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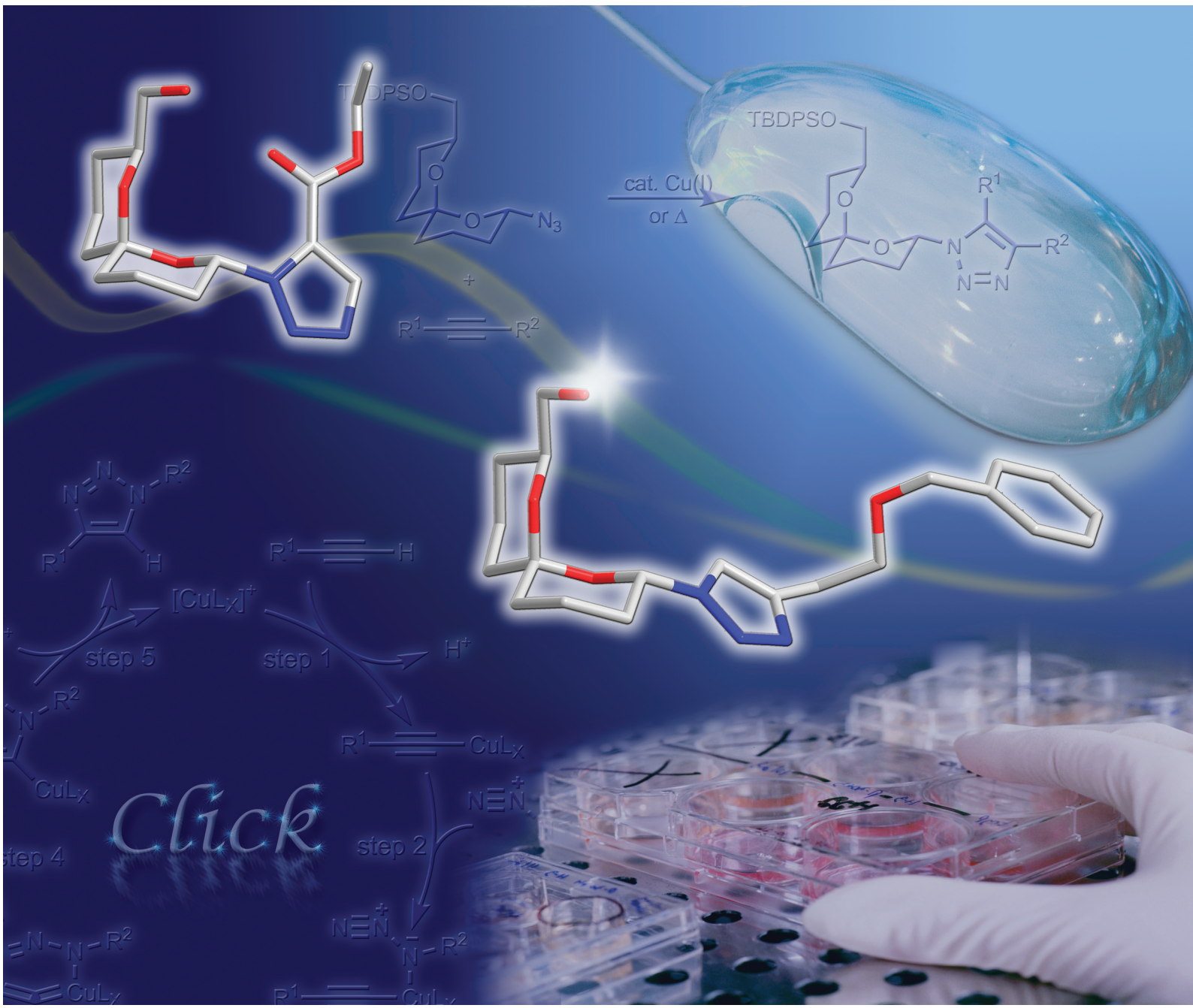

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Synthesis of spiroacetal-triazoles as privileged natural product-like scaffolds using "click chemistry"†‡

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The elaboration of a 6,6-spiroacetal scaffold to incorporate a triazole unit as a peptide bond surrogate at the anomeric position is described. The novel spiroacetal-triazole hybrid structures were generated *via* cycloaddition of a spiroacetal azide to a series of alkynes. The spiroacetal framework was constructed *via* Barbier reaction of bromide **10** with Weinreb amide **11**, followed by acid-catalysed deprotection and cyclisation to afford the 6,6-spiroacetal ring system. The resultant ethoxy-spiroacetal **8** was converted to spiroacetal azide **5**, which was then elaborated into a series of spiroacetal-triazole derivatives **7**.

Introduction

Nature has traditionally been the most important source of lead compounds for the development of new therapeutic agents. Evolutionary selection pressures have resulted in chemical biodiversity that has been exploited extensively by the pharmaceutical industry. By modifying a biologically active lead compound, libraries of structurally similar, but non-natural, synthetic analogues are then synthesised such that the molecular complexity is kept to a minimum whilst improvements are made to the desired pharmacological activity.[1]

The number of biological targets available for screening has increased substantially in recent years through a better understanding of biological pathways and the successful sequencing of the human genome.[2] Hence, it has become increasingly common to subject natural products and their synthetic analogues to broad phenotypic discovery screens to identify any biological activity that is not found in the original natural product. By combining biologically active motifs within a natural product-inspired scaffold system, a library of compounds can be generated for screening of potential bioactivity.[3,4]

Spiroacetals, in particular 1,7-dioxaspiro[5.5]undecanes, are a common structural element in many natural products isolated from a variety of sources that display a wide range of biological activities. For example, many simple spiroacetals are insect pheromones;[5,6] routiennocin is an ionophore antibiotic;[7] okadaic acid and tautomycin are protein phosphatase inhibitors;[8] integramycin is a HIV-1 integrase inhibitor;[9] the milbemycins and avermectins are anthelmintic and insecticidal agents[5] and the spongistatins are antimitotic agents.[10]

More importantly, many truncated synthetic spiroacetals derived from more complex spiroacetal containing natural products, such as spiroacetals **1–3**, provide the basic pharmacophore for the observed biological activity.[11,12] The 6,6-spiroacetal unit has also been used to replace the rigid galactose disaccharide core in a sialyl Lewis X mimetic **4** (Fig. 1).[13]

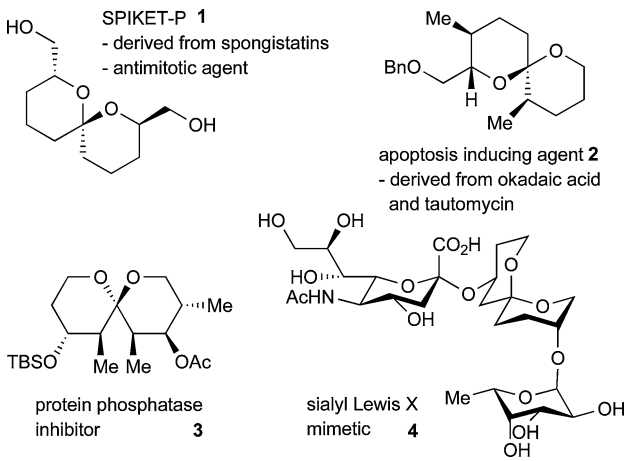

Fig. 1 Privileged 6,6-spiroacetal structures.[11–13]

Several research groups have reported the generation of libraries based on a 6,6-spiroacetal scaffold. For example, Ley *et al.*[3] and Porco *et al.*[14] synthesised a series of 6,6-spiroacetal derivatives containing three sites for further synthetic elaboration to probe for biological activity. A structurally diverse 6,6-spiroacetal-based library constructed by Waldmann *et al.*[12] resulted in the discovery of the lead compound **3** as an inhibitor of several important protein phosphatases (Fig. 1).

The 1,4-disubstituted 1,2,3-triazoles ("triazoles") are used as the mimics (isosteres) of amide/peptide bonds. Being a rigid linker, a triazole ring system holds the substituents in a similar geometry and distance to those of an amide as well as providing a comparable dipole moment. However, unlike the amide counterpart, triazoles are stable towards hydrolytic cleavage (especially under enzymatic conditions), oxidation and reduction.[15]

Our research group has a long standing interest in the synthesis of spiroacetals present in a wide range of biologically significant compounds.[16,17] This synthetic effort has prompted the investigation of elaborating the 6,6-spiroacetal unit to provide novel diverse functionality. In particular, we were interested in the chemical

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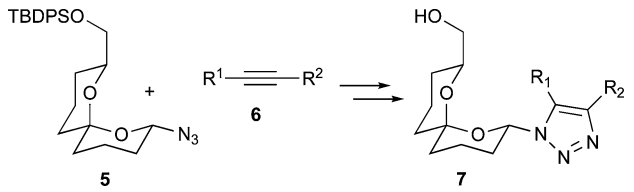
† Dedicated to Professor Andrew B. Holmes on the occasion of his 65th birthday.

