-1-amine

$LiAlH_4$ (79 mg, 97% by weight, 2.02 mmol) was added to a solution of 2-benzyloxy-4-(furan-2-yl)butanenitrile (326 mg, 1.35 mmol) in ether (4.5 mL) at 0 °C and the reaction mixture was stirred at RT for 10 min. The reaction was quenched at 0 °C by sequential addition of water (0.1 mL), NaOH solution (20% aq., 0.1 mL), and a further portion of water (0.6 mL). The suspension was stirred at RT for 10 min then filtered through a pad of Celite and concentrated *in vacuo* to afford the *title compound* as a colourless oil (283 mg, 85%) that was sufficiently pure to use in the next reaction without purification. $R_f$ 0.32 [chloroform–methanol–$NH_3$ solution (conc. aq.), 10 : 1 : 0.1]; $\nu_{max}/cm^{-1}$ (thin film) 3064w, 3031m, 2928s, 2864s, 1672s, 1596s, 1508s, 1497s, 1069s; $\delta_H$ (400 MHz, $CDCl_3$) 1.32 (2 H, br s, $NH_2$), 1.82–1.92 and 1.92–2.03 (2 × 1 H, 2 × m, 2 × H-3), 2.76 (1 H, dd, *J* 13.5, 6.5 Hz, H-1), 2.71–2.77 (2 H, m, 2 × H-4), 2.88 (1 H, dd, *J* 13.5, 4.0 Hz, H-1), 3.44 (1 H, tt, *J* 6.5, 4.0 Hz, H-2), 4.55 and 4.59 (2 × 1 H, 2 × d, *J* 11.5 Hz, $CH_2Ph$), 5.98 (1 H, dd, *J* 3.0, 1.0 Hz, Fu), 6.29 (1 H, dd, *J* 3.0, 2.0 Hz, Fu), 7.28–7.40 (6 H, m, Fu and Ph); $\delta_C$ (100 MHz, $CDCl_3$) 24.0 ($CH_2$); 30.2 ($CH_2$), 44.8 ($CH_2$), 71.5 ($CH_2$), 79.8 (CH), 104.9 (CH), 110.1 (CH), 127.7 (CH), 127.8 (CH), 128.4 (CH), 138.6 (C), 140.9 (CH), 155.7 (C); HRMS ($ESI^+$) found 246.1484; $C_{15}H_{20}NO_2$ ($MH^+$) requires 246.1489.

### *N*-[2-Benzyloxy-4-(furan-2-yl)butyl]-4-methylbenzenesulfonamide (19)

*p*-Toluenesulfonyl chloride (43 mg, 0.226 mmol) was added to a stirred solution of 2-benzyloxy-4-(furan-2-yl)butan-1-amine (50 mg, 0.204 mmol), triethylamine (56 μL, 41 mg, 0.405 mmol) and DMAP (1.0 mg, 0.008 mmol) in dichloromethane (1 mL) at 0 °C. After stirring for 1 h at RT, the reaction mixture was diluted with water (10 mL) and dichloromethane (10 mL). The separated aqueous layer was extracted with dichloromethane (2 × 10 mL) and the combined organic layers were washed sequentially with hydrochloric acid (2.0 M, 15 mL), $NaHCO_3$ solution (sat. aq., 15 mL), and brine (10 mL), then dried over $MgSO_4$, and concentrated *in vacuo*. Purification by column chromatography (petrol–ether, 4 : 1 → 1 : 1) afforded the *title compound* (**19**) as a pale yellow oil (66 mg, 81%). $R_f$ 0.52 (dichloromethane); $\nu_{max}/cm^{-1}$ (thin film) 3288s, 3032s, 2926s, 1598m, 1496s, 1330s, 1162s, 1092s; $\delta_H$ (400 MHz, $CDCl_3$) 1.81 and 1.95 (2 × 1 H, 2 × dtd, *J* 14.0, 7.5, 6.0 Hz, 2 × H-3), 2.43 (3 H, s, $CH_3$), 2.65 (2 H, t, *J* 7.5 Hz, 2 × H-4), 2.94 (1 H, dt, *J* 13.0, 6.0 Hz) and 3.15 (1 H, ddd, *J* 13.0, 6.0, 4.0 Hz, 2 × H-1), 3.51 (1 H, qd, *J* 6.0, 4.0 Hz, H-2), 4.36 and 4.48 (2 × 1 H, 2 × d, *J* 11.5 Hz, $CH_2Ph$), 4.73 (1 H, t, *J* 6.0 Hz, NH), 5.93 (1 H, dd, *J* 3.0, 1.0 Hz, Fu), 6.27 (1 H, dd, *J* 3.0, 2.0 Hz, Fu), 7.23–7.38 (8 H, m, Fu, Ph and Ar), 7.70 (2 H, d, *J* 8.0 Hz, Ar); $\delta_C$ (100 MHz, $CDCl_3$) 21.5 ($CH_3$), 23.6 ($CH_2$), 30.0 ($CH_2$), 45.5 ($CH_2$), 71.5 ($CH_2$), 76.4 (CH), 105.2 (CH), 110.2 (CH), 127.1 (CH), 127.8 (CH), 128.0 (CH), 128.6 (CH), 129.7 (CH), 136.7 (C), 137.8 (C), 141.0 (CH), 143.4 (C), 154.9 (C); HRMS ($ESI^+$) found 422.1396; $C_{22}H_{25}NNaO_4S$ ($MNa^+$) requires 422.1397.

