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Stereoselective bidirectional synthesis of spiroacetals via Rh(II)-catalysed double C–H insertion

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ABSTRACT

The stereoselective synthesis of 5,5-spiroacetals by Rh(II)-catalysed double C–H insertion of methylene acetals bearing two diazo ester substituents is described. The diastereoselectivity of this bidirectional approach can be tuned through appropriate choice of catalyst, and chiral catalysts lead to products with up to 89% *ee*. The diastereoselectivity of the first cyclisation suggests that the second cyclisation proceeds via a non-concerted pathway.

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A large variety of natural products incorporate spirocyclic substructures, the most common being 6,6-, 5,6- and 5,5-spiroacetals.¹ Naturally occurring 5,5-spiroacetals range from simple insect pheromones²⁻⁴ and plant-derived natural products, such as chalcogran (**1**)⁵ and exogonic acid (**2**),⁶ respectively, to much more complex marine-derived natural products,⁷ such as symbiospirol A (**3**)⁸ and halichondrin B (**4**).⁹ There are also a growing number of fungal-derived 5,5-spiroacetal natural products with potent biological activities.¹⁰ 5,5-Spiroacetals have been less thoroughly investigated than their 6,6- and 5,6-counterparts and anomeric effects are often difficult to define or predict in these often conformationally-complex systems.¹

Figure 1: 5,5-Spiroacetal natural products

Common methods for spiroacetal synthesis involve realization of the spirocyclic topology via ring-generating C–O bond-formation events (Scheme 1).¹¹⁻¹³ The most highly utilised methodology is intramolecular acetalisation of appropriately masked dihydroxyketone precursors, which proceeds via intermediate oxonium ions and is generally reversible (eg. **5** → **6**). Nonetheless, there are a growing number of kinetically-controlled, stereoselective synthetic approaches to 5,6- and 6,6-spiroacetals, including those lacking full anomeric stabilisation¹⁴⁻²⁰ and to 5,5-spiroacetals.^{21,22}

Scheme 1: Spiroacetal synthesis via double C–O vs C–C bond formations

We envisaged a mechanistically-novel, bidirectional approach for spiroacetal synthesis, based on generation of the spirocyclic topology by C–C bond-forming reactions of acyclic acetal precursors. We anticipated that methylene acetals with proximal metal carbene groups **7**, would engage in two C–H insertion reactions to deliver the desired 5,5-spiroacetals **6** (Scheme 1).

Furthermore, oxygen atoms adjacent to the C–H bonds undergoing insertion and the 1,5-relationship between the acetal and carbene carbon atoms should predispose these substrates to this reaction manifold.²³ The potential for asymmetric synthesis of spiroacetals with control over absolute configuration through the use of chiral Rh(II)-catalysts was also a highly attractive feature of this new approach.

At the outset of our work, rhodium(II)-catalysed double C–H insertion had been used in the formation of spiro[4.4]nonane-2,7-diones **8** from unsubstituted bis(α-diazo ketones) **9**^{24,25} and 1,1'-spirobi[indan-3,3'-dione] (**10**) from a bis(α-diazo-β-ketoester) **11**, via the corresponding spirocyclic bis(β-ketoester) **12**.²⁶ Notably, the carbenes utilised in these procedures cannot undergo β-elimination. However, before our studies there were no reports of the formation of spiroacetals via double C–H insertion. We now report full details of our earlier work.²⁷

Scheme 2: Previous syntheses of spirocycles by double C–H insertion

2. Results and Discussion

We chose to focus on bis(α-diazoester) substrates due to their ease of preparation and handling, stability towards storage and lack of previous reports on their use in spirocycle formation. Initially, a substrate that lacks activating oxygen atoms, and is therefore a potential precursor for spirocarbacycle synthesis, was prepared (Scheme 3). Reaction of an excess of sodium ethyl acetoacetate (**13**) with 1,7-dibromoheptane (**14**) in refluxing acetonitrile, in the presence of tetra-*n*-butylammonium iodide (TBAI), gave bis(β-ketoester) **15** in modest yield (59%). Double de-acylative diazo transfer using *p*-acetamidobenzenesulfonyl azide (*p*-ABSA) and DBU in MeCN gave the bis(α-diazoester) **16** (65%).

Exposure of **16** to a catalytic quantity of dirhodium(II) tetraacetate, $\text{Rh}_2(\text{OAc})_4$, (2.5 mol%) in CH_2Cl_2 at room temperature afforded mono-cyclised product, cyclopentane **17** (51%), and a complex mixture of side products. Similar results were obtained using $\text{Rh}_2(\text{S-PTAD})_4$ in PhMe, ie. none of the desired spirocycle **18** was produced. The formation of **17** suggests that, subsequent to the first C–H insertion, β-elimination of the second Rh(II) carbene is the dominant reaction pathway. This is perhaps unsurprising, since β-hydride elimination is a well-established alternative pathway to intramolecular C–H insertion for ester-stabilised Rh(II) carbenes, with the relative rates being influenced by substrate and catalyst steric hindrance and electronic factors.^{28,29} Specifically, in this case the second C–H insertion would need to occur at a highly hindered methine position that is also deactivated by the inductive influence of the adjacent carboethoxy group.³⁰

Scheme 3: Attempted synthesis of a spiro[4.4]nonane

Despite the failure of **16** to engage in spirocyclisation to give **18**, the double C–H insertion approach to spiroacetals was pursued with undeterred optimism, since the added oxygen atoms should facilitate development of (partial) positive charge at the α -position, required for C–H insertion, while also destabilising positive charge character at the β -position, thereby retarding the unwanted β -hydride elimination. A series of bis(α -diazoester) methylene acetals were synthesised as substrates for the envisioned double C–H insertion (Scheme 4). Paraformaldehyde was condensed with 2-bromoethanol in the presence of H_2SO_4 under Dean–Stark conditions to give methylene acetal **19**.³¹ An analogous reaction using 3-chloropropanol provided methylene acetal **20** as a potential precursor to 6,6-spiroacetals. Conversion of **19** and **20** to the corresponding diiodides, **21** and **22**, respectively, was readily achieved with NaI in refluxing acetone.

Scheme 4: Synthesis of bis(α -diazoester) methylene acetal substrates

Alkylation of sodium alkyl acetoacetates with **21** and **22** proved to be more challenging than with simple alkyl halides, such as **14**. The reaction is considerably slower, *O*-alkylation is more apparent, and the product bis(β -ketoesters) are difficult to separate, chromatographically, from excess alkyl acetoacetate reagent. Nevertheless, treatment of **21** and **22** with 3.5 equivalents of the sodium salts of methyl, ethyl and *tert*-butyl acetoacetate in refluxing 1,2-dimethoxyethane (DME) minimised *O*-alkylation and gave acceptable yields of bis(β -ketoesters) **23a-c** and **24a-c**, respectively, in reasonable timeframes. These

compounds were converted to the corresponding bis(α -diazoesters) **25a-c** and **26a-c** using *p*-ABSA and DBU.

Interestingly, the diazo transfer reaction on **23a** and **23b** produced varying quantities of mono-diazo byproducts **27a** (15–20%) and **27b** (4–5%), respectively, alongside the desired bis(diazo) products (Figure 2). These may result from base-induced hydrolysis, due to adventitious moisture, and decarboxylation during this diazo transfer step. Fortuitously, these mono-diazo compounds presented an opportunity to later study the first C–H insertion step en route to spiroacetals.

Gratifyingly, treatment of bis(α -diazoester) **25b** with 1 mol% dirhodium(II) tetrakis(trifluoroacetate), $\text{Rh}_2(\text{TFA})_4$, in PhMe provided the desired 5,5-spiroacetal as a ca. 66:17:17 mixture of diastereomers **28b**, **29b** and **30b**, respectively, in 58% yield (Table 1, entry 1). Although the diastereomers were chromatographically inseparable, full characterisation, including determination of relative configurations for each diastereomer, was possible by derivatisation (see below).

