Chemical variation of natural product-like scaffolds: design and synthesis of spiroketal derivatives†

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The design and synthesis of spiroketal structures and their chemical modification, leading to a collection of new small molecules for biological evaluation as orally-bioavailable lead compounds is described. Both [6,5]- and [6,6]-membered ring spiroketal units have been prepared in a stereochemically-varying fashion starting from commercially available (*R*)- or (*S*)-glycidol, in ten, eleven and twelve linear steps, in overall yields of 45, 40 and 20%, respectively. Further elaboration according to Lipinski's guidelines has given a collection of structurally-diverse, new spiroketal derivatives in high yields and with high purity.

Introduction

The successful sequencing of the human genome[1] has improved our understanding of biological pathways, forming a basis for the development of new classes of therapeutics. As a consequence, the number of new biological targets for screening has increased noticeably along with advances in synthetic chemistry tools to map their function through the design of molecularly diverse compounds. Recent studies corroborate the intuitive link between structure and biological activity, where a high degree of molecular shape change within a collection of small molecules is shown to increase the collection's chances of hitting a broader range of biological targets.[2]

Natural products are an extraordinarily valuable source of structural variation.[3] They are often identified as lead compounds in drug discovery programmes, especially in the case of anti-tumour and anti-infective agents,[4] and play an important role in chemical biology studies.[5] Natural products are commonly employed as small molecule chemical probes for the modulation of protein–protein interactions, and as specific binding agents to enzymes and proteins.[6]

In the past decade, libraries built around natural product templates have been used to improve the selectivity, pharmacological properties or potency of the natural compound related to its original biological target.[7,8] For example, compounds based on natural tubulin inhibitors have afforded new anticancer drugs, while a collection of paclitaxel analogues has yielded four second-generation drug candidates which are in clinical trials.[9] Finally, derivatives based on curacin A have generated viable candidates in the anti-infectives therapeutic area.[9] Recently, a growing emphasis has been placed on the generation and use of natural product-like or natural product-derived compounds, for discovery screening processes. Compounds of this kind are screened for the purpose of identifying molecules with new biological activities, distinct from those of the original natural product, and to discover novel lead compounds to address known biological targets.[10,11] For example, Shair and co-workers have identified a new secretory pathway inhibitor of protein trafficking of the Golgi apparatus, using a library based on the core scaffold of galanthamine (an acetylcholinesterase inhibitor) in a broad phenotypic screen, whose activity is unrelated to that of the original natural product.[12]

An important feature regarding compounds based on natural products is that, as substructures or fragments of the parent molecules, they have been shown to retain significant biological activity.[13] Moreover, natural product-like molecules possess readily modifiable structures in terms of skeletal, stereochemical, and side-chain functionality. In fact, appendage variation is a central feature for improving or modulating the biological activity of a compound, and involves coupling of the core structure with a wide range of small chemical units. Stereochemical variation implies the generation of different derivative isomers, and can be achieved through stereoselective synthetic pathways. Skeletal variation results from a change in the atom connectivity or alteration of the shape/3D geometry of the template's core structure. Variation of the appendage, stereochemistry and skeleton of the natural product-inspired scaffold has the potential to change significantly its shape/geometry, resulting in a wide collection of structures that can be used for screening purposes.

The design of compound collections from natural product templates has already demonstrated that a specific, desirable biological property of a natural product can be improved on; even with rather small libraries prepared by simple functional group manipulation (*e.g.* natural product-like libraries of purines, curacin A, vancomycin).[14,15] These early successes motivated further work in skeletal modification of natural product-like compound collections. Armstrong[16] and Bartlett[17] generated widely-varying sets of natural product-like compounds. Schreiber and co-workers[18] later developed a strategy termed diversity-oriented synthesis (DOS). Also, other groups have proposed related synthetic strategies to prepare diverse molecules from a common scaffold.[19] However, aside from stereochemical and appendage variation, skeletal variation has yet to be achieved in an effective manner.

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† Electronic supplementary information (ESI) available: Full experimental details for preparation of the ynals **5** and **6** with characterisation data of each intermediate. Experimental details and characterisation data of compounds **32**, **34a**–**b**, and **46**–**48**. See DOI: 10.1039/b603015g

Spiroketals, in particular 1,6-dioxaspiro[5.5]decanes and 1,7-dioxaspiro[4.5]undecanes, are molecular frameworks found in a variety of complex natural products that possess a wide range of biological activities.[20] The spongistatin family, for example, are tubulin polymerisation inhibitors;[21] okadaic acid is a protein phosphatase inhibitor;[22] tautomycin and integramycin are HIV-1 protease inhibitors;[23] routiennocin is an antibiotic;[24] reveromycins A and B are epidermal growth factor inhibitors;[25] purpuromycin and rubromacyn are human telomerase inhibitors;[26] and bistramide A is a cell proliferation suppressor,[27] amongst many others.[20]

Our group has been interested in spiroketals for a number of years developing several useful methods for preparing the spiroketal framework associated with many complex natural products.[28] Furthermore, in 1995 we showed how it was possible to use a [6,6]-*bis*-anomerically stabilised spiroketal as a rigid scaffold to replace the *N*-acetylglucosamine–galactose disaccharide in a sialyl Lewis X mimetic (Fig. 1a).[29] We later developed a polymer-supported synthetic route to spiroketal units (Fig. 1b).[30] Other groups have subsequently recognised the opportunity of using these concepts for the generation of spiroketal libraries.[31]

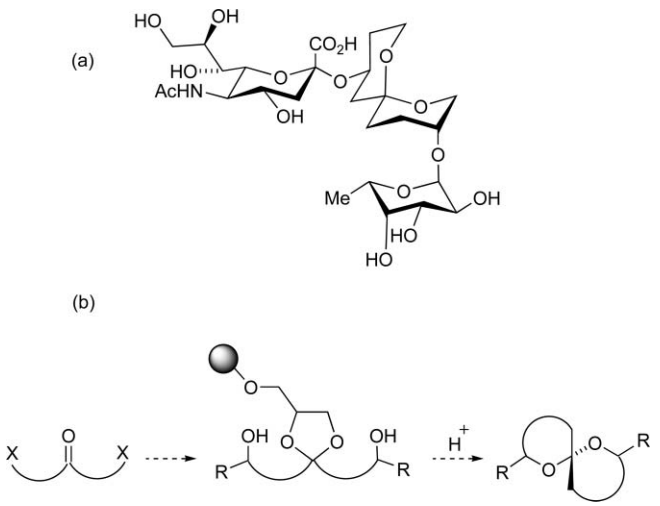


Fig. 1 (a) Spiroketal framework as novel scaffold; (b) a solid-phase synthesis approach to spiroketals.

Further developments have since been reported which clearly demonstrate that promising pharmacological effects (such as phosphatase inhibition, modulation of the tubulin cytoskeleton of breast cancer cells, and cytotoxicity against tumor cell lines) can be achieved through the construction and screening of simple spiroketals (Fig. 2).[32]

Here, we report the design, synthesis, and elaboration of spiroketal units leading to a collection of small molecules that could be used as biological probes in phenotopic assays. Our goal was to generate a wide range of spiroketal derivatives suitable for biological screening towards orally bio-available lead compounds, closely matching the Lipinski rule of five.[33]

Results and discussion

We began the project by focusing on spiroketals with at least three sites amenable to appendage change. Furthermore, we recognised the potential shown by the spiroketal molecular framework to undergo stereochemical and skeletal variation. Hypothetically, the spiroketalisation event can deliver the spiroketal structural unit in four different arrangements (Scheme 1)[34] with the anomeric effect, steric interactions, intramolecular hydrogen bonding and other chelation effects governing their relative configuration and

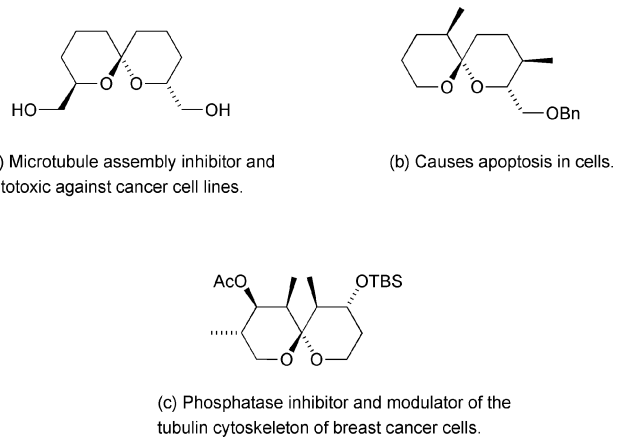
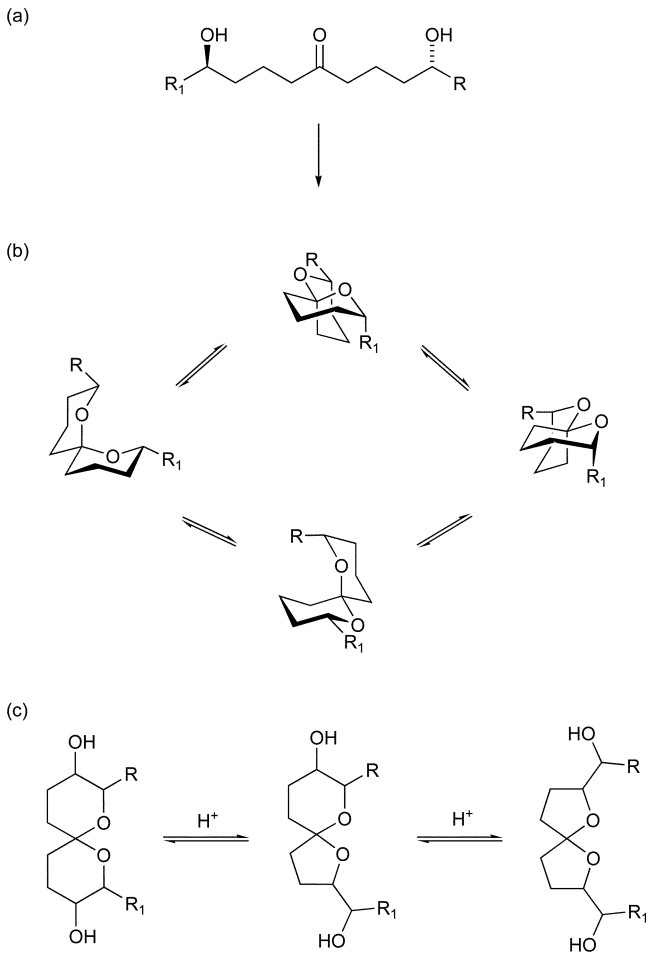


Fig. 2 Unnatural spiroketal derivatives and their associated biological activities.



Scheme 1 (a) Spiroketalisation followed by (b) epimerisation at the spiroketal carbon: sources of stereochemical/configurational variation inherent to the spiroketal molecular framework; (c) acid-catalysed interconversion of [6,6]-, [6,5]- and [5,5]-spiroketal systems as a source of skeletal variation.

stabilities.[35] Epimerisation at the spiroketal carbon can also be considered a source of stereochemical and configurational change by interconverting between isomers (Scheme 1b). Furthermore, the acid-catalysed interconversion of [6,6]-, [6,5]- and [5,5]-spiroketal systems should allow for further structural interconversions (Scheme 1c).

Our initial synthetic efforts focused on the spiroketal scaffolds **1** to **4**, which possess a flexible ketal hinge point and a latent, electrophilic ring-ketone, beta to the spiro-carbon. The spiroketals **1** and **3** contain one benzylic ether and one free primary alcohol (Fig. 3), whereas structure **2** combines a *p*-bromo-substituted benzylic ether with a primary alcohol. The scaffold **4** substitutes the free primary alcohol with a methyl acetylene group, retaining the benzyl-protected alcohol. In principle, **3** also allows for the interconversion of [6,5]- and [6,6]-spiroketal units as a source of skeletal change.

The plan for the preparation of the spiroketals **1** to **4** was based on the spiroketalisation of a *β*-keto-1,3-dithiane precursor (Fig. 3), which could be generated from the ynone through a double-conjugate addition of the requisite dithiol using a method previously developed by our group.[36] The ynone could be derived from the addition of an appropriate Grignard reagent into the ynal, followed by Dess–Martin periodinane oxidation and elaboration of the terminal alkene. Where dihydroxylation would lead ultimately to the spiroketals **1** to **3**, alternatively, epoxidation and nucleophilic addition of the acetylene group could lead to the spiroketal **4**. The ynals would be readily synthesised using reaction sequences established previously, starting from commercially available (*R*)- or (*S*)-glycidol.

We envisaged the use of the ynals as flexible chiral building blocks towards the generation of spiroketals through the addition of nucleophiles at the aldehyde functionality. Furthermore, as shown in previous work from our group,[37] we anticipated that the presence of the dithiane group would influence the isomeric ratio of the resulting spiroketals, slowing the equilibration between spiroketal isomers through the inductive effect of the two sulfur atoms and thus destabilising the interaction of the sulfur lone pair with those on the oxygen of the C–O.

As starting materials for the spiroketals, the ynals **5** and **6** were prepared efficiently on a multigram scale (40–50 g) starting from the enantiopure (*R*)-glycidol (Scheme 2).

In general terms (Scheme 2) the first synthetic step involves the protection of the primary hydroxyl group of glycidol through formation of the benzylic ether derivative.[38] This is followed by ring opening of the epoxide with TMS-protected acetylide and silyl-deprotection, which gives the (*S*)-alcohol in a straightforward

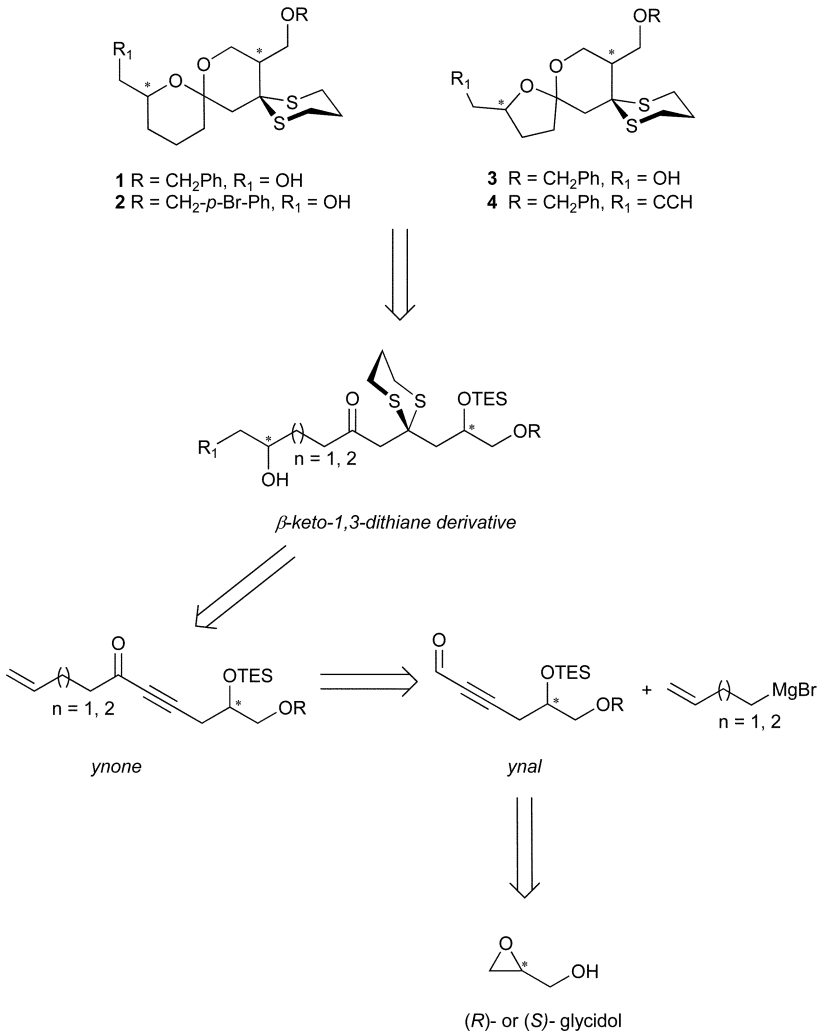
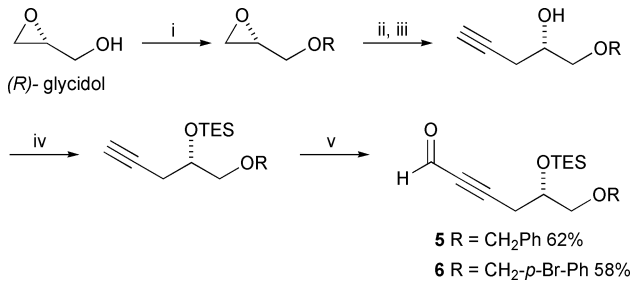


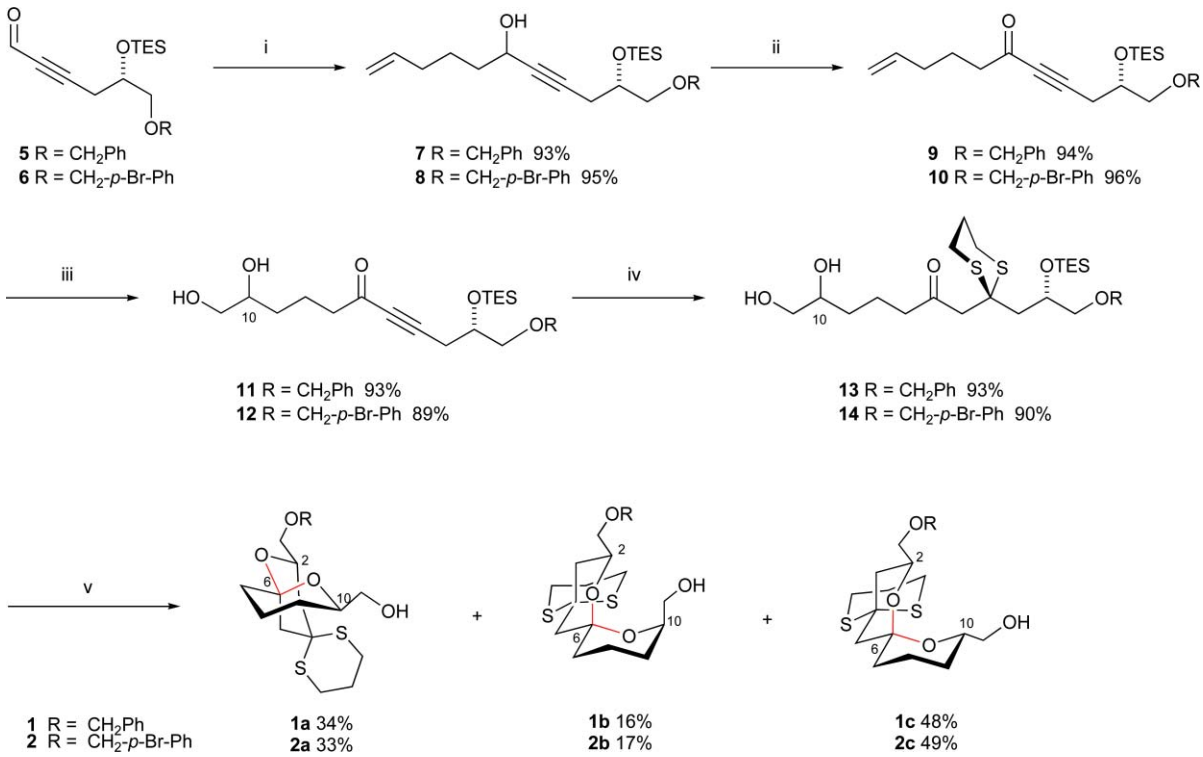
Fig. 3 Spiroketal units and their retrosynthetic analysis.



Scheme 2 Reagents and conditions: (i) NaH, $PhCH_2Br$ or *p*-$BrPhCH_2Br$, TBAI, DMF, 0 °C, 18 h; (ii) TMSCCH, *n*-BuLi, −78 °C, THF, BF_3·THF, 18 h; (iii) K_2CO_3, MeOH, rt, 2 h; (iv) TESCl, imid., THF, rt, 18 h; (v) *n*-BuLi, −78 °C, THF, 30 min then *N*-formylmorpholine, rt, 18 h.

manner. Further silyl-protection and carbonylation of the resultant terminal acetylene affords (*S*)-ynals **5** and **6** in a 62 and 58% overall yield, respectively, with 99% ee over five linear steps. Starting from (*S*)-glycidol, the enantiomer of **5** is also synthesised in the same yield following a similar procedure.

Initially, ynals **5** and **6** were used as starting materials for the synthesis of the spiroketal scaffolds **1** and **2**, respectively. The route involved 1,2-carbonyl addition of the Grignard reagent 4-pentenyl magnesium bromide to ynals **5** or **6**, followed by Dess–Martin periodinane oxidation of the alcohol **7** or **8** to form ynones **9** or **10** (Scheme 3). Dihydroxylation of the terminal olefins with osmium tetroxide was followed by the smooth conversion of the resultant diols **11** and **12** into *β*-keto-1,3-dithiane derivatives **13** and **14** respectively in excellent yields. These precursors were amenable to acid-catalysed spiroketalisation with dilute, aqueous perchloric acid (under thermodynamic conditions) to form spiroketals **1** and **2** in near quantitative yields. For each of the scaffolds, a diastereomeric mixture of the precursor resulted in the formation of three configurationally different spiroketal isomers **1a**–**c** and **2a**–**c**, respectively, with a ratio of 2 : 1 : 3. In particular, the 10*S*-diastereomeric precursors would lead, exclusively, to isomers **1c** and **2c**, whereas the 10*R*-diastereomers would yield a 2 : 1 mixture of **1a**,**2a** and **1b**,**2b**. The isomers **1a** and **2a** exhibited an 'axial-equatorial' arrangement of the acetal oxygen atoms (Fig. 4, C6–O bond in green), resulting in only one stabilising anomeric effect in combination with diequatorial substituents at C2 and C10 (Scheme 3). In contrast, isomers **1b** and **2b** show an 'axial–axial' arrangement with a favourable *bis*-anomeric effect (Fig. 4, C6–O bonds in green), but with high-energy 1,3-diaxial interactions (Scheme 3, substituent at C10). Finally, the most abundant isomers **1c** and **2c** present the most favourable thermodynamic configuration with a double anomeric contribution (Fig. 4, C6–O bonds in green) and diequatorial substituents. Each of the three spiroketal isomers of **1** and **2** were easily isolated by column chromatography. It was possible to determine the absolute configuration of spiroketals **1a**, **1c** and **2c**, all three of which were obtained as white, crystalline solids, by X-ray crystallography experiments (Fig. 5). Looking at the space-filling, 3D impression of isomers **1a** and **1c** (Fig. 5b), the clear differences in molecular shape between the two spiroketals give a strong indication of how such differences could translate into molecular diversity within a collection of small molecule derivatives. The absolute configuration of **1b** was confirmed by extensive spectroscopic studies, most noticeably by analysis of nOe enhancements. NOESY experiments also unequivocally confirmed the configuration at the C6 anomeric centre in spiroketals **2a** and **2b** as shown.



Scheme 3 Reagents and conditions: (i) $CH_2{=}CH(CH_2)_3MgBr$, Et_2O, 30 °C, 4 h; (ii) Dess–Martin periodinane, DCM, rt, 2 h; (iii) OsO_4, NMO, H_2O–^{t}BuOH, 0 °C, 18 h; (iv) $HS(CH_2)_3SH$, NaOMe, MeOH–DCM, −10 °C, 18 h; (v) $HClO_4$ 10% aq., MeCN–DCM, 0 °C, 30 min.

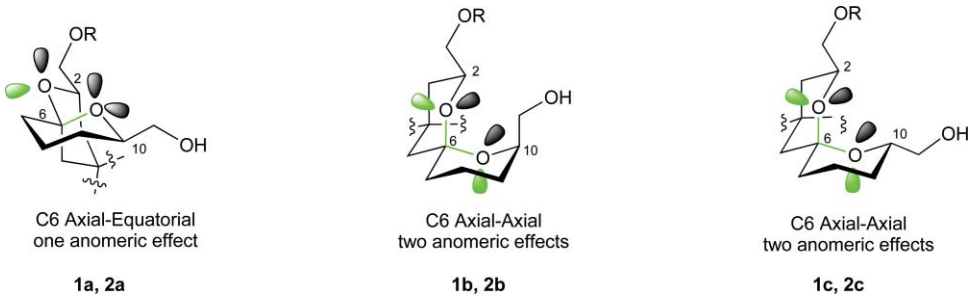


Fig. 4 The anomeric effect in [6,6]-spiroketal units **1a**–**c** and **2a**–**c**.

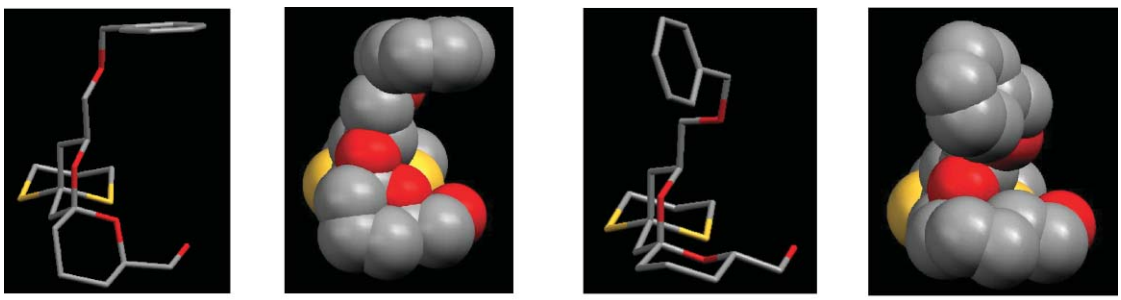
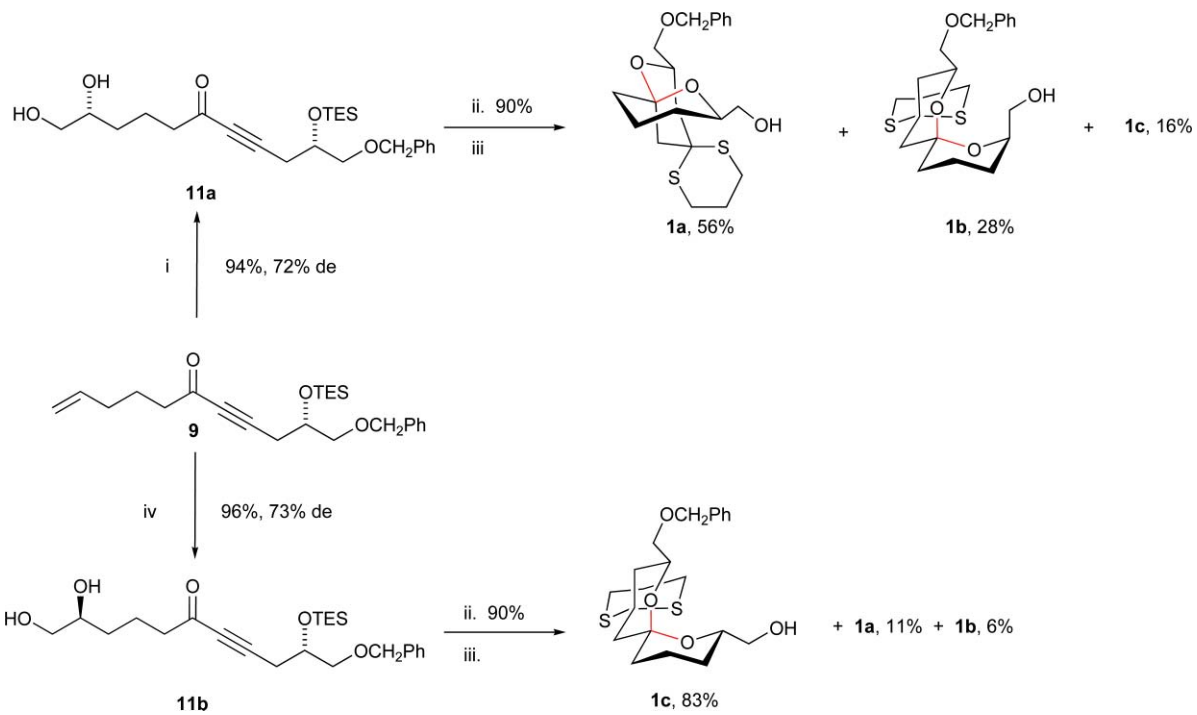


Fig. 5 3D impressions of the spiroketals **1a** and **1c** determined by X-ray crystallography experiments.

This synthetic approach achieved the formation of the [6,6]-membered ring spiroketal units through a series of high yielding and straightforward transformations, with overall yields of 74 and 72% for **1** and **2** starting from ynals **5** and **6**, respectively, in gram quantities. The spiroketalisation event was shown as a key step to incorporating stereochemical change into the spiroketal scaffold with the formation of the three isomers.