### *N*-[2-Isovaleryloxy-4-(2-methoxy-5-oxo-2,5-dihydrofuran-2-yl) butyl]-4-methylbenzenesulfonamide (20)

Oxygen gas was bubbled through a stirred solution of sulfonamide **17** (150 mg, 0.381 mmol) and rose bengal (2.0 mg, 1.97 μmol) in methanol (10 mL) for 2 min. Maintaining a slow stream of oxygen, the solution was cooled to 0 °C and irradiated[39] for 10 min. The reaction mixture was concentrated *in vacuo*, then the crude residue was taken up in pyridine (5 mL) and acetic anhydride (36 μL, 0.382 mmol) added. After stirring for 15 min at RT, the reaction mixture was diluted with water (20 mL), the aqueous layer extracted with dichloromethane (2 × 30 mL), the combined organic layers washed with $CuSO_4$ solution (sat. aq., 2 × 30 mL), water (30 mL), and then dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (methanol–dichloromethane, 1%) afforded the *title compound* (**20**) as a viscous, colourless oil (166 mg, 99%) and as a 1 : 1 mixture of diastereomers. $R_f$ 0.32 (methanol–dichloromethane, 1%); $\nu_{max}/cm^{-1}$ (thin film) 3277br, 2960m, 2873m, 1768s, 1733s, 1495s, 1453s, 1159s; $\delta_H$ (400 MHz, $C_6D_6$) 0.92 (2 peaks, 6 H, d, *J* 6.5 Hz, $CH(CH_3)_2$), 1.62–1.97 (4 H, m, 2 × H-3 and 2 × H-4), 2.04 (3 H, s, $ArCH_3$), 2.06–2.16 (3 H, m, $CHCH_2CO$), 2.87 (2 peaks, 3 H, s, $OCH_3$), 2.99–3.06 (2 H, m, 2 × H-1), 4.92–5.00 (1 H, m, H-2), 5.41/5.43 (1 H, t, *J* 6.5 Hz, NH), 5.74/5.76 (1 H, d, *J* 5.5 Hz,=CHCO), 6.34/6.36 (1 H, d, *J* 5.5 Hz, C*H*=CHCO), 6.97 and 7.92 (2 × 2 H, 2 × d, *J* 8.0 Hz, Ar); $\delta_C$ (100 MHz, $C_6D_6$) 21.1 ($CH_3$), 22.3 ($CH_3$), 25.7 ($CH_2$ and CH), 33.2 ($CH_2$), 43.2 ($CH_2$), 46.0/46.1 ($CH_2$), 50.6 ($CH_3$), 71.6 (2 peaks, CH), 110.1 (C), 125.0 (CH), 127.4 (CH), 129.9 (CH), 138.1 (C), 143.2 (C), 152.8 (2 peaks, CH), 169.3 (2 peaks, C), 172.5 (2 peaks, C); HRMS ($ESI^+$) found 462.1543; $C_{21}H_{29}NNaO_7S$ ($MNa^+$) requires 462.1557.