‡ Electronic supplementary information (ESI) available: Experimental details and characterisation data of triazoles **14a–g** and **7a–g**. See DOI: 10.1039/b808454h

attachment of the spiroacetal scaffold to a biologically relevant 1,2,3-triazole unit. Further incorporation of a hydroxymethyl group on the spiroacetal ring also provides an additional site for further derivatisation. As a result, the combination of these important bioactive motifs generates a novel hybrid of functionality that can be probed for biological activity. The collection of spiroacetal-triazoles reported herein provides novel probes to screen for potential bioactivity in phenotypic assays.

Moreover, these spiroacetal derivatives allow diversification at the anomeric position, providing spiroacetal-based triazoles in which the triazole unit acts as an isostere to mimic the biologically relevant peptide bond. We therefore herein report the synthesis of a series of spiroacetal-triazoles **7** based on the cycloaddition of spiroacetal azide **5** to alkynes **6** (Scheme 1).



Scheme 1 Synthesis of spiroacetal-triazoles **7** based on the cycloaddition of azide **5** to a range of alkynes **6**.

To date, only Ley *et al.*[3] have reported the synthesis of a structurally related spiroacetal-triazole analogue which includes viable procedures for the synthesis of a series of these triazole derivatives. The biological screening of the spiroacetal-triazole unit is currently under evaluation.

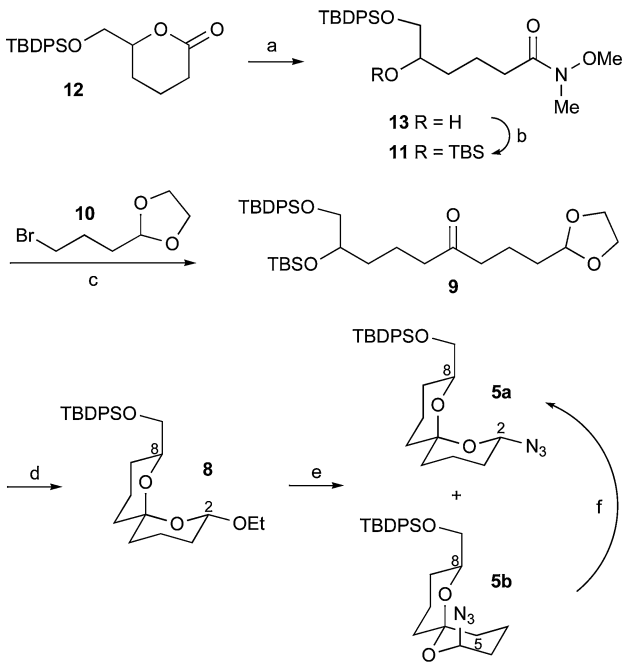
Results and discussion

The retrosynthesis adopted for the key spiroacetal-triazole target **7** hinges on disconnection of the anomeric C–N bond linking the spiroacetal to the triazole motif. Thus, ethoxy-spiroacetal **8** is converted to azide **5** which is then elaborated to a triazole. Ethoxy-spiroacetal **8** is formed *via* acid-catalysed deprotection and cyclisation of ketone **9** which in turn, is available from the Barbier coupling of bromide **10** with Weinreb amide **11**. Weinreb amide **11** is then easily accessed from lactone **12** (Scheme 2).

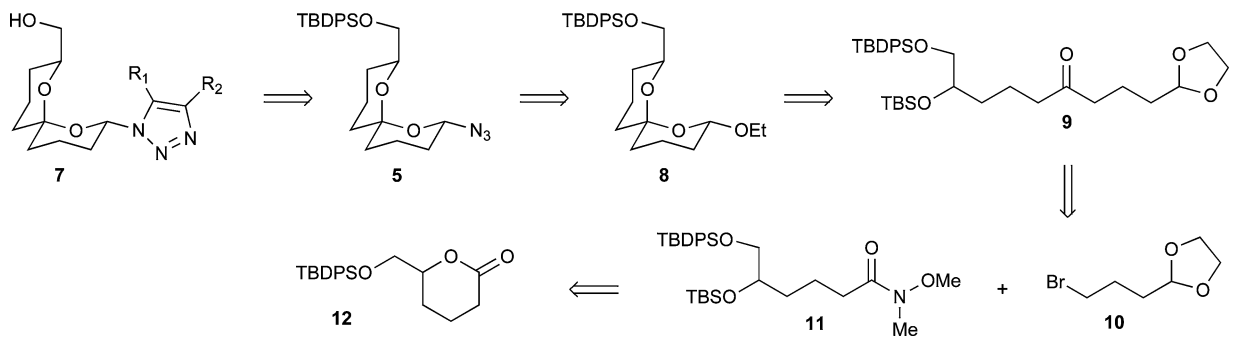
Preparation of spiroacetal-azide 5

Lactone **12** was prepared from commercially available ethyl 2-oxocyclopentanecarboxylate in 87% yield over five steps using procedures adapted from the work reported by Taylor *et al.*[18] Lactone **12** was then treated with the aluminium amide intermediate generated from trimethylaluminium and *N,O*-dimethylhydroxylamine in CH_2Cl_2. Subsequent silylation of the resultant alcohol **13** afforded Weinreb amide **11** in 85% yield over two steps. Bromide **10** was readily prepared from tetrahydrofuran *via* adaptation of the literature procedure.[19]

With bromide **10** and Weinreb amide **11** in hand, attention focused on their union *via* generation of the Grignard reagent derived from bromide **10** (Scheme 3). Due to the instability of the resultant Grignard reagent,[20] utilisation of Barbier conditions was implemented under the reaction conditions that have been successfully used for related reactions by our research group.[17,21] After activation of the magnesium turnings with iodine and 1,2-dibromoethane, Weinreb amide **11** and bromide **10** were added



Scheme 3 Synthesis of spiroacetal azides **5a** and **5b**. *Reagents and conditions:* (a) i. *N,O*-dimethylhydroxylamine hydrochloride, $AlMe_3$, CH_2Cl_2, 0 °C, 20 min; ii. **12**, CH_2Cl_2, 0 °C→rt, 2 h; (b) TBSCl, imidazole, DMAP (cat.), CH_2Cl_2, rt, 3 d, 85% over 2 steps; (c) i. **11**, Mg, I_2 (cat.), 1,2-dibromoethane, THF, rt, 1 h; ii. **10**, 33 °C, 2 h, 80%; (d) CSA, aq. EtOH, rt, 3 h, 86%; (e) $TMSN_3$, TMSOTf, CH_2Cl_2, −10 °C, 3 h, **5a**: 36%, **5b**: 15%; (f) $TMSN_3$, TMSOTf, CH_2Cl_2, −10 °C, 3 h, **5a**: 43%, **5b**: 20%.



Scheme 2 Retrosynthesis of spiroacetal-triazoles **5**.

sequentially and the reaction was triggered with the addition of iodine. Initially, the reaction afforded ketone **9** in only 42–65% yield when the reaction temperature was not carefully controlled. However, it was later found that a higher yield (78–80%) was obtained when the reaction was conducted under concentrated conditions with careful control of the temperature to be less than 33 °C in order to minimise degradation of Grignard reagent. The use of magnesium powder was also attempted, but this reagent only afforded ketone **9** in 12% yield only (Scheme 3).

With the basic spiroacetal skeleton assembled, the carbonyl cascade cyclisation of ketone **9** to ethoxy-spiroacetal **8** was next pursued. Similar deprotection and cyclisation sequences have been used by Mead and Zemribo[22] as well as de Greef and Zard[23] to prepare structurally related spiroacetals. After much experimentation, simultaneous unmasking of the aldehyde and the secondary alcohol in ketone **9** followed by cyclisation and subsequent ethoxylation of the resulting lactol was best carried out using camphorsulfonic acid (CSA) in aqueous ethanol at room temperature for 3 hours. Ethoxy-spiroacetal **8** was then carefully separated from the unreacted ketone **9** by flash chromatography. The crude residue was recycled by subjecting it to the same cyclisation conditions (CSA in aqueous ethanol) to give 86% overall yield of ethoxy-spiroacetal **8** after three iterations of recycling (Scheme 3).

NMR analysis of ethoxy-spiroacetal **8** revealed a characteristic anomeric 2-H resonance at δ_H 4.83 ppm (dd, $J_{2ax,3ax}$ 10.0 Hz and $J_{2ax,3eq}$ 2.3 Hz), which indicated that the ethoxy substituent adopted an equatorial position. A characteristic quaternary spirocarbon C-6 resonated at δ_C 98.1 ppm and a NOESY correlation between 2-H and 8-H confirmed the presence of the bis-anomerically stabilised spiroacetal ring system (Fig. 2).