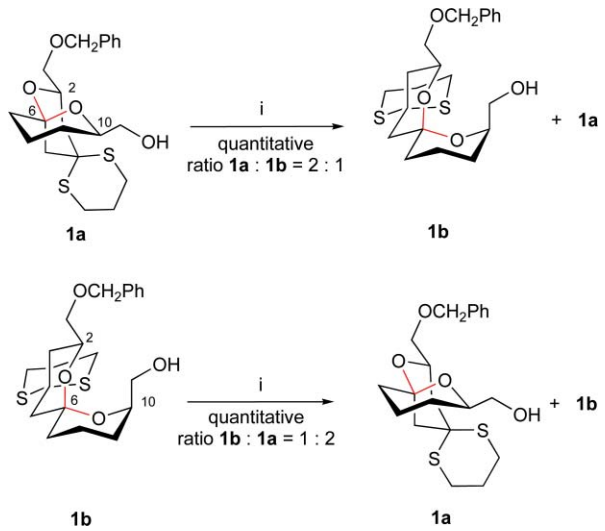
Further studies aimed at understanding the stereochemical outcome of the spiroketal ring formation were also carried out in the form of asymmetric dihydroxylation of **11** to furnish either of the diastereomeric products. Sharpless asymmetric dihydroxylation using AD-mix-α and β furnished the diastereomerically-enriched diols **11a** and **b** with 72 and 73% de, respectively (Scheme 4). Formation of the dithiane derivative occurred in 90%



Scheme 4 Reagents and conditions: (i) AD-mix-β, H_2O–^{t}BuOH, 0 °C, 18 h; (iv) AD-mix-α, H_2O–^{t}BuOH, 0 °C, 18 h; (ii) $HS(CH_2)_3SH$, NaOMe, MeOH–DCM, −10 °C, 18 h; (iii) $HClO_4$ 10% aq., MeCN–DCM, 0 °C, 30 min.

yield on both diastereoisomers and the spiroketalisation events proceeded in a quantitative manner: it also confirmed that the 10*R*-diastereomer **11a** provides a 2 : 1 mixture of **1a** and **1b** (Scheme 4) and the 10*S*-diastereomeric precursor **11b** provides, exclusively, isomer **1c**. The spiroketalisation was therefore performed across a range of temperatures (−30 °C to rt) with no observable change in the configurational outcome.

To investigate the use of stereochemical change within a collection of spiroketal derivatives, we initially looked at the ability of **1a**–**c** and **2a**–**c** to epimerise at the spiroketal carbon C6 under acidic conditions. We found that treating isomers **1a** and **1b** with dilute, aqueous perchloric acid (under thermodynamic conditions), led to successful epimerisation of the starting material as a 2 : 1 mixture of **1a** : **1b** (Scheme 5).



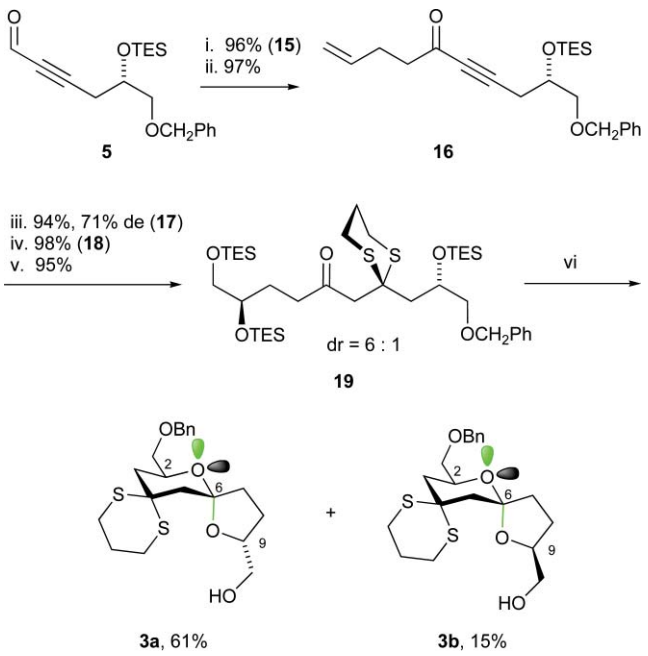
Scheme 5 Reagents and conditions: (i) $HClO_4$ 10% aq., MeCN–DCM, 0 °C, 1 h.

The equilibration was also performed within a range of temperatures (−30 to 30 °C) and reaction times (10 min to 24 h) giving the same **1a** : **1b** isomeric ratio.

Epimerisation at the spiroketal carbon was also performed on spiroketals **2a** and **2b** providing the same outcome. These initial results show the propensity of the compounds derived from [6,6]-membered ring spiroketal scaffolds to undergo stereochemical change using simple and mild reaction conditions.

The preparation of the [6,5]-membered ring spiroketals **3** and **4** (Scheme 6) was achieved following a similar route to the [6,6]-membered ring compounds. It is important to underline that scaffold **3**, due to the presence of the hydroxyl group as the substituent at C9, is set up for skeletal change by conversion into the [6,6]-membered ring spiroketal. In the case of **4**, the presence of the terminal alkyne allows for 1,3-dipolar addition of azide derivatives as an example of click-chemistry.[39]

The synthesis of the common intermediate **16** came as a result of the addition of 4-butenyl magnesium bromide to the ynal **5**, followed by oxidation to give the ynone **16** in 93% yield over two steps. The preparation of the spiroketal **3** involved the formation of the 1,2-diol, which was performed in an asymmetric fashion by Sharpless dihydroxylation with AD-mix-β catalyst in 94% yield and 71% de. The diastereomerically-enriched mixture was subjected to protection of the vicinal diol allowing for the synthesis of the β-keto-1,3-dithiane **19** in 95% yield at rt. The spiroketalisation of the diastereomerically-enriched mixture of β-keto-1,3-dithiane derivative proceeded under the same conditions described above, leading to the formation of the [6,5]-membered ring spiroketals **3a** and **3b** in yields of 65 and 15%, respectively. The two [6,5]-membered ring spiroketals have been isolated enantiomerically pure and their structures determined by NOESY experiments. In the case of both isomers the C6–O bond of the five-membered ring has a pseudo-axial orientation with respect to the six-membered ring, maximising the stabilising anomeric contribution (Scheme 6, C6–O bond in green). The presence of a third spiroketal isomer was detected by ^{1}H and ^{13}C NMR analysis of the crude reaction mixture, but attempts to isolate the compound resulted in its degradation. Evaluation of alternative separation techniques to obtain this isomer are under investigation. The synthesis of spiroketal **4** (Scheme 7) proceeded by epoxidation of the terminal alkene of ketone **16**, in a racemic fashion, to give in 75% yield the oxirane derivative **20**, and this was followed by ring opening with TMS–acetylide in an unoptimised 50% yield. TES-protection of the resulting secondary alcohol and subsequent 1,4-conjugate addition of 1,3-propandithiol afforded the spiroketal precursor **23** in 45% over three steps. Spiroketalisation afforded **4** in quantitative yield as a mixture of two isomers **4a** and **4b**, in a 1 : 1 ratio.

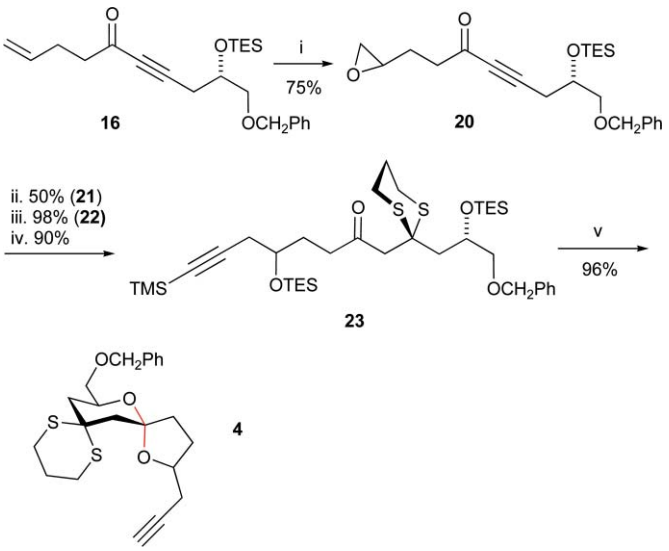


Scheme 6 Reagents and conditions: (i) $CH_2{=}CH(CH_2)_2MgBr$, Et_2O, 30 °C, 4 h; (ii) Dess–Martin periodinane, DCM, rt, 2 h; (iii) AD-mix-β, H_2O–$^{t}BuOH$, 0 °C, 18 h; (iv) TESOTf, py, MeOH–DCM, 0 °C, 30 min; (v) $HS(CH_2)_3SH$, NaOMe, MeOH–DCM, rt, 18 h; (vi) $HClO_4$ 10% aq., MeCN–DCM, 0 °C, 30 min.

In each case NMR studies prove that the six-membered ring bears the oxygen substituent of the five-membered ring axially.

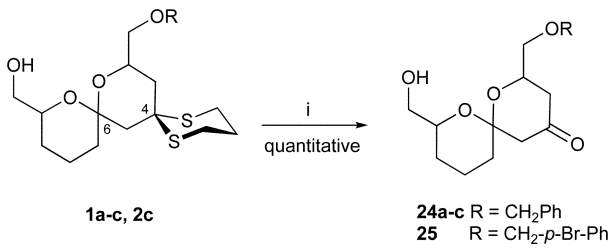
Synthesis of a collection of new spiroketal derivatives: elaboration of the spiroketal units

Dithiane removal to unveil the ketone functionality at carbon C4 was the first synthetic modification performed on the spiroketal



Scheme 7 Reagents and conditions: (i) *m*CPBA, NaH_2PO_4, DCM, rt, 13 h; (ii) TMSCCH, *n*-BuLi, −78 °C, BF_3·THF, rt, 30 min (iii) TESCl, imid., rt, 2 h; (iv) $HS(CH_2)_3SH$, NaOMe, MeOH–DCM, rt, 18 h; (v) $HClO_4$ 10% aq., MeCN–DCM, 0 °C, 30 min.

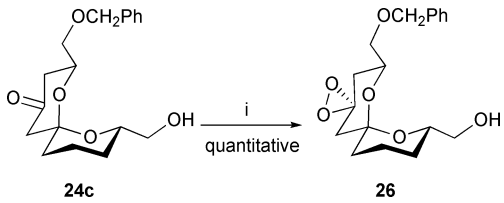
scaffolds **1a**–**c** and **2c**. This was achieved using a mild, chemoselective method[40] to give ketones **24a**–**c** and **25** in high yield, with no undesirable oxidation of the primary alcohol and no epimerisation at spiroketal carbon C6 (Scheme 8).



Scheme 8 Reagents and conditions: (i) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, MeOH–H_2O, rt, 45 min.

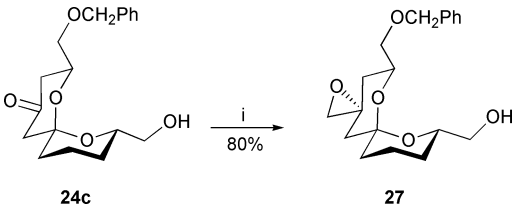
The carbonyl group at carbon C4 is present in a number of natural spiroketals.[20] In its own right this group could be useful for biological evaluation if not ideal in terms of drug development. However it was our intention to explore the reactivity at the ketone centre in an effort to prepare analogues at C4. The literature transformations on similar spiroketal substrates involve stereoselective reduction to the alcohol, or the addition of Grignard reagents (*i.e.* MeMgBr).[41] In our case, reductive amination of **24c** using methylamine, 2-pyridyl-methylamine and 3-morpholin-4-yl-propylamine under a variety of different conditions failed. Efforts to convert **24c** to the corresponding endocyclic ester to form a [7,6]-membered ring spiroketal, under the standard Baeyer–Villiger oxidative conditions (*m*CPBA, pH 7.6 buffer at rt) were also unsuccessful; only starting material was recovered.

Interestingly, treatment with a masked form of hydrogen peroxide,[42] in the presence of different Lewis acid catalysts (Scheme 9), including BF_3·Et_2O, $SnCl_4$ and $(CH_3)_3SiOTf$ afforded dioxirane **26**. The use of **26** as a potential chiral epoxidation catalyst is currently under investigation. Finally, under Corey–



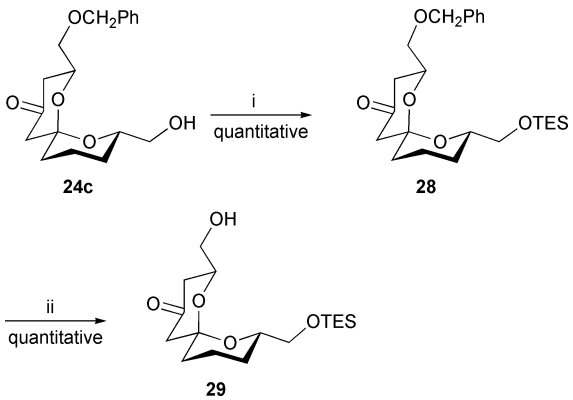
Scheme 9 Reagents and conditions: (i) $(CH_3)_3SiOOSi(CH_3)_3$, BF_3·Et_2O or $SnCl_4$ or $(CH_3)_3SiOTf$, DCM, −40 to −20 °C, 12 h.

Chaykovsky homologative epoxidation conditions (Scheme 10) the preferential formation of one diastereomeric epoxide (**27**) was successfully achieved in good yield. The absolute configuration of the epoxide was determined by NMR, in particular by NOESY experiments. We believe that given its specific reactivity, the C4 ketone may convey interesting properties to the compounds in terms of their activity during bioassay screening.



Scheme 10 Reagents and conditions: (i) $Me_3S(O)^+I^-$, KO^{t}Bu, DMSO, rt, 24 h.

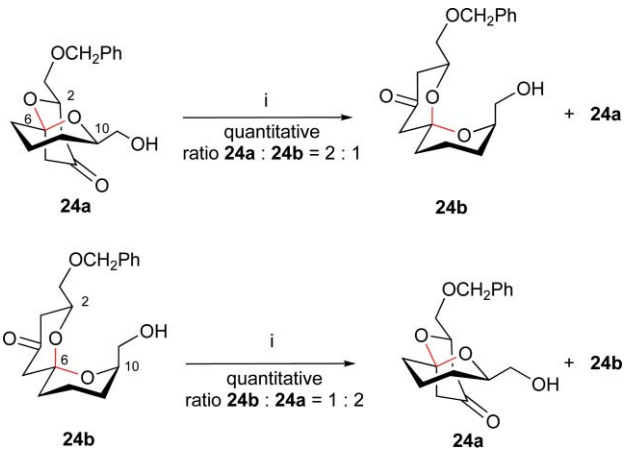
Starting from **24c**, silyl-protection (**28**) followed by debenzylation (**29**) of the resulting silyloxyethers allowed for efficient differentiation of the two primary hydroxyl groups for further elaboration (Scheme 11).



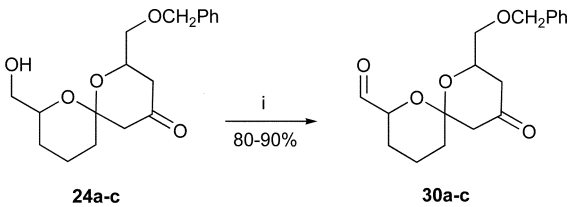
Scheme 11 Reagents and conditions: (i) TESOTf, 2,6-lutidine, DCM, −78 to 0 °C, 5 min; (ii) $Pd(OH)_2$, $CaCO_3$, EtOH, 70 °C, 18 h.

Spiroketal derivatives **24a** and **b** were also shown to be capable of epimerising at carbon C6 under the same mild conditions used for compounds **1a** and **b** (Scheme 12). With the aim of exploring the chemistry of the substituents of the spiroketal ring, the next step was the oxidation of the primary hydroxyl group at C11 of **24a**–**c** to the corresponding aldheydes **30a**–**c**. This transformation was achieved using Dess–Martin periodinane (Scheme 13).

The synthesis of an aldehyde of type **30** (with the carbonyl alpha to a spiroketal system) has very little literature precedent.[43] We successfully managed to isolate the three isomers in good

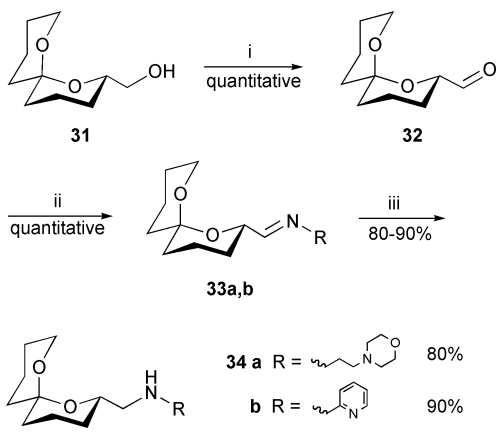


Scheme 12 Reagents and conditions: (i) $HClO_4$ 10% aq., MeCN–DCM, 0 °C, 1 h.



Scheme 13 Reagents and conditions: (i) Dess–Martin periodinane, DCM, rt, 2 h.

yields using specific isolation conditions. With a reliable route to **30**, the target was to install medicinally and synthetically interesting amines *via* regioselective reductive amination at the highly reactive α-alkoxy aldehyde. Initial investigations involved optimisation of the reaction conditions on a simplified spiroketal **31** synthesised previously by our group.[28] Oxidation to aldehyde **32** was performed following the same procedure used for **30**, and gave only the most thermodynamically stable isomer. Condensation with an appropriate primary amine afforded secondary amines **34a**–**b**, after polymer-supported borohydride reduction[44] of the isolable imine intermediates **33a**–**b** (Scheme 14). The reduction of the imine **33a** was also succesfully achieved by catalytic hydrogenation in a continuous flow-reactor.[45]

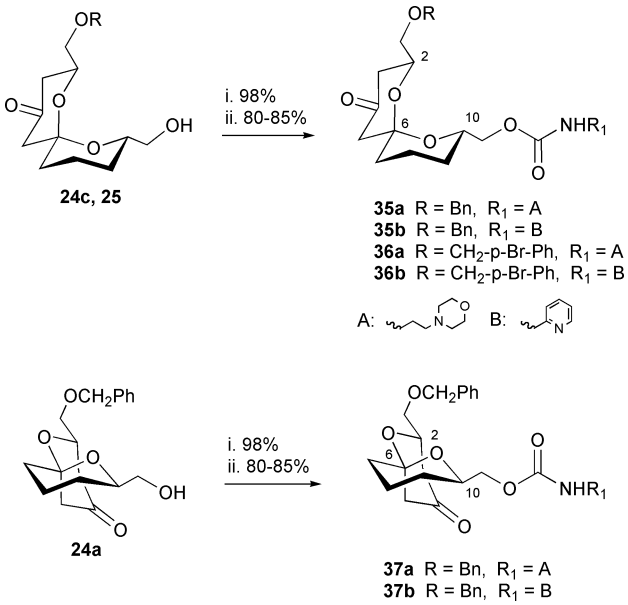


Scheme 14 Reagents and conditions: (i) Dess–Martin periodinane, DCM, rt, 2 h; (ii) RNH_2, EtOH, rt; (iii) PS–borohydride, THF, rt, 18 h.

The chemical variation of the spiroketal scaffolds took into consideration the synthesis of spiroketal-derived small molecules as potential lead compounds.

To this end, elaboration of the alcohol functional group at C11 was performed, leading to a collection of potential orally bioavailable lead compounds.[46]

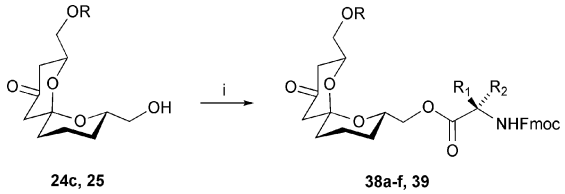
A rapid and clean synthesis of activated carbonate esters of the spiroketal isomers starting from **24a**, **24c**, and **25** (Scheme 15) enabled straightforward access to the *N*-substituted carbamate derivatives **35a**–**b**, **36a**–**b** and **37a**–**b** in good yields. In formation of both the carbonate and the carbamate derivatives, the desired products were isolated enantiomerically pure.



Scheme 15 Reagents and conditions: (i) *p*-nitrophenyl chloroformate, py, THF, rt, 20 min (ii) RNH_2, DMF, rt, 10 min.

The primary hydroxyl group of spiroketals **24** and **25** were then coupled with the carboxylic acid of a series of natural and unnatural *N*-Fmoc-protected α-amino acids. First, the coupling reaction was performed on the double anomeric stabilised isomers **24c** and **25**, as shown in Table 1. A reaction condition screen gave the desired products using *O*-(7-azabenzotriazole-1-yl)-*N*,*N*,*N*′*N*′-tetramethyluronium hexafluorophosphate (HATU) as coupling reagent, 1-hydroxy-7-azabenzotriazole (HOAt) as additive and diisopropylethyl amine (DIEA) as base with the reaction time between 18–48 h. Furthermore, under the selected conditions, all the spiroketal derivatives (Table 1) were isolated enantiomerically pure. Condensation of the primary alcohol with the carboxylic acid of glycine (**38a**, **39**), (*S*)-phenylalanine (**38c**) and (*S*)-2-furyl-glycine (**38e**) gave the desired products in 70–94% yields. Interestingly, phenyl and 2-furyl-glycine coupled in higher yields than alanine, which, despite the increasing steric demand (R_2 = H < CH_3 < CH_2–phenyl-2-furyl), suggests an increase in reactivity due to favourable π-stacking interactions with the spiroketal C2 methyloxybenzylic group. Compounds **38c** and **38f** were isolated in 50 and 44% yield, respectively, by coupling **1c** with (*S*)-alanine and (*S*)-α-cyclobutane glycine. Compound **38d** was formed in a 26% yield as a result of the condensation of the primary alcohol with the carboxylic acid group of (*S*)-α-allyl-glycine. In

Table 1 Coupling reactions of **24c** and **25** with *N*-Fmoc-protected α-amino acids

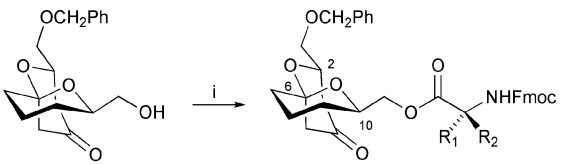


24c, 25 **38a-f, 39**

Entry	R	R_1	R_2	Yield (%)[a]	
1	CH_2Ph	H	H	**38a**	93
2	CH_2Ph	H	CH_2Ph	**38b**	70
3	CH_2Ph	H	CH_3	**38c**	50
4	CH_2Ph	H	$CH_2CH{=}CH_2$	**38d**	26
5	CH_2Ph	H	2-Furyl	**38e**	94
6	CH_2Ph	$R_1{=}R_2$	$-(CH_2)_3-$	**38f**	44
7	CH_2–*p*-Br–Ph	H	H	**39**	92

[a] All compounds have been isolated with 98% de. Reagents and conditions: (i) *N*-Fmoc-protected-α-amino acid, HATU, HOAt, DIEA, DMF, rt, 18–48 h.

Table 2 Coupling reactions of **24a** with *N*-Fmoc-protected-α-amino acids

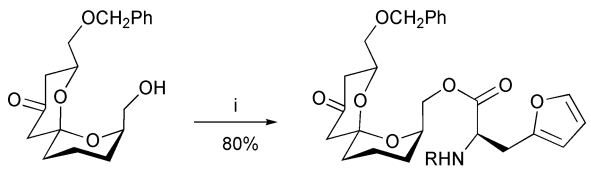


24a **40a-c**

Entry	R_1	R_2	Yield (%)[a]	
1	H	H	**40a**	90
2	H	CH_2Ph	**40b**	65
3	H	2-Furyl	**40c**	95

[a] All compounds have been isolated with 98% de. Reagents and conditions: (i) *N*-Fmoc-protected-α-amino acids, HATU, HOAt, DIEA, DMF, rt, 18–48 h.

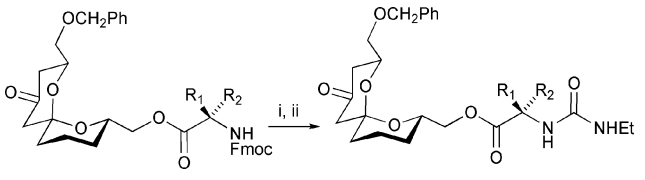
some cases the coupling reactions were not high yielding, but our focus was to synthesise derivatives using a range of diverse α-amino acids of relevance as medicinal chemistry building blocks. Using the same reaction conditions, the coupling of the primary alcohol of spiroketal isomers **24a** (Table 2) and **24b** (Scheme 16) was performed. The compounds **40b–c** and **41** were prepared in good to excellent yields and were also isolated enantiomerically pure. The next synthetic step was the elaboration of the terminal *N*-Fmoc α-amino group to achieve spiroketal derivatives suitable for biological screening.



24b **41**, R = Fmoc, 98% de

Scheme 16 Reagents and conditions: (i) *N*-Fmoc-protected-(*S*)-2-furyl-α-glycine, HATU, HOAt, DIEA, DMF, rt, 18 h.

We therefore prepared a number of selected spiroketal ester derivatives of the three different isomers. Fmoc-deblocking and partial scavenging of the fullvene by-product was performed with polymer-supported piperazine[47] using microwave heating at 120 °C for 30 min. This procedure afforded complete *N*-Fmoc deprotection and avoided the need for a purification step. Instead, direct addition of ethyl isocyanate to the crude amine mixture readily provided urea derivatives **42a–e** (Scheme 17) and **44b** (Scheme 19) in high yields, as a single diastereoisomer. However, epimerisation at the C6 centre was observed in the synthesis of urea derivatives **43a–b** and these were isolated as a mixture with isomers **44a–b** in a *ca.* 3 : 2 product ratio (Scheme 18).



38b-f

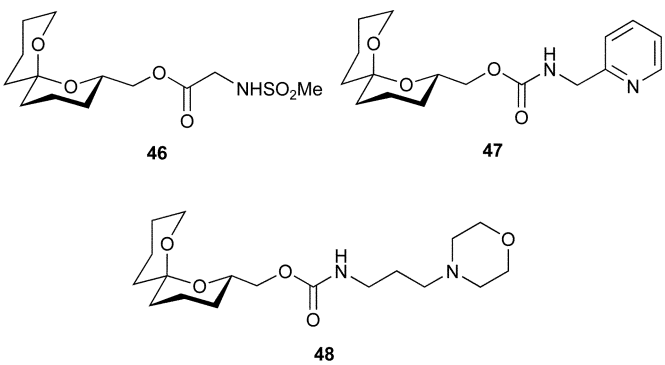
quantitative yield over two steps

42a R_1 = H, R_2 = CH_3,
42b R_1 = H, R_2 = CH_2Ph
42c R_1 = H, R_2 = $CH_2CH{=}CH_2$
42d R_1 = H, R_2 = 2-furyl
42e R_1 = R_2 = $-(CH_2)_3-$

Scheme 17 Reagents and conditions: (i) PS–piperazine, DCM, MW, 120 °C, 30 min; (ii) EtNCO, DCM, rt, 30 min.

Furthermore, mesylation of the crude deprotected primary amines starting from compounds **38a–c** and **38f** provided access to a series of sulfonamide derivatives **45a–d** in quantitative yields (Scheme 20).

As a comparison in terms of potential biological activity, the derivatives **46–48** (Fig. 6) were also prepared quantitatively from the simple spiroketal **31**, using the approaches already described.

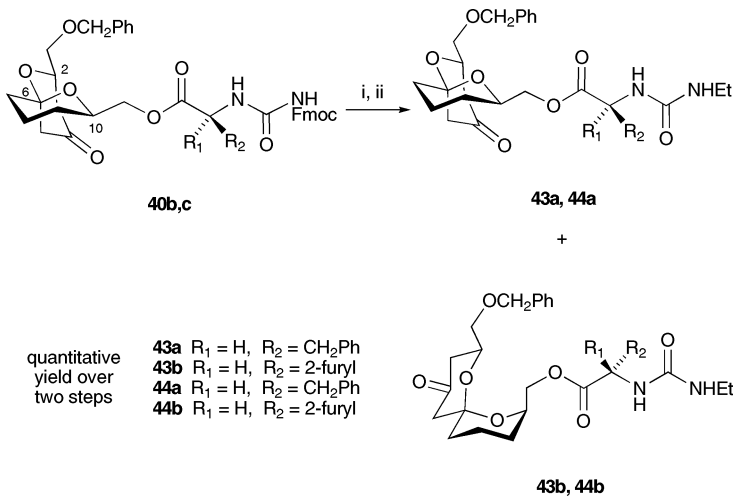


46 **47**

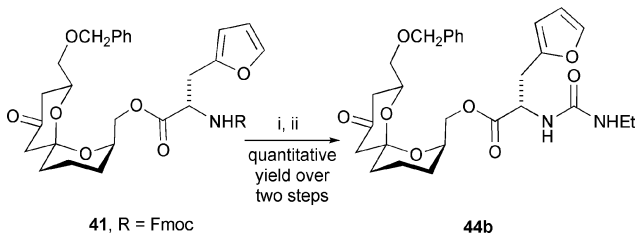
48

Fig. 6 Simple spiroketal derivatives.

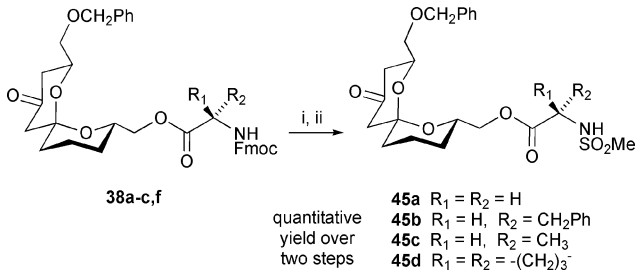
It is important to highlight that the complete series of carbamate, urea and sulfonamide derivatives closely match the Lipinski rule of five.[46] Moreover, the primary alcohol of compound **24c** was oxidised to the corresponding acid as an intermediate for amide coupling studies. By way of illustration, the amide derivative **49** was prepared in an excellent 90% yield over three steps (Scheme 21). Finally, starting from spiroketal **24c**, triazole derivative **51** was obtained in quantitative yield *via* formation of the azide precursor and addition of the requisite alkyne in a click-chemistry fashion[48] (Scheme 22). Both routes to compounds **49** and **51** represent viable procedures for the synthesis of a series of amide and triazole derivatives.