### *N*-[2-Benzyloxy-4-(2-methoxy-5-oxo-2,5-dihydrofuran-2-yl) butyl]-4-methylbenzenesulfonamide (21)

Oxygen gas was bubbled through a stirred solution of sulfonamide **19** (20 mg, 0.05 mmol) and rose bengal (1.0 mg, 0.98 μmol) in methanol (1 mL) for 2 min. Maintaining a slow stream of oxygen, the solution was cooled to 0 °C and irradiated[39] for 10 min. The reaction mixture was concentrated *in vacuo*, then the crude residue was taken up in pyridine (0.6 mL) and acetic anhydride (5.0 μL, 0.049 mmol) added. After stirring for 15 min at RT, the reaction mixture was diluted with water (5 mL), the aqueous layer extracted with dichloromethane (2 × 5 mL), the combined organic layers washed with $CuSO_4$ solution (sat. aq., 2 × 10 mL), water (5 mL), and then dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (methanol–dichloromethane, 1%) afforded the *title compound* (**21**) as a colourless oil (17 mg, 76%) and as a 1 : 1 mixture of diastereomers. $R_f$ 0.17 (methanol–dichloromethane, 0.5%); $\nu_{max}/cm^{-1}$ (thin film) 3288s br, 3061m, 2928s, 1770s, 1599w, 1455m, 1333s, 1267s, 1163s, 1092s; $\delta_H$ (500 MHz, $CDCl_3$) 1.58–1.74 (2 H, m, 2 × H-3), 1.78–1.98 (2 H, m, 2 × H-4), 2.42 (3 H, s, $ArCH_3$), 2.90/2.94 (1 H, dd, *J* 13.0, 6.0 Hz) and 3.04–3.10 (1 H, m, 2 × H-1), 3.17 (3 H, s, $OCH_3$), 3.51/3.52 (1 H, app. quin, *J* 5.5 Hz, H-2), 4.37/4.38 and 4.43/4.45 (2 × 1 H, 2 × d, *J* 11.5 Hz, $CH_2Ph$), 4.93 (1 H, t, *J* 6.0 Hz, NH), 6.20 (1 H, d, *J* 5.5 Hz,=CHCO), 7.07/7.08 (1 H, d, *J* 5.5 Hz, C*H*=CHCO), 7.21–7.36 (7 H, m, Ph and Ar), 7.69 (2 H, d, *J* 8.0 Hz, Ar); $\delta_C$ (125 MHz, $CDCl_3$) 21.5 ($CH_3$), 25.3 ($CH_2$), 32.4/32.5 ($CH_2$), 45.3/45.4 ($CH_2$), 51.2 ($CH_3$), 71.4 (2 peaks, $CH_2$), 76.6 (CH), 110.7 (2 peaks, C), 125.0 (2 peaks, CH), 127.0 (CH), 127.8 (CH), 128.0 (CH), 128.5 (CH), 129.8 (CH), 136.6/136.7 (C), 137.7 (C), 143.5 (C), 153.4 (2 peaks, CH), 169.7 (C); HRMS ($ESI^+$) found 468.1451; $C_{23}H_{27}NNaO_6S$ ($MNa^+$) requires 468.1451.

### (5*R**,8*S**)-8-Isovaleryloxy-6-(4-methylbenzenesulfonyl)-1-oxa-6-azaspiro[4.5]dec-3-en-2-one (23ax) and (5*S**,8*S**)-8-isovaleryloxy-6-(4-methylbenzenesulfonyl)-1-oxa-6-azaspiro[4.5] dec-3-en-2-one (23eq)