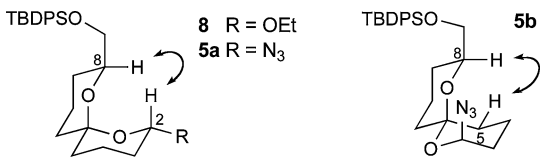


Fig. 2 Structures of azide **5a** and **5b** showing the anomerically stabilised spiroacetal rings and their substituents. NOESY correlations are denoted by arrows.

Conversion of ethoxy-spiroacetal **8** to azide **5** was next performed using TMSOTf and $TMSN_3$ in CH_2Cl_2 at −10 °C to yield a diastereomeric mixture of equatorial azide **5a** and axial azide **5b**. Carefully controlled separation by flash chromatography afforded equatorial azide **5a** and axial azide **5b** in 36% and 15% yield, respectively. Treating pure axial azide **5b** with TMSOTf and $TMSN_3$ in CH_2Cl_2 at −10 °C led to epimerisation of **5b** into a separable 2.2 : 1 mixture of equatorial azide **5a** and axial azide **5b** in 63% yield. Thus, combination of this epimerisation process with the initial displacement reaction afforded equatorial and axial azides **5a** and **5b** in 42% and 3% yield respectively, over two steps from ethoxy-spiroacetal **8** (Scheme 3).

NMR analysis of azide **5a** revealed a characteristic anomeric 2-H resonance at δ_H 4.94 ppm (dd, $J_{2ax,3ax}$ 10.8 Hz and $J_{2ax,3eq}$ 2.5 Hz), which indicated that the azide substituent adopted an equatorial position. A NOESY correlation between 2-H and 8-H also confirmed the presence of the bis-anomerically stabilised spiroacetal ring system (Fig. 2). On the other hand, NMR analysis of azide **5b** revealed a characteristic anomeric 2-H resonance at δ_H 4.61 ppm (t, $J_{2,3}$ 6.4 Hz), which indicated that the azide substituent adopted an axial position. In this case, a NOESY correlation between 5-H and 8-H confirmed the presence of the mono-anomerically stabilised spiroacetal ring system (Fig. 2). The characteristic quaternary spirocarbon C-6 in both equatorial azide **5a** and axial azide **5b** resonated at δ_C 93.2 ppm.

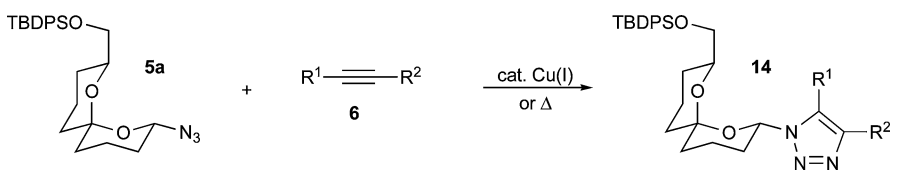
Preparation of spiroacetal-triazoles 14

In 2001, Sharpless *et al.*[24] proposed the concept of "click chemistry" following nature's lead and assembled a set of powerful, highly reliable, and selective reactions for the rapid synthesis of new compounds through carbon–heteroatom linkages. Since the introduction of this concept, the 1,3-dipolar cycloaddition of azides to alkynes is the most extensively studied and applied "click reaction" used. The popularity of this reaction is due to the versatility of triazoles as chemically stable peptide bond surrogates and the introduction of the synthetically useful copper-catalysed azide–alkyne cycloaddition (CuAAC) by Meldal *et al.*[25] and Sharpless *et al.*[26]

With azides **5a** and **5b** in hand, attention next turned to their subsequent cycloaddition to a range of alkynes in order to prepare spiroacetal-triazoles **14** (Scheme 4). The cycloaddition of the major equatorial azide **5a** was carried out using a catalytic quantity of phosphine-stabilised copper(I) salt[27] [CuI·P(OEt)$_3$] in the presence of excess terminal alkynes **6a–d** in toluene under reflux to afford spiroacetal-triazoles **14a–d** in excellent yield (83–98%). It is known that CuAAC only catalyses the cycloaddition of an azide to a terminal alkyne to afford a 1,4-disubstituted triazole as the only regioisomer due to the involvement of the copper acetylide intermediate. This excellent regioselectivity was clearly observed in the formation of triazoles **14a–d** that were prepared using CuAAC (Table 1, entry 1–4).

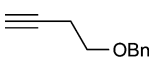
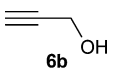
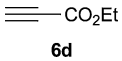
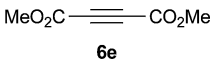
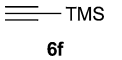
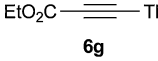
In contrast, the cycloaddition of the major equatorial azide **5a** to the internal alkyne, dimethyl acetylenedicarboxylate (**6e**), was promoted thermally using an excess of alkyne **6e** in toluene at 110 °C, affording spiroacetal-triazoles **14e** in good yield (78%, Table 1, entry 5).

The thermally promoted conditions were also used for the cycloaddition of azide **5a** to trimethylsilyl-substituted alkynes **6f** and **6g** to afford spiroacetal-triazoles **14f** and **14g** in good yield (64–84%). However, prolonged heating in a sealed tube was required



Scheme 4 Cycloadditions of azides **5a** to a range of alkynes under copper(I)-catalysed or thermally-promoted conditions.

Table 1 Summary of reagents and conditions used for the cycloaddition of azide **5a**

Entry	Alkynes	Reagents and conditions	Products			Yield (%)
				R^1	R^2	
1	 **6a**	a	**14a**	H	$(CH_2)_2OBn$	98
2	 **6b**	a	**14b**	H	CH_2OH	83
3	 **6c**	a	**14c**	H	Ph	96
4	 **6d**	a	**14d**	H	CO_2Et	84
5	 **6e**	b	**14e**	CO_2Me	CO_2Me	78
6	 **6f**	c	**14f**	H	TMS	64[a](+ 36% **5a**)
7	 **6g**	c	**14g**	CO_2Et	TMS	84

Reagents and conditions: (a) $CuI{\cdot}P(OEt)_3$ (10 mol%), toluene, reflux, 1 h; (b) toluene, reflux, 1 h; (c) toluene, sealed tube, reflux, 2 d.[a] Azide starting material **5a** was recovered from the cycloaddition due to the high volatility of trimethylsilylacetylene **6f** despite using a large excess of the alkyne in a sealed tube.

for these cycloadditions (Table 1, entry 6 and 7). Although the cycloaddition of azide **5a** to terminal trimethylsilylacetylene (**6f**, Table 1, entry 6) can be catalysed by CuAAC, the thermally promoted conditions were adopted in order to demonstrate the increased reaction times required compared to the use of CuAAC and to demonstrate the regio-directing effect of the silyl substituent on the alkyne.

The regio-directing effect of the silyl substituent in alkynes **6f** and **6g** was clearly observed with 4-trimethylsilyl substituted triazoles **14f** and **14g** being obtained as the sole regioisomers from the cycloadditions (Table 1). This regioselectivity resulted from the steric bulk exerted by the trimethylsilyl substituent and the ability of silicon to stabilise a developing partial positive charge on the alkyne β-carbon in the transition state for the reaction. Mono-substituted triazole **7f** and 1,5-disubstituted triazole **7g** were then obtained upon removal of the 4-trimethylsilyl group in **14f** and **14g**. A 1,5-disubstituted triazole is a stable isostere of a *cis*-peptide bond commonly found in turns and loops of peptide secondary structures.[28]

For all the cycloadditions performed using equatorial azide **5a**, only the corresponding equatorial triazoles **14a–g** resulted from the reaction with no epimerisation at the anomeric or the spiroacetal centre being observed as confirmed by NMR studies. The axial anomeric 2′-H resonance in spiroacetal-triazole **14g** showed characteristic deshielding (δ_H 6.65 ppm) due to the through-space electron withdrawing effect and anisotropic effect exerted by the neighbouring carbonyl group at C-5 of the triazole ring (Fig. 3).