Use of the highly electrophilic dirhodium(II) tetrakis(trifluoroacetate), $\text{Rh}_2(\text{TFA})_4$, as catalyst afforded none of the desired spiroacetals (entry 2). Instead, significant quantities of products resulting from β -elimination were observed – not uncommon when using this catalyst with α -diazoesters.²⁸ Treatment of the bis methyl ester **25a** with 0.1 mol% of the bridged bis(dicarboxylate) catalyst $\text{Rh}_2(\text{esp})_2$,^{32,33} gave a modest yield (36%), yet very high selectivity (ca. >98:<1:<1) for C_2 spiroacetal **28a** (entry 2). The yield was improved (56%) using 0.5 mol% catalyst (entry 3), and under these conditions the reaction could be conducted on a gram scale (entry 4) to give a good yield (77%) of **28a** with high diastereoselectivity (ca. 95:5:<1). Bulkier ester substrates, **25b** and **25c**, resulted in less diastereoselective outcomes (76:24:<1 to 89:11:<1) under a variety of conditions (entries 6–9).

In a reversal of diastereoselectivity, dirhodium(II) tetrakis(triphenylacetate), $\text{Rh}_2(\text{TPA})_4$, gave the C_1 products **29a-c** as the major diastereomer (41:59:<1 to 12:88:<1) (entries 10–12). Use of the chiral catalyst, $\text{Rh}_2(\text{S-PTAD})_4$,³⁴ with bis ethyl ester **25b** delivered the spiroacetals with similar diastereoselectivity to $\text{Rh}_2(\text{oct})_4$ (entries 13–14), although the bis *tert*-butyl ester **25c** gave more of the C_1 product **29c** under these conditions (entry 15). Diastereoselectivity with racemic $\text{Rh}_2(\text{PTAD})_4$ was not significantly different to that achieved with enantiomerically pure catalyst (entries 16–17). By comparison, an alternative chiral catalyst, $\text{Rh}_2(\text{S-DOSP})_4$,³⁵ gave slightly higher diastereoselectivity for **28b** (entries 18–19) that was slightly diminished by use of racemic $\text{Rh}_2(\text{DOSP})_4$ (entry 20). Derivatisation of diastereomeric mixtures from reactions using $\text{Rh}_2(\text{S-PTAD})_4$ and $\text{Rh}_2(\text{S-DOSP})_4$ (entries 13 and 18, respectively) enabled analysis of the major diastereomer **28b** by chiral HPLC and determination of 89 and 74% *ee*, respectively. Curiously, in contrast to previous studies of intramolecular C–H insertion reactions that found these two chiral catalysts gave opposite absolute stereoinduction,³⁴ in the case of **25b**, these catalysts give the same absolute stereoselectivity.

Unfortunately, attempts to synthesise 6,6-spiroacetals **31-33** by treatment of **26a-c** with $\text{Rh}_2(\text{esp})_2$ under optimised conditions, provided none of the desired products. Instead, complex mixtures of products were isolated in each case. Analysis of these mixtures

by ^1H NMR showed evidence of β -elimination to give predominantly α,β -unsaturated esters, some insertion into water to give α -hydroxyesters and possibly oxidation to give α -ketoesters. Given the complete lack of evidence for cyclised, C–H insertion products, the strong preference for 5-membered ring formation in reactions of this type²³ and the known propensity for β -elimination by α -diazoesters, this avenue of investigation was not pursued further.

Table 1. Synthesis of spiroacetals by double C–H insertion.

Entry	SM	Catalyst ^a	Temp (°C)	Ratio (28:29:30) ^b	Yield (%)
1	25b	Rh ₂ (oct) ₄ ^c	−78 → 0	61:17:17	58
2	25b	Rh ₂ (TFA) ₄ ^c	−78 → 0	n.a.	0
3	25a	Rh ₂ (esp) ₂ ^d	−78 → 0	>98:<1:<1	36
4	25a	Rh ₂ (esp) ₂	−78 → 0	>98:<1:<1	56
5	25a	Rh ₂ (esp) ₂ ^e	−78 → 0	95:5:<1	77
6	25b	Rh ₂ (esp) ₂	−60 → 0	87:13:<1	47
7	25b	Rh ₂ (esp) ₂	−78 → 0	81:19:<1	67
8	25c	Rh ₂ (esp) ₂	−78 → 0	76:24:<1	50
9	25c	Rh ₂ (esp) ₂	−78 → 0	89:11:<1	41
10	25a	Rh ₂ (TPA) ₄	−60 → 0	17:83:<1	44
11	25b	Rh ₂ (TPA) ₄	−60 → 0	12:88:<1	55
12	25c	Rh ₂ (TPA) ₄	−60 → 0	41:59:<1	56
13	25b	Rh ₂ (S-PTAD) ₄	−60 → 0	52:32:16	48 ^f
14	25b	Rh ₂ (S-PTAD) ₄	−10 → 0	50:40:10	68
15	25c	Rh ₂ (S-PTAD) ₄	−60 → 0	37:63:<1	64
16	25b	Rh ₂ (rac-PTAD) ₄	−40 → 0	49:37:14	56
17	25b	Rh ₂ (rac-PTAD) ₄	20	41:46:13	71
18	25b	Rh ₂ (S-DOSP) ₄	−60 → 0	74:17:9	52 ^g
19	25b	Rh ₂ (S-DOSP) ₄	−20 → 0	73:18:9	66
20	25b	Rh ₂ (rac-DOSP) ₄	−20 → 0	60:27:13	64
21	26a	Rh ₂ (esp) ₂	−78 → 0	n.a.	0
22	26b	Rh ₂ (esp) ₂	−78 → 0	n.a.	0
23	26c	Rh ₂ (esp) ₂	−78 → 0	n.a.	0

^a All reactions conducted in PhMe using 0.5 mol% catalyst under argon for 2 h, unless otherwise noted.

^b Determined by ^1H NMR integration.

^c Conducted using 1 mol% catalyst.

^d Conducted using 0.1 mol% catalyst.

^e Scaled up to 1.2 g of 25a.

^f Major diastereomer 28b 89% ee by chiral HPLC of a derivative.

^g Major diastereomer 28b 74% ee by chiral HPLC of a derivative.

The spiroacetal diastereomers 28b, 29b and 30b were not chromatographically separable, however they were spectroscopically distinct by ^1H NMR, allowing for measurement of diastereoselectivity by integration of well resolved peaks for tetrahydrofuran protons, eg. δ 3.77 (2H, td), 3.22 (1H, dd) and 3.36 (2H, dd) for 28b, 29b and 30b, respectively. Although the C₁ diastereomer 29b could be readily identified within the mixture, and distinguished from the other diastereomers by ^1H and ^{13}C NMR, the C₂ diastereomers could not be distinguished from each other spectroscopically. To facilitate separation of the diastereomers and allow determination of configurations, the diastereomeric mixtures from Rh₂(oct)₄, Rh₂(S-PTAD)₄ and Rh₂(S-DOSP)₄-catalysed reactions (entries 1, 13 and 18) were treated with LiAlH₄ and the resultant alcohols converted to separable mixtures of *p*-bromobenzoates (Scheme 5). From these mixtures, 34 could be isolated in 35–39% yield. Racemic and enantiomerically-enriched *p*-bromobenzoate 34 was readily analysed by chiral HPLC with UV detection to determine enantiomeric ratios. Furthermore, single crystals of racemic and enantiomerically-enriched 34 (from entry 13) were obtained, allowing relative and absolute configuration to be determined by x-ray crystallography.²⁷

Scheme 5: Derivatisation of the spiroacetal mixture.

The availability of mono-diazo compounds 27a and 27b provided a convenient substrate to investigate the first cyclisation of this bidirectional approach (Table 2). Separate treatment of 27a and 27b with Rh₂(esp)₂ under optimised conditions, provided the cis and trans tetrahydrofuranyl acetals 35a/36a and 35a/36b as chromatographically separable mixtures (ca. 69:31 and 57:43 cis/trans, respectively). Attempts to obtain suitable crystals of the derived 2,4-dinitrophenylhydrazones for x-ray crystallography were unsuccessful. Therefore, the relative configuration of these compounds was assigned on the basis of coupling constants in comparison to molecular mechanics based estimates for the two diastereomers.³⁶ Monte Carlo conformational searches for cis and trans diastereomers 35a and 36a, using the MMFFs force field^{37,38} and a chloroform solvent model, provided 36 and 58 conformers, respectively, within 5.0 kcal mol^{−1} of the global minimum energy conformation. This allowed calculation of Boltzmann-weighted 3J values for H2–H3, which matched well with the experimental values (5.2 vs 4.0 Hz and 1.5 vs 1.1 Hz, respectively).