$H_2SO_4$ (40% aq., 1.0 mL) was added to neat sulfonamide **20** (167 mg, 0.380 mmol) and the suspension stirred at RT for 5 d. The reaction mixture was diluted with $NaHCO_3$ solution (sat. aq., 50 mL), the aqueous layer extracted with ethyl acetate (3 × 50 mL), and the combined organics washed with brine (50 mL) and dried over $MgSO_4$ then concentrated *in vacuo*. Purification by column chromatography (methanol–dichloromethane, 0 → 3%) afforded both diastereomers of the *title compound* (**23ax**/**23eq**, *dr* = 65 : 35) as a pale yellow oil (42 mg, 27%). $R_f$ 0.11 (dichloromethane); $\nu_{max}/cm^{-1}$ (thin film) 2970s, 2922m, 1766s, 1728s, 1345s, 1164s; $\delta_H$ (400 MHz, $CDCl_3$) [ax/eq refer to **23ax**/**23eq**] 0.97 (6 H, d, *J* 6.5 Hz, $CH(CH_3)_2$, eq), 1.02 (6 H, d, *J* 6.5 Hz, $CH(CH_3)_2$, ax), 1.47–1.52 (1 H, m, H-10, both), 1.61–2.40 (4 H, m, H-10, 2 × H-9 and $CH(CH_3)_2$, both), 2.29 (2 H, d, *J* 7.0 Hz, $CH_2CO$, eq) overlapping 2.30 (2 H, d, *J* 7.0 Hz, $CH_2CO$, ax), 2.42 (3 H, s, $ArCH_3$, ax), 2.43 (3 H, s, $ArCH_3$, eq), 3.06 (1 H, t, *J* 11.5 Hz, H-7, eq), 3.27 (1 H, dd, *J* 13.0, 2.0 Hz, H-7, ax), 4.22–4.27 (2 H, m, H-7, both), 5.01 (1 H, tdd, *J* 11.5, 5.5, 5.0 Hz, H-8, eq), 5.13–5.17 (1 H, m, H-8, ax), 6.01 (1 H, d, *J* 5.5 Hz, H-3, eq), 6.02 (1 H, d, *J* 5.5 Hz, H-3, ax), 7.29 (2 H, d, *J* 8.5 Hz, Ar, ax), 7.31 (2 H, d, *J* 8.5 Hz, Ar, eq), 7.48 (2 H, d, *J* 8.5 Hz, Ar, ax), 7.49 (2 H, d, *J* 8.5 Hz, Ar, eq), 7.77 (1 H, d, *J* 5.5 Hz, H-4, eq), 7.85 (1 H, d, *J* 5.5 Hz, H-4, ax); $\delta_C$ (100 MHz, $CDCl_3$) 21.6 ($CH_3$, ax), 21.7 ($CH_3$, eq), 22.3 ($CH_3$, eq), 22.4 ($CH_3$, ax), 25.6 ($CH_2$, eq), 25.7 (CH, both), 25.8 ($CH_2$, ax), 31.9 ($CH_2$, eq), 32.6 ($CH_2$, ax), 43.3 ($CH_2$, eq), 43.5 ($CH_2$, ax), 47.6 ($CH_2$, eq), 48.0 ($CH_2$, ax), 64.7 (CH, ax), 67.3 (CH, eq), 94.2 (C, eq), 94.9 (C, ax), 118.7 (CH, ax), 119.0 (CH, eq), 127.2 (CH, ax), 127.3 (CH, eq), 129.9 (CH, ax), 130.0 (CH, eq), 135.0 (C, eq), 135.3 (C, ax), 144.6 (C, ax), 144.8 (C, eq), 156.6 (CH, eq), 157.1 (CH, ax), 169.3 (C, eq), 169.5 (C, ax), 171.9 (C, eq), 172.5 (C, ax); HRMS ($ESI^+$) found 430.1295; $C_{20}H_{25}NNaO_6S$ ($MNa^+$) requires 430.1295.