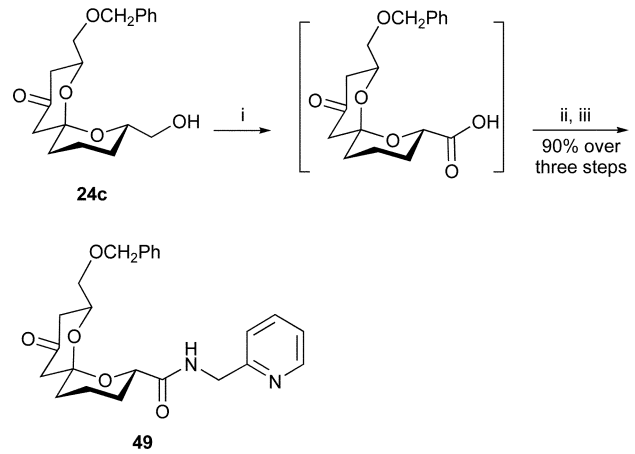
Scheme 18 Reagents and conditions: (i) PS–piperazine, DCM, MW, 120 °C, 30 min; (ii) EtNCO, DCM, rt, 30 min.



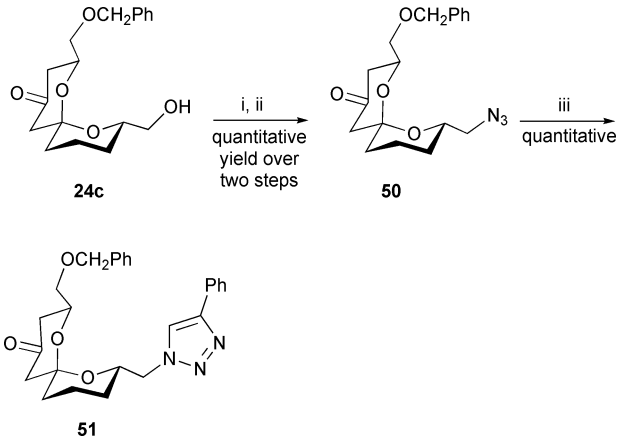
Scheme 19 Reagents and conditions: (i) PS–piperazine, DCM, MW, 120 °C, 30 min; (ii) EtNCO, DCM, rt, 30 min.



Scheme 20 Reagents and conditions: (i) PS–piperazine, DCM, MW, DMF, 120 °C, 30 min; (ii) $MeSO_2Cl$, py, DCM, rt, 2 h.



Scheme 21 Reagents and conditions: (i) PDC, DMF, rt, 18 h; (ii) *p*-nitrophenyl chloroformate, py, THF, rt, 20 min; (iii) 2-picolyl amine, rt, 10 min.



Scheme 22 Reagents and conditions: (i) Tf_2O, py, DCM, −78 °C to rt, 30 min; (ii) NaN_3, DMF, rt, 1 h; (iii) PhCCH, $CuSO_4 \cdot 5H_2O$ 1 mol%, sodium ascorbate 5 mol%, H_2O–^{t}BuOH, rt, 3 h.

Conclusions

In summary, we have synthesized [6,6]- and [6,5]-membered ring spiroketal units containing three independent points of variation geared towards the generation of a collection of natural product-like compounds.

In particular, the spiroketal units **1**–**4** were prepared following an efficient linear route, with the last synthetic steps generating the stereochemical/configurational change through the synthesis of a series of spiroketal isomers with different molecular shapes. Preliminary studies have also shown the potential of the epimerisation event at the spiroketal carbon C6 as a source of stereochemical variation within the collection of spiroketals. In order to increase molecular diversity, the possibility of achieving skeletal change on spiroketal **3** is still under investigation. By successful elaboration of the units **1**, **2** and **31** a collection of structurally-diverse, new spiroketal derivatives (**24a–c**, **25a**, **34a–b**, **35a–b**, **36a–b**, **37a–b**, **42a**, **42e**, **43a–b**, **44a–b**, **45a–d**, **46–49**, **51**) was achieved towards orally-bioavailable lead compounds. Extensive biological screening of all the compounds is currently under evaluation and will be reported separately.

Experimental

General experimental details

All melting points were determined on a Reichert hot stage apparatus, and are uncorrected. Infrared spectra were recorded using a Perkin-Elmer One FTIR spectrometer fitted with an ATR sampling accessory as either liquid films or dilute solutions in spectroscopic grade chloroform or dichloromethane. ^{1}H NMR spectra were recorded on Brüker DPX-400 (400 MHz) and Brüker DRX-600 (600 MHz) instruments as dilute solutions in deuterated chloroform unless otherwise stated. The chemical shifts are reported relative to tetramethylsilane or residual chloroform as an internal standard. The multiplicity of the signals is designated by the following abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; qn, quintet; br, broad; m, multiplet. All coupling constants, J, are reported in Hertz (Hz). ^{13}C-NMR spectra were recorded at 100 and 150 MHz on Bruker DPX-400 and Bruker DRX-600 instruments, respectively. The spectra were recorded as dilute solutions in deuterated chloroform unless otherwise stated, with chemical shifts reported relative to the residual chloroform as an internal standard on a broad band decoupled mode. Mass spectra were obtained on a Kratos MS890MS instrument using electron impact (+EI), a Kratos-QTQF spectrometer using electrospray ionisation (+ESI), or LCT Premier spectrometer by Waters using Micromass MS software by electrospray ionisation (+ESI) at the Department of Chemistry, Cambridge. Optical rotations were measured using a Perkin Elmer Model 343 polarimeter; $[\alpha]_D^{25}$ values are reported in 10^{-1} deg cm^2 g^{-1}. All microwave heating was performed on an Emrys synthesizer Biotage AG, 1725 Discovery Drive, Charlottesville, Virginia 22911. Chiral HPLC analyses were performed on an Agilent 1100 series HPLC with a diode array detection, recording at the specified wavelength and with a Chiracel® OD (25 cm × Ø 0.46 cm), manufactured by Daicel Chemical Industry. X-Ray crystal structures were determined on a Nonius Kappa CCD instrument at the Cambridge University Chemistry Laboratory (CUCL) X-Ray Laboratory, Lensfield Road, Cambridge, CB2 1EW.‡ Gravimetric or flash column chromatography was carried out using Merck Kieselgel 230–400 mesh or Fluka florisil. Analytical thin layer chromatography was performed using pre-coated glass-backed plates (Merck Kieselgel F254) and visualised by exposure to ultra-violet radiation (254 nm) and treatment with acidic ammonium molybdate (VI). All solvents and chemicals were used as provided by the supplier, or were dried and/or purified according to the accepted literature procedures. Petroleum ether refers to the 40–60 °C boiling point fraction unless otherwise stated. All reactions were conducted in oven-dried glassware at room temperature, under an argon atmosphere unless otherwise stated. All organic extracts were dried over anhydrous magnesium sulfate and filtered under gravity. Solvents were removed from the extracts on a Büchi rotary evaporator under water pump or oil pressure.

General procedure for the synthesis of ynols 7, 8 and 15

A solution of ynal **5** or **6** in anhydrous THF (5 M with rinsing × 2) was added, dropwise, to a stirred, *in situ* preparation of either but-1-enyl-4-magnesium bromide or pent-1-enyl-5-magnesium bromide (2.3 eq.) in anhydrous THF (1.0 M), pre-cooled to −78 °C. The reaction mixture was heated at 30 °C for 4 h and then quenched with a saturated, aqueous solution of NH_4Cl followed by aqueous phase extraction using Et_2O (×3). The recombinant organic extracts were washed with distilled water (×2) and brine (×1), dried over anhydrous $MgSO_4$, filtered, and then concentrated *in vacuo*. The resultant crude was then purified by gravimetric column chromatography on silica, using 1 : 4 Et_2O and petroleum ether as eluent.

(10*S*)-11-Benzyloxy-10-triethylsilanyloxyundec-1-en-7-yn-6-ol (7). A clear, colourless oil (93%); R_f 0.16 (1 : 4 Et_2O–petroleum ether); υ_{max}(film)/cm^{-1}: 3387, 2953, 2912, 1641, 1488, 1239, 1010, 910, 727 and 698; δ_H (400 MHz; $CDCl_3$; Me_4Si) 7.26–7.35 (5 H, m, *Ar*), 5.75–5.86 (1 H, m, R–C*H*=CH$_2$), 5.02 (1 H, dd, *J* 17.1 and 1.6, R–CH=C(H$_A$)H), 4.95–4.98 (1 H, m, R–CH=C(H$_B$)H), 4.55 (2 H, s, –OC*H*$_2$Ph), 4.32 (1 H, d, *J* 5.2, *H*$_6$), 3.95–3.98 (1 H, m, *H*$_2$), 3.45–3.53 (2 H, m, *H*$_1$), 2.53 (1 H, ddd, *J* 16.7, 6.2 and 1.7, *H*$_{3A}$), 2.40 (1 H, ddd, *J* 16.7, 5.6 and 1.8, *H*$_{3B}$), 2.06–2.10 (2 H, m, *H*$_9$), 1.76 (1 H, d, *J* 5.2, *OH*), 1.63–1.72 (2 H, m, *H*$_7$), 1.50–1.60 (2 H, m, *H*$_8$), 0.97 (9 H, t, *J* 7.9, –OSi(CH$_2$C*H*$_3$)$_3$) and 0.63 (6 H, q, *J* 7.8, –OSi(C*H*$_2$CH$_3$)$_3$); δ_C (100 MHz; $CDCl_3$; Me_4Si) 138.4, 138.3, 128.3, 127.6, 127.5, 114.7, 82.8, 82.1, 73.4, 73.3, 70.2, 62.5, 37.4, 33.3, 24.9, 24.4, 6.8 and 4.9; *m*/*z* (+ESI) calc. for $C_{24}H_{38}NaO_3Si$ (MNa$^+$) 425.2488, found 425.2498.

(10*S*)-11-(4-Bromobenzyloxy)-10-triethylsilanyloxyundec-1-en-7-yn-6-ol (8). A clear, colourless oil (95%); R_f 0.25 (3 : 7 Et_2O–petroleum ether); υ_{max}(film)/cm^{-1}: 3398, 2952, 2912, 1641, 1594, 1488, 1239, 1205, 1092, 1071, 910, 835, 802 and 698; δ_H (400 MHz; $CDCl_3$; Me_4Si) 7.46 (2 H, d, *J* 8.3, *Ar*), 7.21 (2 H, d, *J* 8.3, *Ar*), 5.80 (1 H, m, R–C*H*=CH$_2$), 5.02 (1 H, d, *J* 17.2, R–CH=C(H$_A$)H), 4.96 (1 H, d, *J* 10.2, R–CH=C(H$_B$)H), 4.49 (2 H, s, –OC*H*$_2$Ph), 4.30–4.33 (1 H, m, *H*$_6$), 3.94–3.97 (1 H, m, *H*$_2$), 3.45–3.51 (2 H, m, *H*$_1$), 2.51 (1 H, ddd, *J* 16.8, 6.5 and 1.7, *H*$_{3A}$), 2.39 (1 H, ddd, *J* 16.7, 5.5 and 1.5, *H*$_{3B}$), 2.08 (2 H, m, *H*$_9$), 1.63–1.70 (2 H, m, *H*$_7$), 1.52–1.58 (2 H, m, *H*$_8$), 0.96 (9 H, t, *J* 7.9, –OSi(CH$_2$C*H*$_3$)$_3$) and 0.62 (6 H, q, *J* 7.8, –OSi(C*H*$_2$CH$_3$)$_3$); δ_C (100 MHz; $CDCl_3$; Me_4Si) 138.4, 137.2, 131.4, 129.2, 128.3, 114.7, 90.8, 82.1, 73.3, 72.6, 70.2, 62.6, 37.4, 33.3, 24.9, 24.4, 6.8 and 4.9; *m*/*z* (+ESI) calc. for $C_{24}H_{37}BrNaO_3Si$ (MNa$^+$) 503.1593, found 503.1584.

(9*S*)-10-Benzyloxy-9-triethylsilanyloxydec-1-en-6-yn-5-ol (15). A clear, colourless oil (96%); R_f 0.18 (1 : 4 Et_2O–petroleum ether); υ_{max}(film)/cm^{-1}: 3439, 2953, 2912, 2876, 1641, 1594, 1488, 1458, 1414, 1361, 1239, 1201, 1094, 1071, 1011, 910, 835, 795, 727, 698 and 673; δ_H (600 MHz; $CDCl_3$; Me_4Si) 7.26–7.36 (5 H, m, *Ar*), 5.75–5.86 (1 H, m, R–C*H*=CH$_2$), 4.97–5.07 (2 H, m, R–CH=C*H*$_2$), 4.55 (2 H, s, –OC*H*$_2$Ph), 4.33 (1 H, d, *J* 5.2, *H*$_6$), 3.99–4.03 (1 H, m, *H*$_2$), 3.44–3.52 (2 H, m, *H*$_1$), 2.53 (1 H, ddd, *J* 16.5, 6.3 and 1.7, *H*$_{3A}$), 2.40 (1 H, ddd, *J* 16.5, 5.8 and 1.9, *H*$_{3B}$), 2.08–2.12 (2 H, m, *H*$_8$), 1.68–1.78 (3 H, m, *H*$_7$ & *OH*), 0.97 (9 H, t, *J* 7.9, –OSi(CH$_2$C*H*$_3$)$_3$) and 0.63 (6 H, q, *J* 7.8, –OSi(C*H*$_2$CH$_3$)$_3$); δ_C (150 MHz; $CDCl_3$; Me_4Si) 138.1, 136.8, 128.3, 127.6, 127.5, 115.2, 82.5, 81.8, 73.4, 73.2, 70.6, 62.4, 37.3, 25.3, 24.6, 6.8 and 4.8; *m*/*z* (+ESI) calc. for $C_{23}H_{36}NaO_3Si$ (MNa$^+$) 411.2331, found 411.2303.

‡ CCDC reference numbers 600002–600004. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b603015g.

General procedure for the synthesis of ynones 9, 10 and 16

To a stirred solution of ynol **7**, **8** or **15** in anhydrous DCM (0.2 M) was added Dess–Martin periodinane reagent (1.5 eq.) at 0 °C. The reaction mixture was allowed to stir at ambient temperature for 2 h then quenched with a 1 : 1 mixture of saturated, aqueous $Na_2S_2O_3$ and $NaHCO_3$ solutions, and left to stir for a further 30 min. The aqueous phase was then extracted with Et_2O (×3) and the recombinant organic extracts washed with distilled water (×2), and brine (×1). Drying over anhydrous $MgSO_4$, followed by filtration and *in vacuo* evaporation yielded a clear, colourless liquid crude, which was purified by gravimetric column chromatography on silica, using 1 : 4 Et_2O and petroleum ether as eluent.

(10*S*)-11-Benzyloxy-10-triethylsilanyloxyundec-1-en-7-yn-6-one (9). A clear, colourless liquid (94%); R_f 0.54 (1 : 4 Et_2O–petroleum ether); $[\alpha]_D^{25}$ −2.9 (*c* 0.47, CH_2Cl_2); υ_{max}(film)/cm^{-1}: 2954, 2912, 2216, 1673, 1642, 1496, 1455, 1413, 1362, 1237, 1093, 1003, 911, 729 and 697; δ_H (400 MHz; $CDCl_3$; Me_4Si) 7.17–7.28 (5 H, m, *Ar*), 5.63–5.73 (1 H, m, R–C*H*=CH_2), 4.95–4.96 (1 H, m, R–CH=C(H_A)H), 4.89–4.92 (1 H, m, R–CH=C(H_B)H), 4.46 (2 H, s, –OCH_2Ph), 3.92–3.97 (1 H, m, H_2), 3.35–3.43 (2 H, m, H_1), 2.61 (1 H, dd, *J* 17.2 and 5.5, H_{3A}), 2.47 (1 H, dd, *J* 17.2 and 5.9, H_{3B}), 2.40–2.44 (2 H, t, *J* 7.4, H_7), 1.97–2.01 (2 H, m, H_9), 1.64–1.68 (2 H, m, H_8), 0.88 (9 H, t, *J* 7.9, –OSi(CH_2CH_3)$_3$) and 0.54 (6 H, q, *J* 7.8, –OSi(CH_2CH_3)$_3$); δ_C (100 MHz; $CDCl_3$; Me_4Si) 187.9, 138.0, 137.6, 128.3, 2 × 127.6, 115.4, 90.9, 82.0, 73.4, 73.2, 69.4, 44.6, 32.8, 25.3, 23.1, 6.7 and 4.8; *m*/*z* (+ESI) calc. for $C_{24}H_{36}NaO_3Si$ (MNa^+) 423.2331, found 423.2322.

(10*S*)-11-(4-Bromobenzyloxy)-10-triethylsilanyloxyundec-1-en-7-yn-6-one (10). A clear, colourless oil (96%); R_f 0.48 (3 : 7 Et_2O–petroleum ether); $[\alpha]_D^{25}$ −0.4 (*c* 2.50, CH_2Cl_2); υ_{max}(film)/cm^{-1}: 2954, 2911, 2876, 2214, 1673, 1641, 1593, 1488, 1458, 1412, 1361, 1237, 1161, 1093, 1071, 1011, 914, 835, 803, 795, 741, 727 and 674; δ_H (400 MHz; $CDCl_3$; Me_4Si) 7.47 (2 H, d, *J* 8.3, *Ar*), 7.20 (2 H, d, *J* 8.2, *Ar*), 5.71–5.82 (1 H, m, R–C*H*=CH_2), 5.03–5.05 (1 H, m, R–CH=C(H_A)H), 5.97–5.01 (1 H, m, R–CH=C(H_B)H), 4.49 (2 H, s, –OCH_2Ph), 4.00–4.04 (1 H, m, H_2), 3.43–3.50 (2 H, m, H_1), 2.67 (1 H, dd, *J* 17.2 and 5.8, H_{3A}), 2.49–2.58 (3 H, m, H_{3B} and H_7), 2.06–2.10 (2 H, m, H_9), 1.73–1.77 (2 H, m, H_8), 0.95 (9 H, t, *J* 7.9, –OSi(CH_2CH_3)$_3$) and 0.62 (6 H, q, *J* 7.8, –OSi(CH_2CH_3)$_3$); δ_C (100 MHz; $CDCl_3$; Me_4Si) 187.7, 137.6, 137.1, 131.5, 129.2, 121.5, 115.4, 90.7, 82.1, 73.4, 72.7, 69.4, 44.7, 33.8, 25.3, 23.1, 6.7 and 4.8; *m*/*z* (+ESI) calc. for $C_{24}H_{35}BrNaO_3Si$ (MNa^+) 501.1436, found 501.1407.

(9*S*)-10-Benzyloxy-9-triethylsilanyloxydec-1-en-6-yn-5-one (16). A clear, colourless oil (97%); R_f 0.60 (1 : 4 Et_2O–petroleum ether); $[\alpha]_D^{25}$ −2.2 (*c* 2.50, CH_2Cl_2); υ_{max}(film)/cm^{-1}: 2955, 2911, 2876, 2214, 1675, 1641, 1497, 1455, 1412, 1360, 1239, 1206, 1239, 1162, 1093, 1003, 971, 915, 861, 730, 697 and 675; δ_H (600 MHz; $CDCl_3$; Me_4Si) 7.26–7.34 (5 H, m, *Ar*), 5.75–5.85 (1 H, m, R–C*H*=CH_2), 5.05 (1 H, dd, *J* 17.1 and 1.5, R–CH=C(H_A)H), 5.00 (1 H, dd, *J* 10.3 and 1.3, R–CH=C(H_B)H), 4.54 (2 H, s, –OCH_2Ph), 3.99–4.04 (1 H, m, H_2), 3.46–3.50 (2 H, m, H_1), 2.70 (1 H, dd, *J* 17.1 and 5.5, H_{3A}), 2.53–2.61 (3 H, m, H_{3B} and H_7), 2.38–2.41 (2 H, m, H_8), 0.96 (9 H, t, *J* 8.1, –OSi(CH_2CH_3)$_3$) and 0.62 (6 H, q, *J* 7.9, –OSi(CH_2CH_3)$_3$); δ_C (150 MHz; $CDCl_3$; Me_4Si) 187.9, 138.0, 136.4, 128.3, 2 × 127.6, 115.5, 91.2, 81.9, 73.4, 73.2, 69.4, 44.5, 27.9, 25.3, 6.7 and 4.8; *m*/*z* (+ESI) calc. for $C_{23}H_{35}O_3Si$ (MH^+) 387.2355, found 387.2356; calc. for $C_{23}H_{34}NaO_3Si$ (MNa^+) 409.2175, found 409.2169.

General procedure for the synthesis of diols 11, 12 and 17

Method A. To a rigorously stirred solution of OsO_4 (5 mol%) and NMO (1.1 eq.) in 1 : 1 distilled water–*t*-butanol (0.02 M) was added ynone **9** or **10** at 0 °C. The resultant heterogeneous mixture was then stirred for 18 h. Reductive work-up involved the slow, portionwise addition of solid Na_2SO_3 (1.5 g mmol^{-1} of **9** or **10**) followed by further stirring for 1 h. The reaction mixture was then diluted with EtOAc and the aqueous phase extracted with EtOAc (×3). The recombinant organic extracts were washed with distilled water (×1) and brine (×1), dried over anhydrous $MgSO_4$, filtered and then concentrated *in vacuo*. Purification of the resultant crude oil was performed by gravimetric column chromatography on silica, using 4 : 1 EtOAc and petroleum ether as eluent.

(2*S*)-1-Benzyloxy-10,11-dihydroxy-2-triethylsilanyloxyundec-4-yn-6-one (11). A clear, colourless oil (93%); R_f 0.34 (EtOAc); υ_{max}(film)/cm^{-1}: 3419, 3056, 2954, 2214, 1670, 1455, 1420, 1362, 1238, 1096, 1006, 896, 731 and 698; δ_H (600 MHz; $CDCl_3$; Me_4Si) 7.26–7.34 (5 H, m, *Ar*), 4.53 (2 H, s, –OCH_2Ph), 3.99–4.03 (1 H, m, H_2), 3.63–3.66 (1 H, m, H_{10}), 3.59 (1 H, d, *J* 11.0, H_{11A}), 3.44–3.49 (2 H, m, H_1), 3.39–3.42 (1 H, m, H_{11B}), 2.95 (1 H, br s, *OH*), 2.78 (1 H, br s, *OH*), 2.68 (1 H, dd, *J* 17.2 and 5.6, H_{3A}), 2.53–2.57 (3 H, m, H_7 and H_{3B}), 1.76–1.80 (1 H, m, H_{8A}), 1.67–1.71 (1 H, m, H_{8B}), 1.39–1.43 (2 H, m, H_9), 0.94 (9 H, t, *J* 7.9, –OSi(CH_2CH_3)$_3$) and 0.61 (6 H, q, *J* 7.9, –OSi(CH_2CH_3)$_3$); δ_C (150 MHz; $CDCl_3$; Me_4Si) 187.9, 138.0, 128.3, 127.7, 127.6, 91.4, 82.0, 73.4, 73.2, 71.7, 69.4, 66.6, 45.1, 32.2, 25.3, 19.8, 6.7 and 4.8; *m*/*z* (+ESI) calc. for $C_{24}H_{38}NaO_5Si$ (MNa^+) 457.2386, found 457.2391.

(2*S*)-1-(4-Bromobenzyloxy)-10,11-dihydroxy-2-triethylsilanyloxyundec-4-yn-6-one (12). A clear, colourless oil (89%); R_f 0.24 (EtOAc); υ_{max}(film)/cm^{-1}: 3398, 2954, 2911, 2875, 2213, 1671, 1593, 1488, 1457, 1410, 1361, 1238, 1092, 1070, 1010, 925, 873, 835, 803, 728, 698 and 673; δ_H (600 MHz; $CDCl_3$; Me_4Si) 7.45 (2 H, d, *J* 8.2, *Ar*), 7.20 (2 H, d, *J* 8.2, *Ar*), 4.48 (2 H, s, –OCH_2Ph), 3.98–4.03 (1 H, m, H_2), 3.66–3.69 (1 H, m, H_{10}), 3.62–3.64 (1 H, m, H_{11A}), 3.42–3.48 (3 H, m, H_1 and H_{11B}), 2.65–2.69 (1 H, dd, *J* 17.2 and 6.0, H_{3A}), 2.52–2.57 (3 H, m, H_{3B} and H_7), 1.71–1.82 (2 H, m, H_8), 1.41–1.45 (2 H, m, H_9), 0.95 (9 H, t, *J* 8.0, –OSi(CH_2CH_3)$_3$) and 0.61 (6 H, q, *J* 7.9, –OSi(CH_2CH_3)$_3$); δ_C (150 MHz; $CDCl_3$; Me_4Si) 187.7, 137.0, 131.5, 129.2, 121.5, 91.1, 82.0, 73.3, 72.7, 71.7, 69.4, 66.6, 45.1, 32.2, 25.3, 19.7, 6.7 and 4.8; *m*/*z* (+ESI) calc. for $C_{24}H_{37}BrNaO_5Si$ (MNa^+) 535.1491, found 535.1494.

Method B. To a rigorously stirred solution of either AD-mix-α or AD-mix-β (1.45 g mmol^{-1} of **9**, **10** or **16**) in 1 : 1 distilled water–*t*-butanol (0.02 M) was added ynone **9**, **10** or **16** at 0 °C. The resultant heterogeneous mixture was then stirred for 18 h. Reductive work-up involved the slow, portionwise addition of solid Na_2SO_3 (1.5 g mmol^{-1} of **9**, **10** or **16**), followed by further stirring for 1 h. The reaction mixture was then diluted with EtOAc and the aqueous phase extracted with EtOAc (×3). The recombinant organic extracts were washed with distilled water (×1) and brine (×1), dried over anhydrous $MgSO_4$, filtered and then evaporated *in vacuo*. Purification of the resultant crude oil was performed by gravimetric column chromatography on silica, using 4 : 1 EtOAc and petroleum ether as eluent.

(2*S*),(10*R*)-1-Benzyloxy-10,11-dihydroxy-2-triethylsilanyloxy-undec-4-yn-6-one (11a). A clear, colourless oil (94%), Chiral HPLC: Chiracel® OD, 9 : 1 hexanes–*i*-PrOH: 10.5 min (2*S*, 10*S*), 11.7 min (2*S*, 10*R*) gave 72% de.

(2*S*),(10*S*)-1-Benzyloxy-10,11-dihydroxy-2-triethylsilanyloxy-undec-4-yn-6-one (11b). A clear, colourless oil (96%), Chiral HPLC: Chiracel® OD, 9 : 1 hexanes–*i*-PrOH: 10.6 min (2*S*, 10*S*), 11.6 min (2*S*, 10*R*) gave 73% de.

(2*S*),(9*R*)-10-Benzyloxy-1,2-dihydroxy-9-triethylsilanyloxydec-6-yn-5-one (17). A clear, colourless oil (94%); R_f 0.38 (EtOAc); υ_{max}(film)/cm^{-1}: 3396, 2953, 2911, 2876, 2214, 1670, 1496, 1455, 1412, 1361, 1238, 1206, 1093, 1003, 872, 844, 731, 697 and 674; δ_H (600 MHz; $CDCl_3$; Me_4Si) 7.25–7.34 (5 H, m, *Ar*), 4.54 (2 H, s, –OCH_2Ph), 4.10–4.13 (1 H, m, H_2), 3.66–3.69 (1 H, m, H_9), 3.60–3.62 (1 H, m, H_{10A}), 3.41–3.51 (3 H, m, H_1 and H_{10B}), 2.64–2.72 (3 H, m, H_{3A} and H_7), 2.53–2.60 (1 H, m, H_{3B}), 1.71–1.81 (2 H, m, H_8), 0.95 (9 H, t, *J* 8.0, –OSi(CH$_2$CH_3)$_3$) and 0.61 (6 H, q, *J* 7.8, –OSi(CH_2CH$_3$)$_3$); δ_C (150 MHz; $CDCl_3$; Me_4Si) 187.8, 138.0, 128.4, 128.3, 127.7, 127.6, 91.8, 81.9, 73.4, 73.1, 71.2, 69.4, 66.5, 41.6, 26.9, 25.3, 6.8 and 4.8; *m*/*z* (+ESI) calc. for $C_{23}H_{37}O_5Si$ (MH$^+$) 421.2410, found 421.2393; Chiracel® OD, 9 : 1 hexanes–*i*-PrOH: 29.5 min (2*S*, 9*S*), 31.6 min (2*S*, 9*R*) gave 71% de.

General procedure for the synthesis of dithianes 13 and 14

To a stirred solution of NaOMe (1.35 eq.) and ynone **11** or **12** in 3 : 1 anhydrous MeOH–DCM (0.08 M) was added propane-1,3-dithiol (1.25 eq.) at −10 °C. The temperature was then maintained at −10 °C and the yellow solution left to stir for 18 h, after which a 1 : 1 mixture of distilled water and saturated, aqueous $NaHCO_3$ solution was added, dropwise. The reaction mixture was then diluted with Et_2O, the aqueous phase extracted with Et_2O (×3) and the recombinant organic extracts washed with distilled water (×2) and brine (×1). Drying over anhydrous $MgSO_4$, filtration, and *in vacuo* evaporation yielded a yellow, liquid crude, which was purified by gravimetric column chromatography on silica, using EtOAc as eluent.