The cycloaddition of axial azide **5b** to alkynes **6a** and **6c** was also attempted. However, in these cases, only complex mixtures were obtained. It was postulated that the steric clash between

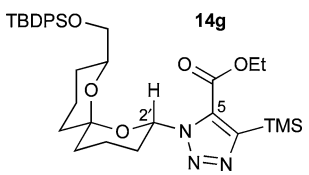
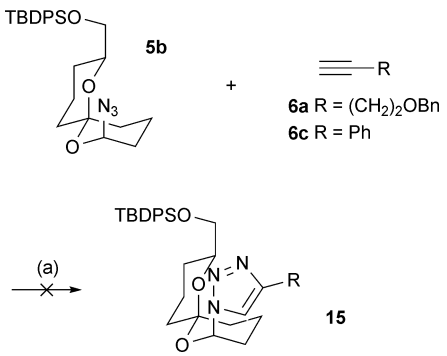


Fig. 3 The characteristic deshielding of 2′-H resonance in trisubstituted triazole **14g** was due to the through-space electron withdrawing effect and anisotropic effect exerted by the neighbouring carbonyl group.

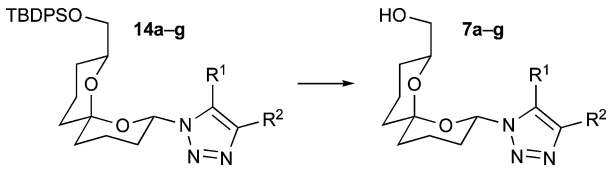
the newly formed axial triazole substituent at C-2′ and the TBDPS-protected hydroxymethyl substituent at C-8′ destabilised the resulting triazole **15** leading to degradation and a complex mixture of products (Scheme 5).



Scheme 5 Attempted cycloaddition of azides **5b** to alkynes **6a** or **6c**. *Reagents and conditions:* (a) **6a** or **6c**, $CuI{\cdot}P(OEt)_3$ (cat.), toluene, reflux, 1 h, complex mixture.

Deprotection of the silyl ether group in spiroacetal-triazoles 7

Deprotection of the silyl ether group in spiroacetal-triazoles **14a–g** was effected using a variety of reagents (Scheme 6). Firstly, desilylation of TBDPS ethers **14a** and **14c** was effected using TBAF in the presence of molecular sieves to give triazoles **7a** and **7c** in 74% and 82% yield, respectively. However, the use of TBAF could not be extended to the desilylation of TBDPS ethers **14e** and **14g**, which only resulted in complex mixtures presumably due to the basicity of the fluoride reagent used (Table 2).



Scheme 6 Desilylations of spiroacetal-triazoles **14a–g**.

Secondly, the less basic reagent, HF·pyridine was used to successfully effect desilylation of TBDPS ethers **14b** and **14d** in 70–71% yield. The use of HF·pyridine for the deprotection of TBDPS ethers **14a** proceeded in a comparable yield (72–75%) to that observed using TBAF (74%). However, these reaction conditions were found to be too harsh for the deprotection of TBDPS ethers **14e** and **14f**, only affording triazoles **7e** and **7f** in 23–26% yield (Table 2).

Finally, the mild reagent, HF·triethylamine,[29] was used to effect desilylation of the sensitive triazoles **14e–g**. Using the deprotection of TBDPS ether **14a** as a trial reaction, desilylation using HF·triethylamine in THF at room temperature afforded triazole **7a** in 99% yield although a long reaction time was required (2 days). Satisfied with the high yield obtained for this reaction, the desilylation of the sensitive triazoles **14e** and **14f** using HF·triethylamine was next carried out. Pleasingly, triazoles **7e** and **7f** were afforded in 69% and 86% yield, respectively. The 4-silyl group in **14f** was also simultaneously removed to give the monosubstituted compound **7f** (Table 2).

Use of HF·triethylamine was found to be too harsh to effect the deprotection of **14g** and only a complex mixture was obtained. Subsequently, excess triethylamine was added to buffer the reaction, and gratifyingly, the desired triazole **7g** was afforded in 93% yield (Table 2). The 4-silyl group in **14g** was also simultaneously removed to give the 1,5-disubstituted compound **7g**. The use of non-fluoride based desilylation reagents was also investigated. However, use of catalytic HCl,[30] generated *in situ* from the addition of acetyl chloride to methanol, failed to give triazole **7g** and only a complex mixture resulted.

Conclusion

In conclusion, the elaboration of a 6,6-spiroacetal ring system to incorporate a triazole unit at the anomeric position together with a synthetic useful hydroxymethyl group has been successfully accomplished. Given the importance of a triazole unit as a practical isostere/surrogate of a peptide bond, the assembly of a spiroacetal and a triazole unit demonstrated herein generates a novel series of spiroacetal-containing peptide bond mimics. The knowledge gleaned in this synthetic study also provides momentum for future elaboration of 6,6-spiroacetals to incorporate other biologically active motifs. In addition to the chemical diversity reflected by this series of spiroacetal hybrids, compounds prepared in this study can also be used as probes to screen for potential bioactivity in broad phenotypic assays.

Experimental

General

Experiments requiring anhydrous conditions were performed under a dry nitrogen or argon atmosphere using oven- or flame-dried apparatus and standard techniques in handling air- and/or moisture-sensitive materials unless otherwise stated. Solvents used (except for Et_2O) for reactions, work-up extractions and chromatographic purifications were distilled, unless otherwise stated. Commercial reagents were analytical grade or were purified by standard procedures prior to use.[31] Separation of mixtures was performed by flash chromatography using Kieselgel S 63–100 μm (Riedel-de-Hahn) silica gel with the indicated eluent. Mass spectra were recorded on a VG-70SE mass spectrometer at a nominal accelerating voltage of 70 eV for low resolution and at a nominal resolution of 5000 to 10 000 as appropriate for high resolution. Ionisation was effected using electron impact (EI^+), fast atom bombardment (FAB^+) using 3-nitrobenzyl alcohol as the matrix or chemical ionisation (CI^+) using ammonia as a carrier gas. Major and significant fragments are quoted in the form x (y), where x is the mass to charge ratio (m/z) and y is the percentage abundance relative to the base peak (100%). Infrared spectra were obtained using a Perkin Elmer Spectrum 1000 Fourier Transform

Table 2 Summary of reagents and conditions used for the desilylations of spiroacetal-triazoles **14a–g**

		Products			Yield (%)		
Entry	TBDPS ether		R^1	R^2	(a) TBAF	(b) HF·py	(c) 3HF·NEt_3
1	**14a**	**7a**	H	$(CH_2)_2OBn$	74	72–75	99
2	**14b**	**7b**	H	CH_2OH	—	71	—
3	**14c**	**7c**	H	Ph	82	—	—
4	**14d**	**7d**	H	CO_2Et	—	70	—
5	**14e**	**7e**	CO_2Me	CO_2Me	c. mixture	23	69
6	**14f**	**7f**	H	H	—	26	86
7	**14g**	**7g**	CO_2Et	H	c. mixture	—	93[a]

Reagents and conditions: (a) TBAF, 3 Å molecular sieves, THF, rt, 4 h; (b) HF·pyridine, THF, rt, 18–24 h; (c) 3HF·NEt_3, THF, rt, 2–3 d.[a] Excess NEt_3 was added to buffer the reaction mixture. A complex mixture resulted when NEt_3 was not used.

Infrared spectrometer as a thin film between sodium chloride plates. Absorption peaks are reported as wavenumbers (ν, cm^{-1}). NMR spectra were recorded on either a Bruker DRX300 spectrophotometer operating at 300 MHz for ^1H nuclei and 75 MHz for ^{13}C nuclei, or on a Bruker DRX400 spectrophotometer operating at 400 MHz for ^1H nuclei and 100 MHz for ^{13}C nuclei, at ambient temperature. ^1H NMR chemical shifts are reported in parts per million (ppm) relative to the tetramethylsilane peak (δ 0.00 ppm). ^1H NMR values are reported as chemical shift δ, relative integral, multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; quintet; m, multiplet), coupling constant (J, Hz) and assignment. Coupling constants were taken directly from the spectra. ^{13}C NMR chemical shifts are reported in ppm relative to the chloroform peak (δ 77.0 ppm). ^{13}C NMR values are reported as chemical shifts δ, multiplicity and assignment. Assignments were made with the aid of DEPT, COSY, HSQC, HMBC and NOESY experiments.