### (5*R**,8*S**)-8-Benzyloxy-6-(4-methylbenzenesulfonyl)-1-oxa-6-azaspiro[4.5]dec-3-en-2-one (24ax) and (5*S**,8*S**)-8-Benzyloxy-6-(4-methylbenzenesulfonyl)-1-oxa-6-azaspiro[4.5]dec-3-en-2-one (24eq)

$H_2SO_4$ (40% aq., 1.0 mL) was added to neat sulfonamide **21** (177 mg, 0.397 mmol) and the suspension stirred at RT for 2 d. The reaction mixture was diluted with $NaHCO_3$ solution (sat. aq., 20 mL), the aqueous layer extracted with ethyl acetate (3 × 20 mL), and the combined organics washed with brine (20 mL)

and dried over $MgSO_4$ then concentrated *in vacuo*. Purification by column chromatography (methanol–dichloromethane, 0 → 1%) afforded both diastereomers of the *title compound* (**24ax**/**24eq**, *dr* = 15 : 85) as a pale yellow solid (130 mg, 79%). $R_f$ 0.47 (methanol–dichloromethane, 0.5%); m.p. 164–166 °C; $\nu_{max}/cm^{-1}$ (thin film) 3030s, 2922s, 1770s, 1580m, 1341s, 1161s, 1101s; NMR data for **24ax**: $\delta_H$ (400 MHz, $CDCl_3$) 1.40 (1 H, ddd, *J* 13.5, 4.5, 2.5 Hz, H-10), 1.92 (1 H, tdd, *J* 13.5, 4.5, 3.0 Hz) and 1.97–2.03 (1 H, m, 2 × H-9), 2.42 (3 H, s, $CH_3$), 2.50 (1 H, td, *J* 13.5, 4.5 Hz, H-10), 3.14 (1 H, dd, *J* 13.0, 1.5 Hz, H-7), 3.73–3.82 (1 H, m, H-8), 4.39 (1 H, ddd, *J* 13.0, 3.0, 2.0 Hz, H-7), 4.55 and 4.78 (2 × 1 H, 2 × d, *J* 12.0 Hz, C$H_2$Ph), 5.99 (1 H, d, *J* 5.5 Hz, H-3), 7.29 (2 H, d, *J* 8.5 Hz, Ar), 7.30–7.44 (5 H, m, Ph), 7.52 (2 H, d, *J* 8.5 Hz, Ar), 7.80 (1 H, d, *J* 5.5 Hz, H-4); $\delta_C$ (100 MHz, $CDCl_3$) 21.6 ($CH_3$), 25.2 ($CH_2$), 32.4 ($CH_2$), 46.6 ($CH_2$), 68.7 (CH), 69.9 ($CH_2$), 95.4 (C), 118.6 (CH), 127.2 (CH), 127.7 (CH), 127.8 (CH), 128.5 (CH), 129.9 (CH), 135.7 (C), 137.9 (C), 144.4 (C), 157.5 (CH), 169.9 (C); NMR data for **24eq**: $\delta_H$ (400 MHz, $CDCl_3$) 1.63 (1 H, ddd, *J* 13.5, 4.0, 3.0 Hz, H-10), 1.79 (1 H, tdd, *J* 13.5, 11.0, 4.0 Hz, H-9), 2.04 (1 H, td, *J* 13.5, 4.5 Hz, H-10), 2.11–2.17 (1 H, m, H-9), 2.42 (3 H, s, $CH_3$), 2.94 (1 H, t, *J* 11.0 Hz, H-7), 3.72 (1 H, tt, *J* 11.0, 4.5 Hz, H-8), 4.29 (1 H, ddd, *J* 11.0, 4.5, 1.5 Hz, H-7), 4.65 (2 H, s, C$H_2$Ph), 5.99 (1 H, d, *J* 5.5 Hz, H-3), 7.29 (2 H, d, *J* 8.5 Hz, Ar), 7.31–7.41 (5 H, m, Ph), 7.46 (2 H, d, *J* 8.5 Hz, Ar), 7.74 (1 H, d, *J* 5.5 Hz, H-4); $\delta_C$ (100 MHz, $CDCl_3$) 21.6 ($CH_3$), 26.9 ($CH_2$), 36.1 ($CH_2$), 48.7 ($CH_2$), 71.0 ($CH_2$), 72.8 (CH), 94.4 (C), 118.8 (CH), 127.3 (CH), 127.6 (CH), 127.9 (CH), 128.5 (CH), 129.9 (CH), 135.0 (C), 138.0 (C), 144.7 (C), 156.9 (CH), 169.5 (C); HRMS ($ESI^+$) found 436.1175; $C_{22}H_{23}NNaO_5S$ ($MNa^+$) requires 436.1189.