(2″*S*)-1-[2-(3-Benzyloxy-2-triethylsilanyloxy-propyl)[1,3]-dithian-2-yl]-6,7-dihydroxy-heptan-2-one (13). A clear, colourless oil (93%); R_f 0.23 (EtOAc); υ_{max}(film)/cm^{-1}: 3421, 2953, 2876, 1709, 1560, 1455, 1415, 1364, 1265, 1239, 1091, 1005, 908, 872, 731 and 699; δ_H (600 MHz; $CDCl_3$; Me_4Si) 7.22–7.29 (5 H, m, *Ar*), 4.47 (2 H, s, –OCH_2Ph), 4.19–4.21 (1 H, m, H_2), 3.58–3.62 (1 H, m, H_{10}), 3.52–3.54 (1 H, m, H_{11A}), 3.33–3.43 (3 H, m, H_1, and H_{11B}), 3.12 (1 H, d, *J* 15.3, H_{5A}), 2.98 (1 H, d, *J* 15.3, H_{5B}), 2.68–2.84 (4 H, m, –S–CH_2–CH$_2$–CH_2–S–), 2.49–2.51 (2 H, m, H_7), 2.42–2.45 (1 H, m, H_{3A}), 2.28 (1 H, dd, *J* 15.1 and 7.3, H_{3B}), 1.85–1.89 (2 H, m, –S–CH$_2$–CH_2–CH$_2$–S–), 1.62–1.69 (1 H, m, H_{8A}), 1.53–1.60 (1 H, m, H_{8B}), 1.33–1.37 (2 H, m, H_9), 0.89 (9 H, t, *J* 8.2, –OSi(CH$_2$CH_3)$_3$) and 0.57 (6 H, q, *J* 7.9, –OSi(CH_2CH$_3$)$_3$); δ_C (150 MHz; $CDCl_3$; Me_4Si) 206.8, 138.2, 128.2, 127.6, 127.5, 74.9, 73.2, 71.8, 69.6, 66.5, 51.0, 49.4, 44.5, 42.7, 32.4, 26.5, 26.2, 24.7, 19.4, 7.0 and 5.3; *m*/*z* (+ESI) calc. for $C_{27}H_{46}NaO_5S_2Si$ (MNa$^+$) 565.2454, found 565.2546.

(2″*S*)-1-{2-[3-(4-Bromobenzyloxy)-2-triethylsilanyloxy-propyl]-[1,3]dithian-2-yl}-6,7-dihydroxy-heptan-2-one (14). A clear, colourless oil (90%); R_f 0.15 (EtOAc); υ_{max}(film)/cm^{-1}: 3439, 2950, 2910, 2874, 1712, 1671, 1552, 1488, 1457, 1414, 1362, 1238, 1166, 1088, 1070, 1010, 908, 838, 803, 728 and 675; δ_H (600 MHz; $CDCl_3$; Me_4Si) 7.42–7.49 (2 H, m, *Ar*), 7.17–7.22 (2 H, m, *Ar*), 4.46–4.48 (2 H, m, –OCH_2Ph), 4.21–4.23 (1 H, m, H_2), 3.59–3.65 (1 H, m, H_{10}), 3.52–3.58 (1 H, m, H_{11A}), 3.36–3.51 (3 H, m, H_1 and H_{11B}), 3.13–3.19 (1 H, m, H_{5A}), 2.98–3.05 (1 H, m, H_{5B}), 2.68–2.85 (4 H, m, –S–CH_2–CH$_2$–CH_2–S–), 2.41–2.65 (3 H, m, H_{3A} and H_7), 2.28–2.41 (1 H, m, H_{3B}), 1.88–1.94 (2 H, m, –S–CH$_2$–CH_2–CH$_2$–S–), 1.52–1.87 (2 H, m, H_8), 1.36–1.50 (2 H, m, H_9), 0.90–0.98 (9 H, m, –OSi(CH$_2$CH_3)$_3$) and 0.56–0.64 (6 H, m, –OSi(CH_2CH$_3$)$_3$); δ_C (150 MHz; $CDCl_3$; Me_4Si) 205.6, 137.6, 131.5, 129.3, 121.4, 75.1, 74.5, 71.7, 69.5, 66.6, 51.0, 49.5, 44.4, 42.6, 32.4, 26.6, 26.5, 24.9, 19.1, 6.9 and 5.3; *m*/*z* (+ESI) calc. for $C_{27}H_{45}BrNaO_5S_2Si$ (MNa$^+$) 643.1559, found 643.1563.

(2*R*),(9*S*)-10-Benzyloxy-1,2,9-tristriethylsilanyloxydec-6-yn-5-one (18). A stirred solution of diol **17** (146 mg, 0.35 mmol) in anhydrous DCM (2 cm^3) was cooled to −78 °C and treated sequentially with 2,6-lutidine (230 mg, 1.05 mmol, 3.0 eq.) and TESOTf (230 mg, 0.87 mmol, 1.5 eq.). The reaction was immediately warmed to 0 °C over 5 min, quenched with a saturated, aqueous solution of $NaHCO_3$ (10 cm^3) and then extracted with Et_2O (4 × 10 cm^3). The recombinant organic extracts were washed with distilled water (2 × 10 cm^3) and brine (1 × 10 cm^3), dried over anhydrous $MgSO_4$ and then concentrated *in vacuo*. The subsequent crude oil was purified by gravimetric column chromatography on silica, using 1 : 19 Et_2O and petroleum ether as eluent to afford the title compound **18** as a clear, colourless oil (221 mg, 98%): R_f 0.70 (1 : 9 Et_2O–petroleum ether); υ_{max}(film)/cm^{-1}: 2945, 2912, 1672, 1550, 1459, 1420, 1362, 1229, 1087, 1001, 913, 819, 726 and 697; δ_H (400 MHz; $CDCl_3$; Me_4Si) 7.26–7.36 (5 H, m, *Ar*), 4.55 (2 H, s, –OCH_2Ph), 3.95–4.01 (1 H, m, H_2), 3.68–3.72 (1 H, m, H_9), 3.45–3.56 (4 H, m, H_1 and H_{10}), 2.45–2.70 (2 H, m, H_7), 2.31–2.44 (1 H, m, H_{3A}), 2.15–2.30 (1 H, m, H_{3B}), 1.09–1.38 (2 H, m, H_8), 0.90–1.01 (27 H, m, 3 × –OSi(CH$_2$CH_3)$_3$) and 0.52–0.66 (18 H, m, 3 × –OSi(CH_2CH$_3$)$_3$); δ_C (100 MHz; $CDCl_3$; Me_4Si) 187.6, 138.4, 128.3, 127.5, 89.5, 80.2, 73.8, 73.4, 73.0, 70.2, 67.2, 33.2, 30.7, 25.6, 6.8, 2 × 6.7, 5.1, 4.9 and 4.8; *m*/*z* (+ESI) calc. for $C_{35}H_{64}NaO_5Si_3$ (MNa$^+$) 671.3959, found 671.3945.

(2′*S*),(5*R*)-1-[2-(3-Benzyloxy-2-triethylsilanyloxypropyl)[1,3]-dithian-2-yl]-5,6-bistriethylsilanyloxy-hexan-2-one (19). To a stirred solution of NaOMe (190 mg, 0.35 mmol, 1.35 eq.) and ynone **18** (169 mg, 0.26 mmol) in 3 : 1 anhydrous MeOH–DCM (1.3 cm^3) was added propane-1,3-dithiol (35 mg, 0.33 mmol, 1.25 eq.) at −10 °C. The temperature was then maintained at −10 °C for 1 h and the yellow solution then left to reach ambient temperature over 18 h, at which point a 1 : 1 mixture of distilled water and saturated, aqueous $NaHCO_3$ solution (2 cm^3) was added, dropwise. The reaction mixture was then diluted with Et_2O (1 × 5 cm^3), the aqueous phase extracted with Et_2O (3 × 5 cm^3) and the recombinant organic extracts washed with distilled water (2 × 5 cm^3) and brine (1 × 5 cm^3). Drying over anhydrous $MgSO_4$, filtration, and *in vacuo* evaporation yielded a clear, colourless oil, which was purified by gravimetric column chromatography on silica using 1 : 9 Et_2O and petroleum ether as eluent to afford the title compound **19** as a clear, colourless oil (253 mg, 95%): R_f 0.59 (1 : 9 Et_2O–petroleum ether); υ_{max}(film)/cm^{-1}: 2953, 2909, 2875, 1713, 1670, 1547, 1456, 1414, 1364, 1238, 1086, 1003, 909, 814, 725, 697 and 673; δ_H (600 MHz; $CDCl_3$; Me_4Si) 7.26–7.36

(5 H, m, *Ar*), 4.50–4.57 (2 H, s, –OCH_2Ph), 4.24–4.25 (1 H, m, H_2), 3.67–3.74 (1 H, m, H_9), 3.52–3.54 (1 H, m, H_{10A}), 3.33–3.43 (3 H, m, H_1 and H_{10B}), 3.12 (1 H, d, *J* 15.3, H_{5A}), 2.98 (1 H, d, *J* 15.3, H_{5B}), 2.68–2.84 (4 H, m, –S–CH_2–CH_2–CH_2–S–), 2.49–2.51 (2 H, m, H_7), 2.42–2.45 (1 H, m, H_{3A}), 2.28 (1 H, dd, *J* 15.1 and 7.3, H_{3B}), 1.85–1.89 (2 H, m, –S–CH$_2$–CH_2–CH$_2$–S–), 1.62–1.69 (1 H, m, H_{8A}), 1.53–1.60 (1 H, m, H_{8B}), 0.89–1.01 (27 H, m, 3 × –OSi(CH$_2$CH_3)$_3$) and 0.51–0.65 (18 H, m, 3 × –OSi(CH_2CH$_3$)$_3$); δ_C (150 MHz; $CDCl_3$; Me_4Si) 206.3, 138.3, 128.3, 127.7, 127.6, 127.5, 75.0, 73.2, 72.2, 69.6, 66.9, 51.0, 49.5, 42.5, 40.3, 27.9, 26.3, 24.8, 22.8, 7.0, 6.9, 6.8, 5.4, 5.0, and 4.3; *m*/*z* (+ESI) calc. for $C_{38}H_{72}NaO_5S_2Si_3$ (MNa^+) 779.4027, found 779.4025.

(7*S*)-8-Benzyloxy-1-oxiranyl-7-triethylsilanyloxyoct-4-yn-3-one (20). To a stirred solution of ynone **16** (180 mg, 0.47 mmol) in anhydrous DCM (5 cm^3) were successively added Na_2HPO_4 (248 mg, 1.40 mmol, 3.0 eq.) and *m*CPBA (*ca.* 77% purity, 157 mg, 0.70 mmol, 1.5 eq.). After stirring at ambient temperature for 13 h, the reaction mixture was then quenched with a saturated aqueous solution of Na_2SO_4 (2 cm^3) and distilled water (4 cm^3) and the mixture extracted with DCM (3 × 10 cm^3). The recombinant organic layers were then dried over anhydrous $MgSO_4$ and concentrated *in vacuo.* The resultant crude was purified by column chromatography on silica, using 1 : 4 Et_2O and petroleum ether as eluent to give the title compound **20** (162 mg, 75%) as a clear, colourless oil: R_f 0.22 (1 : 4 Et_2O–petroleum ether); υ_{max}(film)/cm^{-1}: 2954, 2911, 2876, 2215, 1674, 1455, 1412, 1362, 1239, 1167, 1092, 1004, 976, 910, 857, 840, 824, 739 and 698; δ_H (600 MHz; $CDCl_3$; Me_4Si) 7.25–7.37 (5 H, m, *Ar*), 4.54 (2 H, s, –OCH_2Ph), 4.00–4.04 (1 H, m, H_2), 3.45–3.50 (2 H, m, H_1), 2.92–2.96 (1 H, m, H_9), 2.73–2.77 (1 H, m, H_{10A}), 2.64–2.72 (3 H, m, H_{3A} and H_7), 2.57 (1 H, dd, *J* 17.2 and 5.9, H_{3B}), 2.48 (1 H, dd, *J* 4.8 and 2.6, H_{10B}), 1.96–2.02 (1 H, m, H_{8A}), 1.73–1.79 (1 H, m, H_{8B}), 0.95 (9 H, t, *J* 8.0, –OSi(CH$_2$CH_3)$_3$) and 0.62 (6 H, q, *J* 8.0, –OSi(CH_2CH$_3$)$_3$); δ_C (150 MHz; $CDCl_3$; Me_4Si) 186.3, 138.0, 128.4, 127.7, 127.6, 91.6, 81.8, 73.4, 73.1, 69.3, 51.0, 47.0, 41.3, 26.4, 25.3, 6.7 and 4.8; *m*/*z* (+ESI) calc. for $C_{23}H_{35}O_4Si$ (MH^+) 403.2305, found 403.2313; calc. for $C_{23}H_{34}NaO_4Si$ (MNa^+) 425.2124, found 425.2150.

(2*S*)-1-Benzyloxy-9-hydroxy-2-triethylsilanyloxy-12-trimethylsilanyldodeca-4,11-diyn-6-one (21). To a solution of TMS–acetylene (20 mg, 0.20 mmol, 2.0 eq.) in anhydrous THF (0.5 cm^3) at −78 °C was added *n*-BuLi (0.13 cm^3, 0.20 mmol of a 1.6 M solution in hexanes, 2.0 eq.). After stirring at −78 °C for 30 min, BF_3·THF (28 mg, 0.20 mmol, 2.0 eq.) was added. After stirring at −78 °C for a further 30 min, a pre-prepared solution of oxirane **20** (40 mg, 0.10 mmol) in anhydrous THF (0.3 cm^3 with rinsing × 2) was added, dropwise, and the reaction left to reach ambient temperature, with stirring, over 30 min, then quenched with a saturated, aqueous solution of NH_4Cl (1 cm^3) and extracted with Et_2O (3 × 5 cm^3). The recombinant organic extracts were washed with distilled water (2 × 5 cm^3) and brine (1 × 5 cm^3), dried over anhydrous $MgSO_4$, filtered, and then evaporated *in vacuo.* The resultant crude was purified by gravimetric column chromatography on silica, using 1 : 4 Et_2O and petroleum ether as eluent to afford the title compound **21** (25 mg, 50%) as a clear colourless oil: R_f 0.15 (1 : 4 Et_2O–petroleum ether); υ_{max}(film)/cm^{-1}: 3434, 2956, 2913, 2877, 2216, 2177, 1674, 1455, 1412, 1361, 1249, 1094, 1005, 842, 739 and 698; δ_H (400 MHz; $CDCl_3$; Me_4Si) 7.26–7.37 (5 H, m, *Ar*), 4.55 (2 H, s, –OCH_2Ph), 4.00–4.04 (1 H, m, H_2), 3.70–3.77 (1 H, m, H_9), 3.44–3.51 (2 H, m, H_1), 2.67–2.73 (3 H, m, H_{3A} and H_7), 2.56 (1 H, dd, *J* 17.2 and 5.8, H_{3B}), 2.29–2.33 (2 H, m, H_{10}), 2.14 (1 H, d, *J* 4.8, *OH*), 1.75–1.94 (2 H, m, H_8), 0.96 (9 H, t, *J* 8.0, –OSi(CH$_2$CH_3)$_3$), 0.62 (6 H, q, *J* 7.9, –OSi(CH_2CH$_3$)$_3$) and 0.16 (9 H, s, –Si(CH_3)$_3$); δ_C (100 MHz; $CDCl_3$; Me_4Si) 187.4, 138.0, 128.4, 127.7, 102.6, 92.1, 91.5, 88.0, 73.4, 73.2, 69.4, 69.0, 41.7, 30.0, 29.0, 25.4, 6.7, 4.8 and −0.02; *m*/*z* (+ESI) calc. for $C_{28}H_{44}NaO_4Si_2$ (MNa^+) 523.2676, found 523.2656.

(2*S*)-1-Benzyloxy-2,9-bistriethylsilanyloxy-12-trimethylsilanyldodeca-4,11-diyn-6-one (22). To a stirred solution of ynone **21** (145 mg, 0.28 mmol) in anhydrous THF (0.5 cm^3) were added, sequentially, imidazole (92 mg, 1.35 mmol, 4.8 eq.) and TESCl (89 mg, 0.59 mmol, 2.1 eq.) at ambient temperature. After 2 h the reaction was quenched with a saturated, aqueous solution of $NaHCO_3$ (2 cm^3) and then extracted with Et_2O (4 × 5 cm^3). The recombinant organic extracts were washed with distilled water (2 × 5 cm^3) and brine (1 × 5 cm^3), dried over anhydrous $MgSO_4$ and then concentrated *in vacuo.* Subsequent purification by gravimetric column chromatography on silica, using 1 : 9 Et_2O and petroleum ether as eluent, afforded the title compound **22** (170 mg, 98%) as a clear, colourless oil: R_f 0.39 (1 : 9 Et_2O–petroleum ether); υ_{max}(film)/cm^{-1}: 2955, 2913, 2877, 2360, 2339, 1638, 1459, 1416, 1240, 1097, 1005 and 744; δ_H (400 MHz; $CDCl_3$; Me_4Si) 7.26–7.35 (5 H, m, *Ar*), 4.52 (2 H, s, –OCH_2Ph), 4.01–4.05 (1 H, m, H_2), 3.85–3.89 (1 H, m, H_9), 3.47–3.51 (2 H, m, H_1), 2.53–2.76 (4 H, m, H_3 and H_7), 2.28–2.45 (2 H, m, H_{10}), 1.99–2.03 (1 H, m, H_{8A}), 1.81–1.85 (1 H, m, H_{8B}), 0.90–0.96 (18 H, m, –OSi(CH$_2$CH_3)$_3$), 0.55–0.63 (12 H, m, –OSi(CH_2CH$_3$)$_3$) and 0.17 (9 H, s, –Si(CH_3)$_3$); δ_C (100 MHz; $CDCl_3$; Me_4Si) 187.8, 138.2, 128.3, 127.6, 127.5, 103.8, 92.8, 90.8, 87.8, 73.4, 73.3, 69.9, 69.0, 41.0, 30.7, 25.3, 6.8, 6.7, 5.0, 4.8 and −0.004; *m*/*z* (+ESI) calc. for $C_{34}H_{58}NaO_4Si_3$ (MNa^+) 637.3541, found 637.3536.

(2″*S*)-1-[2-(3-Benzyloxy-2-triethylsilanyloxypropyl)-[1,3] dithian-2-yl]-5-triethylsilanyloxy-8-trimethylsilanyl-oct-7-yn-2-one (23). To a stirred solution of NaOMe (14 mg, 0.26 mmol, 1.35 eq.) and ynone **22** (118 mg, 0.19 mmol) in 3 : 1 anhydrous MeOH–DCM (3.6 cm^3) was added propane-1,3-dithiol (26 mg, 0.24 mmol, 1.25 eq.) at 0 °C. The reaction was then warmed to ambient temperature and the yellow solution left to stir for 18 h, after which a 1 : 1 mixture of distilled water and saturated, aqueous $NaHCO_3$ solution was added (1.5 cm^3), dropwise. The reaction mixture was then diluted with Et_2O (5 cm^3), the aqueous phase extracted with Et_2O (3 × 5 cm^3) and the recombinant organic extracts washed with distilled water (2 × 5 cm^3) and brine (1 × 5 cm^3). Drying over anhydrous $MgSO_4$, filtration, and *in vacuo* evaporation yielded a yellow, liquid crude, which was purified by gravimetric column chromatography on silica, using EtOAc as eluent to afford the title compound **23** (125 mg, 90%) as a clear, colourless oil: R_f 0.10 (1 : 9 Et_2O–petroleum ether); υ_{max}(film)/cm^{-1}: 2954, 2911, 2876, 2178, 1710, 1455, 1414, 1364, 1249, 1102, 1005, 842, 739 and 699; δ_H (600 MHz; $CDCl_3$; Me_4Si) 7.26–7.35 (5 H, m, *Ar*), 4.50–4.56 (2 H, s, –OCH_2Ph), 4.24–4.26 (1 H, m, H_2), 3.84–3.88 (1 H, m, H_9), 3.36–3.49 (2 H, m, H_1), 3.17 (1 H, dd, *J* 15.3 and 7.2, H_{5A}), 3.03 (1 H, dd, *J* 15.3 and 5.3, H_{5B}), 2.81–2.94 (2 H, m, –S–CH(H_A)–CH$_2$–CH$_2$–S– and –S–CH$_2$–CH$_2$–CH(H_A)–S–), 2.71–2.80 (2 H, m, –S–CH(H_B)–CH$_2$–CH$_2$–S– and –S–CH$_2$–CH$_2$–CH(H_B)–S–), 2.60–2.70 (1 H, m, H_{7A}), 2.46–2.59 (2 H, m, H_{3A} and H_{7B}), 2.25–2.39 (3 H, m, H_{3B} and H_{10}), 1.87–1.99 (3 H,

m, H_{8A} and –S–CH_2–CH_2–CH_2–S–), 1.72–1.82 (1 H, m, H_{8B}), 0.90–0.98 (18 H, m, 2 × –OSi(CH_2CH_3)$_3$), 0.58–0.65 (12 H, m, 2 × –OSi(CH_2CH_3)$_3$) and 0.14 (9 H, s, –Si(CH_3)$_3$); δ_C (150 MHz; $CDCl_3$; Me_4Si) 206.1, 138.2, 128.7, 127.7, 127.5, 91.5, 88.2, 74.9, 73.2, 69.8, 69.6, 51.2, 49.4, 42.6, 40.2, 30.1, 27.3, 26.6, 26.3, 24.8, 7.0, 6.9, 5.4, 4.9 and −0.004; *m/z* (+ESI) calc. for $C_{37}H_{67}O_4S_2Si_3$ (MH^+) 723.3789, found 723.3823, $C_{37}H_{66}NaO_4S_2Si_3$ (MNa^+) 745.3608, found 745.3622.

General procedure for the synthesis of dithiane-protected spiroketal units 1a–c and 2a–c

To a stirred solution of dithiane precursor **13** in 1 : 1 DCM–MeCN (0.09 M) at 0 °C was added, dropwise, perchloric acid solution (1 cm^3 $mmol^{-1}$ of **13**, 10% *v*/*v* in H_2O). After 30 min, the reaction was diluted with Et_2O and neutralised using a saturated, aqueous solution of $NaHCO_3$. The aqueous phase was extracted with Et_2O (×4), and the recombinant organic extracts were washed with distilled water (×2) and brine (×1). Drying over anhydrous $MgSO_4$, filtration and *in vacuo* evaporation yielded a crude oil, which was purified by gravimetric column chromatography on florisil, using 3 : 2 EtOAc and petroleum ether as eluent.

(15-Benzyloxymethyl-9,14-dioxa-1,5-dithiadispiro[5.1.5.3]-hexadec-10-yl)methanol isomer (1a). A white crystalline solid (34%, starting from racemic **13**; 56%, starting from diastereomerically-enriched **13a**; 11%, starting from diastereomerically-enriched **13b**); R_f 0.24 (3 : 2 EtOAc–petroleum ether); mp 117 °C (from pentane); $[\alpha]_D^{25}$ +16.7 (*c* 0.12, CH_2Cl_2); υ_{max}(film)/cm^{-1} 3467, 2941, 2866, 1496, 1453, 1360, 1217, 1096, 1023, 1013, 736 and 697; δ_H (600 MHz; $CDCl_3$; Me_4Si) 7.26–7.35 (5 H, m, *Ar*), 4.56–4.61 (2 H, m, –OCH_2Ph), 4.49–4.51 (1 H, m, H_2), 3.82–3.84 (1 H, m, H_{10}), 3.50–3.61 (4 H, m, H_1 and H_{11}), 3.07 (1 H, t, *J* 11.9, –S–CH(H_A)–CH_2–CH_2–S–), 2.88 (1 H, t, *J* 12.0, –S–CH_2–CH_2–CH(H_A)–S–), 2.70–2.77 (2 H, m, H_{5A} and –S–CH(H_B)–CH_2–CH_2–S–), 2.62–2.64 (2 H, m, –S–CH_2–CH_2–CH(H_A)–S– and *OH*), 2.54 (1 H, d, *J* 13.7, H_{3A}), 2.00–2.04 (1 H, m, –S–CH_2–CH(H_A)–CH_2–S–), 1.85–1.89 (1 H, m, –S–CH_2–CH(H_B)–CH_2–S–), 1.77–1.82 (2 H, m, H_{3B} and H_{8A}), 1.65–1.67 (1 H, m, H_{7A}), 1.48–1.60 (4 H, m, H_{5B}, H_{7B}, H_{8B} and H_{9A}) and 1.28–1.35 (1 H, m, H_{9B}); δ_H (150 MHz; $CDCl_3$; Me_4Si) 138.2, 128.3, 127.7, 127.6, 98.0, 74.2, 73.5, 72.6, 66.8, 66.4, 46.8, 40.8, 39.2, 36.7, 26.4, 26.3, 25.9, 25.3 and 19.0; *m/z* (+ESI) calc. for $C_{21}H_{30}NaO_4S_2$ (MNa^+) 433.1483, found 433.1482; Crystal structure determination of spiroketal unit **1a**: Single crystals of **1a** were recrystallised from pentane, mounted in inert oil and transferred to the cold gas stream of the diffractometer. Crystal data. $C_{21}H_{30}O_4S_2$, M = 410.57, orthorhombic, a = 8.18360(10), b = 11.8557(2), c = 21.3327(4) Å, U = 2069.75(6) Å^3, T = 180(2) K, space group $P2_12_12_1$, Z = 4, μ(Mo Kα) = 0.281 mm^{-1}, 13637 reflections measured, 4721 unique (R_{int} = 0.0445) which were used in all calculations. The final R_1 and wR_2 indices were 0.0489 and 0.1178, respectively (all data).

(15-Benzyloxymethyl-9,14-dioxa-1,5-dithiadispiro[5.1.5.3]hexadec-10-yl)methanol isomer (1b). A clear, colourless oil (16%, starting from racemic **13**; 28%, starting from diastereomerically-enriched **13a**; 6%, starting from diastereome-rically-enriched **13b**); R_f 0.34 (3 : 2 EtOAc–petroleum ether); $[\alpha]_D^{25}$ −25.5 (*c* 0.11, CH_2Cl_2); υ_{max}(film)/cm^{-1} 3467, 2941, 2866, 1423, 1362, 1276, 1238, 1211, 1123, 1091, 1028, 1009, 960, 914, 874, 739 and 699; δ_H (600 MHz; $CDCl_3$; Me_4Si) 7.26–7.37 (5 H, m, *Ar*), 4.60 (2 H, s, –OCH_2Ph), 4.03–4.06 (2 H, m, H_{10} and H_2), 3.63 (1 H, dd, *J* 10.0 and 5.7, H_{1A}), 3.52–3.56 (2 H, m, H_{1B} and H_{11A}), 3.41–3.44 (1 H, m, H_{11B}), 2.95–3.03 (2 H, m, –S–CH_2–CH_2–CH_2–S–), 2.69–2.77 (2 H, m, –S–CH_2–CH_2–CH_2–S–), 2.48 (1 H, dd, *J* 13.8 and 2.0, H_{3A}), 2.27–2.34 (1 H, m, *OH*), 2.19 (1 H, dd, *J* 13.8 and 11.2, H_{3B}), 2.08–2.14 (3 H, m, H_5 and H_{7A}), 2.03–2.07 (1H, m, –S–CH_2–CH(H_A)–CH_2–S–), 1.81–1.95 (2H, m, H_{8A} and –S–CH_2–CH(H_B)–CH_2–S–), 1.55–1.62 (1 H, m, H_{8B}), 1.43–1.48 (1 H, m, H_{9A}), 1.33 (1 H, td, *J* 13.5 and 4.3, H_{7B}) and 1.24 (1 H, td, *J* 12.9 and 4.3, H_{9B}); δ_C (150 MHz; $CDCl_3$; Me_4Si) 138.3, 128.4, 2 × 127.6, 97.2, 73.4, 73.0, 70.2, 69.5, 66.2, 47.7, 45.6, 39.0, 33.9, 26.9, 26.7, 26.2, 25.1 and 17.9; *m/z* (+ESI) calc. for $C_{21}H_{31}O_4S_2$ (MH^+) 411.1664 found 411.1671; calc. for $C_{21}H_{30}NaO_4S_2$ (MNa^+) 433.1483, found 433.1481.