Synthesis towards spiroacetal azides 5a and 5b

6-(*tert*-Butyldiphenylsilyloxy)-5-hydroxy-*N*-methoxy-*N*-methylhexanamide (13)

To a suspension of *N,O*-dimethylhydroxylamine (2.20 g, 22.5 mmol) in anhydrous CH_2Cl_2 (80 mL) at 0 °C was added dropwise a solution of $AlMe_3$ (11.3 mL, 2.0 mol L^{-1} in toluene, 22.5 mmol). The mixture was stirred until the solid dissolved. A solution of valerolactone **12** (3.97 g, 10.8 mmol) in anhydrous CH_2Cl_2 (40 mL) was added and the mixture was warmed to room temperature. After 3 h, the reaction was carefully poured into an ice-cold 1 : 1 solution mixture of saturated NH_4Cl and Rochelle's salt (80 mL). The resulting mixture was stirred vigorously for 30 min with warming to room temperature. The aqueous phase was extracted with Et_2O (3 × 60 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo* to yield the crude *title compound* **13** as a yellow oil (4.85 g, 100%) that was used in the hydroxyl protection step without further purification. Purification by flash chromatography was performed using hexane–EtOAc (7 : 3 to 3 : 2) as eluent to yield the *title compound* **13** as a colourless oil. HRMS (CI): found MH^+, 430.2415, $C_{24}H_{36}NO_4Si$ requires 430.2414. ν_{max} (film)/cm^{-1}: 3430 br (O–H), 2931 (C–H), 1651 (C=O), 1427, 1112 (C–O), 703. δ_H (300 MHz; $CDCl_3$): 1.07 (9 H, s, OSi$Ph_2{}^t$Bu), 1.47 (2 H, dt, $J_{4,5}$ 7.7 and $J_{4,3}$ 6.5, 4-H), 1.62–1.83 (2 H, m, 3-H), 2.43 (2 H, t, $J_{2,3}$ 7.4, 2-H), 2.64 (1 H, br s, OH), 3.16 (3 H, s, NMe), 3.51 (1 H, dd, J_{AB} 10.0 and $J_{6A,5}$ 7.4, 6-H_A), 3.66 (1 H, dd, J_{AB} 10.0 and $J_{6B,5}$ 3.6, 6-H_B), 3.66 (3 H, s, OMe), 3.71–3.77 (1 H, m, 5-H), 7.35–7.47 (6 H, m, Ph), 7.63–7.68 (4 H, m, Ph). δ_C (75 MHz; $CDCl_3$): 19.2 (C, OSi$Ph_2{}^t$Bu), 20.5 (CH_2, C-3), 26.8 (CH_3, OSi$Ph_2{}^t$Bu), 31.6 (CH_2, C-2), 32.2 (CH_3, NMe), 32.4 (CH_2, C-4), 61.1 (CH_3, OMe), 68.0 (CH_2, C-6), 71.6 (CH, C-5), 127.7 (CH, Ph), 129.8 (CH, Ph), 133.2 (C, Ph), 135.5 (CH, Ph), 174.3 (C, C=O). m/z (CI): 430 (MH^+, 38%), 412 (M − OH, 3), 372 (M − ^{t}Bu, 22), 353 (26), 352 (M − Ph, 100), 322 (52), 291 (31), 264 (17), 199 (29), 78 (24).

5-(*tert*-Butyldimethylsilyloxy)-6-(*tert*-butyldiphenylsilyloxy)-*N*-methoxy-*N*-methylhexanamide (11)

To a solution of crude alcohol **13** (*ca.* 4.85 g, 10.8 mmol) in anhydrous CH_2Cl_2 (50 mL) at room temperature was added imidazole (1.69 g, 24.9 mmol), DMAP (276 mg, 2.26 mmol) and TBSCl (1.87 g, 12.4 mmol). After 24 h, a second portion of TBSCl (170 mg, 1.13 mmol) was added and the mixture was concentrated *in vacuo* to half of its volume. After 2 h, saturated $NaHCO_3$ solution (25 mL) was added. The aqueous phase was extracted with Et_2O (3 × 25 mL) and the combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography (twice) using hexane–EtOAc (19 : 1 to 3 : 2) as eluent yielded the *title compound* **11** (4.80 g, 82% from valerolactone **12** over 2 steps) as a colourless oil and valerolactone **12** (0.56 g, 14%). HRMS (FAB): found MH^+, 544.3273, $C_{30}H_{50}NO_4Si_2$ requires 544.3278. ν_{max} (film)/cm^{-1}: 2930 (C–H), 1667 (C=O), 1428, 1254 (C–O), 1112 (C–O), 702. δ_H (400 MHz; $CDCl_3$): −0.08 (3 H, s, OSi$Me_2{}^t$Bu), 0.00 (3 H, s, OSi$Me_2{}^t$Bu), 0.83 (9 H, s, OSi$Me_2{}^t$Bu), 1.04 (9 H, s, OSi$Ph_2{}^t$Bu), 1.45–1.55 (1 H, m, 4-H_A), 1.58–1.77 (3 H, m, 3-H and 4-H_B), 2.43 (2 H, m, 2-H), 3.17 (3 H, s, NMe), 3.47 (1 H, dd, J_{AB} 10.0 and $J_{6A,5}$ 6.7, 6-H_A), 3.57 (1 H, dd, J_{AB} 10.0 and $J_{6B,5}$ 5.1, 6-H_B), 3.66 (3 H, s, OMe), 3.68–3.79 (1 H, m, 5-H), 7.34–7.42 (6 H, m, Ph), 7.64–7.68 (4 H, m, Ph). δ_C (100 MHz; $CDCl_3$): −4.83 (CH_3, OSi$Me_2{}^t$Bu), −4.48 (CH_3, OSi$Me_2{}^t$Bu), 18.0 (C, OSi$Me_2{}^t$Bu), 19.2 (C, OSi$Ph_2{}^t$Bu), 20.3 (CH_2, C-3), 25.8 (CH_3, OSi$Me_2{}^t$Bu), 26.8 (CH_3, OSi$Ph_2{}^t$Bu), 32.3 (CH_3 and CH_2, NMe and C-2), 34.1 (CH_2, C-4), 61.1 (CH_3, OMe), 67.5 (CH_2, C-6), 72.6 (CH, C-5), 127.6 (CH, Ph), 129.6 (CH, Ph), 133.6 (C, Ph), 133.6 (C, Ph), 135.6 (CH, Ph), 174.6 (C, C=O). m/z (FAB): 544 (MH^+, 20%), 528 (M − Me, 5), 486 (M − ^{t}Bu, 72), 412 (M − OTBDMS, 39), 217 (25), 209 (50), 197 (45), 193 (30), 147 (23), 135 (100), 73 (98).

8′-(*tert*-Butyldimethylsilyloxy)-9′-(*tert*-butyldiphenylsilyloxy)-1′-(1,3-dioxolan-2-yl)nonan-4′-one (9)

To a mixture of Mg turnings§ (1.07 g, 44.0 mmol) in THF (5.0 mL) at room temperature under an atmosphere of argon were added I_2 (1 crystal) and 1,2-dibromoethane (228 μL, 2.64 mmol). The mixture was stirred until the yellow colour faded. Weinreb amide **11** (4.79 g, 8.80 mmol) in THF (31 mL) was added to the above activated magnesium *via* cannula followed by addition of bromide **10** (2.87 mL, 17.6 mmol) dropwise. The reaction was initiated with the addition of I_2 (1 crystal) and the internal reaction temperature was regulated carefully to be less than 33 °C. After 1 h, a second portion of bromide **10** (1.44 mL, 8.80 mmol) was added dropwise. After 1 h, saturated $NaHCO_3$ solution (30 mL) was added and the aqueous phase was extracted with Et_2O (3 × 50 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography using hexane–EtOAc (19 : 1 to 9 : 1) as eluent yielded the *title compound* **9** (4.23 g, 80%) as a pale yellow oil. HRMS (CI): found MH^+, 599.3562, $C_{34}H_{55}O_5Si_2$ requires 599.3588. ν_{max} (film)/cm^{-1}: 2930 (C–H), 1714 (C=O), 1428, 1254 (C–O), 1112 (C–O), 836, 703. δ_H (300 MHz; $CDCl_3$): −0.08 (3 H, s, OSi$Me_2{}^t$Bu), −0.01 (3 H, s, OSi$Me_2{}^t$Bu), 0.83 (9 H, s, OSi$Me_2{}^t$Bu), 1.04 (9 H, s, OSi$Ph_2{}^t$Bu), 1.40–1.46 (1 H, m, 7′-H_A), 1.60–1.78 (7 H, m, 1′-H_A, 1′-H_B, 2′-H_A, 2′-H_B, 6′-H_A, 6′-H_B and 7′-H_B), 2.38 (2 H, t, $J_{5',6'}$ 6.9, 5′-H), 2.45 (2 H, t, $J_{3',2'}$ 7.1, 3′-H), 3.45 (1 H, dd, J_{AB} 10.0 and $J_{9'A,8'}$ 6.8, 9′-H_A), 3.57 (1 H, dd, J_{AB} 10.0 and $J_{9'B,8'}$ 5.0, 9′-H_B), 3.64–3.74 (1 H, m, 8′-H), 3.81–3.89 (2 H, m, 4-H), 3.89–3.98 (2 H, m, 5-H),

§ The Mg turnings were pre-washed with aqueous HCl (0.10 mol L^{-1}) and water then flame-dried *in vacuo*.