## Equilibration experiments

Single butenolide spiroacetals (**6–9**) or spiro-*N*,*O*-acetals (**23, 24**) (5–20 mg) were dissolved in $CD_3CN$ (0.6 mL) in a standard NMR tube. Hydriodic acid (aq., 57% by weight, 1 mol%) was then added and equilibration monitored by NMR spectroscopy. Equilibrium was usually reached within 30 min–24 h.

## Notes and references


1 (*a*) A. A. Ponomarev and I. A. Markushina, *Dokl. Akad. Nauk SSSR*, 1959, **126**, 99; (*b*) V. Dedek, P. Trska and R. Hofeditz, *Collect. Czech. Chem. Commun.*, 1968, **33**, 3565; (*c*) H. Fukuda, M. Takeda, Y. Sato and O. Mitsunobu, *Synthesis*, 1979, 368; (*d*) B. L. Feringa and R. J. Butselaar, *Tetrahedron Lett.*, 1982, **23**, 1941; (*e*) P. DeShong, R. E. Waltermire and H. L. Ammon, *J. Am. Chem. Soc.*, 1988, **110**, 1901; (*f*) F. Perron and K. F. Albizati, *J. Org. Chem.*, 1989, **54**, 2044; (*g*) P. J. Kocienski, Y. Fall and R. Whitby, *J. Chem. Soc., Perkin Trans. 1*, 1989, 841; (*h*) R. C. D. Brown and P. J. Kocienski, *Synlett*, 1994, 417; (*i*) P. J. Kocienski, R. C. D. Brown, A. Pommier, M. Procter and B. Schmidt, *J. Chem. Soc., Perkin Trans. 1*, 1998, 9; (*j*) S. Bartlett, R. Hodgson, J. M. Holland, M. Jones, C. Kilner, A. Nelson and S. Warriner, *Org. Biomol. Chem.*, 2003, **1**, 2393.
2 Y. Lefebvre, *Tetrahedron Lett.*, 1972, **13**, 133.
3 J. Robertson, P. Meo, J. W. P. Dallimore, B. M. Doyle and C. Hoarau, *Org. Lett.*, 2004, **6**, 3861.
4 J. Robertson, K. Stevens and S. Naud, *Synlett*, 2008, 2083.
5 J. Robertson, P. T. Chovatia, T. G. Fowler, J. M. Withey and D. J. Woollaston, *Org. Biomol. Chem.*, 2010, **8**, 226.
6 (*a*) Y. Nakamura, Y. Ohto, A. Murakami, S. Jiwajinda and H. Ohigashi, *J. Agric. Food Chem.*, 1998, **46**, 5031; (*b*) Y. Nakamura, N. Kawamoto, Y. Ohto, K. Torikai, A. Murakami and H. Ohigashi, *Cancer Lett.*, 1999, **140**, 37.
7 The authors in Ref. 6a state that their AL-1 is identical to that isolated by Bohlmann *et al*. from *Artemisia douglasiana* although in Bohlmann's paper the enol ether stereochemistry is represented as *Z*- rather than *E*-. F. Bohlmann, N. Ates, J. Jakupovic, R. M. King and H. Robinson, *Phytochemistry*, 1982, **21**, 2691.
8 E. L. Eliel, K. D. Hargrave, K. M. Pietrusiewicz and M. Manoharan, *J. Am. Chem. Soc.*, 1982, **104**, 3635.
9 For example: L. Ma, F. Ge, C.-P. Tang, C.-Q. Ke, X.-Q. Li, A. Althammer and Y. Ye, *Tetrahedron*, 2011, **67**, 3533.
10 B. Wallnofer, O. Hofer and H. Greger, *Phytochemistry*, 1989, **28**, 2687.
11 (*a*) The situation arises commonly in the total synthesis of natural products containing the 1,7-dioxaspiro[5.5]undecane core as articulated, for example, in: K. Mori, H. Watanabe, K. Yanagi and M. Minobe, *Tetrahedron*, 1985, **41**, 3663; (*b*) For more general discussion see: F. Perron and K. F. Albizati, *Chem. Rev.*, 1989, **89**, 1617.
12 M. G. Nonato, M. J. Garson, R. J. W. Truscott and J. A. Carver, *Phytochemistry*, 1993, **34**, 1159.
13 S. J. Hobson and R. Marquez, *Org. Biomol. Chem.*, 2006, **4**, 3808.
14 V. VanRheenan, R. C. Kelly and D. Y. Cha, *Tetrahedron Lett.*, 1976, **17**, 1973.
15 A. S. Pilcher and P. DeShong, *J. Org. Chem.*, 1993, **58**, 5130.