Table 2. Cyclisation of mono-diazo compounds.

Entry	SM	Ratio ^a	cis ³ J _{H2-H3} (Hz) ^b	trans ³ J _{H2-H3} (Hz) ^b	Yield (%)
1	27a	69:31	5.2 (4.0)	1.5 (1.1)	55
2	27b	57:43	5.2 (4.0)	1.5 (1.1)	45

^a Determined by ¹H NMR of the crude mixture.^b Calculated values are in parentheses.

The discrepancy between the very high levels of diastereoselectivity achieved in the double C–H insertion of **25a** and **25b** with Rh₂(esp)₂ (≥95% ds and ≥80% ds, respectively) and the low diastereoselectivity in the mono C–H insertion of **27a** and **27b** under the same conditions (69% ds and 57% ds, respectively) is intriguing. It suggests that the second C–H insertion, and perhaps both, does not occur via a concerted pathway (Scheme 6, path A), since a concerted C–H insertion should transform the trans mono-cyclic intermediate into diastereomers **29** and **30**. This suggests the reaction may occur via transfer of hydride from the acetal carbon to the rhodium carbene, then recombination of the thus formed enolate with the oxonium ion via both faces (Scheme 6, path B). Related mechanisms have previously been suggested to account for the formation of anomalous products in the Rh(II)-catalysed C–H insertion adjacent to cation-stabilising oxygen atoms.^{39–44} Further work is ongoing to investigate the mechanism of this bidirectional reaction, including computational modelling of the reaction pathways, with particular interest in whether one or both of the C–H insertion steps proceed via a non-concerted mechanism involving hydride transfer from the acetal carbon to the carbene, since this has important ramifications for the stereochemical course of the reaction.

Scheme 6: Concerted vs non-concerted pathways to spiroacetal products.

3. Conclusion

Chiral 5,5-spiroacetals can be synthesised from acyclic methylene acetal precursors via double Rh(II)-catalysed C–H insertion reactions. This complexity-building method creates two rings in a spirocyclic topology, and three new stereogenic centres

in one pot from readily available achiral precursors. Through appropriate choice of catalyst, the diastereoselectivity of the reaction can be altered and chiral catalysts can be used to provide the major diastereomer in good to excellent enantioselectivity. By comparison to a non-acetal precursor to spirocarbacycles precursor, the beneficial effect of oxygen atoms adjacent to the site of C–H insertion is noted. A limitation of the present bidirectional approach to spiroacetals is the inability to form 6-membered rings, and hence 6,6-spiroacetals. Nevertheless, the product 5,5-spiroacetals represent interesting chiral, 3-dimensional scaffolds for future drug discovery, asymmetric synthesis and catalysis. An investigation of the cyclisation of a mono-diazo compound suggests that the spiroacetal formation may proceed in a stepwise manner, rather than a concerted C–H insertion. Work is ongoing to investigate the mechanism of this reaction and extend this bidirectional C–H insertion strategy to the synthesis of other bicyclic compounds.

4. Experimental Section

4.1. General

All reactions were performed under an atmosphere of nitrogen unless otherwise indicated. Temperatures quoted as –78 °C, –60 °C, –40 °C and –20 °C were obtained by cooling the reaction vessel in bath of dry ice/acetone/water. Anhydrous solvents were dried on molecular sieves prior to use. All other reagents and solvents were used as purchased from commercial suppliers unless otherwise noted. Reaction progress was monitored by thin layer chromatography (TLC) on aluminum backed silica gel plates, visualising with UV light, and plates were developed using vanillin or potassium permanganate. Flash chromatography was performed using silica gel (230 – 400 mesh). NMR spectra were acquired on Varian INOVA or Bruker Avance III HD NMR spectrometers at 500 MHz and 125 MHz for ¹H and ¹³C respectively. ¹H NMR spectra were referenced to the residual forms of the solvent with one less deuterium than the perdeuterated solvent (CHCl₃ = 7.26 ppm) ¹³C NMR spectra were referenced to the internal perdeuterated solvent resonance (CDCl₃ = 77.16 ppm & C₆D₆ = 128.06 ppm). Coupling constants (*J*) are in Hz. The multiplicities of the signals are described using the following abbreviations: s = singlet, d = doublet, t = triplet q = quadruplet, br = broad. Low resolution electrospray mass spectra (LRESIMS) were recorded on an Agilent 6120 quadrupole LCMS system. High resolution mass spectra (HRMS) were acquired on a Bruker Bruker QTOF MaXis II ETD.

4.2. General procedure for the synthesis of bis(iodoalkyl) methylene acetals

Haloalcohol (2.0 equiv.) and paraformaldehyde (3.60 g, 120 mmol, 1.00 eq) were dissolved in toluene (20 mL) in a round-bottom flask equipped with a Dean-Stark apparatus. Concentrated sulfuric acid (1 drop, cat.) was added and the mixture was refluxed for 1.5 h, until approximately the expected amount of water had been collected. After cooling, sodium bicarbonate (approx. 2 g) was added and the mixture was filtered. The filtrate was concentrated *in vacuo* and purified by flash chromatography (95:5, PS/EtOAc) to provide the bis(bromoalkyl) or bis(chloroalkyl) methylene acetal.

The dibromo or dichloro compound (1.0 equiv.) and sodium iodide (2.05 eq) were dissolved in acetone (0.66 mL/mmole substrate) and heated to reflux for 3 h. The acetone was removed *in vacuo*, water and Et₂O were added and the layers were separated. The organic layer was washed with brine, dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*, to yield the bis(iodoalkyl) methylene acetal.

4.2.1. 1-Bromo-2-[(2-bromoethoxy)methoxy]ethane (**19**)

Yield 77%, colourless oil. R_f 0.60 (95:5 PS/Et₂O); ¹H NMR (500 MHz, CDCl₃) δ 4.78 (2H, s, OCH₂O), 3.92 (4H, t, J = 6.0 Hz, BrCH₂CH₂O), 3.51 (4H, t, J = 6.0 Hz, BrCH₂CH₂O); ¹³C NMR (126 MHz, CDCl₃) δ 95.6 (OCH₂O), 68.3 (BrCH₂CH₂O), 30.8 (BrCH₂CH₂O).

4.2.2. 1-Chloro-3-[(3-chloropropoxy)methoxy]propane (**20**)

Yield 83%, colourless oil. R_f 0.72 (90:10 PS/EtOAc); ¹H NMR (500 MHz, CDCl₃) δ 4.68 (2H, s, OCH₂O), 3.68 (4H, t, J = 5.9 Hz, ClCH₂CH₂CH₂O), 3.65 (4H, t, J = 6.4 Hz, ClCH₂CH₂CH₂O), 2.04 (4H, app p, J = 6.2 Hz); ¹³C NMR (126 MHz, CDCl₃) δ 95.6 (OCH₂O), 64.4 (ClCH₂CH₂CH₂O), 41.9 (ClCH₂CH₂CH₂O), 32.8 (ClCH₂CH₂CH₂O).

4.2.3. 1-Iodo-2-[(2-iodoethoxy)methoxy]ethane (**21**)

Yield 92%, orange-brown oil. R_f 0.60 (95:5 PS/Et₂O); ¹H NMR (500 MHz, CDCl₃) δ 4.77 (2H, s, OCH₂O), 3.86 (4H, t, J = 6.5 Hz, ICH₂CH₂O), 3.29 (4H, t, J = 6.5 Hz, ICH₂CH₂O); ¹³C NMR (126 MHz, CDCl₃) δ 95.3 (OCH₂O), 69.1 (ICH₂CH₂O), 3.1 (ICH₂CH₂O).