(15-Benzyloxymethyl-9,14-dioxa-1,5-dithiadispiro[5.1.5.3]hexadec-10-yl)methanol isomer (1c). A white crystalline solid (48%, starting from racemic **13**; 16%, starting from diastereomerically-enriched **13a**; 83%, starting from diastereomerically-enriched **13b**); R_f 0.53 (3 : 2 EtOAc–petroleum ether); mp 127 °C (from pentane); $[\alpha]_D^{25}$ +65.3 (*c* 0.17, CH_2Cl_2); υ_{max}(film)/cm^{-1} 3503, 2944, 2866, 1453, 1438, 1370, 1281, 1216, 1167, 1125, 1091, 1040, 1022, 1006, 992, 947, 910, 827, 802, 739 and 699; δ_H (600 MHz; $CDCl_3$; Me_4Si) 7.26–7.36 (5 H, m, *Ar*), 4.59–4.64 (2 H, m, –OCH_2Ph), 4.13–4.15 (1 H, m, H_2), 3.73–3.77 (1 H, m, H_{10}), 3.54–3.60 (2 H, m, H_1), 3.47–3.51 (1 H, m, H_{11A}), 3.40–3.45 (1 H, m, H_{11B}), 3.09–3.14 (1 H, m, –S–CH(H_A)–CH_2–CH_2–S–), 3.01 (1 H, d, *J* 11.2, *OH*), 2.88–2.93 (1 H, m, –S–CH_2–CH_2–CH(H_A)–S–), 2.65–2.69 (1 H, m, –S–CH_2–CH_2–CH(H_B)–S–), 2.56–2.61 (2 H, m, H_{3A} and –S–CH_2–CH_2–CH(H_B)–S–), 2.16 (1 H, d, *J* 14.0, H_{5A}), 2.04–2.08 (1 H, m, –S–CH_2–CH(H_A)–CH_2–S–), 1.85–1.95 (2 H, m, H_{8A} and –S–CH_2–CH(H_B)–CH_2–S–), 1.80 (1 H, dd, *J* 13.6 and 11.5, H_{3B}), 1.71 (1 H, d, *J* 14.1, H_{5B}), 1.64–1.67 (1 H, m, H_{7A}), 1.58–1.61 (1 H, m, H_{8B}), 1.42–1.48 (2 H, m, H_{7B} and H_{9A}) and 1.12–1.16 (1 H, m, H_{9B}); δ_C (150 MHz; $CDCl_3$; Me_4Si) 138.4, 128.3, 127.6, 127.5, 96.8, 73.3, 72.5, 70.4, 66.1, 65.9, 47.3, 46.6, 38.5, 34.6, 26.7, 26.2, 25.7, 25.3 and 18.1; *m/z* (+ESI) calc. for $C_{21}H_{30}NaO_4S_2$ (MNa^+) 433.1483, found 433.1486; Crystal structure determination of spiroketal unit **1c**: Single crystals of **1c** were recrystallised from pentane, mounted in inert oil and transferred to the cold gas stream of the diffractometer. Crystal data. $C_{21}H_{30}O_4S_2$, M = 410.57, orthorhombic, a = 8.13710(10), b = 9.73410(10), c = 26.6319(4) Å, U = 2109.44(5) Å^3, T = 180(2) K, space group $P2_12_12_1$, Z = 4, μ(Mo Kα) = 0.276 mm^{-1}, 17628 reflections measured, 4759 unique (R_{int} = 0.0471) which were used in all calculations. The final R_1 and wR_2 indices were 0.0438 and 0.0821, respectively (all data).

[15-(4-Bromobenzyloxymethyl)-9,14-dioxa-1,5-dithiadispiro-[5.1.5.3]hexadec-10-yl]methanol isomer (2a). A clear, colourless oil (33%, starting from racemic **14**); R_f 0.18 (3 : 2 EtOAc–petroleum ether); $[\alpha]_D^{25}$ +4.4 (*c* 0.88, CH_2Cl_2); υ_{max}(film)/cm^{-1} 3493, 2941, 2866, 1454, 1363, 1217, 1092, 1041, 739 and 699; δ_H (600 MHz; $CDCl_3$; Me_4Si) 7.44 (2 H, d, *J* 8.2, *Ar*), 7.21 (2 H, d, *J* 8.1, *Ar*), 4.54–4.59 (2 H, m, –OCH_2Ph), 4.48–4.51 (1 H, m, H_2), 3.82–3.85 (1 H, m, H_{10}), 3.50–3.63 (4 H, m, H_1 and H_{11}), 3.05–3.09 (1 H, m, –S–CH(H_A)–CH_2–CH_2–S–), 2.85–2.89 (1 H, m, –S–CH_2–CH_2–CH(H_A)–S–), 2.70–2.77 (2 H, m, H_{5A} and –S–CH(H_B)–CH_2–CH_2–S–), 2.60–2.63 (2 H, m, –S–CH_2–CH_2–CH(H_B)–S– and *OH*), 2.52–2.55 (1 H, m, H_{3A}), 2.00–2.04 (1 H, m, –S–CH_2–CH(H_A)–CH_2–S–),

1.84–1.89 (1 H, m, –S–CH_2–CH(H_B)–CH_2–S–), 1.77–1.81 (2 H, m, H_{3B} and H_{8A}), 1.65–1.67 (1 H, m, H_{7A}), 1.51–1.60 (4 H, m, H_{5B}, H_{7B}, H_{8B} and H_{9A}) and 1.30–1.35 (1 H, m, H_{9B}); δ_C (150 MHz; $CDCl_3$; Me_4Si) 137.3, 131.5, 129.3, 128.4, 121.5, 98.0, 74.2, 2 × 72.7, 66.8, 66.5, 46.8, 40.7, 39.1, 36.7, 26.5, 26.3, 25.9, 25.3 and 19.0; *m/z* (+ESI) calc. for $C_{21}H_{30}BrO_4S_2$ (MH^+) 489.0769, found 489.0783; calc. for $C_{21}H_{29}BrNaO_4S_2$ (MNa^+) 511.0588, found 511.0618.

[15-(4-Bromobenzyloxymethyl)-9,14-dioxa-1,5-dithiadispiro-[5.1.5.3]hexadec-10-yl]methanol isomer (2b). A clear, colourless oil (17%, starting from racemic **14**); R_f 0.25 (3 : 2 EtOAc–petroleum ether); $[\alpha]_D^{25}$ −11.3 (*c* 0.60, CH_2Cl_2); υ_{max}(film)/cm^{-1} 3493, 2940, 2866, 1454, 1424, 1364, 1274, 1243, 1212, 1169, 1089, 1028, 1009, 960, 910, 872, 739 and 699; δ_H (600 MHz; $CDCl_3$; Me_4Si) 7.44 (2 H, d, *J* 8.3, *Ar*), 7.22 (2 H, d, *J* 8.1, *Ar*), 4.60 (2 H, s, –OCH_2Ph), 4.03–4.06 (2 H, m, H_{10} and H_2), 3.63 (1 H, dd, *J* 10.0 and 5.7, H_{1A}), 3.52–3.56 (2 H, m, H_{1B} and H_{11A}), 3.41–3.44 (1 H, m, H_{11B}), 2.95–3.03 (2 H, m, –S–CH_2–CH_2–CH_2–S–), 2.69–2.77 (2 H, m, –S–CH_2–CH_2–CH_2–S–), 2.48 (1 H, dd, *J* 13.8 and 2.0, H_{3A}), 2.27–2.34 (1 H, m, *OH*), 2.19 (1 H, dd, *J* 13.8 and 11.2, H_{3B}), 2.08–2.14 (3 H, m, H_5 and H_{7A}), 2.03–2.07 (1 H, m, –S–CH_2–CH(H_A)–CH_2–S–), 1.90–1.95 (1 H, m, –S–CH_2–CH(H_B)–CH_2–S–), 1.81–1.86 (1 H, m, H_{8A}), 1.55–1.62 (1 H, m, H_{8B}), 1.43–1.48 (1 H, m, H_{9A}), 1.33 (1 H, td, *J* 13.5 and 4.3, H_{7B}) and 1.24 (1 H, td, *J* 12.9 and 4.3, H_{9B}); δ_C (150 MHz; $CDCl_3$; Me_4Si) 137.4, 131.5, 129.2, 128.4, 121.4, 97.2, 73.1, 72.6, 70.2, 69.5, 66.2, 47.6, 45.5, 39.0, 33.9, 26.9, 26.7, 26.2, 25.1 and 17.9; *m/z* (+ESI) calc. for $C_{21}H_{30}BrO_4S_2$ (MH^+) 489.0769, found 489.0782; calc. for $C_{21}H_{29}BrNaO_4S_2$ (MNa^+) 511.0588, found 511.0609.

[15-(4-Bromobenzyloxymethyl)-9,14-dioxa-1,5-dithiadispiro-[5.1.5.3]hexadec-10-yl]methanol isomer (2c). A white, crystalline (49%, starting from racemic **14**); R_f 0.40 (3 : 7 EtOAc–petroleum ether); $[\alpha]_D^{25}$ +48.2 (*c* 0.11, CH_2Cl_2); υ_{max}(film)/cm^{-1} 3499, 2940, 2867, 1453, 1439, 1375, 1280, 1216, 1168, 1125, 1089, 1039, 1023, 1006, 992, 947, 909, 828, 802, 735 and 700; δ_H (600 MHz; $CDCl_3$; Me_4Si) 7.43 (2 H, d, *J* 8.2, *Ar*), 7.23 (2 H, d, *J* 8.3, *Ar*), 4.52–4.57 (2 H, m, –OCH_2Ph), 4.11–4.14 (1 H, m, H_2), 3.71–3.75 (1 H, m, H_{10}), 3.52–3.57 (2 H, m, H_1), 3.46–3.50 (1 H, m, H_{11A}), 3.40–3.44 (1 H, m, H_{11B}), 3.08–3.12 (1 H, m, –S–CH(H_A)–CH_2–CH_2–S–), 3.01 (1 H, d, *J* 11.3, *OH*), 2.86–2.91 (1 H, m, –S–CH_2–CH_2–CH(H_A)–S–), 2.65–2.69 (1 H, m, –S–CH_2–CH_2–CH(H_B)–S–), 2.53–2.61 (2 H, m, H_{3A} and –S–CH_2–CH_2–CH(H_B)–S–), 2.15 (1 H, d, *J* 15.9, H_{5A}), 2.04–2.06 (1 H, m, –S–CH_2–CH(H_A)–CH_2–S–), 1.83–1.93 (2 H, m, H_{8A} and –S–CH_2–CH(H_B)–CH_2–S–), 1.78 (1 H, dd, *J* 13.6 and 11.5, H_{3B}), 1.70 (1 H, d, *J* 14.1, H_{5B}), 1.57–1.66 (2 H, m, H_{7A} and H_{8B}), 1.40–1.46 (2 H, m, H_{7B} and H_{9A}) and 1.12–1.16 (1 H, m, H_{9B}); δ_C (150 MHz; $CDCl_3$; Me_4Si) 137.4, 131.4, 129.2, 122.2, 96.8, 72.6, 72.5, 70.4, 66.0, 65.9, 47.2, 46.6, 38.4, 34.6, 26.7, 26.2, 25.7, 25.3 and 18.1; *m/z* (+ESI) calc. for $C_{21}H_{30}BrO_4S_2$ (MH^+) 489.0769, found 489.0789; calc. for $C_{21}H_{29}BrNaO_4S_2$ (MNa^+) 511.0588, found 511.0610; Crystal structure determination of spiroketal unit (**2c**): Single crystals of **2c** were recrystallised from pentane, mounted in inert oil and transferred to the cold gas stream of the diffractometer. Crystal data. $C_{21}H_{29}BrO_4S_2$, $M = 489.47$, orthorhombic, $a = 13.4354(4)$, $b = 16.5257(6)$, $c = 9.9835(3)$ Å, $U = 2216.63(12)$ Å^3, $T = 180(2)$ K, space group $P2_12_12$, $Z = 4$, μ(Mo Kα) = 2.067 mm^{-1}, 13524 reflections measured, 3866 unique ($R_{int} = 0.0547$) which were used in all calculations. The final R_1 and wR_2 indices were 0.0601 and 0.1457, respectively (all data).

General procedure for the synthesis of dithiane-protected spiroketal units 3a,b and 4

To a stirred solution of dithiane precursor **19** or **23** in 1 : 1 DCM–MeCN (0.09 M) at 0 °C was added, dropwise, perchloric acid solution (1 cm^3 $mmol^{-1}$ of **19** or **23**, 10% *v*/*v* in H_2O). After 30 min, the reaction was diluted with Et_2O and neutralised using a saturated, aqueous solution of $NaHCO_3$. The aqueous phase was extracted with Et_2O (×4), and the recombinant organic extracts washed with distilled water (×2) and brine (×1). Drying over anhydrous $MgSO_4$, filtration and *in vacuo* evaporation yielded a crude oil, which was purified by gravimetric column chromatography on florisil using EtOAc and petroleum ether as eluent.

(14-Benzyloxymethyl-1,15-dioxa-8,12-dithiadispiro[4.1.5.3]-pentadec-2-yl)methanol isomer (3a). A clear, colourless oil (61%); R_f 0.52 (1 : 4 EtOAc–petroleum ether); $[\alpha]_D^{25}$ +33.0 (*c* 0.11, CH_2Cl_2); υ_{max}(film)/cm^{-1} 3434, 2906, 1454, 1361, 1209, 1091, 868, 738 and 698; δ_H (600 MHz; $CDCl_3$; Me_4Si) 7.26–7.35 (5 H, m, *Ar*), 4.55–4.61 (2 H, m, –OCH_2Ph), 4.37–4.44 (2 H, m, H_2 and H_9), 3.78 (1 H, d, *J* 12.0, H_{10A}), 3.44–3.50 (3 H, m, H_1 and H_{10B}), 3.03–3.08 (1 H, m, –S–CH(H_A)–CH_2–CH_2–S–), 2.84–2.88 (1 H, m, –S–CH(H_B)–CH_2–CH_2–S–), 2.67–2.73 (2 H, m, –S–CH_2–CH_2–CH(H_A)–S– and *OH*), 2.58–2.65 (1 H, m, –S–CH_2–CH_2–CH(H_B)–S–), 2.43 (1 H, d, *J* 13.6, H_{8A}), 2.20 (1 H, dd, *J* 14.2 and 1.7, H_{7A}), 2.08–2.14 (1 H, m, H_{3A}), 2.00–2.07 (3 H, m, H_5 and –S–CH_2–CH(H_A)–CH_2–S–), 1.82–1.88 (2 H, m, H_{3B} and –S–CH_2–CH(H_B)–CH_2–S–) and 1.67–1.71 (2 H, m, H_{7B} and H_{8B}); δ_C (150 MHz; $CDCl_3$; Me_4Si) 138.0, 128.4, 127.7, 127.6, 105.7, 82.6, 73.4, 72.4, 67.4, 65.6, 47.0, 45.0, 39.8, 38.4, 26.4, 26.3, 25.1 and 23.3; *m/z* (+ESI) calc. for $C_{20}H_{29}O_4S_2$ (MH^+) 397.1507, found 397.1494; calc. for $C_{20}H_{28}NaO_4S_2$ (MNa^+) 419.1327, found 419.1313.

(14-Benzyloxymethyl-1,15-dioxa-8,12-dithiadispiro[4.1.5.3]-pentadec-2-yl)methanol isomer (3b). A clear, colourless oil (15%); R_f 0.48 (1 : 4 EtOAc–petroleum ether); $[\alpha]_D^{25}$ +14.4 (*c* 0.13, CH_2Cl_2); υ_{max}(film)/cm^{-1} 3434, 2906, 1454, 1361, 1209, 1091, 868, 738 and 698; δ_H (600 MHz; $CDCl_3$; Me_4Si) 7.26–7.35 (5 H, m, *Ar*), 4.55–4.62 (2 H, m, –OCH_2Ph), 4.30–4.34 (1 H, m, H_2), 4.00–4.08 (1 H, m, H_9), 3.67–3.69 (1 H, m, H_{10A}), 3.45–3.54 (3 H, m, H_1 and H_{10B}), 2.95–3.03 (1 H, m, –S–CH(H_A)–CH_2–CH_2–S–), 2.81–2.92 (2 H, m, –S–CH(H_B)–CH_2–CH_2–S– and –S–CH_2–CH_2–CH(H_A)–S–), 2.67–2.75 (2 H, m, –S–CH_2–CH_2–CH(H_B)–S– and *OH*), 2.32–2.45 (m), 2.18–2.25 (m), 2.10–2.16 (m), 2.00–2.09 (m), 1.82–1.99 (m) and 1.68–1.81 (m); δ_C (150 MHz; $CDCl_3$; Me_4Si) 138.2, 128.4, 2 × 127.7, 106.9, 78.2, 73.6, 72.9, 69.7, 65.0, 47.2, 45.4, 39.2, 35.1, 26.3, 26.2, 25.2 and 24.5; *m/z* (+ESI) calc. for $C_{20}H_{29}O_4S_2$ (MH^+) 397.1507, found 397.1494; calc. for $C_{20}H_{28}NaO_4S_2$ (MNa^+) 419.1327, found 419.1313.

14-Benzyloxymethyl-2-prop-2-ynyl-1,15-dioxa-8,12-dithiadispiro-[4.1.5.3]pentadecane 1 : 1 diastereomeric mixture (4). A colourless oil (96%); R_f 0.53 (3 : 7 EtOAc–petroleum ether); υ_{max}(film)/cm^{-1} 3288, 2905, 1423, 1362, 1242, 1094, 846, 738 and 698; δ_H (600 MHz; $CDCl_3$; Me_4Si) 7.26–7.35 (5 H, m, *Ar*), 4.55–4.59 (2 H, m, –OCH_2Ph), 4.29–4.35 (2 H, m, H_2 and H_9), 3.47–3.53

(2 H, m, H_1), 3.05–3.16 (1 H, m, –S–CH(H_A)–CH_2–CH_2–S–), 2.86–2.91 (1 H, m, –S–CH(H_B)–CH_2–CH_2–S–), 2.67–2.75 (1 H, m, –S–CH_2–CH_2–CH(H_A)–S–), 2.61–2.65 (m), 2.50–2.55 (m), 2.34–2.49 (m), 2.14–2.25 (m), 1.97–2.24 (m), 1.85–1.96 (m) and 1.67–1.87 (m); δ_C (150 MHz; $CDCl_3$; Me_4Si) 138.4, 138.3, 2 × 128.3, 127.60, 2 × 127.5, 106.4, 106.1, 81.2, 80.9, 79.4, 77.4, 73.3, 73.2, 2 × 72.6, 69.4, 69.3, 67.1, 66.7, 65.8, 47.2, 47.1, 45.1, 44.9, 39.4, 2 × 38.8, 38.1, 28.6, 27.8, 27.1, 26.5, 26.4, 26.3, 25.4 and 2 × 25.2; *m/z* (+ESI) calc. for $C_{22}H_{29}O_3S_2$ (MH^+) 405.1558, found 405.1553; calc. for $C_{22}H_{28}NaO_3S_2$ (MNa^+) 427.1378, found 427.1367.

General procedure for the epimerisation of dithiane-protected spiroketal units 1a and 1b

To a stirred solution of **1a** or **1b** in 1 : 1 DCM–MeCN (0.09 M) at 0 °C was added, dropwise, perchloric acid solution (1 cm^3 $mmol^{-1}$ of **1a** or **1b**, 10% *v*/*v* in H_2O). After 1 h, the reaction was diluted with Et_2O and neutralised using a saturated, aqueous solution of $NaHCO_3$. The aqueous phase was extracted with Et_2O (×4), and the recombinant organic extracts were washed with distilled water (×2) and brine (×1). Drying over anhydrous $MgSO_4$, filtration and *in vacuo* evaporation yielded a crude oil (quant.): ratio **1a** : **1b** = 1 : 2 by ^1H NMR studies.

General procedure for the formation of spiroketal units 24a–c and 25

To a stirred solution of spiroketal alcohol **1a**–**c** or **2a** in 3 : 1 MeOH–H_2O (0.1 M) was added, at ambient temperature, 2-methyl-2-butene (1.7 eq.) and NaH_2PO_4 (2.0 eq.). After cooling to 0 °C, $NaClO_2$ (6.0 eq.) was added, portionwise, and the resultant suspension was stirred at ambient temperature for 45 min. The reaction mixture was then diluted with distilled water and the aqueous phase extracted with EtOAc (×5). The recombinant organic extracts were washed with distilled water (×2) and brine (×1), dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. Purification was performed by gravimetric column chromatography on florisil, using 3 : 2 EtOAc and petroleum ether as eluent.

2-Benzyloxymethyl-8-hydroxymethyl-1,7-dioxaspiro[5.5]undecan-4-one isomer (24a). A clear, colourless oil (quant.); R_f 0.24 (3 : 2 EtOAc–petroleum ether); $[\alpha]_D^{25}$ +10.8 (*c* 5.00, CH_2Cl_2); υ_{max}(film)/cm^{-1} 3493, 2941, 2866, 1736, 1496, 1453, 1424, 1371, 1275, 1242, 1214, 1177, 1167, 1087, 1025, 1007, 958, 908, 870, 844, 804, 734 and 698; δ_H (600 MHz; $CDCl_3$; Me_4Si) 7.26–7.34 (5 H, m, *Ar*), 4.59–4.64 (2 H, m, –OCH_2Ph), 4.54–4.56 (1 H, m, H_2), 3.71–3.75 (1 H, m, H_{10}), 3.56–3.65 (4 H, m, H_1 and H_{11}), 2.90 (1 H, d, *J* 14.3, H_{5A}), 2.48 (1 H, dd, *J* 14.3 and 11.7, H_{3A}), 2.34–2.39 (2 H, m, H_{3B} and H_{5B}), 1.89–1.92 (1 H, m, H_{8A}), 1.76–1.79 (2 H, m, H_7), 1.56–1.62 (2 H, m, H_{8B} and H_{9A}) and 1.50–1.53 (1 H, m, H_{9B}); δ_C (150 MHz; $CDCl_3$; Me_4Si) 205.3, 137.8, 128.4, 127.8, 127.7, 100.6, 74.2, 73.5, 72.1, 69.5, 65.7, 47.9, 43.3, 35.2, 25.4 and 18.0; *m/z* (+ESI) calc. for $C_{18}H_{25}O_5$ (MH^+) 321.1702, found 321.1703; calc. for $C_{18}H_{24}NaO_5$ (MNa^+) 343.1521, found 343.1522.

2-Benzyloxymethyl-8-hydroxymethyl-1,7-dioxaspiro[5.5]undecan-4-one isomer (24b). A clear, colourless oil (quant.); R_f 0.18 (1 : 1 EtOAc–petroleum ether); $[\alpha]_D^{25}$ −3.8 (*c* 2.50, CH_2Cl_2); υ_{max}(film)/cm^{-1} 3453, 2941, 2867, 1722, 1603, 1497, 1454, 1400, 1365, 1310, 1288, 1272, 1248, 1208, 1126, 1090, 1040, 983, 955, 935, 903, 865, 844, 738 and 698; δ_H (600 MHz; $CDCl_3$; Me_4Si) 7.26–7.36 (5 H, m, *Ar*), 4.57–4.62 (2 H, m, –OCH_2Ph), 4.21–4.24 (1 H, m, H_2), 4.03–4.10 (1 H, m, H_{10}), 3.57–3.62 (2 H, m, H_1), 3.50–3.53 (1 H, m, H_{11A}), 3.40–3.44 (1 H, m, H_{11B}), 2.70 (1 H, dd, *J* 16.4 and 11.5, H_{3A}), 2.53–2.60 (2 H, m, H_5), 2.41 (1 H, dd, *J* 16.4 and 3.5, H_{3B}), 1.84–1.91 (2 H, m, H_{8A} and H_{7A}), 1.70–1.74 (1 H, m, H_{8B}), 1.48–1.52 (1 H, m, H_{9A}), 1.39 (1 H, td, *J* 13.0 and 3.9, H_{7B}) and 1.30–135 (1 H, m, H_{9B}); δ_C (150 MHz; $CDCl_3$; Me_4Si) 206.1, 137.9, 128.4, 127.8, 127.7, 98.9, 73.4, 72.7, 71.2, 70.9, 65.9, 51.0, 41.6, 33.7, 25.9 and 17.9; *m/z* (+ESI) calc. for $C_{18}H_{25}O_5$ (MH^+) 321.1702, found 321.1702; calc. for $C_{18}H_{24}NaO_5$ (MNa^+) 343.1521, found 343.1526.

2-Benzyloxymethyl-8-hydroxymethyl-1,7-dioxaspiro[5.5]undecan-4-one isomer (24c). A clear, colourless oil (quant.); R_f 0.30 (1 : 1 EtOAc–petroleum ether); $[\alpha]_D^{25}$ +42.7 (*c* 0.52, CH_2Cl_2); υ_{max}(film)/cm^{-1} 3439, 2941, 2870, 1717, 1604, 1497, 1454, 1439, 1405, 1364, 1310, 1277, 1254, 1224, 1208, 1151, 1124, 1079, 1041, 980, 904, 883, 834, 738 and 698; δ_H (600 MHz; $CDCl_3$; Me_4Si) 7.26–7.35 (5 H, m, *Ar*), 4.59–4.66 (2 H, m, –OCH_2Ph), 4.09–4.14 (1 H, m, H_2), 3.68–3.70 (1 H, m, H_{10}), 3.63 (1 H, dd, *J* 10.9 and 3.6, H_{1A}), 3.58 (1 H, dd, *J* 9.9 and 4.9, H_{1B}), 3.51–3.55 (1 H, m, H_{11A}), 3.43–3.49 (1 H, m, H_{11B}), 2.48 (1 H, dd, *J* 11.8 and 11.6, H_{3A}), 2.44 (2 H, s, H_5), 2.35 (1 H, dd, *J* 14.3 and 2.6, H_{3B}), 1.86–2.03 (2 H, m, H_{7A} and H_{8A}), 1.64–1.73 (1 H, m, H_{8B}), 1.43–1.54 (2 H, m, H_{7B} and H_{9A}) and 1.25–1.32 (1 H, m, H_{9B}); δ_C (150 MHz; $CDCl_3$; Me_4Si) 205.8, 138.1, 128.4, 127.7, 127.5, 99.5, 73.4, 72.0, 71.0, 68.4, 65.8, 51.7, 43.1, 34.4, 25.6 and 18.3; *m/z* (+ESI) calc. for $C_{18}H_{25}O_5$ (MH^+) 321.1702, found 321.1707.

2-(4-Bromobenzyloxymethyl)-8-hydroxymethyl-1,7-dioxaspiro-[5.5]undecan-4-one isomer (25). A clear, colourless oil (quant.); R_f 0.25 (1 : 1 EtOAc–petroleum ether); $[\alpha]_D^{25}$ +29.4 (*c* 0.14, CH_2Cl_2); υ_{max}(film)/cm^{-1} 3493, 2941, 2867, 1735, 1593, 1488, 1424, 1372, 1273, 1240, 1214, 1168, 1086, 1069, 1028, 1009, 960, 909, 871, 840, 804, 739 and 699; δ_H (600 MHz; $CDCl_3$; Me_4Si) 7.43 (2 H, d, *J* 8.2, *Ar*), 7.20 (2 H, d, *J* 8.3, *Ar*), 4.52–4.56 (2 H, m, –OCH_2Ph), 4.09–4.13 (1 H, m, H_2), 3.67–3.71 (1 H, m, H_{10}), 3.54–3.61 (2 H, m, H_1), 3.51–3.54 (1 H, m, H_{11A}), 3.43–3.48 (1 H, m, H_{11B}), 2.41–2.49 (3 H, m, H_{3A} and H_5), 2.33 (1 H, dd, *J* 14.5 and 2.6, H_{3B}), 2.13 (1 H, bs, *OH*), 1.91–1.98 (1 H, m, H_{8A}), 1.85–1.89 (1 H, m, H_{7A}), 1.65–1.69 (1 H, m, H_{8B}), 1.43–1.51 (2 H, m, H_{7B} and H_{9A}) and 1.23–1.32 (1 H, m, H_{9B}); δ_C (150 MHz; $CDCl_3$; Me_4Si) 205.7, 137.1, 131.5, 129.1, 121.5, 99.5, 73.4, 72.1, 71.1, 68.3, 65.7, 51.7, 43.0, 34.4, 25.5 and 18.3; *m/z* (+ESI) calc. for $C_{18}H_{23}BrNaO_5$ (MNa^+) 421.0627, found 421.0615.

(12-Benzyloxymethyl-1,2,6,11-tetraoxadispiro[2.1.5.3]tridec-7-yl)methanol (26). A stirred solution of spiroketal **24c** (20 mg, 62.5 μmol) in anhydrous DCM (1 cm^3) was cooled to −60 °C and treated, sequentially, with bis(trimethylsilyl)peroxide (11 mg, 62.5 μmol, 1.0 eq.) and $(CH_3)_3SiOTf$ or $BF_3{\cdot}Et_2O$ or $SnCl_4$ (31.2 μmol, 5 mol%). The reaction was warmed to −40 °C over 18 h, quenched with a saturated, aqueous solution of $NaHCO_3$ (2 cm^3) and then extracted with Et_2O (4 × 5 cm^3). The recombinant organic extracts were washed with distilled water (2 × 5 cm^3) and brine (1 × 5 cm^3), dried over anhydrous $MgSO_4$ and then concentrated *in vacuo*. Gravimetric column chromatography on florisil, using EtOAc as eluent, afforded the title compound **26**

as a clear, colourless oil (21 mg, quant.): R_f 0.44 (EtOAc); $[\alpha]_D^{25}$ +23.5 (*c* 0.20, CH_2Cl_2); υ_{max}(film)/cm^{-1} 3310, 2937, 1454, 1314, 1217, 1088, 1043; $CDCl_3$; Me_4Si) 7.25–7.34 (5 H, m, Ar), 4.58–4.64 (2 H, m, –OCH_2Ph), 4.02–4.04 (1 H, m, H_2), 3.80–3.84 (1 H, m, H_{10}), 3.64 (1 H, d, *J* 11.3, H_{11A}), 3.52–3.56 (3 H, m, H_1 and H_{11B}), 2.41 (1 H, d, *J* 14.4, H_{5A}), 2.18 (1 H, d, *J* 13.8, H_{3A}), 1.94–1.98 (1 H, m, H_{8A}), 1.70–1.74 (1 H, m, H_{7A}), 1.60–1.64 (3 H, m, H_{3B}, H_{5B} and H_{8B}), 1.46–1.51 (2 H, m, H_{7B} and H_{9A}) and 1.24–1.30 (1 H, m, H_{9B}); δ_C (150 MHz; $CDCl_3$; Me_4Si) 138.1, 128.4, 127.6, 127.5, 108.4, 96.8, 73.4, 72.3, 70.6, 66.9, 65.9, 37.4, 34.9, 32.1, 25.9 and 18.1; *m*/*z* (+EI) calc. for $C_{18}H_{25}O_6$ (MH^+) 337.2, found 337.1.