16 Crystal data for compound **6ax**: (colourless plate, 0.16 × 0.20 × 0.24 mm): $C_8H_{10}O_4$ $M_r$ = 170.16; orthorhombic, space group *Pbca*; *a* = 7.0008(2) Å, *b* = 9.0561(2) Å, *c* = 24.0388(5) Å, $\beta$ = 90°, *V* = 1524.06 (6) Å$^3$; *Z* = 8; $\mu$ = 0.120 mm$^{-1}$; $D_{calc}$ = 1.483 g cm$^{-3}$; Reflections collected = 3461; independent reflections = 1723 ($R_{int}$ = 0.024); *R* values [$I > 2\sigma(I)$, 1276 reflections]: $R_1$ = 0.0363, w$R_2$ = 0.0972; $\rho_{min/max}$ = −0.34/0.32 e Å$^{-3}$; CCDC 842957. Crystal data for compound **6eq**: (colourless block, 0.10 × 0.10 × 0.10 mm): $C_8H_{10}O4$ $M_r$ = 170.16; monoclinic, space group *P*21/*n*; *a* = 7.5000(3) Å, *b* = 6.0089(2) Å, *c* = 17.9334 (7) Å, $\beta$ = 94.8761(15)°, *V* = 805.28(5) Å$^3$; *Z* = 4; $\mu$ = 0.113 mm$^{-1}$; $D_{calc}$ = 1.403 g cm$^{-3}$; Reflections collected = 3347; independent reflections = 1822 ($R_{int}$ = 0.023); *R* values [$I > 2\sigma(I)$, 1492 reflections]: $R_1$ = 0.0484, w$R_2$ = 0.1581; $\rho_{min/max}$ = −0.27/0.34 e Å$^{-3}$; CCDC 842958.
17 (*a*) M. A. Ciufolini and C. Y. Wood, *Tetrahedron Lett.*, 1986, **27**, 5085; (*b*) M. A. Ciufolini, C. Y. W. Hermann, Q. Dong, T. Shimizu, S. Swaminathan and N. Xi, *Synlett*, 1998, 105.
18 W.-S. Zhou, Z.-H. Lu and Z.-M. Wang, *Tetrahedron*, 1993, **49**, 2641.
19 B. S. Nash, *Chemistry Part II thesis*, University of Oxford, 2007.
20 S. Macnaughton, *D.Phil. thesis*, University of Oxford, 2011.
21 A. D. Kosal and B. L. Ashfeld, *Org. Lett.*, 2010, **12**, 44.
22 *Cf.* C.-C. Li, S. Liang, X.-H. Zhang, Z.-X. Xie, J.-H. Chen, Y.-D. Wu and Z. Yang, *Org. Lett.*, 2005, **7**, 3709 in which hydrogenation of aldehyde **14** in the presence of Lindlar catalyst led to competitive reduction of the aldehyde, necessitating re-oxidation of the so-formed 2-(3-hydroxypropyl)furan.
23 K. Iwanami and T. Oriyama, *Chem. Lett.*, 2004, **33**, 1324.
24 Y. Mei, P. A. Bentley and J. Du, *Tetrahedron Lett.*, 2009, **50**, 4199.
25 T. Miura and Y. Masaki, *J. Chem. Soc., Perkin Trans. 1*, 1995, 2155.
26 H. Fujioka, A. Goto, K. Otake, O. Kubo, K. Yahata, Y. Sawama and T. Maegawa, *Chem. Commun.*, 2010, **46**, 3976.
27 (*a*) C. S. Foote, M. T. Wuesthoff, S. Wexler, I. G. Burstain, R. Denny, G. O. Schenck and K.-H. Schulte-Elte, *Tetrahedron*, 1967, **23**, 2583; (*b*) $Ac_2O$ work-up details: Y. Fall, B. Vidal, D. Alonso and G. Gómez, *Tetrahedron Lett.*, 2003, **44**, 4467.
28 D. Woollaston, *D.Phil. thesis*, University of Oxford, 2007.
29 *Cf.* E. Pavlakos, T. Georgiou, M. Tofi, T. Montagnon and G. Vassilikogiannakis, *Org. Lett.*, 2009, **11**, 4556.
30 Using $I_2$ in the presence of an excess of triethylamine (in $CD_3CN$) led to no isomerisation.
31 (*a*) S. Wolfe, *Acc. Chem. Res.*, 1972, **5**, 102; (*b*) K. B. Wiberg, M. A. Murcko, K. E. Laidig and P. J. MacDougall, *J. Phys. Chem.*, 1990, **94**, 6956; (*c*) A. J. Kirby and N. H. Williams, in *The Anomeric Effect and Associated Stereoelectronic Effects*, ed. G. R. J. Thatcher, American Chemical Society, ACS Symposium Series, Washington, DC, 1993, pp. 55–69.
32 C. Thibaudeau, J. Plavec, N. Garg, A. Papchikhin and J. Chattopadhyaya, *J. Am. Chem. Soc.*, 1994, **116**, 4038.
33 Spartan '10, Wavefunction, Inc., Irvine, CA; Y. Shao, L. F. Molnar, Y. Jung, J. Kussmann, C. Ochsenfeld, S. T. Brown, A. T. B. Gilbert, L. V. Slipchenko, S. V. Levchenko, D. P. O'Neill, R. A. DiStasio Jr., R.