4.2.4. 1-Iodo-3-[(3-iodopropoxy)methoxy]propane (**22**)

Yield 98%, orange-brown oil. R_f 0.84 (95:5 PS/EtOAc); ¹H NMR (500 MHz, CDCl₃) δ 4.68 (2H, s, OCH₂O), 3.61 (4H, t, J = 5.85 Hz, ICH₂CH₂CH₂O), 3.29 (4H, t, J = 6.7 Hz, ICH₂CH₂CH₂O), 2.08 (4H, app p, J = 6.3 Hz, ICH₂CH₂CH₂O); ¹³C NMR (126 MHz, CDCl₃) δ 95.6 (OCH₂O), 67.4 (ICH₂CH₂CH₂O), 33.5 (ICH₂CH₂CH₂O), 3.3 (ICH₂CH₂CH₂O).

4.3. General procedure for double nucleophilic substitution with sodium alkyl acetoacetates

Diiodo compound (1.0 equiv.) and alkyl acetoacetate sodium salt (3.5 equiv.) were dissolved in DME (0.75 M in diiodide) and then heated to reflux for 16 h (overnight). The reaction was quenched with sat. NH₄Cl(aq)/water (1:1 v/v) and extracted with ethyl acetate (3 times). The organic layer was washed with brine and dried over magnesium sulfate, then filtered and solvent was removed *in vacuo*. The crude residue was purified by flash chromatography (90:10, PS/EtOAc) to yield the desired compound.

4.3.1. 1,11-diethyl 2,10-diacetylundecanedioate (**15**)

General procedure modified to use 1,7-dibromoheptane (**14**) in MeCN with tetra-*n*-butylammonium iodide, TBAI (5 mol%) at reflux for 3 h. Yield 59%, colourless oil. ¹H NMR (500 MHz, CDCl₃) δ 4.19 (4H, q, J = 7.1 Hz), 3.38 (2H, t, J = 7.4 Hz), 2.22 (6H, s), 1.89 – 1.76 (4H, m), 1.33 – 1.22 (16H, m).

4.3.2. Methyl 2-{2-[(3-acetyl-4-methoxy-4-oxobutoxy)methoxy]ethyl}-3-oxobutanoate (**23a**)

Yield 68%, yellow oil. R_f 0.15 (90:10 PS/EtOAc); ¹H NMR (500 MHz, CDCl₃) δ 4.54 (2H, s, OCH₂O), 3.72 (6H, s, CH₃OC(O)), 3.64 (2H, t, J = 6.9 Hz, OCH₂CH₂CH), 3.50 (4H, m, OCH₂CH₂CH), 2.23 (6H, s, (CO)CH₃), 2.11 (4H, m, CH₂CH₂CH); ¹³C NMR (126 MHz, CDCl₃) δ 202.8 (C(O)CH₃), 170.2 (C(O)OMe), 95.4 (OCH₂O), 65.4 (OCH₂CH₂CH), 56.6 (CH₃OC(O)), 52.6 (OCH₂CH₂CH), 29.3 (OCH₂CH₂CH), 28.3 (C(O)CH₃); LRMS (ESI +) m/z 355 ([M + Na]⁺, 100); HRMS (ESI +) m/z calculated for C₁₅H₂₄NaO₈ 355.1363, found 355.1363.

4.3.3. Ethyl 2-{2-[(3-acetyl-4-ethoxy-4-oxobutoxy)methoxy]ethyl}-3-oxobutanoate (**23b**)

Yield 76%, yellow oil. R_f 0.29 (90:10 PS/EtOAc); ¹H NMR (500 MHz, CDCl₃) δ 4.53 (2H, s, OCH₂O), 4.19 (4H, app dtt, J_1 = 10.8 Hz, J_2 = 6.6 Hz, J_3 = 3.7 Hz, CH₃CH₂CO₂), 3.62 (2H, t, J = 7.1 Hz, CH₂CH₂CH), 3.51 (4H, app hept, J_1 = 5.2 Hz, J_2 = 4.5 Hz, OCH₂CH₂CH), 2.25 (6H, s, (CO)CH₃), 2.12 (4H, dt, J_1 = 11.3 Hz, J_2 = 6.2 Hz, OCH₂CH₂CH), 1.27 (6H, t, J = 7.4 Hz, CH₃CH₂CO₂); ¹³C NMR (126 MHz, CDCl₃) δ 202.70 (C(O)CH₃), 169.51 (C(O)OEt), 95.14 (OCH₂O), 65.19 (OCH₂CH₂CH), 61.39 (CH₃CH₂OC(O)), 56.61 (OCH₂CH₂CH), 29.03 (OCH₂CH₂CH), 28.07 (C(O)CH₃), 14.04 (CH₃CH₂OC(O)); MS (ESI +) m/z 383.16 ([M + Na]⁺, 100); HRMS (ESI +) m/z calculated for C₁₇H₂₈NaO₈ 383.1676, found 383.1680.

4.3.4. *tert*-Butyl 2-(2-{[3-acetyl-4-(*tert*-butoxy)-4-oxobutoxy]methoxy}ethyl)-3-oxobutanoate (**23c**)

Yield 52%, yellow oil. R_f 0.44 (90:10 PS/EtOAc); ¹H NMR (500 MHz, CDCl₃) δ 4.56 (2H, s, OCH₂O), 3.54-3.50 (3H, m, CH₂CH₂CH, CH₂CH₂CH), 2.24 (6H, s, (CO)CH₃), 2.08 (4H, app p, J = 6.7 Hz, CH₂CH₂CH), 1.46 (9H, s, (CH₃)₃COC(O)); ¹³C NMR (126 MHz, CDCl₃) δ 203.22 (C(O)CH₃), 168.82 (C(O)Ot-Bu), 95.31 (OCH₂O), 82.09 (C(O)OC(CH₃)₃), 65.46 (OCH₂CH₂CH), 57.93 (OCH₂CH₂CH), 29.15 (OCH₂CH₂CH), 28.19 (C(O)CH₃), 28.06 (C(O)OC(CH₃)₃); MS (ESI +) m/z 408.92 ([M + Na - 30]⁺, 100); HRMS (ESI +) m/z calculated for C₂₁H₃₆NaO₈ 439.2302, found 439.2307.

4.3.5. Methyl 2-acetyl-5-[(4-acetyl-5-methoxy-5-oxopentyl)oxy]methoxy pentanoate (**24a**)

Yield 62%, yellow oil. R_f 0.20 (90:10 PS/EtOAc); ¹H NMR (500 MHz, CDCl₃) δ 4.61 (2H, s, OCH₂O), 3.73 (6H, s, CH₃OC(O)), 3.51 (4H, t, J = 6.2 Hz, OCH₂CH₂CH₂CH), 3.47 (2H, t, J = 7.4 Hz, OCH₂CH₂CH₂CH), 2.22 (6H, s, (CO)CH₃), 1.92 (4H, app q, J = 7.7 Hz, CH₂CH₂CH₂CH), 1.56 (4H, app dq, J_1 = 13.6 Hz, J_2 = 6.7 Hz, CH₂CH₂CH₂CH); ¹³C NMR (126 MHz, CDCl₃) δ 202.8 (C(O)CH₃), 170.3 (C(O)OCH₃), 95.5 (OCH₂O), 67.4 (CHCH₂CH₂CH₂O), 59.4 (C(O)OCH₃), 52.5 (CHCH₂CH₂CH₂O), 29.1 (C(O)CH₃), 27.6 (CHCH₂CH₂CH₂O), 25.3 (CHCH₂CH₂CH₂O).

4.3.6. Ethyl 2-acetyl-5-[(4-acetyl-5-ethoxy-5-oxopentyl)oxy]methoxy pentanoate (**24b**)

Yield 64%, yellow oil. R_f 0.23 (90:10 PS/EtOAc); ¹H NMR (500 MHz, CDCl₃) δ 4.62 (2H, s, OCH₂O), 4.19 (4H, q, J = 7.1 Hz, CH₃CH₂OC(O)), 3.51 (4H, t, J = 6.3 Hz, OCH₂CH₂CH₂CH), 3.44 (2H, t, J = 7.4 Hz, CH₂CH₂CH₂CH), 2.22 (6H, s, (CO)CH₃), 1.92 (4H, app q, J = 7.7 Hz, OCH₂CH₂CH₂CH), 1.57 (4H, app dq, J_1 = 13.9 Hz, J_2 = 6.5 Hz, OCH₂CH₂CH₂CH), 1.27 (6H, t, J = 7.1 Hz, CH₃CH₂OC(O)); ¹³C NMR (126 MHz, CDCl₃) δ 202.9 (C(O)CH₃), 169.9 (C(O)OCH₂CH₃), 95.4 (OCH₂O), 67.36 (CHCH₂CH₂CH₂O), 61.5 (C(O)OCH₂CH₃), 59.7 (CHCH₂CH₂CH₂O), 29.0 (C(O)CH₃), 27.6 (CHCH₂CH₂CH₂O), 25.2 (CHCH₂CH₂CH₂O), 14.3 (C(O)OCH₂CH₃).