(12-Benzyloxymethyl-1,6,11-trioxadispiro[2.1.5.3]tridec-7-yl)-methanol (27). A stirred solution of spiroketal **24c** (58 mg, 181 μmol) in anhydrous DMSO (1 cm^3) was treated with a pre-prepared mixture of trimethylsulfonium oxide (60 mg, 270 μmol, 1.5 eq.) and potassium *t*-butoxide (30 mg, 270 μmol, 1.5 eq.) at room temperature. After stirring over 18 h, EtOAc (1 cm^3) and distilled water (1 cm^3) were added, and the subsequent aqueous phase extracted with EtOAc (3 × 1 cm^3). The recombinant organic extracts were washed with distilled water (2 × 1 cm^3) and brine (1 × 1 cm^3), dried over anhydrous $MgSO_4$, filtered and then evaporated *in vacuo*. Gravimetric column chromatography on florisil, using EtOAc as eluent, afforded the title compound **27** as a clear, colourless oil (21 mg, 80%); R_f 0.22 (EtOAc); $[\alpha]_D^{25}$ +72.7 (*c* 0.13, CH_2Cl_2); υ_{max}(film)/cm^{-1} 3455, 2921, 1720, 1595, 1454, 1364, 1231, 1168, 1086, 1048, 989; δ_H (600 MHz; $CDCl_3$; Me_4Si) 7.26–7.35 (5 H, m, *Ar*), 4.58–4.64 (2 H, m, –OCH_2Ph), 4.20–4.24 (1 H, m, H_2), 3.79–3.83 (1 H, m, H_{10}), 3.51–3.59 (4 H, m, H_1 and H_{11}), 2.55–2.59 (2 H, m, epoxide–CH_2–), 2.03–2.07 (2 H, m, H_{3A} and H_{5A}), 1.93–2.03 (1 H, m, H_{7A}), 1.70–1.74 (1 H, m, H_{8A}), 1.60–1.64 (1 H, m, H_{7B}), 1.43–1.53 (2 H, m, H_{8B} and H_{9A}), 1.33 (1 H, dd, *J* 14.2 and 1.8, H_{5B}) 1.23–1.28 (1 H, m, H_{9B}), and 1.19–1.21 (1 H, m, H_{3B}); δ_C (150 MHz; $CDCl_3$; Me_4Si) 138.4, 128.4, 127.5, 97.1, 73.3, 72.5, 70.3, 66.3, 66.0, 54.8, 50.6, 41.6, 34.6, 34.1, 26.0 and 18.2; *m*/*z* (+ESI) calc. for $C_{19}H_{26}NaO_5$ (MNa^+) 357.1678, found 357.1678.

2-Benzyloxymethyl-8-triethylsilanyloxymethyl-1,7-dioxaspiro-[5.5]undecan-4-one isomer (28). A stirred solution of spiroketal **24c** (20 mg, 62.5 μmol) in anhydrous DCM (1 cm^3) was cooled to −78 °C and treated, sequentially, with 2,6-lutidine (20 mg, 188 μmol, 3.0 eq.) and TESOTf (25 mg, 93.8 μmol, 1.5 eq.). The reaction was immediately warmed to 0 °C over 5 min, quenched with a saturated, aqueous solution of $NaHCO_3$ (2 cm^3) and then extracted with Et_2O (4 × 5 cm^3). The recombinant organic extracts were washed with distilled water (2 × 5 cm^3) and brine (1 × 5 cm^3), dried over anhydrous $MgSO_4$ and then concentrated *in vacuo*. The subsequent crude oil was purified by gravimetric column chromatography on florisil, using Et_2O and petroleum ether as eluent to afford the title compound **28** as a clear, colourless oil (27 mg, quant.): R_f 0.63 (2 : 3 Et_2O–petroleum ether); υ_{max}(film)/cm^{-1} 2950, 2907, 2873, 1718, 1455, 1274, 1212, 1155, 1092, 1072, 1010, 871, 812, 733, 697; δ_H (600 MHz; $CDCl_3$; Me_4Si) 7.26–7.36 (5 H, m, *Ar*), 4.58–4.64 (2 H, m, –OCH_2Ph), 4.13–4.17 (1 H, m, H_2), 3.60–3.69 (2 H, m, H_{1A} and H_{10}), 3.53–3.58 (2 H, m, H_{1B} and H_{11A}), 3.44–3.48 (1 H, m, H_{11B}), 2.30–2.46 (4 H, m, H_3 and H_5), 1.90–1.98 (1 H, m, H_{8A}), 1.80–1.89 (1 H, m, H_{7A}), 1.60–1.68 (2 H, m, H_{8B} and H_{9A}), 1.36–1.47 (1 H, m, H_{7B}), 1.15–1.25 (1 H, m, H_{9B}), 0.91 (9 H, t, *J* 8.1, –OSi(CH_2CH_3)$_3$) and 0.55 (6 H, q, *J* 7.9, –OSi(CH_2CH$_3$)$_3$); δ_C (150 MHz; $CDCl_3$; Me_4Si) 205.5, 138.2, 128.3, 127.6, 127.5, 99.3, 73.3, 72.1, 71.3, 67.9, 66.1, 51.6, 43.0, 34.4, 26.4, 18.7, 6.6 and 4.4; *m*/*z* (+EI) calc. for $C_{24}H_{39}O_5Si$ (MH^+) 435.3, found 435.3.

2-Hydroxymethyl-8-triethylsilanyloxymethyl-1,7-dioxaspiro-[5.5]undecan-4-one isomer (29). To a stirred solution of TES-protected spiroketal **28** (10 mg, 23 μmol) and 2-methylcyclohexadiene (0.5 cm^3) in anhydrous EtOH (0.5 cm^3) was added $CaCO_3$ (23 mg, 230 μmol, 10.0 eq.) and Pd(OH)$_2$/C (12 mg, 20 mol%) The reaction was refluxed for 18 h then cooled to ambient temperature, filtered and evaporated *in vacuo*. The subsequent crude oil was purified by gravimetric column chromatography on florisil, using EtOAc as eluent to afford the title compound **29** as a clear, colourless oil (8 mg, quant.): R_f 0.15 (EtOAc); υ_{max}(film)/cm^{-1} 3349, 1722, 1500, 1478, 1269, 1078, 1050, 1092, 1060, 1000; δ_H (600 MHz; $CDCl_3$; Me_4Si) 4.06–4.10 (1 H, m, H_2), 3.80–3.84 (1 H, m, H_{1A}), 3.55–3.64 (3 H, m, H_{1B}, H_{10} and H_{11A}), 3.45–3.49 (1 H, m, H_{11B}), 2.48 (1 H, dd, *J* 14.4 and 11.7, H_{3A}), 2.36–2.44 (2 H, m, H_5), 2.26–2.30 (1 H, m, H_{3B}), 1.84–1.95 (3 H, m, H_{7A}, H_{8A} and *OH*), 1.64–1.71 (2 H, m, H_{8B} and H_{9A}), 1.48 (1 H, dd, *J* 13.3 and 4.7, H_{7B}), 1.18–1.24 (1 H, m, H_{9B}), 0.93 (9 H, t, *J* 7.9, –OSi(CH_2CH_3)$_3$) and 0.56 (6 H, q, *J* 7.9, –OSi(CH_2CH$_3$)$_3$); δ_C (150 MHz; $CDCl_3$; Me_4Si) 205.3, 99.4, 71.4, 68.9, 66.0, 65.0, 51.6, 42.1, 34.3, 26.3, 18.6, 6.7 and 4.4; *m*/*z* (+EI) calc. for $C_{17}H_{33}O_5Si$ (MH^+) 345.2, found 345.2.

General procedure for the synthesis of aldehydes 30a–c

To a stirred solution of the spiroketal alcohol in anhydrous DCM (0.13 M) was added Dess–Martin periodinane reagent (2.0 eq.) at ambient temperature. The resultant reaction suspension was left stirring under a positive argon atmosphere for 2 h, then quenched through dropwise addition of a 1 : 1 mixture of saturated, aqueous $NaHCO_3$ and $Na_2S_2O_3$ solutions at 0 °C, followed by further stirring at ambient temperature for 20 min. The aqueous phase was then extracted with Et_2O (×3), and the recombinant organic extracts washed with distilled water (×2) and brine (×1). Drying over anhydrous $MgSO_4$, filtration, and *in vacuo* evaporation afforded a liquid oil, which was purified immediately by gravimetric, column chromatography on florisil, using Et_2O and petroleum ether as eluent. [For the formation of **30a** and **30b**, solid, anhydrous $NaHCO_3$ (10.0 eq.) was added, and the pH of the solution monitered (pH *ca.* 8) before the addition of Dess–Martin periodinane.

8-Benzyloxymethyl-10-oxo-1,7-dioxaspiro[5.5]undecane-2-carbaldehyde isomer (30a). A clear, colourless oil (83%); R_f 0.24 (3 : 7 EtOAc–petroleum ether); δ_H (600 MHz; $CDCl_3$; Me_4Si) 9.80 (1 H, s, H_{11}), 7.26–7.37 (5 H, m, *Ar*), 4.55–4.61 (3 H, m, H_2 and –OCH_2Ph), 4.06–4.10 (1 H, m, H_{10}), 3.54–3.59 (2 H, m, H_1), 2.73 (1 H, d, *J* 15.2, H_{5A}), 2.45–2.53 (3 H, m, H_3 and H_{5B}), 2.00–2.05 (1 H, m, H_{9A}), 1.80–1.91 (2 H, m, H_{8A} and H_{7A}), 1.64–1.73 (2 H, m, H_{7B} and H_{9B}) and 1.51–1.61 (1 H, m, H_{8B}); δ_C (150 MHz; $CDCl_3$; Me_4Si) 204.9, 202.5, 137.9, 128.4, 127.7, 127.6, 100.2, 78.2, 73.5, 71.8, 70.2, 50.4, 43.1, 35.8, 23.2 and 15.9; *m*/*z* (+EI) calc. for $C_{18}H_{23}O_5$ (MH^+) 319.2, found 319.1.

8-Benzyloxymethyl-10-oxo-1,7-dioxaspiro[5.5]undecane-2-carbaldehyde isomer (30b). A clear, colourless oil (80%); R_f 0.60 (1 : 1 EtOAc–petroleum ether); δ_H (600 MHz; $CDCl_3$; Me_4Si) 9.48

(1 H, s, H_{11}), 7.26–7.36 (5 H, m, *Ar*), 4.53–4.61 (2 H, m, –OCH_2Ph), 4.43–4.47 (1 H, m, H_{10}), 4.21–4.26 (1 H, m, H_2), 3.52–3.62 (2 H, m, H_1), 2.79–2.85 (1 H, m, H_{3A}), 2.60–2.66 (2 H, m, H_5), 2.37–2.42 (1 H, m, H_{3B}), 1.82–2.02 (3 H, m, H_{7A}, H_{8A} and H_{9A}), 1.68–1.78 (1 H, m, H_{8B}), 1.40–1.54 (1 H, m, H_{7B}) and 1.26–1.35 (1 H, m, H_{9B}); δ_C (150 MHz; $CDCl_3$; Me_4Si) 205.5, 201.6, 137.7, 128.5, 127.8, 127.7, 99.0, 75.3, 73.4, 72.2, 71.2, 50.3, 41.3, 33.7, 24.8 and 17.7; *m/z* (+EI) calc. for $C_{18}H_{23}O_5$ (MH^+) 319.2, found 319.1.

8-Benzyloxymethyl-10-oxo-1,7-dioxaspiro[5.5]undecane-2-carbaldehyde isomer (30c). A clear, colourless oil (90%.); R_f 0.53 (1 : 1 EtOAc–petroleum ether); δ_H (600 MHz; $CDCl_3$; Me_4Si) 9.55 (1 H, s, H_{11}), 7.26–7.37 (5 H, m, *Ar*), 4.57–4.64 (2 H, m, –OCH_2Ph), 4.07–4.11 (1 H, m, H_2), 4.01 (1 H, dd, *J* 12.3 and 2.4, H_{10}), 3.51–3.63 (2 H, m, H_1), 2.49 (1 H, dd, *J* 14.8 and 1.5, H_{3A}), 2.44–2.50 (2 H, m, H_{3B} and H_{5A}), 2.36–2.43 (1 H, m, H_{5B}), 1.98–2.08 (1 H, m, H_{8A}), 1.90–1.97 (1 H, m, H_{7A}), 1.83–1.89 (1 H, m, H_{9A}), 1.73–1.78 (1 H, m, H_{8B}), 1.48–1.58 (1 H, m, H_{7B}) and 1.32–1.42 (1 H, m, H_{9B}); δ_C (150 MHz; $CDCl_3$; Me_4Si) 208.9, 204.7, 137.9, 128.4, 127.7, 127.5, 99.7, 74.9, 73.5, 71.9, 68.8, 51.2, 42.9, 34.2, 24.7 and 17.9; *m/z* (+EI) calc. for $C_{18}H_{23}O_5$ (MH^+) 319.2, found 319.1.

General procedure for the synthesis of spiroketal-derived carbamates 35a,b, 36a,b and 37a,b

To an anhydrous DMF solution (0.25 M) of the spiroketal alcohol derivative was added, sequentially, pyridine (1.5 eq.) and *p*-nitrophenylchloroformate (1.5 eq.) in one portion at 0 °C. The reaction was then left to stir at ambient temperature for 20 min, at which point the requisite amine (1.0 eq.) was added dropwise. After stirring for 10 min, EtOAc and distilled water were added, and the subsequent aqueous phase extracted with EtOAc (×3). The recombinant organic extracts were washed with distilled water (×1) and brine (×1), dried over anhydrous $MgSO_4$, filtered and then evaporated *in vacuo*. The resultant crude was purified by gravimetric column chromatography on silica gel, using 3 : 7 EtOAc and petroleum ether as eluent.

(3-Morpholin-4-yl-propyl)carbamic acid 8-benzyloxymethyl-10-oxo-1,7-dioxaspiro[5.5]undec-2-ylmethyl ester isomer (35a). A colourless oil (80%); R_f 0.20 (EtOAc); $[a]_D^{25}$ +30.0 (*c* 0.81, CH_2Cl_2); υ_{max}(film)/cm^{-1} 3344, 2943, 2857, 1715, 1521, 1454, 1360, 1334, 1255, 1087, 1041, 983, 914, 861, 737 and 698; δ_H (600 MHz; $CDCl_3$; Me_4Si) 7.23–7.38 (5 H, m, *Ar*), 5.80 (1 H, s, –O(CO)N*H*–), 4.59–4.65 (2 H, m, –OCH_2Ph), 4.08–4.12 (1 H, m, H_2), 3.92–3.98 (2 H, m, H_{11}), 3.80–3.84 (1 H, m, H_{10}), 3.65–3.67 (4 H, m, –CH_2–N(–CH_2–CH_2–)$_2$O), 3.57–3.63 (2 H, m, H_1), 3.20–3.24 (2 H, m, H_{12}), 2.34–2.46 (10 H, m, H_3, H_5 and –CH_2–N(–CH_2–CH_2–)$_2$O), 1.93–1.99 (1 H, m, H_{8A}), 1.84–1.88 (1 H, m, H_{7A}), 1.62–1.69 (3 H, m, H_{8B} and H_{13}), 1.54–1.59 (1 H, m, H_{9A}), 1.42–1.50 (1 H, m, H_{7B}), 1.23–1.30 (1 H, m, H_{9B}); δ_C (150 MHz; $CDCl_3$; Me_4Si) 205.4, 156.4, 138.1, 128.4, 127.7, 127.5, 99.3, 73.4, 2 × 72.1, 68.7, 68.2, 67.1, 67.0, 2 × 53.6, 51.5, 43.1, 40.5, 34.2, 26.1, 25.6 and 18.4; *m/z* (+ESI) calc. for $C_{26}H_{39}N_2O_7$ (MH^+) 491.2757, found 491.2774.

Pyridin-2-ylmethylcarbamic acid 8-benzyloxymethyl-10-oxo-1,7-dioxaspiro[5.5]undec-2-ylmethyl ester isomer (35b). A colourless oil (85%); R_f 0.30 (EtOAc); $[a]_D^{25}$ +45.0 (*c* 0.87, CH_2Cl_2); υ_{max}(film)/cm^{-1} 2942, 1798, 1720, 1592, 1517, 1500, 1454, 1336, 1290, 1246, 1110, 1043, 993, 851, 754 and 699; δ_H (600 MHz; $CDCl_3$; Me_4Si) 8.50–8.53 (1 H, m, *Ar*), 7.64 (1 H, t, *J* 7.6, *Ar*), 7.23–7.34 (6 H, m, *Ar*), 7.16–7.19 (1 H, m, *Ar*), 5.73 (1 H, s, –O(CO)N*H*–), 4.58–4.65 (2 H, m, –OCH_2Ph), 4.47 (2 H, d, *J* 5.0, H_{12}), 4.09–4.11 (1 H, m, H_2), 4.03 (2 H, d, *J* 4.6, H_{11}), 3.82–3.84 (1 H, m, H_{10}), 3.54–3.58 (1 H, m, H_{1A}), 3.59–3.62 (1 H, m, H_{1B}), 2.32–2.47 (4 H, m, H_3 and H_5), 1.93–1.98 (1 H, m, H_{8A}), 1.86–1.90 (1 H, m, H_{7A}), 1.66–1.70 (1 H, m, H_{8B}), 1.57–1.61 (1 H, m, H_{9A}), 1.45–1.51 (1 H, m, H_{7B}), 1.25–1.32 (1 H, m, H_{9B}); δ_C (150 MHz; $CDCl_3$; Me_4Si) 205.5, 156.8, 156.4, 149.1, 138.1, 136.7, 128.4, 127.7, 127.5, 122.3, 121.7, 99.4, 73.4, 72.0, 68.8, 68.2, 67.4, 51.4, 46.0, 42.9, 34.2, 26.1 and 18.4; *m/z* (+EI) calc. for $C_{25}H_{30}N_2NaO_6$ (MNa^+) 477.2002, found 477.1989.

(3-Morpholin-4-yl-propyl)carbamic acid 8-(4-bromobenzyloxymethyl)-10-oxo-1,7-dioxaspiro[5.5]undec-2-ylmethyl ester isomer (36a). A colourless oil (80%); R_f 0.25 (EtOAc); $[a]_D^{25}$ +56.0 (*c* 0.43, CH_2Cl_2); υ_{max}(film)/cm^{-1} 3324, 2943, 1719, 1529, 1488, 1457, 1359, 1258, 1117, 1088, 1041, 1011, 984 and 804; δ_H (600 MHz; $CDCl_3$; Me_4Si) 7.47 (2 H, d, *J* 8.3, *Ar*), 7.21 (2 H, d, *J* 8.1, *Ar*), 5.82 (1 H, s, –O(CO)N*H*–), 4.54–4.59 (2 H, m, –OCH_2Ph), 4.07–4.13 (1 H, m, H_2), 3.90–4.00 (2 H, m, H_{11}), 3.76–3.82 (1 H, m, H_{10}), 3.64–3.68 (4 H, m, –CH_2–N(–CH_2–CH_2–)$_2$O), 3.55–3.62 (2 H, m, H_1), 3.20–3.24 (2 H, m, H_{12}), 2.33–2.45 (10 H, m, H_3, H_5 and –CH_2–N(–CH_2–CH_2–)$_2$O), 1.92–1.96 (1 H, m, H_{8A}), 1.83–1.88 (1 H, m, H_{7A}), 1.62–1.69 (3 H, m, H_{8B} and H_{13}), 1.55–1.59 (1 H, m, H_{9A}), 1.45–1.49 (1 H, m, H_{7B}), 1.22–1.29 (1 H, m, H_{9B}); δ_C (150 MHz; $CDCl_3$; Me_4Si) 205.2, 162.5, 156.4, 137.2, 131.5, 129.1, 121.5, 99.3, 72.6, 2 × 72.1, 68.7, 68.2, 67.1, 67.0, 2 × 53.6, 51.5, 43.0, 40.5, 34.2, 26.1, 25.6 and 18.4; *m/z* (+ESI) calc. for $C_{26}H_{38}BrN_2O_7$ (MH^+) 569.1862, found 569.1899; calc. for $C_{26}H_{37}BrN_2NaO_7$ (MNa^+) 591.1682, found 591.1687.

Pyridin-2-ylmethylcarbamic acid 8-(4-bromobenzyloxymethyl)-10-oxo-1,7-dioxaspiro[5.5]undec-2-ylmethyl ester isomer (36b). A colourless oil (85%); R_f 0.35 (EtOAc); $[a]_D^{25}$ +62.0 (*c* 0.50, CH_2Cl_2) υ_{max}(film)/cm^{-1} 3336, 3245, 2987, 1756, 1578, 1495, 1378, 1280, 1120, 1045, 1020, 988 and 810; δ_H (600 MHz; $CDCl_3$; Me_4Si) 8.50–8.51 (1 H, m, *Ar*), 7.68 (1 H, t, *J* 7.5, *Ar*), 7.46 (2 H, d, *J* 8.2, *Ar*), 7.26–7.30 (1 H, m, *Ar*), 7.19–7.24 (3 H, m, *Ar*), 5.78 (1 H, s, –O(CO)N*H*–), 4.51–4.59 (2 H, m, –OCH_2Ph), 4.47 (2 H, d, *J* 5.2, H_{12}), 4.08–4.14 (1 H, m, H_2), 3.98–4.03 (2 H, m, H_{11}), 3.78–3.83 (1 H, m, H_{10}), 3.53–3.60 (2 H, m, H_1), 2.33–2.47 (3 H, m, H_{3A} and H_5), 2.33 (1 H, d, *J* 14.3, H_{3B}), 1.90–1.97 (1 H, m, H_{8A}), 1.84–1.88 (1 H, m, H_{7A}), 1.66–1.70 (1 H, m, H_{8B}), 1.56–1.60 (1 H, m, H_{9A}), 1.45–1.50 (1 H, m, H_{7B}), 1.25–1.30 (1 H, m, H_{9B}); δ_C (150 MHz; $CDCl_3$; Me_4Si) 205.6, 162.8, 156.8, 148.8, 137.1, 131.5, 129.1, 128.4, 126.2, 122.6, 115.7, 99.4, 72.6, 72.1, 68.7, 68.2, 67.4, 51.4, 45.8, 42.9, 34.2, 26.0 and 18.4; *m/z* (+ESI) calc. for $C_{25}H_{29}BrN_2NaO_6$ (MNa^+) 555.1107, found 555.1091.

(3-Morpholin-4-yl-propyl)carbamic acid 8-benzyloxymethyl-10-oxo-1,7-dioxaspiro[5.5]undec-2-ylmethyl ester isomer (37a). A colourless oil (80%); R_f 0.10 (EtOAc); $[a]_D^{25}$ +2.0 (*c* 0.30, CH_2Cl_2); υ_{max}(film)/cm^{-1} 3344, 2943, 2857, 1715, 1521, 1454, 1360, 1334, 1255, 1087, 1041, 983, 914, 861, 737 and 698; δ_H (600 MHz; $CDCl_3$; Me_4Si) 7.26–7.35 (5 H, m, *Ar*), 5.71–5.75 (1 H, s, –O(CO)N*H*–), 4.50–4.64 (3 H, m, H_2 and –OCH_2Ph), 4.10–4.13 (2 H, m, H_{11}), 3.83–3.88 (1 H, m, H_{10}), 3.67–3.71 (4 H, m, –CH_2–N(–CH_2–CH_2–)$_2$O), 3.56–3.63 (2 H, m, H_1), 3.22–3.24 (2 H, m, H_{12}), 2.81–2.88 (1 H, m, H_{5A}), 2.34–2.52 (9 H, m, H_3, H_{5B} and –CH_2–N(–CH_2–CH_2–)$_2$O), 1.86–1.88 (2 H, m, H_{7A} and H_{8A}), 1.76–1.79 (1 H, m,

H_{7B}), 1.58–1.68 (4 H, m, H_{8B}, H_{9A} and H_{13}), 1.24–1.27 (1 H, m, H_{9B}); δ_C (150 MHz; $CDCl_3$; Me_4Si) 205.5, 156.4, 154.4, 138.0, 128.4, 127.7, 100.5, 73.4, 2 × 72.0, 69.3, 66.9, 66.6, 53.6, 48.1, 43.4, 40.4, 35.0, 25.7, 25.6 and 17.6 *m/z* (+ESI) calc. for $C_{26}H_{38}N_2NaO_7$ (MNa^+) 513.2577, found 513.2578.

Pyridin-2-ylmethylcarbamic acid 8-benzyloxymethyl-10-oxo-1,7-dioxaspiro[5.5]undec-2-ylmethyl ester isomer (37b). A colourless oil (85%); R_f 0.15 (EtOAc); $[\alpha]_D^{25}$ +4.0 (*c* 0.25, CH_2Cl_2); υ_{max}(film)/cm^{-1} 2942, 1798, 1720, 1592, 1517, 1500, 1454, 1336, 1290, 1246, 1110, 1043, 993, 851, 754 and 699; δ_H (600 MHz; $CDCl_3$; Me_4Si) 8.51–8.54 (1 H, m, *Ar*), 7.65–7.68 (1 H, t, *J* 7.5, *Ar*), 7.20–7.33 (7 H, m, *Ar*), 5.82 (1 H, s, –O(CO)N*H*–), 4.45–4.62 (5 H, m, H_2, H_{12} and –OCH_2Ph), 4.11–4.18 (2 H, m, H_{11}), 3.84–3.88 (1 H, m, H_{10}), 3.53–3.63 (2 H, m, H_1), 2.79–2.83 (1 H, m, H_{5A}), 2.49–2.56 (1 H, m, H_{3A}), 2.30–2.41 (2 H, m, H_{3B} and H_{5B}), 1.83–1.92 (1 H, m, H_{8A}), 1.72–1.82 (2 H, m, H_7), 1.52–1.63 (2 H, m, H_{8B} and H_{9A}), 1.42–1.52 (1 H, m, H_{9B}); δ_C (150 MHz; $CDCl_3$; Me_4Si) 205.5, 157.0, 156.6, 148.8, 138.0, 137.2, 128.4, 127.6, 126.2, 122.6, 121.9, 100.5, 73.4, 72.0, 71.8, 69.3, 67.0, 48.3, 45.9, 43.3, 34.9, 25.6 and 17.5; *m/z* (+ESI) calc. for $C_{25}H_{30}N_2NaO_6$ (MNa^+) 477.2002, found 477.1979.

General procedure for the synthesis of spiroketal esters 38a–f, 39, 40a–c and 41

To a stirred, argon-flushed solution of the spiroketal-derived primary alcohol in anhydrous DMF (12.5 μM) was added at ambient temperature, in the order written: Hünigs base (5.0 eq.), the requisite *N*-Fmoc-protected α-amino acid (1.0 eq.), and HOAt (3.0 eq.). The resultant yellow solution was then cooled to 0 °C, and treated with HATU (3.0 eq.), through a portion-wise addition, and left to reach ambient temperature with overnight stirring under a positive argon atmosphere. After 48 h, the reaction was diluted with EtOAc and the resultant organic phase extracted with a saturated, aqueous solution of $NaHCO_3$ (×3) with the combined, basic, aqueous phases subject to further extraction using EtOAc (×3). The recombinant organic extracts were then washed with distilled water (×1) and brine (×1), dried over anhydrous $MgSO_4$, filtered and evaporated *in vacuo*. The resultant pale-pellow/light-brown crude was purified by gravimetric column chromatography on silica gel, using EtOAc and petroleum ether as eluent. [For formation of **38a**, **39** and **40a** 1.25 eq. of HATU and HOAt, as well as 2.00 eq. of Hünigs base were used with a reaction time of 18 h; all de were verified by Chiral HPLC.]

(9*H*-Fluoren-9-ylmethoxycarbonylamino)acetic acid 8-benzyloxymethyl-10-oxo-1,7-dioxaspiro[5.5]undec-2-ylmethyl ester isomer (38a). A clear, colourless oil (93%); R_f 0.41 (1 : 1 EtOAc–petroleum ether); υ_{max}(film)/cm^{-1} 3297, 2918, 2354, 2202, 1953, 1718, 1529, 1451, 1250, 1084, 1031, 740, 669; δ_H (600 MHz; $CDCl_3$; Me_4Si) 7.76 (2 H, d, *J* 7.5, *Ar*), 7.60 (2 H, d, *J* 7.4, *Ar*), 7.40 (2 H, t, *J* 7.5, *Ar*), 7.26–7.34 (7 H, m, *Ar*), 5.25–5.29 (1 H, m, *NH*), 4.56–4.62 (2 H, m, –OCH_2Ph), 4.40 (2 H, d, *J* 7.1, H_{13}), 4.23 (1 H, t, *J* 7.1, H_{14}), 4.12 (1 H, dd, *J* 11.4 and 6.9, H_{11A}), 4.05–4.08 (2 H, m, H_2 and H_{11B}), 3.99 (1 H, dd, *J* 18.2 and 5.8, H_{12A}), 3.91 (1 H, dd, *J* 18.2 and 5.3, H_{12B}), 3.82–3.87 (1 H, m, H_{10}), 3.56–3.60 (2 H, m, H_1), 2.34–2.46 (4 H, m, H_3 and H_5), 1.93–2.02 (1 H, m, H_{8A}), 1.84–1.88 (1 H, m, H_{7A}), 1.68–1.72 (1 H, m, H_{8B}), 1.54–1.58 (1 H, m, H_{9A}), 1.45–1.55 (1 H, m, H_{7B}) and 1.25–1.32 (1 H, m, H_{9B}); δ_C (150 MHz; $CDCl_3$; Me_4Si) 205.3, 166.9, 156.5, 143.8, 141.3, 138.0, 128.4, 127.7, 127.5, 127.1, 125.1, 120.0, 99.4, 73.4, 72.0, 68.5, 68.2, 67.5, 67.2, 51.4, 47.1, 43.0, 42.7, 34.1, 25.6 and 18.4; *m/z* (+EI) calc. for $C_{35}H_{38}NO_8$ (MH^+) 600.3, found 600.2.