C. Lochan, T. Wang, G. J. O. Beran, N. A. Besley, J. M. Herbert, C. Y. Lin, T. Van Voorhis, S. H. Chien, A. Sodt, R. P. Steele, V. A. Rassolov, P. E. Maslen, P. P. Korambath, R. D. Adamson, B. Austin, J. Baker, E. F. C. Byrd, H. Dachsel, R. J. Doerksen, A. Dreuw, B. D. Dunietz, A. D. Dutoi, T. R. Furlani, S. R. Gwaltney, A. Heyden, S. Hirata, C.-P. Hsu, G. Kedziora, R. Z. Khalliulin, P. Klunzinger, A. M. Lee, M. S. Lee, W. Z. Liang, I. Lotan, N. Nair, B. Peters, E. I. Proynov, P. A. Pieniazek, Y. M. Rhee, J. Ritchie, E. Rosta, C. D. Sherrill, A. C. Simmonett, J. E. Subotnik, H. L. Woodcock III, W. Zhang, A. T. Bell, A. K. Chakraborty, D. M. Chipman, F. J. Keil, A. Warshel, W. J. Hehre, H. F. Schaefer, J. Kong, A. I. Krylov, P. M. W. Gill and M. Head-Gordon, *Phys. Chem. Chem. Phys.*, 2006, **8**, 3172.

34 E. L. Eliel and S. H. Wilen, *Stereochemistry of Organic Compounds*, Wiley, 1994.

35 I. García, M. Pérez, P. Besada, G. Gómez and Y. Fall, *Tetrahedron Lett.*, 2008, **49**, 1344.

36 A. Okano, K. Tsukamoto, S. Kosaka, H. Maeda, S. Oishi, T. Tanaka, N. Fujii and H. Ohno, *Chem.–Eur. J.*, 2010, **16**, 8410.

37 C. Rogers and B. A. Keay, *Can. J. Chem.*, 1992, **70**, 2929.

38 (*a*) V. C. Arsenijevic and D. D. Stefanovic, *C. R. Chim.*, 1956, **243**, 964; (*b*) J. S. Ng, J. R. Behling, A. L. Campbell, D. Nguyen and B. Lipshutz, *Tetrahedron Lett.*, 1988, **29**, 3045.

39 Light source: 160 W daylight 'Solar Glo Sun Simulating' lamp (www.exo-terra.com).