4.85 (1 H, t, $J_{2,1'}$ 4.4, 2-H), 7.34–7.44 (6 H, m, Ph), 7.64–7.68 (4 H, m, Ph). δ_C (75 MHz; $CDCl_3$): −4.81 (CH_3, OSi$Me_2{}^t$Bu), −4.46 (CH_3, OSi$Me_2{}^t$Bu), 18.0 (C, OSiMe$_2{}^t$Bu), 18.2 (CH_2, C-2′), 19.2 (C, OSiPh$_2{}^t$Bu), 19.5 (CH_2, C-6′), 25.8 (CH_3, OSiMe$_2{}^t$Bu), 26.9 (CH_3, OSiPh$_2{}^t$Bu), 33.1 (CH_2, C-1′), 33.9 (CH_2, C-7′), 42.2 (CH_2, C-3′), 43.1 (CH_2, C-5′), 64.8 (2 × CH_2, C-4 and C-5), 67.5 (CH_2, C-9′), 72.6 (CH, C-8′), 104.3 (CH, C-2), 127.6 (CH, Ph), 129.6 (CH, Ph), 133.7 (C, Ph), 135.6 (CH, Ph), 210.5 (C, C=O). *m/z* (CI): 599 (MH^+, 17%), 541 (26), 412 (M − OSiMe$_2{}^t$Bu, 100), 343 (M − OSiPh$_2{}^t$Bu, 11), 211 (27), 197 (16), 149 (20), 135 (24), 121 (36), 99 (40), 91 (20), 78 (37), 73 (94).

(2*S**,6*S**,8*S**)-8-(*tert*-Butyldiphenylsilyloxymethyl)-2-ethoxy-1,7-dioxaspiro[5.5]undecane (8)

To a solution of ketone **9** (750 mg, 1.25 mmol) in a 99 : 1 mixture of EtOH–H_2O (15 mL) at room temperature was added (+)-10-camphorsulfonic acid monohydrate (628 mg, 2.51 mmol) in small portions. After 3 h, solid $NaHCO_3$ (220 mg, 2.63 mmol) was added and the mixture was concentrated *in vacuo.* The resulting thick yellow oil was dissolved in saturated $NaHCO_3$ solution (10 mL) and Et_2O (10 mL) and the aqueous phase was extracted with Et_2O (3 × 10 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo.* Purification by flash chromatography using hexane–EtOAc (99 : 1, 97 : 3 to 9 : 1) as eluent yielded the *title compound* **8** (356 mg, 61%) as a pale yellow oil and a mixture of starting materials (264 mg). The recovered starting materials were subjected to the above reaction cycle several times to yield the *title compound* **8** (503 mg, 86% overall yield after 3 cycles) after purification. HRMS (FAB): found MH^+, 467.2618, $C_{28}H_{39}O_4Si$ requires 467.2618. ν_{max} (film)/cm^{-1}: 2934 (C–H), 1428, 1221, 1187, 1112 (C–O), 1083 (C–O), 973, 955, 702. δ_H (300 MHz; $CDCl_3$): 1.05 (9 H, s, OSiPh$_2{}^t$Bu), 1.17–1.22 (1 H, m, 9-H_A), 1.26 (3 H, t, $J_{CH3,CH2}$ 7.1, OCH$_2$*CH*$_3$), 1.33–1.50 (3 H, m, 3-H_A, 5-H_A and 11-H_A), 1.56–1.66 (4 H, m, 4-H_A, 5-H_B or 11-H_B, 9-H_B and 10-H_A), 1.71–1.81 (2 H, m, 3-H_B and 5-H_B or 11-H_B), 1.87–2.06 (2 H, m, 4-H_B and 10-H_B), 3.53 (1 H, dq, J_{AB} 9.4 and $J_{CH2,CH3}$ 7.1, O*CH*$_A$H$_B$CH$_3$), 3.59 (1 H, dd, J_{AB} 10.4 and $J_{8\text{-}CH2,8}$ 4.2, 8-*CH*$_A$H$_B$O), 3.68 (1 H, dd, J_{AB} 10.4 and $J_{8\text{-}CH2,8}$ 6.5, 8-CH$_A$*H*$_B$O), 3.86–3.95 (1 H, m, 8-H), 4.00 (1 H, dq, J_{AB} 9.4 and $J_{CH2,CH3}$ 7.1, OCH$_A$*H*$_B$CH$_3$), 4.83 (1 H, dd, $J_{2ax,3ax}$ 10.0 and $J_{2ax,3eq}$ 2.3, 2-H_{ax}), 7.33–7.46 (6 H, m, Ph), 7.69–7.76 (4 H, m, Ph). δ_C (75 MHz; $CDCl_3$): 15.3 (CH_3, OCH$_2$*CH*$_3$), 17.8 (CH_2, C-4 or C-10), 18.5 (CH_2, C-4 or C-10), 19.2 (C, OSiPh$_2{}^t$Bu), 26.7 (CH_3, OSiPh$_2{}^t$Bu), 27.0 (CH_2, C-9), 30.9 (CH_2, C-3), 34.8 (CH_2, C-5 or C-11), 35.2 (CH_2, C-5 or C-11), 64.3 (CH_2, O*CH*$_2$CH$_3$), 67.5 (CH_2, 8-CH_2O), 70.9 (CH, C-8), 96.6 (CH, C-2), 98.1 (C, C-6), 127.6 (CH, Ph), 127.6 (CH, Ph), 129.5 (CH, Ph), 129.6 (CH, Ph), 133.8 (C, Ph), 133.8 (C, Ph), 135.6 (CH, Ph), 135.7 (CH, Ph). *m/z* (FAB): 467 (MH^+, 3%), 423 (M − OEt, 27), 411 (M − ^{t}Bu, 10), 391 (M − Ph, 11), 365 (25), 207 (33), 199 (65), 197 (47), 167 (22), 149 (37), 137 (35), 135 (98), 85 (100), 75 (22).

(2*S**,6*S**,8*S**)-2-Azido-8-(*tert*-butyldiphenylsilyloxymethyl)-1,7-dioxaspiro[5.5]undecane (5a) and (2*S**,6*R**,8*S**)-2-azido-8-(*tert*-butyldiphenylsilyloxymethyl)-1,7-dioxaspiro[5.5]undecane (5b)

To a solution of ethoxy-spiroacetal **8** (293 mg, 624 μmol) and $TMSN_3$ (414 μL, 3.12 mmol) in anhydrous CH_2Cl_2 (9.7 mL) at −10 °C was added freshly prepared TMSOTf solution (1.16 mL, 0.70 mol L^{-1} in CH_2Cl_2, 811 μmol) dropwise. After 3 h, ice-cold saturated $NaHCO_3$ solution (3 mL) was added and the mixture was warmed to room temperature. Saturated $NaHCO_3$ (10 mL) and CH_2Cl_2 (10 mL) were added and the aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were filtered through a pad of silica and concentrated *in vacuo.* Purification by flash chromatography using hexane–Et_2O–EtOAc (99 : 1 : 0, 49 : 1 : 0 to 97 : 0 : 3) as eluent yielded the *title equatorial azido-spiroacetal* **5a** (106 mg, 36%) and *axial azido-spiroacetal* **5b** (42.9 mg, 15%) as pale yellow oils. Unreacted ethoxy-spiroacetal **8** (13.6 mg, 5%) was also recovered.

Epimerisation of axial azido-spiroacetal 5b

To a solution of axial azido-spiroacetal **5b** (50 mg, 107 μmol) and $TMSN_3$ (71 μL, 535 μmol) in anhydrous CH_2Cl_2 (2.0 mL) at −10 °C was added freshly prepared TMSOTf solution (0.2 mL, 0.70 mol L^{-1} in CH_2Cl_2, 139 μmol) dropwise. After 3 h, ice-cold saturated $NaHCO_3$ solution (1.5 mL) was added and the mixture was warmed to room temperature. Saturated $NaHCO_3$ (2 mL) and CH_2Cl_2 (2 mL) were added and the aqueous phase was extracted with CH_2Cl_2 (3 × 4 mL). The combined organic extracts were filtered through a pad of silica and concentrated *in vacuo.* Purification by flash chromatography using hexane–Et_2O–EtOAc (99 : 1 : 0, 49 : 1 : 0 to 97 : 0 : 3) as eluent yielded the *title equatorial azido-spiroacetal* **6a** (21.5 mg, 43%) and *axial azido-spiroacetal* **5b** (10.1 mg, 20%) as pale yellow oils.