2-(9*H*-Fluoren-9-ylmethoxycarbonylamino)-3-phenylpropionic acid 8-benzyloxymethyl-10-oxo-1,7-dioxaspiro[5.5]undec-2-ylmethyl ester isomer (38b). A clear, colourless oil (70%); R_f 0.44 (2 : 3 EtOAc–petroleum ether); υ_{max}(film)/cm^{-1} 3294, 2916, 2350, 2198, 1985, 1720, 1530, 1451, 1249, 1212, 1078, 988, 759, 741; δ_H (600 MHz; $CDCl_3$; Me_4Si) 7.77 (2 H, d, *J* 7.5, *Ar*), 7.55 (2 H, t, *J* 7.2, *Ar*), 7.40 (2 H, t, *J* 7.4, *Ar*), 7.21–7.34 (10 H, m, *Ar*), 7.07 (2 H, d, *J* 7.1, *Ar*), 5.23 (1 H, m, *NH*), 4.62–4.65 (1 H, m, H_{12}), 4.56–4.62 (2 H, m, –OCH_2Ph), 4.43 (1 H, dd, *J* 10.4 and 7.3, H_{13A}), 4.29 (1 H, dd, *J* 10.4 and 7.1, H_{13B}), 4.19 (1 H, t, *J* 7.0, H_{14}), 4.11–4.14 (1 H, m, H_2), 4.01–4.05 (2 H, m, H_{11}), 3.83–3.87 (1 H, m, H_{10}), 3.54–3.58 (2 H, m, H_1), 3.10 (1 H, dd, *J* 13.9 and 5.4, –CH(H_A)Ph), 2.98 (1 H, dd, *J* 13.9 and 6.3, –CH(H_B)Ph), 2.39–2.47 (3 H, m, H_{3A} and H_5), 2.31–2.34 (1 H, m, H_{3B}), 1.92–2.02 (1 H, m, H_{8A}), 1.84–1.92 (1 H, m, H_{7A}), 1.67–1.70 (1 H, m, H_{8B}), 1.43–1.56 (2 H, m, H_{7B} and H_{9A}) and 1.20–1.24 (1 H, m, H_9); δ_C (150 MHz; $CDCl_3$; Me_4Si) 205.0, 171.3, 155.5, 143.8, 143.7, 141.3, 138.1, 135.6, 129.3, 128.6, 128.4, 127.7, 127.5, 127.1, 127.0, 125.1, 125.0, 120.0, 119.9, 99.4, 73.4, 72.0, 68.5, 68.1, 67.8, 66.9, 54.7, 51.4, 47.1, 42.9, 38.2, 34.1, 26.1 and 18.3; *m/z* (+EI) calc. for $C_{42}H_{44}NO_8$ (MH^+) 690.3, found 690.2.

2-(9*H*-Fluoren-9-ylmethoxycarbonylamino)propionic acid 8-benzyloxymethyl-10-oxo-1,7-dioxaspiro[5.5]undec-2-ylmethyl ester isomer (38c). A clear, colourless oil (50%); R_f 0.37 (2 : 3 EtOAc–petroleum ether); υ_{max}(film)/cm^{-1} 3290, 2943, 2378, 2203, 1945, 1721, 1530, 1451, 1234, 1212, 997, 743, 688; δ_H (600 MHz; $CDCl_3$; Me_4Si) 7.76 (2 H, d, *J* 7.4, *Ar*), 7.55–7.63 (2 H, m, *Ar*), 7.40 (2 H, t, *J* 7.4, *Ar*), 7.26–7.36 (7 H, m, *Ar*), 5.34 (1 H, d, *J* 7.5, *NH*), 4.56–4.62 (2 H, m, –OCH_2Ph), 4.34–4.41 (3 H, m, H_{12} and H_{13}), 4.22 (1 H, t, *J* 7.0, H_{14}), 4.10–4.14 (2 H, m, H_2 and H_{11A}), 4.04 (1 H, d, *J* 11.2, H_{11B}), 3.85–3.88 (1 H, m, H_{10}), 3.55–3.60 (2 H, m, H_1), 2.36–2.50 (3 H, m, H_3 and H_{5A}), 2.33 (1 H, d, *J* 14.4, H_{5B}), 1.95–2.01 (1 H, m, H_{8A}), 1.85–1.92 (1 H, m, H_{7A}), 1.68–1.71 (1 H, m, H_{8B}), 1.56–1.60 (1 H, m, H_{9A}), 1.45–1.53 (1 H, m, H_{7B}), 1.36 (3 H, d, *J* 6.8, –CH_3) and 1.21–1.28 (1 H, m, H_{9B}); δ_C (150 MHz; $CDCl_3$; Me_4Si) 205.2, 172.7, 155.6, 143.9, 143.8, 141.2, 138.1, 128.4, 127.7, 127.6, 127.5, 127.1, 125.1, 120.0, 99.4, 73.4, 72.0, 68.5, 68.1, 67.5, 66.9, 51.4, 49.6, 47.1, 43.0, 34.1, 26.0, 18.6 and 18.3; *m/z* (+EI) calc. for $C_{36}H_{40}NO_8$ (MH^+) 614.3, found 614.2.

2-(9*H*-Fluoren-9-ylmethoxycarbonylamino)pent-4-enoic acid 8-benzyloxymethyl-10-oxo-1,7-dioxaspiro[5.5]undec-2-ylmethyl ester isomer (38d). A clear, yellow oil (26%); R_f 0.32 (7 : 13 EtOAc–petroleum ether); υ_{max}(film)/cm^{-1} 3298, 2954, 2359, 2192, 2022, 1721, 1524, 1453, 1249, 988, 743, 688; δ_H (600 MHz; $CDCl_3$; Me_4Si) 7.77 (2 H, d, *J* 7.4, *Ar*), 7.55 (2 H, d, *J* 7.1, *Ar*), 7.39 (2 H, t, *J* 7.3, *Ar*), 7.26–7.36 (7 H, m, *Ar*), 5.61–5.71 (1 H, m, –CH_2–C*H*=CH_2), 5.26–5.35 (1 H, m, *NH*), 5.07–5.17 (2 H, m, –CH_2–CH=CH_2), 4.59 (2 H, m, –OCH_2Ph), 4.37–4.49 (2 H, m, H_{12} and H_{13A}), 4.30–4.37 (1 H, m, H_{13B}), 4.19–4.26 (1 H, t, *J* 7.0, H_{14}), 4.02–4.15 (3 H, m, H_2 and H_{11}), 3.82–3.92 (1 H, m, H_{10}), 3.53–3.62 (2 H, m, H_1), 2.51–2.62 (1 H, m, –CH(H_A)–CH=CH_2), 2.30–2.50 (5 H, m, H_3, H_5 and –CH(H_B)–CH=CH_2), 1.92–2.03 (1 H, m, H_{8A}), 1.84–1.91 (1 H, m, H_{7A}), 1.66–1.73 (1 H, m, H_{8B}), 1.54–1.61 (1 H, m, H_{9A}), 1.43–1.53

(1 H, m, H_{7B}) and 1.22–1.38 (1 H, m, H_{9B}); δ_C (150 MHz; $CDCl_3$; Me_4Si) 205.0, 171.7, 156.4, 143.9, 143.8, 141.3, 138.1, 128.4, 127.7, 127.5, 127.1, 125.1, 120.0, 119.9, 119.5, 99.4, 73.4, 72.0, 68.4, 68.1, 67.7, 67.0, 53.3, 51.4, 47.1, 42.9, 36.7, 34.1, 26.1 and 18.3; *m/z* (+EI) calc. for $C_{38}H_{42}NO_8$ (MH^+) 640.3, found 640.2.

2-(9*H*-Fluoren-9-ylmethoxycarbonylamino)-3-furan-2-yl-propionic acid 8-benzyl-oxymethyl-10-oxo-1,7-dioxaspiro[5.5]undec-2-ylmethyl ester isomer (38e). A clear, colourless oil (94%); R_f 0.36 (2 : 3 EtOAc–petroleum ether); υ_{max}(film)/cm^{-1} 3290, 2943, 2323, 2192, 2022, 1719, 1529, 1453, 1212, 988, 743, 668; δ_H (600 MHz; $CDCl_3$; Me_4Si) 7.76 (2 H, d, *J* 7.4, *Ar*), 7.55–7.62 (2 H, m, *Ar*), 7.39 (2 H. t, *J* 7.4, *Ar*), 7.23–7.36 (8 H, m, *Ar*), 6.21 (1 H, s, *Ar*), 6.05–6.07 (1 H, m, *Ar*), 5.40–5.46 (1 H, m, *NH*), 4.58–4.63 (3 H, m, H_{12} and $-OCH_2Ph$), 4.40–4.44 (1 H, m, H_{13A}), 4.28–4.32 (1 H, m, H_{13B}), 4.19–4.24 (1 H, m, H_{14}), 4.04–4.14 (3 H, m, H_2 and H_{11}), 3.81–3.90 (1 H, m, H_{10}), 3.51–3.61 (2 H, m, H_1), 3.05–3.25 (2 H, m, $-CH_2$–furan), 2.30–2.40 (4 H, m, H_3 and H_5), 1.93–2.03 (1 H, m, H_{8A}), 1.83–1.92 (1 H, m, H_{7A}), 1.67–1.71 (1 H, m, H_{8B}), 1.58–1.62 (1 H, m, H_{9A}), 1.46–1.53 (1 H, m, H_{7B}) and 1.23–1.40 (1 H, m, H_{9B}); δ_C (150 MHz; $CDCl_3$; Me_4Si) 205.2, 170.8, 155.5, 150.1, 143.9, 143.8, 142.2, 141.3, 138.1, 132.5, 130.9, 128.8, 128.4, 127.7, 127.5, 127.1, 125.2, 125.1, 120.0, 110.4, 108.1, 99.4, 73.4, 72.0, 68.5, 68.1, 67.7, 67.1, 53.1, 51.4, 47.1, 42.9, 34.1, 30.8, 26.2 and 18.4; *m/z* (+ESI) calc. for $C_{40}H_{42}NO_9$ (MH^+) 680.2860, found 680.2882.

1-(9*H*-Fluoren-9-ylmethoxycarbonylamino)cyclobutane carboxylic acid 8-benzyloxymethyl-10-oxo-1,7-dioxaspiro[5.5]undec-2-ylmethyl ester (38f). A clear, colourless oil (44%); R_f 0.31 (7 : 13 EtOAc–petroleum ether); υ_{max}(film)/cm^{-1} 3288, 2932, 2356, 2145, 2022, 1720, 1523, 1453, 1212, 1078, 988, 743, 668; δ_H (600 MHz; $CDCl_3$; Me_4Si) 7.76 (2 H, d, *J* 7.1, *Ar*), 7.56–7.64 (2 H, m, *Ar*), 7.37–7.41 (2 H, m, *Ar*), 7.26–7.35 (7 H, m, *Ar*), 5.49 (1 H, s, *NH*), 4.54–4.61 (2 H, m, $-OCH_2Ph$), 4.34–4.38 (2 H, m, H_{13}), 4.20–4.24 (1 H, m, H_{14}) 4.06–4.15 (3 H, m, H_2 and H_{11}), 3.83–3.94 (1 H, m, H_{10}), 3.54–3.59 (2 H, m, H_1), 2.48–2.63 (2 H, m, cyclobutyl–CH_2–), 2.33–2.46 (6 H, m, H_3, H_5 and cyclobutyl–CH_2–), 1.95–2.05 (3 H, m, H_{8A} and cyclobutyl–CH_2–), 1.87 (1 H, d, *J* 13.4, H_{7A}), 1.65–1.71 (1 H, m, H_{8B}), 1.56–1.62 (1 H, m, H_{9A}), 1.44–1.50 (1 H, m, H_{7B}) and 1.26–1.36 (1 H, m, H_{9B}); δ_C (150 MHz; $CDCl_3$; Me_4Si) 205.3, 171.1, 155.5, 2 × 143.9, 141.3, 138.1, 128.4, 127.7, 127.5, 127.0, 125.1, 2 × 119.9, 99.4, 73.4, 72.0, 68.4, 68.2, 67.6, 66.6, 51.5, 47.2, 43.1, 34.1, 31.2, 26.0, 18.4 and 15.0; *m/z* (+EI) calc. for $C_{38}H_{42}NO_8$ (MH^+) 640.3, found 640.2.

(9*H*-Fluoren-9-ylmethoxycarbonylamino)acetic acid 8-(4-bromo-benzyloxymethyl)-10-oxo-1,7-dioxaspiro[5.5]undec-2-ylmethyl ester (39). A clear, colourless oil (92%); R_f 0.27 (1 : 1 EtOAc–petroleum ether); υ_{max}(film)/cm^{-1} 3327, 2954, 2358, 2192, 1719, 1529, 1453, 1245, 988, 759, 743, 668; δ_H (600 MHz; $CDCl_3$; Me_4Si) 7.76 (2 H, d, *J* 11.0, *Ar*), 7.60 (2 H, dd, *J* 11.1 and 7.8, *Ar*), 7.44–7.48 (2 H, m, *Ar*), 7.39 (2 H, t, *J* 7.5, *Ar*), 7.28–7.34 (2 H, m, *Ar*), 7.17–7.22 (2 H, m, *Ar*), 5.30–5.34 (1 H, m, *NH*), 4.53–4.60 (2 H, m, $-OCH_2Ph$), 4.36–4.40 (2 H, m, H_{13}), 4.23 (1 H, t, *J* 7.1, H_{14}), 4.09–4.14 (1 H, m, H_{11A}), 3.96–4.08 (3 H, m, H_2, H_{11B} and H_{12A}), 3.87–3.94 (1 H, m, H_{12B}), 3.80–3.86 (1 H, m, H_{10}), 3.53–3.64 (2 H, m, H_1), 2.32–2.50 (4 H, m, H_3 and H_5), 1.84–1.95 (1 H, m, H_{7A}), 1.63–1.74 (2 H, m, H_8), 1.44–1.51 (2 H, m, H_{7B} and H_{9A}) and 1.28–1.35 (1 H, m, H_{9B}); δ_C (150 MHz; $CDCl_3$; $MeSi_4$) 205.6, 171.1, 156.7, 143.9, 141.3, 137.1, 131.5, 129.1, 127.6, 127.1, 125.1, 121.5, 120.0, 99.5, 73.4, 72.1, 68.4, 68.2, 67.5, 67.2, 51.7, 47.1, 43.0, 42.7, 34.1, 25.5 and 18.3; *m/z* (+EI) calc. for $C_{35}H_{37}BrNO_8$ (MH^+) 678.2, found 678.2.

(9*H*-Fluoren-9-ylmethoxycarbonylamino)acetic acid 8-benzyl-oxymethyl-10-oxo-1,7-dioxaspiro[5.5]undec-2-ylmethyl ester isomer (40a). A clear, colourless oil (90%); R_f 0.24 (1 : 1 EtOAc–petroleum ether); υ_{max}(film)/cm^{-1} 3290, 2354, 2202, 2158, 2053, 1985, 1953, 1719, 1529, 1451, 1245, 1084, 1031, 743, 668; δ_H (600 MHz; $CDCl_3$; Me_4Si) 7.76 (2 H, d, *J* 7.5, *Ar*), 7.53–7.62 (2 H, m, *Ar*), 7.40 (2 H, t, *J* 7.5, *Ar*), 7.23–7.36 (7 H, m, *Ar*), 6.25–6.27 (1 H, m, *NH*), 4.61 (2 H, m, $-OCH_2Ph$), 4.40 (2 H, d, *J* 7.1, H_{13}), 4,23 (1 H, t, *J* 7.1, H_{14}), 4.12 (1 H, m, H_{11A}), 4.06 (2 H, m, H_2 and H_{11B}), 3.98 (1 H, dd, *J* 18.2 and 5.9, H_{12A}), 3.93 (1 H, dd, *J* 18.3 and 5.9, H_{12B}), 3.83–3.87 (1 H, m, H_{10}), 3.55–3.59 (2 H, m, H_1), 2.35–2.43 (4 H, m, H_3 and H_5), 1.96–2.00 (1 H, m, H_{8A}), 1.83–1.86 (1 H, m, H_{7A}), 1.68–1.71 (1 H, m, H_{8B}), 1.57–1.61 (1 H, m, H_{9A}), 1.45–1.50 (1 H, m, H_{7B}) and 1.30–1.35 (1 H, m, H_{9B}); δ_C (150 MHz; $CDCl_3$; Me_4Si) 205.3, 169.9, 156.1, 143.8, 141.3, 138.0, 128.4, 127.7, 127.5, 127.1, 125.1, 120.0, 99.4, 73.4, 72.0, 68.5, 68.2, 67.5, 67.2, 51.4, 47.1, 43.0, 42.7, 34.1, 25.6 and 18.4; *m/z* (+EI) calc. for $C_{35}H_{38}NO_8$ (M^+) 600.3, found 600.2.

2-(9*H*-Fluoren-9-ylmethoxycarbonylamino)-3-phenylpropionic acid 8-benzyloxymethyl-10-oxo-1,7-dioxaspiro[5.5]undec-2-ylmethyl ester isomer (40b). A clear, colourless oil (65%); R_f 0.29 (2 : 3 EtOAc–petroleum ether); υ_{max}(film)/cm^{-1} 3278, 2359, 2196, 2150, 2053, 1945, 1713, 1520, 1478, 1221, 1033, 743, 668; δ_H (600 MHz; $CDCl_3$; Me_4Si) 7.76 (2 H, d, *J* 7.3, *Ar*), 7.53–7.60 (2 H, m, *Ar*), 7.38–7.42 (2 H, m, *Ar*), 7.19–7.35 (10 H, m, *Ar*), 7.13 (2 H, d, *J* 6.9, *Ar*), 5.23 (1 H, m, *NH*), 4.62 (1 H, m, H_{12}), 4.56–4.62 (2 H, m, $-OCH_2Ph$), 4.41–4.45 (1 H, m, H_{13A}), 4.27–4.31 (1 H, m, H_{13B}), 4.19 (1 H, t, *J* 7.0, H_{14}), 4.10–4.15 (1 H, m, H_2), 4.00–4.05 (2 H, m, H_{11}), 3.84–3.88 (1 H, m, H_{10}), 3.53–3.59 (2 H, m, H_1), 3.10 (1 H, dd, *J* 13.9 and 5.4, $-CH(H_A)Ph$), 2.98 (1 H, dd, *J* 13.9 and 6.3, $-CH(H_B)Ph$), 2.36–2.42 (4 H, m, H_3 and H_5), 1.95–1.99 (1 H, m, H_{8A}), 1.82–1.88 (1 H, m, H_{7A}), 1.67–1.72 (1 H, m, H_{8B}), 1.57–1.61 (1 H, m, H_{9A}), 1.45–1.49 (1 H, m, H_{7B}) and 1.30–1.35 (1 H, m, H_{9B}); δ_C (150 MHz; $CDCl_3$; Me_4Si) 205.0, 171.3, 155.5, 143.8, 143.7, 141.3, 138.1, 135.6, 129.31, 128.6, 128.4, 127.6, 127.5, 127.1, 127.0, 125.1, 125.0, 2 × 120.0, 99.4, 73.4, 72.0, 68.5, 68.1, 67.8, 66.9, 54.7, 51.4, 47.1, 42.9, 38.2, 34.1, 26.1 and 18.3; *m/z* (+EI) calc. for $C_{42}H_{44}NO_8$ (MH^+) 690.3, found 690.2.

2-(9*H*-Fluoren-9-ylmethoxycarbonylamino)-3-furan-2-yl-propionic acid 8-benzyl-oxymethyl-10-oxo-1,7-dioxaspiro[5.5]undec-2-ylmethyl ester isomer (40c). A clear colourless oil (95%); R_f 0.40 (2 : 3 EtOAc–petroleum ether); υ_{max}(film)/cm^{-1} 3297, 2355, 2196, 2158, 1953, 1721, 1534, 1465, 1210, 1100, 786, 743, 668; δ_H (600 MHz; $CDCl_3$; Me_4Si) 7.76 (2 H, d, *J* 7.4, *Ar*), 7.55–7.62 (2 H, m, *Ar*), 7.39 (2 H, t, *J* 7.4, *Ar*), 7.23–7.36 (8 H, m, *Ar*), 6.19–6.23 (1 H, m, *Ar*), 6.05–6.07 (1 H, m, *Ar*), 5.40–5.46 (1 H, m, *NH*), 4.58–4.63 (3 H, m, H_{12} and $-OCH_2Ph$), 4.40–4.44 (1 H, m, H_{13A}), 4.28–4.32 (1 H, m, H_{13B}), 4.19–4.24 (1 H, m, H_{14}), 4.04–4.14 (3 H, m, H_2 and H_{11}), 3.81–3.90 (1 H, m, H_{10}), 3.51–3.61 (2 H, m, H_1), 3.05–3.25 (2 H, m, $-CH_2$–furan), 2.30–2.40 (4 H, m, H_3 and H_5), 1.93–2.03 (1 H, m, H_{8A}), 1.83–1.92 (1 H, m, H_{7A}), 1.67–1.71 (1 H, m, H_{8B}), 1.58–1.62 (1 H, m, H_{9A}), 1.46–1.53 (1 H, m, H_{7B}) and 1.23–1.40 (1 H, m, H_{9B}); δ_C (150 MHz; $CDCl_3$; Me_4Si) 205.2, 170.8, 155.5,

150.1, 143.9, 143.8, 142.2, 141.3, 138.1, 132.5, 130.9, 128.8, 128.4, 127.7, 127.5, 127.1, 125.2, 125.1, 120.0, 110.4, 108.1, 99.4, 73.4, 72.0, 68.5, 68.1, 67.7, 67.1, 53.1, 51.4, 47.1, 42.9, 34.1, 30.8, 26.2 and 18.4; *m/z* (+ESI) calc. for $C_{40}H_{42}NO_9$ (MH^+) 680.2860, found 680.2882.

2-(9*H*-Fluoren-9-ylmethoxycarbonylamino)-3-furan-2-yl-propionic acid 8-benzyl-oxymethyl-10-oxo-1,7-dioxaspiro[5.5]undec-2-yl methyl ester isomer (41). A clear colourless oil (80%); R_f 0.45 (2 : 3 EtOAc–petroleum ether); υ_{max}(film)/cm^{-1} 3301, 2347, 2187, 2123, 1912, 1717, 1534, 1455, 1210, 1100, 786, 743, 650; δ_H (600 MHz; $CDCl_3$; Me_4Si) 7.77 (2 H, d, *J* 7.5, *Ar*), 7.54–7.61 (2 H, m, *Ar*), 7.40 (2 H, t, *J* 7.4, *Ar*), 7.24–7.37 (10 H, m, *Ar*), 6.20–6.22 (1 H, m, *Ar*), 6.04–6.07 (1 H, m, *Ar*), 5.39–5.47 (1 H, m, *NH*), 4.56–4.62 (3 H, m, H_{12} and $-OCH_2Ph$), 4.39–4.44 (1 H, m, H_{13A}), 4.26–4.32 (1 H, m, H_{13B}), 4.20–4.25 (1 H, m, H_{14}), 4.05–4.15 (3 H, m, H_2 and H_{11}), 3.79–3.88 (1 H, m, H_{10}), 3.51–3.60 (2 H, m, H_1), 3.06–3.23 (2 H, m, $-CH_2$–furan), 2.29–2.39 (4 H, m, H_3 and H_5), 1.94–2.03 (1 H, m, H_{8A}), 1.84–1.91 (1 H, m, H_{7A}), 1.68–1.71 (1 H, m, H_{8B}), 1.57–1.63 (1 H, m, H_{9A}), 1.45–1.54 (1 H, m, H_{7B}) and 1.22–1.40 (1 H, m, H_{9B}); δ_C (150 MHz; $CDCl_3$; Me_4Si) 204.8, 170.9, 155.2, 150.0, 143.8, 143.7, 142.3, 141.2, 137.9, 132.5, 131.0, 128.9, 128.5, 127.7, 127.5, 127.0, 125.0, 124.9, 120.0, 110.5, 108.2, 99.8, 73.5, 72.0, 68.3, 68.1, 67.8, 67.5, 53.0, 51.4, 47.5, 43.2, 34.2, 30.6, 26.1 and 18.5; *m/z* (+ESI) calc. for $C_{40}H_{42}NO_9$ (MH^+) 680.2860, found 680.2883.

General procedure for the synthesis of urea derivatives 42a–e, 43a,b and 44a,b

Polymer-bound piperazine (10.0 eq.) was added to a solution of the spiroketal-derived ester in anhydrous DCM (0.1 M), and subjected to microwave heating at 120 °C for 30 min. Sequestration of the polymer reagent, followed by evaporation of the resultant filtrate *in vacuo* yielded the crude amine intermediate, which was subsequently re-dissolved in anhydrous DCM (0.1 M) and treated with ethyl isocyanate (1.0 eq.) at ambient temperature. The resultant reaction mixture was then left to stir for 30 min at ambient temperature. Evaporation *in vacuo* was then followed by purification of the resultant crude liquid by gravimetric column chromatography on silica gel, using EtOAc and petroleum ether.

2-(3-Ethylureido)propionic acid 8-benzyloxymethyl-10-oxo-1,7-dioxaspiro[5.5]undec-2-ylmethyl ester isomer (42a). A clear, colourless oil (quant. over two steps); R_f 0.48 (EtOAc); $[\alpha]_D^{25}$ +7.8 (*c* 0.09, CH_2Cl_2); υ_{max}(film)/cm^{-1} 3380, 2951, 2879, 1776, 1720, 1663, 1564, 1500, 1436, 1348, 1301, 1272, 1212, 1178, 1153, 1144, 1059, 1050, 975, 878, 807, 732, 721 and 680; δ_H (600 MHz; $CDCl_3$; Me_4Si) 7.26–7.36 (5 H, m, *Ar*), 4.66–4.73 (1 H, m, *NH*), 4.59–4.66 (2 H, m, $-OCH_2Ph$), 4.42–4.53 (2 H, m, H_{12} and *NH*), 3.97–4.14 (3 H, m, H_2 and H_{11}), 3.80–3.88 (1 H, m, H_{10}), 3.58–3.65 (2 H, m, H_1), 3.13–3.26 (2 H, m, H_{13}), 2.42–2.50 (3 H, m, H_{3A} and H_5), 2.32–2.38 (1 H, m, H_{3B}), 1.94–2.03 (1 H, m, H_{8A}), 1.89 (1 H, d, *J* 11.8, H_{7A}), 1.70 (1 H, d, *J* 13.2, H_{8B}), 1.55–1.59 (1 H, m, H_{9A}), 1.45–1.50 (1 H, m, H_{7B}), 1.31–1.37 (3 H, m, $-CH_3$), 1.22–1.29 (1 H, m, H_{9B}) and 1.10–1.14 (3 H, m, H_{14}); δ_C (150 MHz; $CDCl_3$; Me_4Si) 205.6, 171.1, 157.0, 146.5, 138.0, 128.4, 127.7, 127.5, 99.6, 73.4, 72.0, 68.6, 68.1, 67.1, 51.6, 49.0, 43.0, 35.3, 34.1, 26.0, 19.2, 18.3 and 15.3; *m/z* (+ESI) calc. for $C_{24}H_{34}N_2NaO_7$ (MNa^+) 485.2264, found 485.2253.

2-(3-Ethylureido)-3-phenylpropionic acid 8-benzyloxy methyl-10-oxo-1,7-dioxaspiro[5.5]undec-2-ylmethyl ester isomer (42b). A clear, colourless oil (quant. over two steps); R_f 0.65 (EtOAc); $[\alpha]_D^{25}$ +10.1 (*c* 0.15, CH_2Cl_2); υ_{max}(film)/cm^{-1} 3379, 2950, 2880, 1773, 1724, 1641, 1562, 1498, 1440, 1356, 1300, 1269, 1213, 1178, 1156, 1143, 1078, 1043, 980, 882, 811, 730, 720 and 684; δ_H (600 MHz; $CDCl_3$; Me_4Si) 7.06–7.40 (10 H, m, *Ar*), 4.74–4.48 (1 H, m, H_{12}), 4.57–4.68 (3 H, m, $-OCH_2Ph$ and *NH*), 4.44–4.48 (1 H, m, *NH*), 3.98–4.14 (3 H, m, H_2 and H_{11}), 3.78–3.82 (1 H, m, H_{10}), 3.56–3.64 (2 H, m, H_1), 2.97–3.18 (4 H, m, H_{13} and $-CH_2$–Ph), 2.41–2.48 (3 H, m, H_{3A} and H_5), 2.29–2.37 (1 H, m, H_{3B}), 1.92–2.04 (1 H, m, H_{8A}), 1.85–1.91 (1 H, m, H_{7A}), 1.66–1.75 (1 H, m, H_{8B}), 1.52–1.56 (1 H, m, H_{9A}), 1.43–1.53 (1 H, m, H_{7B}), 1.16–1.24 (1 H, m, H_{9B}) and 1.08 (3 H, t, *J* 7.2, H_{14}); δ_C (150 MHz; $CDCl_3$; Me_4Si) 205.7, 171.9, 156.9, 138.0, 136.2, 129.4, 128.5, 128.4, 127.7, 127.6, 127.5, 126.9, 99.6, 73.5, 72.0, 68.6, 68.1, 67.1, 54.1, 51.5, 43.1, 38.6, 35.3, 34.1, 26.0, 18.3 and 15.3; *m/z* (+ESI) calc. for $C_{30}H_{39}N_2O_7$ (MH^+) 539.2757, found 539.2733, calc. for $C_{30}H_{38}N_2NaO_7$ (MNa^+) 561.2577, found 561.2563.