4.3.7. *tert*-Butyl 2-acetyl-5-[(4-acetyl-5-(*tert*-butoxy)-5-oxopentyl)oxy]methoxy pentanoate (**24c**)

Yield 79%, yellow oil. R_f 0.37 (90:10 PS/EtOAc); ¹H NMR (500 MHz, CDCl₃) δ 4.63 (2H, s, OCH₂O), 3.52 (4H, t, J = 6.3 Hz, OCH₂CH₂CH₂CH), 3.34 (2H, t, J = 7.4 Hz, CH₂CH₂CH₂CH), 2.21 (6H, s, (CO)CH₃), 1.87 (4H, app q, J = 7.7 Hz, OCH₂CH₂CH₂CH), 1.60-1.53 (4H, m, OCH₂CH₂CH₂CH), 1.46 (18H, s, (CH₃)₃COC(O)); ¹³C NMR (126 MHz, CDCl₃) δ 203.4 (C(O)CH₃), 169.0 (C(O)OC(CH₃)₃), 95.4 (OCH₂O), 82.1 (C(O)OC(CH₃)₃), 67.4 (CHCH₂CH₂CH₂O), 60.7 (CHCH₂CH₂CH₂O), 28.9 (C(O)CH₃), 28.1 (C(O)OC(CH₃)₃), 27.6 (CHCH₂CH₂CH₂O), 25.1 (CHCH₂CH₂CH₂O).

4.4. General procedure for diazo transfer

Bis(β -ketoester) (1.0 equiv.) and *p*-ABSA (2.4 equiv.) were dissolved in acetonitrile (0.15 M in diester). The mixture was cooled to 0 °C (ice bath) and DBU (2.4 equiv.) was added dropwise. The reaction mixture was allowed to warm to room temperature and stirred for 24 h. The reaction was quenched with Et₂O/water (1:1 v/v) and extracted with ethyl acetate (3 times). The organic layer was washed with brine and dried over magnesium sulfate, then filtered and the solvent was evaporated under vacuum. The crude residue was purified by flash chromatography (90:10, PS/EtOAc) to yield the desired compound.

4.4.1. Diethyl 2,10-bis(diazo)undecanedioate

Yield 65%, bright yellow oil. *R*_f 0.31 (90:10 PS/EtOAc); ¹H NMR (500 MHz, CDCl₃) δ 4.22 (4H, q, *J* = 7.1 Hz), 2.29 (4H, t, *J* = 7.5 Hz), 1.49 (4H, m), 1.35 (6H, m), 1.27 (6H, t, *J* = 7.1 Hz).

4.4.2. Methyl 2-diazo-4-[(3-diazo-4-methoxy-4-oxobutoxy)methoxy]butanoate (25a)

Yield 57%, bright yellow oil. *R*_f 0.68 (70:30 PS/EtOAc); ¹H NMR (500 MHz, CDCl₃) δ 4.66 (2H, s, OCH₂O), 3.77 (6H, s, (CO)OCH₃), 3.68 (4H, t, *J* = 5.9 Hz, OCH₂CH₂C(N₂)), 2.56 (4H, t, *J* = 5.9 Hz, OCH₂CH₂C(N₂)); ¹³C NMR (126 MHz, CDCl₃) δ 95.57 (CH₂), 66.28 (CH₂), 52.09 (CH₃), 24.34 (CH₂), OC(O)C(N₂) and OC(O)C(N₂) not detected.

4.4.3. Ethyl 2-diazo-4-[(3-diazo-4-ethoxy-4-oxobutoxy)methoxy]butanoate (25b)

Yield 48%, bright yellow oil. *R*_f 0.53 (85:15 PS/EtOAc); ¹H NMR (500 MHz, CDCl₃) δ 4.66 (2H, s, OCH₂O), 4.22 (4H, t, *J* = 7.1 Hz, (CO)OCH₂CH₃), 3.68 (4H, t, *J* = 5.9 Hz, OCH₂CH₂C(N₂)), 2.56 (4H, t, *J* = 5.9 Hz, OCH₂CH₂C(N₂)), 1.27 (6H, t, *J* = 7.1 Hz, (CO)OCH₂CH₃); ¹³C NMR (126 MHz, CDCl₃) δ 95.61 (CH₂), 66.32 (CH₂), 60.97 (CH₂), 24.35 (CH₂), 14.67 (CH₃), OC(O)C(N₂) and OC(O)C(N₂) not detected.

4.4.4. *tert*-Butyl 4-[[4-(*tert*-butoxy)-3-diazo-4-oxobutoxy]methoxy]-2-diazobutanoate (25c)

Yield 57%, bright yellow oil. *R*_f 0.45 (95:5 PS/EtOAc); ¹H NMR (500 MHz, CDCl₃) δ 4.66 (2H, s, OCH₂O), 3.67 (4H, t, *J* = 6.0 Hz, OCH₂CH₂C(N₂)), 2.51 (4H, t, *J* = 6.0 Hz, OCH₂CH₂C(N₂)), 1.48 (18H, s, (CO)OC(CH₃)₃); ¹³C NMR (126 MHz, CDCl₃) δ 95.41 (CH₂), 81.19 (C_{quat}), 66.15 (CH₂), 28.39 (CH₃), 24.15 (CH₂), OC(O)C(N₂) and OC(O)C(N₂) not detected.

4.4.5. Methyl 2-diazo-5-[[4-diazo-5-methoxy-5-oxopentyl]oxy]methoxy]pentanoate (26a)

Yield 45%, bright yellow oil. *R*_f 0.73 (75:25 PS/EtOAc); ¹H NMR (500 MHz, CDCl₃) δ 4.65 (2H, s, OCH₂O), 3.76 (6H, s, (CO)OCH₃), 3.57 (4H, t, *J* = 6.1 Hz, OCH₂CH₂CH₂C(N₂)), 2.42 (4H, t, *J* = 7.3 Hz, OCH₂CH₂CH₂C(N₂)), 1.80 (4H, app p, *J* = 6.6 Hz, OCH₂CH₂CH₂C(N₂)); ¹³C NMR (126 MHz, CDCl₃) δ 110.2 (OC(O)C(N₂)), 95.7 (OCH₂O), 66.6 (OCH₂CH₂CH₂C(N₂)), 52.0 (C(O)OCH₃), 28.0 (OCH₂CH₂CH₂C(N₂)), 20.6 (OCH₂CH₂CH₂C(N₂)), OC(O)C(N₂) not detected.

4.4.6. Ethyl 2-diazo-5-[[4-diazo-5-ethoxy-5-oxopentyl]oxy]methoxy]pentanoate (26b)

Yield 39%, bright yellow oil. *R*_f 0.84 (75:25 PS/EtOAc); ¹H NMR (500 MHz, CDCl₃) δ 4.65 (2H, s, OCH₂O), 4.22 (4H, q, *J* = 7.1 Hz, CH₃CH₂OC(O)), 3.57 (4H, t, *J* = 6.1 Hz, OCH₂CH₂CH₂C(N₂)), 2.41 (4H, t, *J* = 7.3 Hz, OCH₂CH₂CH₂C(N₂)), 1.80 (4H, app p, *J* = 6.4 Hz, OCH₂CH₂CH₂C(N₂)), 1.27 (6H, t, *J* = 7.1 Hz, CH₃CH₂OC(O)); ¹³C NMR (126 MHz, CDCl₃) δ 95.6 (OCH₂O), 66.7 (OCH₂CH₂CH₂C(N₂)), 60.9 (C(O)OCH₂CH₃), 28.0 (OCH₂CH₂CH₂C(N₂)), 20.6 (OCH₂CH₂CH₂C(N₂)), 14.7 (C(O)OCH₂CH₃), OC(O)C(N₂) and OC(O)C(N₂) not detected.