Equatorial azido-spiroacetal 5a. HRMS (FAB): found [M − N_3]$^+$, 423.2351, $C_{26}H_{35}O_3Si$ requires 423.2356. ν_{max} (film)/cm^{-1}: 2929 (C–H), 2104 (N_3), 1428, 1248 (C–O), 1112 (C–O), 702. δ_H (400 MHz; $CDCl_3$): 1.05 (9 H, s, OSiPh$_2{}^t$Bu), 1.16–1.26 (1 H, m, 9-H_A), 1.37–1.48 (3 H, m, 3-H_A, 5-H_A and 11-H_A), 1.58–1.66 (4 H, m, 4-H_A, 5-H_B or 11-H_B, 9-H_B, and 10-H_A), 1.71–1.77 (2 H, m, 3-H_B and 5-H_B or 11-H_B), 1.90–2.02 (2 H, m, 4-H_B and 10-H_B), 3.58 (1 H, dd, J_{AB} 10.5 and $J_{8\text{-}CH2,8}$ 4.2, 8-*CH*$_A$H$_B$O), 3.66 (1 H, dd, J_{AB} 10.5 and $J_{8\text{-}CH2,8}$ 6.6, 8-CH$_A$*H*$_B$O), 3.81–3.87 (2 H, m, 8-H), 4.94 (1 H, dd, $J_{2ax,3ax}$ 10.8 and $J_{2ax,3eq}$ 2.5, 2-H_{ax}), 7.35–7.44 (6 H, m, Ph), 7.68–7.74 (4 H, m, Ph). δ_C (75 MHz; $CDCl_3$): 17.8 (CH_2, C-4 or C-10), 18.3 (CH_2, C-4 or C-10), 19.2 (C, OSiPh$_2{}^t$Bu), 26.7 (CH_2, C-9), 26.7 (CH_3, OSiPh$_2{}^t$Bu), 30.2 (CH_2, C-3), 34.4 (CH_2, C-5 or C-11), 34.8 (CH_2, C-5 or C-11), 67.2 (CH_2, 8-CH_2O), 71.0 (CH, C-8), 83.2 (CH, C-2), 98.4 (C, C-6), 127.6 (CH, Ph), 127.6 (CH, Ph), 129.6 (CH, Ph), 129.6 (CH, Ph), 133.7 (C, Ph), 135.6 (CH, Ph). *m/z* (FAB): 423 ([M − N_3]$^+$, 13%), 199 (57), 197 (39), 139 (18), 137 (35), 135 (100), 105 (16), 91(17), 75(17).

Axial azido-spiroacetal 5b. HRMS (FAB): found MH^+, 466.2513, $C_{26}H_{36}N_3O_3Si$ requires 466.2526. ν_{max} (film)/cm^{-1}: 2956 (C–H), 2858, 2105 (N_3), 1428, 1250 (C–O), 1113 (C–O), 1072, 847, 702. δ_H (300 MHz; $CDCl_3$): 1.06 (9 H, s, OSiPh$_2{}^t$Bu), 1.19–1.32 (1 H, m, 9-H_A), 1.32–1.44 (1 H, m, 3-H_A), 1.53–1.63 (3 H, m, 3-H_B, 10-H_A and 10-H_B), 1.65–1.81 (7 H, m, 4-H_A, 4-H_B, 5-H_A, 5-H_B, 9-H_B, 11-H_A and 11-H_B), 3.54 (1 H, dd, J_{AB} 10.5 and $J_{8\text{-}CH2,8}$ 4.8, 8-*CH*$_A$H$_B$O), 3.62 (1 H, dd, J_{AB} 10.5 and $J_{8\text{-}CH2,8}$ 5.3, 8-CH$_A$*H*$_B$O), 3.85–3.94 (2 H, m, 8-H), 4.61 (1 H, t, $J_{2,3}$ 6.4, 2-H_{eq}), 7.35–7.44 (6 H, m, Ph), 7.66–7.74 (4 H, m, Ph). δ_C (75 MHz; $CDCl_3$): 18.7 (CH_2, C-4), 19.1 (CH_2, C-10), 19.3 (C, OSiPh^{t}Bu), 26.8 (CH_2, C-9), 26.8 (CH_3, OSiPh^{t}Bu), 32.0 (CH_2, C-3), 34.1 (CH_2, C-5), 39.8 (CH_2,

C-11), 67.0 (CH_2, 8-CH_2O), 73.3 (CH, C-8), 77.8 (CH, C-2), 93.2 (C, C-6), 127.6 (CH, Ph), 129.6 (CH, Ph), 133.6 (C, Ph), 133.7 (C, Ph), 135.6 (CH, Ph). *m/z* (FAB): 466 (MH^+, 1%), 423 (M − N_3, 2), 239 ($SiPh_2{}^tBu$, 7), 214 (32), 207 (13), 199 (38), 197 (37), 183 (13), 137 (24), 135 (100), 121 (14), 105 (14).

General procedures for 1,3-dipolar cycloaddition of azide 5a to alkynes 6

Method A: For terminal alkynes with catalysis by CuI·P(OEt)$_3$. To a solution of azide **5a** and alkyne **6** (50.0–100 μL) in anhydrous toluene (250–500 μL) under an atmosphere of argon was added CuI·P(OEt)$_3$ (0.10–0.12 equiv.). The resulting mixture was heated to reflux for 1 h. After cooling to room temperature, the mixture was purified directly by flash chromatography using hexane–EtOAc as eluent to give the spiroacetal containing a 1,4-disubstituted triazole substituent.

Method B: For symmetrical internal alkynes. A solution of azide **5a** and alkyne **6** (100 μL) in anhydrous toluene (500 μL) was heated to reflux for 1 h. The reaction mixture was purified directly by flash chromatography using hexane–EtOAc as eluent to give the spiroacetal containing a 1,4,5-trisubstituted triazole substituent.

Method C: For trimethylsilylacetylenes. A solution of azide **5a** and trimethylsilylacetylene **6** (50.0–100 μL) in anhydrous toluene (500 μL) was heated at 110 °C in a sealed vessel. If the cycloaddition was not complete in 18 h (TLC), a second portion of trimethylsilylacetylene **6** (50.0–100 μL) was added and the mixture was heated at 110 °C overnight. The reaction mixture was purified directly by flash chromatography using hexane–EtOAc as eluent to give the spiroacetal containing a 1,4,5-trisubstituted triazole substituent.

General procedures for deprotection of silyl protected spiroacetal-triazoles 14

Method A: Desilylation using TBAF. To a solution of TBDPS-protected triazole **14** in anhydrous THF (1.0 mL) under an atmosphere of argon at room temperature was added activated molecular sieves (0.20 g) and TBAF solution (1.0 mol L^{-1} in THF, 2.0–10 equiv.). After 1–3 h, saturated NH_4Cl solution (1 mL) was added. The aqueous phase was extracted with Et_2O (3 × 2 mL) and the combined organic extracts were concentrated *in vacuo.* Purification by flash chromatography using the appropriate eluent yielded hydroxymethyl spiroacetal-triazole **7**.

Method B: Desilylation using HF·pyridine. To a solution of TBDPS-protected triazole **14** in anhydrous THF (1.0–2.0 mL) in a plastic vial under an atmosphere of argon was added HF·pyridine (1.5–3.4 μL per micromole of triazole) and the mixture was stirred at room temperature. If the desilylation was not complete within 18 h (TLC), a second portion of HF·pyridine (1.3–2.0 μL per micromole of triazole) was added and the mixture was stirred at room temperature for another 18 h. Saturated $NaHCO_3$ solution (4 mL) was added dropwise. The aqueous phase was extracted with Et_2O (4 × 4 mL) and the combined organic extracts were concentrated *in vacuo.* Purification by flash chromatography using the appropriate eluent yielded hydroxymethyl spiroacetal-triazole **7**.

Method C: Desilylation using 3HF·NEt$_3$. A solution of TBDPS-protected triazole **14** and 3HF·NEt_3 (2.0–3.0 μL per micromole of triazole) in anhydrous THF (300 μL–1.0 mL) was stirred at room temperature under an atmosphere of argon. If the desilylation was not complete within 18 h (TLC), a second portion of 3HF·NEt_3 (2.0–2.5 μL per micromole of triazole) was added and the mixture was stirred at room temperature for another 18 h. Saturated $NaHCO_3$ solution (4 mL) was added dropwise. The aqueous phase was extracted with Et_2O (4 × 4 mL) and the combined organic extracts were concentrated *in vacuo.* Purification by flash chromatography using the appropriate eluent yielded hydroxymethyl spiroacetal-triazole **7**.