2-(3-Ethylureido)pent-4-enoic acid 8-benzyloxymethyl-10-oxo-1,7-dioxaspiro[5.5]undec-2-ylmethyl ester isomer (42c). A clear, colourless oil (quant. over two steps); R_f 0.60 (EtOAc); $[\alpha]_D^{25}$ +4.5 (*c* 0.10, CH_2Cl_2); υ_{max}(film)/cm^{-1} 3365, 2941, 2870, 1770, 1730, 1642, 1565, 1503, 1452, 1360, 1300, 1281, 1255, 1214, 1190, 1162, 1148, 1094, 1045, 986, 890, 810, 736, 724 and 700; δ_H (600 MHz; $CDCl_3$; Me_4Si) 7.26–7.37 (5 H, m, *Ar*), 5.64–5.70 (1 H, m, $-CH_2-CH{=}CH_2$), 5.09 (2 H, d, *J* 15.1, $-CH_2-CH{=}CH_2$), 4.71 (1 H, d, *J* 7.8, *NH*), 4.59–4.66 (2 H, m, $-OCH_2Ph$), 4.53–4.57 (1 H, m, H_{12}), 4.48–4.53 (1 H, m, *NH*), 4.01–4.13 (3 H, m, H_2 and H_{11}), 3.80–3.88 (1 H, m, H_{10}), 3.57–3.64 (2 H, m, H_1), 3.15–3.21 (2 H, m, H_{13}), 2.42–2.54 (5 H, m, $-CH_2-CH{=}CH_2$, H_{3A} and H_5), 2.32–2.38 (1 H, m, H_{3B}), 1.95–2.01 (1 H, m, H_{8A}), 1.86–1.92 (1 H, m, H_{7A}), 1.66–1.73 (1 H, m, H_{8B}), 1.54–1.62 (1 H, m, H_{9A}), 1.46–1.50 (1 H, m, H_{7B}), 1.22–1.31 (1 H, m, H_{9B}) and 1.09–1.13 (3 H, m, H_{14}); δ_C (150 MHz; $CDCl_3$; Me_4Si) 205.6, 172.3, 157.0, 138.0, 132.6, 128.4, 127.7, 127.5, 127.5, 119.0, 99.5, 73.5, 72.0, 68.6, 68.2, 67.4, 52.6, 51.5, 43.1, 37.1, 35.3, 34.1, 26.0, 18.3 and 15.3; *m/z* (+ESI) calc. for $C_{26}H_{37}N_2O_7$ (MH^+) 489.2601, found 489.2589; calc. for $C_{26}H_{36}N_2NaO_7$ (MNa^+) 551.2420, found 551.2408.

2-(3-Ethylureido)-3-furan-2-ylpropionic acid 8-benzyloxymethyl-10-oxo-1,7-dioxaspiro[5.5]undec-2-ylmethyl ester isomer (42d). A clear, colourless oil (quant. over two steps); R_f 0.67 (EtOAc); $[\alpha]_D^{25}$ −0.3 (*c* 1.52, CH_2Cl_2); υ_{max}(film)/cm^{-1} 3368, 2943, 2875, 1772, 1726, 1641, 1563, 1505, 1454, 1362, 1303, 1279, 1256, 1213, 1189, 1161, 1146, 1089, 1043, 986, 886, 813, 738, 721 and 699; δ_H (600 MHz; $CDCl_3$; Me_4Si) 7.25–7.35 (6 H, m, *Ar*), 6.22–6.24 (1 H, m, *Ar*), 6.04–6.06 (1 H, m, *Ar*), 5.00–5.03 (1 H, m, *NH*), 4.70–4.76 (2 H, m, H_{12} and *NH*), 4.56–4.64 (2 H, m, $-OCH_2Ph$), 3.97–4.09 (3 H, m, H_2 and H_{11}), 3.78–3.85 (1 H, m, H_{10}), 3.54–3.63 (2 H, m, H_1), 3.01–3.19 (4 H, m, $-CH_2$–furan and H_{13}), 2.38–2.46 (3 H, m, H_{3A} and H_5), 2.32–2.36 (1 H, m, H_{3B}), 1.90–2.00 (1 H, m, H_{8A}), 1.85–1.91 (1 H, m, H_{7A}), 1.66–1.70 (1 H, m, H_{8B}), 1.54–1.59 (1 H, m, H_{9A}), 1.45–1.49 (1 H, m, H_{7B}), 1.24–1.31 (1 H, m, H_{9B}) and 1.08 (3 H, t, *J* 7.2, H_{14}); δ_C (150 MHz; $CDCl_3$; Me_4Si) 205.8, 172.0, 168.3, 157.1, 150.8, 138.0, 132.7, 128.4, 127.7, 127.6, 127.5, 110.3, 107.8, 99.5, 73.4, 71.9, 68.5, 68.1, 67.4, 52.4, 51.5, 43.0, 35.3, 34.1, 31.3, 26.1, 18.3 and 15.3; *m/z* (+ESI) calc. for $C_{28}H_{37}N_2O_8$

(MH$^+$) 529.2550, found 529.2526; calc. for $C_{28}H_{36}N_2NaO_8$ (MNa$^+$) 551.2369, found 551.2347.

1-(3-Ethylureido)cyclobutanecarboxylic acid 8-benzyloxymethyl-10-oxo-1,7-dioxaspiro[5.5]undec-2-ylmethyl ester isomer (42e). A clear, colourless oil (quant. over two steps); R_f 0.62 (EtOAc); $[\alpha]_D^{25}$ +12.5 (*c* 0.40, CH_2Cl_2); υ_{max}(film)/cm^{-1} 3360, 2938, 2875, 1773, 1728, 1663, 1560, 1501, 1450, 1370, 1300, 1252, 1210, 1190, 1160, 1143, 1089, 1038, 989, 887, 805, 730, 725 and 701; δ_H (600 MHz; $CDCl_3$; Me_4Si) 7.26–7.36 (5 H, m, *Ar*), 4.82 (1 H, s, *NH*), 4.59–4.65 (2 H, m, –OCH_2Ph), 4.43–4.45 (1 H, m, *NH*), 4.10–4.15 (2 H, m, H_2 and H_{11A}), 4.01–4.05 (1 H, m, H_{11B}), 3.85–3.90 (1 H, m, H_{10}), 3.59–3.64 (2 H, m, H_1), 3.14–3.20 (2 H, m, H_{13}), 2.48–2.58 (2 H, m, cyclobutyl–CH_2–), 2.41–2.47 (3 H, m, H_{3A} and H_5), 2.30–2.37 (3 H, m, H_{3B} and cyclobutyl–CH_2–), 1.92–2.03 (3 H, m, H_{8A} and cyclobutyl–CH_2–), 1.86–1.92 (1 H, m, H_{7A}), 1.67–1.71 (1 H, m, H_{8B}), 1.58–1.62 (1 H, m, H_{9A}), 1.45–1.50 (1 H, m, H_{7B}), 1.23–1.32 (1 H, m, H_{9B}) and 1.10 (3 H, t, *J* 7.2, H_{14}); δ_C (150 MHz; $CDCl_3$; Me_4Si) 205.6, 174.2, 157.1, 138.0, 128.4, 127.7, 127.5, 99.5, 73.5, 72.1, 68.4, 68.3, 67.4, 58.5, 51.6, 43.2, 35.2, 34.1, 31.6, 26.0, 18.3, 15.3 and 15.1; *m*/*z* (+ESI) calc. for $C_{26}H_{37}N_2O_7$ (MH$^+$) 489.2601, found 489.2585; calc. for $C_{26}H_{36}N_2NaO_7$ (MNa$^+$) 511.2420, found 511.2404.

2-(3-Ethylureido)-3-furan-2-yl-propionic acid 8-benzyloxy methyl-10-oxo-1,7-dioxaspiro[5.5]undec-2 ylmethyl ester isomer (44b). A clear, colourless oil (quant. over two steps); R_f 0.54 (EtOAc); $[\alpha]_D^{25}$ +10.5 (*c* 0.05, CH_2Cl_2); υ_{max}(film)/cm^{-1} 3368, 2943, 2875, 1772, 1726, 1641, 1563, 1505, 1454, 1362, 1303, 1279, 1256, 1213, 1189, 1161, 1146, 1089, 1043, 986, 886, 813, 738, 721 and 699; δ_H (600 MHz; $CDCl_3$; Me_4Si) 7.25–7.35 (m), 6.23–6.26 (m), 6.04–6.09 (m), 5.32–5.35 (m), 5.27–5.29 (m), 5.08–5.12 (m), 4.94–4.99 (m), 4.72–4.82 (m), 4.53–4.63 (m), 4.34–4.36 (m), 4.15–4.24 (m), 4.06–4.13 (m), 3.94–4.03 (m), 3.12–3.21 (m), 2.96–3.10 (m), 2.69–2.79 (m), 2.48–2.58 (m), 2.35–2.44 (m), 1.98–2.02 (m), 1.79–1.91 (1 H, m), 1.50–1.67 (3 H, m), 1.21–1.35 (1 H, m) and 1.05–1.18 (3 H, m); δ_C (150 MHz; $CDCl_3$; Me_4Si) 206.1, 171.1, 168.1, 157.1, 142.0, 141.5, 129.7, 128.5, 128.4, 127.7, 127.6, 127.5, 110.4, 107.9, 99.3, 73.5, 71.7, 68.2, 68.1, 60.4, 53.4, 49.8, 41.3, 36.9, 35.8, 33.1, 27.7, 18.4 and 15.4; *m*/*z* (+ESI) calc. for $C_{28}H_{37}N_2O_8$ (MH$^+$) 529.2550, found 529.2562; calc. for $C_{28}H_{36}N_2NaO_8$ (MNa$^+$) 551.2369, found 551.2369.

General procedure for the synthesis of spiroketal-derived sulfonamides 45a–d

Polymer-supported piperazine (10.0 eq.) was added to a solution of the spiroketal-derived ester in anhydrous DCM (0.1 M), and subjected to microwave heating at 120 °C for 30 min. Sequestration of the polymer reagent, followed by evaporation of the resultant filtrate *in vacuo* yielded the crude amine intermediate, which was subsequently re-dissolved in anhydrous DCM (0.1 M) and treated, first with pyridine (1.05 eq.) at ambient temperature, then with $MeSO_2Cl$ (1.05 eq.) at 0 °C. The resultant reaction mixture was then left to warm to ambient temperature and stirred for 2 h. Evaporation *in vacuo* was then followed by purification of the resultant crude liquid by gravimetric column chromatography on silica gel, using EtOAc and petroleum ether.

Methanesulfonylaminoacetic acid 8-benzyloxymethyl-10-oxo-1,7-dioxaspiro[5.5]undec-2-ylmethyl ester isomer (45a). A clear colourless oil (quant. over two steps); R_f 0.16 (1 : 1 EtOAc–petroleum ether); $[\alpha]_D^{25}$ +9.2 (*c* 0.12, CH_2Cl_2); υ_{max}(film)/cm^{-1} 3295, 2939, 1748, 1721, 1454, 1410, 1323, 1212, 1123, 970, 843, 738 and 699; δ_H (600 MHz; $CDCl_3$; Me_4Si) 7.25–7.39 (5 H, m, *Ar*), 4.89 (1 H, br s, *NH*), 4.61–4.65 (2 H, m, –OCH_2Ph), 4.16 (1 H, dd, *J* 11.4 and 7.3, H_{11A}), 4.03–4.09 (2 H, m, H_2 and H_{11B}), 3.94 (1 H, d, *J* 18.3, H_{12A}), 3.84–3.88 (2 H, m, H_{10} and H_{12B}), 3.59–3.64 (2 H, m, H_1), 2.99 (3 H, s, –NHSO$_2$CH_3), 2.41–2.46 (3 H, m, H_{3A} and H_5), 2.38 (1 H, dd, *J* 14.5 and 2.8, H_{3B}), 1.93–2.04 (1 H, m, H_{8A}), 1.86–1.92 (1 H, m, H_{7A}), 1.68–1.74 (1 H, m, H_{8B}), 1.56–1.60 (1 H, m, H_{9A}), 1.47–1.51 (1 H, m, H_{7B}) and 1.25–1.29 (1 H, m, H_{9B}); δ_C (150 MHz; $CDCl_3$; Me_4Si) 205.4, 169.4, 138.0, 128.4, 127.8, 127.5, 99.6, 73.5, 72.1, 68.8, 68.1, 67.7, 51.5, 44.3, 43.1, 41.4, 34.0, 25.9 and 18.3; *m*/*z* (+ESI) calc. for $C_{21}H_{30}NO_8S$ (MH$^+$) 456.1692, found 456.1723, $C_{21}H_{29}NNaO_8S$ (MNa$^+$) 478.1512, found 478.1530.

2-Methanesulfonylamino-3-phenylpropionic acid 8-benzyloxy-methyl-10-oxo-1,7-dioxaspiro[5.5]undec-2-ylmethyl ester isomer (45b). A clear colourless oil (quant. over two steps); R_f 0.25 (1 : 1 EtOAc–petroleum ether); $[\alpha]_D^{25}$ +12.2 (*c* 0.10, CH_2Cl_2); υ_{max}(film)/cm^{-1} 3296, 2933, 1749, 1723, 1455, 1410, 1325, 1279, 1213, 1106, 981, 841, 739 and 701; δ_H (600 MHz; $CDCl_3$; Me_4Si) 7.08–7.45 (10 H, m, *Ar*), 4.82 (1 H, d, *J* 9.2, *NH*), 4.60–4.65 (2 H, m, –OCH_2Ph), 4.32–4.38 (1 H, m, H_{12}), 4.07–4.13 (3 H, m, H_2 and H_{11}), 3.78–3.95 (1 H, m, H_{10}), 3.60–3.64 (2 H, m, H_1), 3.05–3.15 (1 H, m, –CH(H_A)Ph), 2.88–2.94 (1 H, m, –CH(H_B)Ph), 2.60 (3 H, s, –NHSO$_2$CH_3), 2.42–2.48 (3 H, m, H_{3A} and H_5), 2.36–2.41 (1 H, m, H_{3B}), 1.93–2.04 (1 H, m, H_{8A}), 1.86–1.92 (1 H, m, H_{7A}), 1.66–1.75 (1 H, m, H_{8B}), 1.45–1.62 (2 H, m, H_{7B} and H_{9A}) and 1.24–1.30 (1 H, m, H_{9B}); δ_C (150 MHz; $CDCl_3$; Me_4Si) 205.1, 171.2, 138.1, 135.5, 129.5, 128.8, 128.4, 127.7, 127.5, 127.4, 99.5, 73.5, 72.1, 68.7, 68.1, 68.0, 57.2, 51.4, 43.0, 41.3, 39.4, 34.1, 25.9 and 18.3; *m*/*z* (+ESI) calc for $C_{28}H_{35}NNaO_8S$ (MNa$^+$) 568.1981, found 568.2030.

2-Methanesulfonylaminopropionic acid 8-benzyloxymethyl-10-oxo-1,7-dioxaspiro[5.5]undec-2-ylmethyl ester isomer (45c). A clear colourless oil (quant. over two steps); R_f 0.20 (1 : 1 EtOAc–petroleum ether); $[\alpha]_D^{25}$ +3.8 (*c* 0.15, CH_2Cl_2); υ_{max}(film)/cm^{-1} 3298, 2940, 1757, 1721, 1465, 1406, 1320, 1265, 1210, 1106, 832, 739 and 678; δ_H (600 MHz; $CDCl_3$; Me_4Si) 7.26–7.36 (5 H, m, *Ar*), 4.95 (1 H, d, *J* 8.2, *NH*), 4.60–4.65 (2 H, m, –OCH_2Ph), 4.05–4.17 (4 H, m, H_2, H_{11} and H_{12}), 3.85–3.89 (1 H, m, H_{10}), 3.58–3.64 (2 H, m, H_1), 2.94 (3 H, s, –NHSO$_2$CH_3), 2.40–2.46 (3 H, m, H_{3A} and H_5), 2.36 (1 H, dd, *J* 14.5 and 2.9, H_{3B}), 1.94–2.04 (1 H, m, H_{8A}), 1.86–1.92 (1 H, m, H_{7A}), 1.66–1.75 (1 H, m, H_{8B}), 1.53–1.61 (1 H, m, H_{9A}), 1.46–1.50 (1 H, m, H_{7B}), 1.40 (3 H, d, *J* 7.2, –CH_3) and 1.25–1.33 (1 H, m, H_{9B}); δ_C (150 MHz; $CDCl_3$; Me_4Si) 205.1, 171.3, 138.0, 128.4, 2 × 127.7, 127.5, 99.5, 73.5, 72.2, 68.7, 68.1, 67.9, 65.8, 51.7, 43.1, 41.7, 34.0, 25.9, 19.7 and 18.3; *m*/*z* (+ESI) calc for $C_{22}H_{31}NNaO_8S$ (MNa$^+$) 492.1668, found 492.1674.

1-Methanesulfonylaminocyclobutanecarboxylic acid 8-benzyl-oxymethyl-10-oxo-1,7-dioxaspiro[5.5]undec-2-ylmethyl ester (45d). A clear colourless oil (quant. over two steps); R_f 0.26 (1 : 1 EtOAc–petroleum ether); $[\alpha]_D^{25}$ −7.6 (*c* 0.98, CH_2Cl_2); υ_{max}(film)/cm^{-1} 3298, 2931, 1754, 1721, 1450, 1411, 1321, 1268, 1212, 1106, 978, 831, 721 and 701; δ_H (600 MHz; $CDCl_3$; Me_4Si) 7.26–7.36 (5 H, m, *Ar*), 5.07 (1 H, s, *NH*), 4.60–4.64 (2 H, m, –OCH_2Ph), 4.07–4.17 (3 H, m, H_2 and H_{11}), 3.90–3.95 (1 H, m, H_{10}), 3.58–3.64 (2 H, m, H_1),

2.98 (3 H, s, –NHSO$_2$CH_3), 2.52–2.57 (2 H, m, cyclobutyl–CH_2–), 2.34–2.46 (6 H, m, H_3, H_5 and cyclobutyl–CH_2–), 1.96–2.05 (3 H, m, H_{8A} and cyclobutyl–CH_2–), 1.86–1.92 (1 H, m, H_{7A}), 1.68–1.74 (1 H, m, H_{8B}), 1.57–1.62 (1 H, m, H_{9A}), 1.47–1.52 (1 H, m, H_{7B}) and 1.30–1.35 (1 H, m, H_{9B}); δ_C (150 MHz; $CDCl_3$; Me_4Si) 205.3, 173.1, 138.1, 128.4, 127.7, 127.5, 99.5, 73.4, 72.1, 68.5, 68.3, 68.0, 60.6, 51.5, 43.6, 43.1, 34.1, 32.2, 25.9, 18.3 and 15.3; *m/z* (+ESI) calc. for $C_{24}H_{34}NO_8S$ (MH^+) 496.2005, found 496.2020.

8-Benzyloxymethyl-10-oxo-1,7-dioxaspiro[5.5]undecane-2-carboxylic acid(pyridine-2-ylmethyl)amide isomer (49). To an anhydrous DMF solution (2 cm^3) of spiroketal-derived alcohol **24c** (28 mg, 0.089 mmol) was added solid pyridinium dichromate salt (334 mg, 0.888 mmol, 10.0 eq.), in one portion, at ambient temperature. The reaction was then stirred at ambient temperature for 18 h, at which point the reaction was diluted with EtOAc (2 cm^3) and distilled water (2 cm^3), and the aqueous phase extracted with EtOAc (4 × 5 cm^3). The recombinant organic extracts were then dried over anhydrous $MgSO_4$, filtered and then evaporated *in vacuo* to afford the crude carboxylic acid intermediate, which was immediately redissolved in anhydrous DMF (1 cm^3). Pyridine was then added (11 µl, 0.134 mmol) at ambient temperature followed by *p*-nitrophenylchloroformate (27 mg, 0.134 mmol) in one portion, at 0 °C. The reaction was then held at ambient temperature for 20 min, at which point 2-picolylamine was added, drop-wise, and the reaction left to stir for a further 10 min. The reaction mixture was diluted with EtOAc (4 cm^3), then distilled water was added (4 cm^3), and the aqueous phase extracted with EtOAc (3 × 4 cm^3). The recombinant organic extracts were washed with distilled water (1 × 10 cm^3) and brine (1 × 10 cm^3), dried over anhydrous $MgSO_4$, filtered and then evaporated *in vacuo.* Gravimetric column chromatography of the resultant crude on silica, using EtOAc as eluent, afforded the title compound **49** as a clear, faint yellow oil (90% over 3 steps); R_f 0.23 (EtOAc); $[\alpha]_D^{25}$ +47.0 (*c* 0.42, CH_2Cl_2); υ_{max}(film)/cm^{-1} 3350, 2932, 1722, 1672, 1592, 1571, 1528, 1477, 1438, 1369, 1310, 1274, 1255, 1213, 1118, 1095, 1074, 1049, 979, 953, 932, 910, 893, 851, 833, 751, 700 and 666; δ_H (600 MHz; $CDCl_3$; Me_4Si) 8.57 (1 H, d, *J* 4.6, *Ar*), 7.64 (1 H, t, *J* 7.7, *Ar*), 7.47–7.53 (1 H, m, *NH*), 7.26–7.36 (5 H, m, *Ar*), 7.17–7.22 (2 H, m, *Ar*), 4.57–4.64 (3 H, m, H_{12A} and –OCH_2Ph), 4.49 (1 H, dd, *J* 16.2 and 5.3, H_{12B}), 4.15–4.20 (1 H, m, H_{10}), 4.02–4.06 (1 H, m, H_2), 3.62 (1 H, dd, *J* 10.4 and 3.9, H_{1A}), 3.57 (1 H, dd, *J* 10.4 and 4.6, H_{1B}), 2.48–2.58 (3 H, m, H_{3A} and H_5), 2.38–2.42 (1 H, m, H_{3B}), 2.16–2.22 (1 H, m, H_{9A}), 1.99–2.05 (1 H, m, H_{8A}), 1.93 (1 H, m, H_{7A}), 1.72–1.76 (1 H, m, H_{8B}), 1.50–1.56 (1 H, m, H_{7B}), 1.38–1.43 (1 H, m, H_{9B}); δ_C (150 MHz; $CDCl_3$; Me_4Si) 204.9, 173.6, 156.3, 149.3, 137.9, 136.7, 128.4, 127.8, 122.3, 121.7, 100.3, 73.5, 71.7, 70.8, 68.9, 51.4, 43.9, 43.0, 34.3, 27.6 and 18.6; *m/z* (+ESI) calc. for $C_{24}H_{29}N_2O_5$ (MH^+) 425.2076, found 425.2074, calc. for $C_{24}H_{28}N_2NaO_5$ (MNa^+) 447.1896, found 447.1895.

8-Azidomethyl-2-benzyloxymethyl-1,7-dioxaspiro[5.5]undecan-4-one (50). A stirred solution of spiroketal-derived alcohol **24c** (40.0 mg, 125 µmol) in anhydrous DCM (0.5 cm^3) was cooled to −78 °C and treated, sequentially, with anhydrous pyridine (22 µl, 273 µmol, 2.2 eq.) and Tf_2O (14 µl, 139 µmol, 1.1 eq.). The reaction was allowed to warm to room temperature over 1 h, then the mixture was quenched with a saturated, aqueous solution of $NaHCO_3$ (0.2 cm^3) and then extracted with Et_2O (4 × 2 cm^3). The recombinant organic extracts were washed with distilled water (1 × 2 cm^3) and brine (1 × 2 cm^3), dried over anhydrous $MgSO_4$ and then concentrated *in vacuo.* The resultant crude was re-dissolved in anhydrous DMF (1 cm^3) and treated with NaN_3 (8.5 mg, 131 µmol, 1.1 eq.) stirring at room temperature for 5 h, then EtOAc (2 cm^3) and distilled water (2 cm^3) were added, and the subsequent aqueous phase extracted with EtOAc (4 × 2 cm^3). The recombinant organic extracts were washed with distilled water (1 × 2 cm^3) and brine (1 × 2 cm^3), dried over anhydrous $MgSO_4$, filtered and then evaporated *in vacuo.* Gravimetric column chromatography on florisil, using EtOAc as eluent, afforded the title compound **50** as a clear, colourless oil (42 mg, quant.); R_f 0.30 (EtOAc); δ_H (600 MHz; $CDCl_3$; Me_4Si) 7.26–7.35 (5 H, m, *Ar*), 4.60–4.66 (2 H, m, –OCH_2Ph), 4.12–4.17 (1 H, m, H_2), 3.78–3.81 (1 H, m, H_{10}), 3.57–3.65 (2 H, m, H_1), 3.22 (1 H, dd, *J* 12.8 and 7.4, H_{11A}), 3.06 (1 H, dd, *J* 12.8 and 3.3, H_{11B}), 2.34–2.47 (4 H, m, H_3 and H_5), 1.96–2.00 (1 H, m, H_{8A}), 1.87–1.91 (1 H, m, H_{7A}), 1.66–1.72 (1 H, m, H_{8B}), 1.53–1.62 (1 H, m, H_{9A}), 1.46–1.50 (1 H, m, H_{7B}) and 1.26–1.32 (1 H, m, H_{9B}); δ_C (150 MHz; $CDCl_3$; Me_4Si) 205.0, 138.1, 128.4, 127.7, 127.5, 99.7, 73.4, 72.0, 70.4, 68.5, 54.9, 51.4, 42.9, 34.1, 27.1 and 18.4; *m/z* (+ESI) calc. for $C_{18}H_{24}N_3O_4$ (MH^+) 346.1767, found 346.1762, calc. for $C_{18}H_{23}N_3NaO_4$ (MNa^+) 368.1586, found 368.1588.

2-Benzyloxymethyl-8-(4-phenyl[1,2,3]triazol-1-ylmethyl)-1,7-dioxaspiro[5.5]undecan-4-one (51). A stirred solution of azide **50** (54.0 mg, 156 µmol) in 2 : 1 distilled water and *t*-butanol (1 cm^3) was treated, sequentially, with phenylacetylene (17 µl, 156 µmol, 1.0 eq.), $CuSO_4 \cdot 5H_2O$ (0.4 mg, 1.56 µmol, 1 mol%) and sodium ascorbate (1.5 mg 7.8 µmol, 5 mol%). The reaction was stirred at room temperature for 3 h, and then the mixture was extracted with EtOAc (4 × 2 cm^3). The recombinant organic extracts were washed with distilled water (2 × 1 cm^3) and brine (1 × 1 cm^3), dried over anhydrous $MgSO_4$ and then concentrated *in vacuo.* Gravimetric column chromatography on silica gel, using EtOAc as eluent, afforded the title compound **51** as a white, crystalline solid (68 mg, quant.); R_f 0.23 (EtOAc); mp 168 °C (from pentane); $[\alpha]_D^{25}$ +30.0 (*c* 0.35, CH_2Cl_2); υ_{max}(film)/cm^{-1} 2998, 1720, 1455, 1364, 1309, 1223, 1127, 1077, 1049, 768, 743 and 698; δ_H (600 MHz; $CDCl_3$; Me_4Si) 7.77–7.83 (2 H, m, *Ar*), 7.75–7.77 (1 H, m, *Ar*), 7.37–7.41 (2 H, m, *Ar*), 7.23–7.32 (3 H, m, *Ar*), 7.18–7.23 (3 H, m, *Ar*), 4.40–4.52 (3 H, m, H_{11A} and –OCH_2Ph), 4.16–4.21 (1 H, m, H_{11B}), 3.84–3.87 (1 H, m, H_{10}), 3.40–3.43 (1 H, m, H_{1A}), 3.32–3.35 (1 H, m, H_{1B}), 3.28–3.30 (1 H, m, H_2), 2.36–2.48 (3 H, m, H_{3A} and H_5), 1.99–2.05 (1 H, m, H_{3B}), 1.87–1.96 (2 H, m, H_{7A} and H_{8A}), 1.67–1.71 (2 H, m, H_{8B} and H_{9A}), 1.40–1.45 (1 H, m, H_{7B}) and 1.18–1.24 (1 H, m, H_{9B}); δ_C (150 MHz; $CDCl_3$; Me_4Si) 206.1, 147.6, 137.7, 130.2, 128.9, 128.3, 128.1, 127.6, 127.5, 125.7, 121.6, 100.2, 73.2, 71.4, 69.4, 68.7, 54.4, 51.7, 42.8, 33.7, 26.7 and 18.1; *m/z* (+ESI) calc. for $C_{26}H_{30}N_3O_4$ (MH^+) 448.2236, found 448.2210, calc. for $C_{26}H_{29}N_3NaO_4$ (MNa^+) 470.2056, found 470.2068.

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