4.4.7. *tert*-Butyl 5-[[5-(*tert*-butoxy)-4-diazo-5-oxopentyl]oxy]methoxy]-2-diazopentanoate (26c)

Yield 35%, bright yellow oil. *R*_f 0.93 (75:25 PS/EtOAc); ¹H NMR (500 MHz, CDCl₃) δ 4.65 (2H, s, OCH₂O), 3.56 (4H, t, *J* = 6.2 Hz, OCH₂CH₂CH₂C(N₂)), 2.36 (4H, t, *J* = 7.4 Hz, OCH₂CH₂CH₂C(N₂)), 1.79 (4H, app p, *J* = 6.6 Hz, OCH₂CH₂CH₂C(N₂)), 1.47 (18H, s, (CO)OC(CH₃)₃); ¹³C NMR (126 MHz, CDCl₃) δ 160.7 (OC(O)C(N₂)), 110.1 (OC(O)C(N₂)), 95.3 (OCH₂O), 84.0 (C(O)OC(CH₃)₃), 66.7 (OCH₂CH₂CH₂C(N₂)), 28.4 (OCH₂CH₂CH₂C(N₂)), 28.0 (C(O)OC(CH₃)₃), 23.8 (OCH₂CH₂CH₂C(N₂)).

4.4.8. Methyl 2-diazo-4-[[4-(4-oxopentyl]oxy]methoxy]butanoate (27a)

Yield 15-20%, bright yellow oil. *R*_f 0.47 (75:25 PS/EtOAc); ¹H NMR (500 MHz, CDCl₃) δ 4.64 (2H, s, OCH₂O), 3.77 (3H, s, OC(O)CH₃), 3.67 (2H, t, *J* = 5.9 Hz, OCH₂CH₂C(N₂)), 3.52 (2H, t, *J* = 6.2 Hz, OCH₂CH₂CH₂C(O)), 2.56 (2H, t, *J* = 5.9 Hz, OCH₂CH₂C(N₂)), 2.52 (2H, t, *J* = 7.2 Hz, OCH₂CH₂CH₂C(O)), 2.15 (3H, s, CH₃C(O)CH₃), 1.85 (2H, app p, *J* = 6.7 Hz, OCH₂CH₂CH₂C(O)); ¹³C NMR (126 MHz, CDCl₃) δ 207.4 (CH₃C(O)), 94.5 (OCH₂O), 66.2 (OCH₂CH₂CH₂C(O)), 66.1 (OCH₂CH₂C(N₂)), 52.6 (C(O)OCH₃), 39.4 (OCH₂CH₂CH₂C(O)), 29.1 (CH₃C(O)CH₃), 23.4 (OCH₂CH₂C(N₂)), 23.0 (OCH₂CH₂CH₂C(O)).

4.4.9. Ethyl 2-diazo-4-[[4-(4-oxopentyl]oxy]methoxy]butanoate (27b)

Yield 4-5%, bright yellow oil. *R*_f 0.53 (75:25 PS/EtOAc); ¹H NMR (500 MHz, CDCl₃) δ 4.64 (2H, s, OCH₂O), 4.22 (2H, q, *J* = 7.1 Hz, OC(O)CH₂CH₃), 3.68 (2H, t, *J* = 5.9 Hz, OCH₂CH₂C(N₂)), 3.52 (2H, t, *J* = 6.2 Hz, OCH₂CH₂CH₂C(O)), 2.56 (2H, t, *J* = 5.9 Hz, OCH₂CH₂C(N₂)), 2.52 (2H, t, *J* = 7.3 Hz, OCH₂CH₂CH₂C(O)), 2.15 (3H, s, CH₃C(O)CH₃), 1.86 (2H, app p, *J* = 6.7 Hz, OCH₂CH₂CH₂C(O)), 1.27 (3H, t, *J* = 7.2 Hz, OC(O)CH₂CH₃).

4.5. General procedure for the Rh(II)-catalysed C-H insertion

Diazo compound (1 equiv.) was dissolved in dry toluene (0.1 M) under argon atmosphere and then the solution was degassed by bubbling argon with vigorous stirring at -78 °C (dry ice in acetone). The rhodium catalyst (0.5 mol%) was added quickly and then the mixture was progressively warmed until 0 °C was reached. The solvent was removed *in vacuo* and the crude mixture was purified by flash chromatography (85:15, PS/EtOAc) to yield the desired compounds.

4.5.1. Ethyl 2-[(3Z)-5-ethoxy-5-oxopent-3-en-1-yl]cyclopentane-1-carboxylate (17)

Reaction conducted with Rh₂(OAc)₄ (5 mol%) in CH₂Cl₂ at room temperature. Yield 51%, colourless oil. ¹H NMR (600 MHz, CDCl₃) δ 6.20 (1H, dt, *J* = 11.5, 7.5 Hz), 5.75 (1H, dt, *J* = 11.5, 1.6 Hz), 4.15 (2H, q, *J* = 7.1 Hz), 4.14 – 4.10 (2H, m), 2.65 (2H, m), 2.33 (1H, app. q, *J* = 8.5 Hz), 2.15 – 2.07 (1H, m), 1.98 – 1.87 (2H, m), 1.85 – 1.78 (1H, m), 1.70 – 1.62 (3H, m), 1.48 – 1.35 (2H, m), 1.28 (3H, t, *J* = 7.2 Hz), 1.25 (3H, t, *J* = 7.1 Hz).

4.5.2. 4,9-Dimethyl 1,6-dioxaspiro[4.4]nonane-4,9-dicarboxylate

Yield and diastereomeric ratio per Table 1, colourless oil, diastereomers separable by flash chromatography for characterisation purposes. MS (ESI +) *m/z* 267.15 ([M + Na]⁺, 100); HRMS (ESI +) *m/z* calculated for C₁₁H₁₆NaO₆ 267.0839, found 267.0836.

4.5.2.1. (4*S**,5*S**,9*S**)-diastereomer (28a)

^1H NMR (500 MHz, CDCl_3) δ 4.05 (2H, td, $J = 8.5, 3.8$ Hz), 3.77 (2H, td, $J = 8.4, 7.3$ Hz), 3.73 (6H, s), 3.59 (2H, dd, $J = 10.3, 9.1$ Hz), 2.53 (2H, ddt, $J = 12.4, 10.4, 8.7$ Hz), 2.12 (2H, dddd, $J = 12.6, 9.0, 7.3, 3.9$ Hz); ^{13}C NMR (126 MHz, CDCl_3) δ 170.21 (C_{carbox}), 112.45 (C_{spiro}), 66.99 (CH_2), 52.11 (CH_3), 49.58 (CH), 26.50 (CH_2).

4.5.2.2. (4*R**,5*S**,9*S**)-diastereomer (29a)

^1H NMR (500 MHz, CDCl_3) δ 4.04 – 3.96 (2H, m), 3.93 – 3.86 (2H, m), 3.76 (3H, s), 3.66 (3H, s), 3.54 (1H, dd, $J = 9.7, 8.1$ Hz), 3.23 (1H, dd, $J = 8.0, 6.5$ Hz), 2.54 (1H, dtd, $J = 12.5, 8.2, 6.2$ Hz), 2.35 (1H, dtd, $J = 12.4, 7.8, 6.5$ Hz), 2.23 – 2.12 (2H, m); ^{13}C NMR (126 MHz, CDCl_3) δ 171.63 (C_{carbox}), 170.40 (C_{carbox}), 114.01 (C_{spiro}), 66.90 (CH_2), 65.92 (CH_2), 52.26 (CH_3), 51.99 (CH_3), 51.87 (CH), 47.82 (CH), 27.96 (CH_2), 27.53 (CH_2).