Method D: Desilylation using 3HF·NEt$_3$ and buffered with NEt$_3$. A solution of TBDPS-protected triazole **14**, 3HF·NEt_3 (2.0 μL per micromole of triazole) and NEt_3 (2.5 μL per micromole of triazole) in anhydrous THF (700 μL) was stirred at 40 °C for 48 h under an atmosphere of argon. A second portion of 3HF·NEt_3 (1.0 μL micromole of triazole) and NEt_3 (1.3 μL per micromole of triazole) were added and the mixture was stirred at 40 °C for 18 h. Saturated $NaHCO_3$ solution (2 mL) was added dropwise. The aqueous phase was extracted with EtOAc (3 × 3 mL) and the combined organic extracts were concentrated *in vacuo.* Purification by flash chromatography using hexane–EtOAc as eluent yielded hydroxymethyl spiroacetal-triazole **7**.

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References

1 I. Paterson and E. A. Anderson, *Science*, 2005, **310**, 451–453.
2 J. C. Venter, *et al.*, *Science*, 2001, **291**, 1304–1351.
3 G. Zinzalla, L.-G. Milroy and S. V. Ley, *Org. Biomol. Chem.*, 2006, **4**, 1977–2002.
4 R. I. Anegundi, V. G. Puranik and S. Hotha, *Org. Biomol. Chem.*, 2008, **6**, 779–786.
5 F. Perron and K. F. Albizati, *Chem. Rev.*, 1989, **89**, 1617–1661.
6 W. Francke and W. Kitching, *Curr. Org. Chem.*, 2001, **5**, 233–251.
7 *U.S. Pat.*, US 4547523, 1985; W. P. Cullen, *et al.*, *J. Ind. Microbiol.*, 1988, **2**, 349–357; N. R. Kotecha, S. V. Ley and S. Mantegani, *Synlett*, 1992, 395–399.
8 K. Tachibana, P. J. Scheuer, Y. Tsukitani, H. Kikuchi, D. Van Engen, J. Clardy, Y. Gopichand and F. J. Schmitz, *J. Am. Chem. Soc.*, 1981, **103**, 2469–2471; R. E. Honkanen and T. Golden, *Curr. Med. Chem.*, 2002, **9**, 2055–2075; A. B. Dounay and C. J. Forsyth, *Curr. Med. Chem.*, 2002, **9**, 1939–1980; X. C. Cheng, *et al.*, *J. Antibiot.*, 1987, **40**, 907–909; M. Ubukata, X.-C. Cheng, M. Isobe and K. Isono, *J. Chem. Soc., Perkin Trans. 1*, 1993, 617–624; H. Oikawa, *Curr. Med. Chem.*, 2002, **9**, 2033–2054.
9 S. B. Singh, D. L. Zink, B. Heimbach, O. Genilloud, A. Teran, K. C. Silverman, R. B. Lingham, P. Felock and D. J. Hazuda, *Org. Lett.*, 2002, **4**, 1123–1126.
10 G. R. Pettit, Z. A. Cichacz, F. Gao, C. L. Herald, M. R. Boyd, J. M. Schmidt and J. N. A. Hooper, *J. Org. Chem.*, 1993, **58**, 1302–1304; J. S. Guo, K. J. Duffy, K. L. Stevens, P. I. Dalko, R. M. Roth, M. M. Hayward and Y. Kishi, *Angew. Chem., Int. Ed.*, 1998, **37**, 187–192; M. M. Hayward, R. M. Roth, K. J. Duffy, P. I. Dalko, K. L. Stevens, J. S. Guo and Y. Kishi, *Angew. Chem., Int. Ed.*, 1998, **37**, 192–196.
11 F. M. Uckun, *Curr. Pharm. Des.*, 2001, **7**, 1627–1639; F. M. Uckun, C. Mao, A. O. Vassilev, H. Huang and S.-T. Jan, *Bioorg. Med. Chem. Lett.*, 2000, **10**, 541–545; H. Huang, C. Mao, S.-T. Jan and F. M.

Uckun, *Tetrahedron Lett.*, 2000, **41**, 1699–1702; S. Mitsuhashi, H. Shima, T. Kawamura, K. Kikuchi, M. Oikawa, A. Ichihara and H. Oikawa, *Bioorg. Med. Chem. Lett.*, 1999, **9**, 2007–2012.
12 O. Barun, K. Kumar, S. Sommer, A. Langerak, T. U. Mayer, O. Müller and H. Waldmann, *Eur. J. Org. Chem.*, 2005, 4773–4788.
13 A. A. Birkbeck, S. V. Ley and J. C. Prodger, *Bioorg. Med. Chem. Lett.*, 1995, **5**, 2637–2642.
14 B. A. Kulkarni, G. P. Roth, E. Lobkovsky and J. A. Porco, Jr., *J. Comb. Chem.*, 2002, **4**, 56–72.
15 H. C. Kolb and K. B. Sharpless, *Drug Discovery Today*, 2003, **8**, 1128–1137; V. D. Bock, H. Hiemstra and J. H. van Maarseveen, *Eur. J. Org. Chem.*, 2006, 51–68; W. S. Horne, M. K. Yadav, C. D. Stout and M. R. Ghadiri, *J. Am. Chem. Soc.*, 2004, **126**, 15366–15367.
16 J. E. Robinson and M. A. Brimble, *Chem. Commun.*, 2005, 1560–1562; R. Halim, M. A. Brimble and J. Merten, *Org. Biomol. Chem.*, 2006, **4**, 1387–1399; M. A. Brimble, C. L. Flowers, M. Trzoss and K. Y. Tsang, *Tetrahedron*, 2006, **62**, 5883–5896; M. A. Brimble and C. J. Bryant, *Chem. Commun.*, 2006, 4506–4508; M. A. Brimble and C. V. Burgess, *Synthesis*, 2007, 754–760; M. A. Brimble and C. J. Bryant, *Org. Biomol. Chem.*, 2007, **5**, 2858–2866; J. E. Robinson and M. A. Brimble, *Org. Biomol. Chem.*, 2007, **5**, 2572–2582; K. Y. Tsang and M. A. Brimble, *Tetrahedron*, 2007, **63**, 6015–6034.
17 K. Meilert and M. A. Brimble, *Org. Lett.*, 2005, **7**, 3497–3500; K. Meilert and M. A. Brimble, *Org. Biomol. Chem.*, 2006, **4**, 2184–2192.
18 R. J. K. Taylor, K. Wiggins and D. H. Robinson, *Synthesis*, 1990, 589–590.
19 P. C. Wälchli and C. H. Eugster, *Helv. Chim. Acta*, 1978, **61**, 885–898; E. Vedejs, M. J. Arnost and J. P. Hagen, *J. Org. Chem.*, 1979, **44**, 3230–3238; M. Segi, M. Takahashi, T. Nakajima, S. Suga and N. Sonoda, *Synth. Commun.*, 1989, **19**, 2431–2439; D. Wenkert, S. B. Ferguson, B. Porter, A. Qvarnstrom and A. T. McPhail, *J. Org. Chem.*, 1985, **50**, 4114–4119.
20 C. P. Forbes, G. L. Wenteler and A. Wiechers, *J. Chem. Soc., Perkin Trans. 1*, 1977, 2353–2355.
21 M. A. Brimble and D. P. Furkert, *Org. Biomol. Chem.*, 2004, **2**, 3573–3583.
22 K. T. Mead and R. Zemribo, *Synlett*, 1996, 1063–1064.
23 M. de Greef and S. Z. Zard, *Org. Lett.*, 2007, **9**, 1773–1776.
24 H. C. Kolb, M. G. Finn and K. B. Sharpless, *Angew. Chem., Int. Ed.*, 2001, **40**, 2004–2021.
25 C. W. Tornøe, C. Christensen and M. Meldal, *J. Org. Chem.*, 2002, **67**, 3057–3064.
26 V. V. Rostovtsev, L. G. Green, V. V. Fokin and K. B. Sharpless, *Angew. Chem., Int. Ed.*, 2002, **41**, 2596–2599.
27 J. M. Casas-Solvas, A. Vargas-Berenguel, L. F. Capitan-Vallvey and F. Santoyo-Gonzalez, *Org. Lett.*, 2004, **6**, 3687–3690.
28 S. J. Coats, J. S. Link, D. Gauthier and D. J. Hlasta, *Org. Lett.*, 2005, **7**, 1469–1472.
29 M. C. Pirrung, S. W. Shuey, D. C. Lever and L. Fallon, *Bioorg. Med. Chem. Lett.*, 1994, **4**, 1345–1346; D. K. Ress, S. N. Baytas, Q. Wang, E. M. Munoz, K. Tokuzoki, H. Tomiyama and R. J. Linhardt, *J. Org. Chem.*, 2005, **70**, 8197–8200.
30 A. T. Khan and E. Mondal, *Synlett*, 2003, 694–698.
31 W. L. F. Armarego and D. D. Perrin, *Purification of Laboratory Chemicals*, Pergamon, Oxford, UK, 4th edn, 1997.