4.5.3. 4,9-Diethyl 1,6-dioxaspiro[4.4]nonane-4,9-dicarboxylate

Yield and diastereomeric ratio per Table 1, colourless oil, diastereomers partially separable by flash chromatography for characterisation purposes. MS (ESI +) m/z 295.11 ($[\text{M} + \text{Na}]^+$, 100); HRMS (ESI +) m/z calculated for $\text{C}_{13}\text{H}_{20}\text{NaO}_6$ 295.1152, found 295.1152.

4.5.3.1. (4*S**,5*S**,9*S**)-diastereomer (28b)

^1H NMR (500 MHz, CDCl_3) δ 4.24 (2H, q, $J = 7.1$ Hz), 4.16 (2H, q, $J = 7.1$ Hz), 4.05 (2H, td, $J = 8.6, 4.0$ Hz), 3.77 (2H, td, $J = 8.3, 7.3$ Hz), 3.59 (2H, dd, $J = 10.3, 9.0$ Hz), 2.53 (2H, ddt, $J = 12.5, 10.4, 8.7$ Hz), 2.11 (2H, dddd, $J = 12.6, 9.0, 7.3, 3.9$ Hz), 1.27 (6H, t, $J = 7.1$ Hz); ^{13}C NMR (126 MHz, CDCl_3) δ 169.77 (C_{carbox}), 112.63 (C_{spiro}), 67.04 (CH_2), 60.87 (CH_2), 49.74 (CH), 26.51 (CH_2), 14.45 (CH_3).

4.5.3.2. (4*R**,5*S**,9*S**)-diastereomer (29b)

^1H NMR (500 MHz, CDCl_3) δ 4.22 (2H, q, $J = 7.2$ Hz), 4.18 – 4.07 (2H, m), 3.99 (2H, td, $J = 8.4, 5.5$ Hz), 3.89 (2H, dtd, $J = 8.7, 7.7, 7.1, 5.6$ Hz), 3.56 (1H, dd, $J = 9.7, 7.9$ Hz), 3.22 (1H, t, $J = 7.6$ Hz), 2.54 (1H, dtd, $J = 12.0, 8.0, 6.2$ Hz), 2.36 (1H, dq, $J = 12.3, 7.8$ Hz), 2.22 – 2.08 (2H, m), 1.31 (3H, t, $J = 7.1$ Hz), 1.23 (3H, t, $J = 7.1$ Hz); ^{13}C NMR (126 MHz, CDCl_3) δ 171.00 (C_{carbox}), 170.04 (C_{carbox}), 114.10 (C_{spiro}), 66.80 (CH_2), 65.92 (CH_2), 61.14 (CH_2), 60.87 (CH_2), 52.00 (CH), 49.90 (CH), 28.12 (CH_2), 27.55 (CH_2), 14.31 (CH_3), 14.22 (CH_3).

4.5.4. 4,9-Di-tert-butyl 1,6-dioxaspiro[4.4]nonane-4,9-dicarboxylate

Yield and diastereomeric ratio per Table 1, colourless oil, diastereomers partially separable by flash chromatography for characterisation purposes. MS (ESI +) m/z 351.10 ($[\text{M} + \text{Na}]^+$, 100); HRMS (ESI +) m/z calculated for $\text{C}_{17}\text{H}_{28}\text{NaO}_6$ 351.1778, found 351.1769.

4.5.4.1. (4*S**,5*S**,9*S**)-diastereomer (28c)

^1H NMR (500 MHz, CDCl_3) δ 4.04 (2H, td, $J = 8.5, 4.1$ Hz), 3.77 (2H, q, $J = 8.2$ Hz), 3.49 (2H, dd, $J = 10.1, 9.1$ Hz), 2.49 (2H, ddt, $J = 12.6, 10.3, 8.6$ Hz), 2.05 (2H, dddd, $J = 11.7, 9.1, 7.3, 4.1$ Hz), 1.47 (18H, s); ^{13}C NMR (126 MHz, CDCl_3) δ 168.85 (C_{carbox}), 112.95 (C_{spiro}), 80.87 (C_q), 66.83 (CH_2), 50.40 (CH), 28.13 (CH_2), 26.36 (CH_3).

4.5.4.2. (4*R**,5*S**,9*S**)-diastereomer (29c)

^1H NMR (500 MHz, CDCl_3) δ 3.98 (1H, td, $J = 8.2, 6.3$ Hz), 3.95 (1H, td, $J = 8.1, 1.9$ Hz), 3.88 (1H, td, $J = 8.0, 6.1$ Hz), 3.84 (1H, ddd, $J = 10.9, 8.3, 5.6$ Hz), 2.53–2.45 (1H, m), 2.32 (1H, dtd, $J = 12.2, 10.7, 7.9$ Hz), 2.13–2.02 (2H, m), 1.50 (9H, s), 1.45

4.5.5. Methyl 2-[(4-oxopentyl)oxy]oxolane-3-carboxylate

Yield and diastereomeric ratio as per Table 2, colourless oil, diastereomers separable by flash chromatography for characterisation purposes.

4.5.5.1. cis Diastereomer (35a)

R_f 0.36 (80:20 PS/EtOAc); ^1H NMR (500 MHz, CDCl_3) δ 5.18 (1H, d, $J = 5.2$ Hz, H), 4.05 (1H, td, $J_1 = 8.8$ Hz, $J_2 = 4.8$ Hz), 3.91 (1H, app q, $J = 8.0$ Hz), 3.71 (3H, s, $\text{C}(\text{O})\text{OCH}_3$), 3.65 (1H, dt, $J_1 = 9.8$ Hz, $J_2 = 6.1$ Hz, $\text{OCH}_2\text{CH}_2\text{CH}_2\text{C}(\text{O})\text{CH}_3$), 3.39 (1H, dt, $J_1 = 9.7$ Hz, $J_2 = 6.2$ Hz, $\text{OCH}_2\text{CH}_2\text{CH}_2\text{C}(\text{O})\text{CH}_3$), 3.09 (1H, td, $J_1 = 9.5$ Hz, $J_2 = 5.1$ Hz, H), 2.44 (2H, t, $J = 7.3$ Hz, $\text{OCH}_2\text{CH}_2\text{CH}_2\text{C}(\text{O})\text{CH}_3$), 2.14 (3H, s, $\text{C}(\text{O})\text{CH}_3$), 2.04 (2H, m, CH_2), 1.80 (2H, app p, $J = 6.9$ Hz, $\text{OCH}_2\text{CH}_2\text{CH}_2\text{C}(\text{O})\text{CH}_3$).

4.5.5.2. trans Diastereomer (36a)

R_f 0.36 (80:20 PS/EtOAc); ^1H NMR (500 MHz, CDCl_3) δ 5.25 (1H, d, $J = 1.5$ Hz, H), 4.01 (1H, td, $J_1 = 8.1$ Hz, $J_2 = 5.3$ Hz, H^c or H^d), 3.90 (1H, app q, $J = 7.8$ Hz), 3.72 (3H, s, $\text{C}(\text{O})\text{OCH}_3$), 3.65 (1H, dt, $J_1 = 10.3$ Hz, $J_2 = 6.2$ Hz, $\text{OCH}_2\text{CH}_2\text{CH}_2\text{C}(\text{O})\text{CH}_3$), 3.43 (1H, dt, $J_1 = 9.6$ Hz, $J_2 = 6.2$ Hz, $\text{OCH}_2\text{CH}_2\text{CH}_2\text{C}(\text{O})\text{CH}_3$), 3.03 (1H, t, $J = 7.1$ Hz, H^b), 2.50 (2H, t, $J = 7.3$ Hz, $\text{OCH}_2\text{CH}_2\text{CH}_2\text{C}(\text{O})\text{CH}_3$), 2.20 (2H, ddd, $J_1 = 12.7$ Hz, $J_2 = 7.0$ Hz, $J_3 = 5.0$ Hz, CH_2), 2.14 (3H, s, $\text{C}(\text{O})\text{CH}_3$), 1.85 (2H, app p, $J = 6.7$ Hz, $\text{OCH}_2\text{CH}_2\text{CH}_2\text{C}(\text{O})\text{CH}_3$).

4.5.6. Ethyl 2-[(4-oxopentyl)oxy]oxolane-3-carboxylate

Yield and diastereomeric ratio as per Table 2, colourless oil, diastereomers partially separable by flash chromatography for characterisation purposes.

4.5.6.1. cis Diastereomer (35b)

R_f 0.25 (75:25 PS/EtOAc); ^1H NMR (500 MHz, CDCl_3) δ 5.18 (1H, d, $J = 5.1$ Hz, H), 4.17 (2H, q, $J = 7.1$ Hz, $\text{C}(\text{O})\text{OCH}_2\text{CH}_3$), 4.04 (1H, td, $J_1 = 8.7$ Hz, $J_2 = 4.9$ Hz), 3.91 (1H, app q, $J = 7.8$ Hz), 3.64 (1H, dt, $J_1 = 9.8$ Hz, $J_2 = 6.1$ Hz, $\text{OCH}_2\text{CH}_2\text{CH}_2\text{C}(\text{O})\text{CH}_3$), 3.39 (1H, dt, $J_1 = 9.7$ Hz, $J_2 = 6.1$ Hz, $\text{OCH}_2\text{CH}_2\text{CH}_2\text{C}(\text{O})\text{CH}_3$), 3.07 (1H, td, $J_1 = 9.5$ Hz, $J_2 = 5.2$ Hz, H), 2.45 (2H, t, $J = 7.3$ Hz, $\text{OCH}_2\text{CH}_2\text{CH}_2\text{C}(\text{O})\text{CH}_3$), 2.12 (3H, s, $\text{C}(\text{O})\text{CH}_3$), 2.03 (2H, dt, $J_1 = 6.7$ Hz, $J_2 = 3.7$ Hz, CH_2), 1.79 (2H, app p, $J = 6.6$ Hz, $\text{OCH}_2\text{CH}_2\text{CH}_2\text{C}(\text{O})\text{CH}_3$), 1.27 (3H, t, $J = 7.1$ Hz, $\text{C}(\text{O})\text{OCH}_2\text{CH}_3$); ^{13}C NMR (126 MHz, CDCl_3) δ 189.0 ($\text{C}(\text{O})\text{OCH}_2\text{CH}_3$), 102.7 (OCHO), 67.1 ($\text{OCH}_2\text{CH}_2\text{CH}_2\text{C}(\text{O})\text{CH}_3$), 66.7 (OCH_2), 60.8 ($\text{C}(\text{O})\text{OCH}_2\text{CH}_3$), 49.8 ($\text{OCH}_2\text{CH}_2\text{CH}$), 40.3 ($\text{OCH}_2\text{CH}_2\text{CH}_2\text{C}(\text{O})$), 30.0 ($\text{CH}_2\text{C}(\text{O})\text{CH}_3$), 25.0 ($\text{OCH}_2\text{CH}_2\text{CH}$), 23.9 ($\text{OCH}_2\text{CH}_2\text{CH}_2\text{C}(\text{O})$), 14.4 ($\text{C}(\text{O})\text{OCH}_2\text{CH}_3$).

4.5.6.2. trans Diastereomer (36b)

R_f 0.25 (90:10 PS/EtOAc); ^1H NMR (500 MHz, CDCl_3) δ 5.25 (1H, d, $J = 1.5$ Hz, H), 4.17 (2H, q, $J = 7.1$ Hz, $\text{C}(\text{O})\text{OCH}_2\text{CH}_3$), 4.00 (1H, td, $J_1 = 7.8$ Hz, $J_2 = 5.3$ Hz), 3.90 (1H, app q, $J = 7.5$ Hz), 3.65 (1H, dt, $J_1 = 9.8$ Hz, $J_2 = 6.1$ Hz, $\text{OCH}_2\text{CH}_2\text{CH}_2\text{C}(\text{O})\text{CH}_3$), 3.43 (1H, dt, $J_1 = 9.7$ Hz, $J_2 = 6.1$ Hz, $\text{OCH}_2\text{CH}_2\text{CH}_2\text{C}(\text{O})\text{CH}_3$), 3.00 (1H, t, $J = 7.1$ Hz, H^b), 2.50 (2H, t, $J = 7.3$ Hz, $\text{OCH}_2\text{CH}_2\text{CH}_2\text{C}(\text{O})\text{CH}_3$), 2.19 (2H, ddd, $J_1 = 12.8$ Hz, $J_2 = 6.9$ Hz, $J_3 = 5.7$ Hz, CH_2), 2.14 (3H, s, $\text{C}(\text{O})\text{CH}_3$), 1.85 (2H, app p, $J = 6.7$ Hz, $\text{OCH}_2\text{CH}_2\text{CH}_2\text{C}(\text{O})\text{CH}_3$), 1.27 (3H, t, $J = 7.1$ Hz, $\text{C}(\text{O})\text{OCH}_2\text{CH}_3$); ^{13}C NMR (126 MHz, CDCl_3) δ 189.1

(C(O)OCH₂CH₃), 105.6 (OCHO), 67.1 (OCH₂CH₂CH₂C(O)CH₃), 66.8 (CH₂), 61.2 (C(O)OCH₂CH₃), 51.2 (OCH₂CH₂CH^b), 40.5 (OCH₂CH₂CH₂C(O)), 30.1 (CH₂C(O)CH₃), 27.7 (CH₂C(O)CH₃), 27.6 (OCH₂CH₂CH^b), 24.1 (OCH₂CH₂CH₂C(O)), 14.3 (C(O)OCH₂CH₃).

4.5.7. General procedure for the derivatisation of the 5,5-spiroacetal diesters

A mixture of spiroacetals **28b**, **29b** and **30b** was dissolved in dry THF (0.15 M) under argon atmosphere. Lithium aluminium hydride powder (8 equiv.) was dissolved in the same volume of dry THF under argon atmosphere. Both solutions were cooled to 0 °C and the spiroacetal solution was added dropwise to the LiAlH₄ solution with vigorous stirring. The resultant mixture was allowed to warm to room temperature and stirred overnight. The reaction was quenched with Na₂SO₄•10H₂O, filtered and the solvent was removed *in vacuo*. The residue was dissolved in CH₂Cl₂ (0.1 M) with triethylamine (2 equiv.) and DMAP (cat.), cooled to 0 °C, and a solution of *p*-bromobenzoyl chloride (4 equiv.) in toluene (0.2 M) was added dropwise. The mixture was allowed to warm to room temperature and stirred overnight. The reaction was quenched with water and extracted three times with ethyl acetate. The organic layers were combined, washed with aq. HCl (5%), aq. sat. NaHCO₃, then brine, dried over anhydrous MgSO₄, the solvent was removed *in vacuo* and the crude residue was purified by flash chromatography (98:2 to 95:5, PS/EtOAc), to yield the title compound.

4.5.7.1. {(4*R*,9*R*)-9-[(4-bromobenzoyloxy)methyl]-1,6-dioxaspiro[4.4]nonan-4-yl)methyl 4-bromobenzoate (**34**)}

[α]_D²⁴ -17.7 (c 0.634, CHCl₃); R_f 0.43 (85:15 PS/EtOAc); ¹H NMR (500 MHz, CDCl₃) δ 7.83 (4H, dt, *J* = 8.6, 1.9 Hz), 7.55 (4H, dt, *J* = 8.6, 1.9 Hz), 4.49 (2H, dd, *J* = 11.1, 7.1 Hz), 4.42 (2H, dd, *J* = 11.1, 6.6 Hz), 4.05 (2H, td, *J* = 8.8, 3.3 Hz), 3.83 (2H, dt, *J* = 8.5, 7.4 Hz), 2.74 (2H, ddt, *J* = 11.1, 8.4, 6.8 Hz), 2.17 (2H, dddd, *J* = 11.9, 8.4, 7.3, 3.3 Hz), 1.95 (2H, ddt, *J* = 12.0, 11.1, 8.9 Hz); ¹³C NMR (126 MHz, CDCl₃) δ 165.75 (ArC(O)O), 131.94 (C_{Ar}), 131.15 (C_{Ar}), 129.11 (C_{Ar}), 128.33 (C_{Ar}), 112.69 (C_{spiro}), 66.23 (CH₂), 64.74 (CH₂), 43.51 (CH), 28.66 (CH₂); HRMS (ESI +) *m/z* calculated for C₂₃H₂₂Br₂NaO₆ 574.9675, found 574.9664.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at...

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