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PAPER

Enantioselective synthesis of *C*-linked spiroacetal-triazoles as privileged natural product-like scaffolds†‡

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The enantioselective synthesis of novel *C*-linked spiroacetal-triazoles **10** is reported. The key step involves reaction of acetylenic spiroacetal **11** with several azides by the Copper-Catalysed Azide–Alkyne Cycloaddition (CuAAC). The biologically privileged spiroacetal scaffold **11** was prepared from silyl-protected Weinreb amide **19** using several reliable Grignard additions and a highly diastereoselective enzymatic kinetic resolution.

Introduction

Nature continues to be an important source of lead compounds for the development of new therapeutic agents, with approximately 63% of clinically used drugs derived directly or indirectly from natural products.[1] The extreme evolutionary selection processes experienced in nature over billions of years results in complex bioactive natural products with diverse structures that are optimised to interact with various biological systems. The potency and structural diversity of natural products is actively exploited by the pharmaceutical industry for the development of new therapeutic agents.[2]

Spiroacetals, in particular 6,6-spiroacetals, are common structural motifs found in many natural products that exhibit a wide range of biological activities. For example, simple 6,6-spiroacetals function as insect pheromones,[3] spongistatin 1 exhibits antimotitic activity,[4] alotaketal A activates the cAMP cell signalling pathway,[5] the avermectins are anthelmintic and insecticidal agents,[6] and both the bistramides and virgatolides have potential anti-tumour activity.[7]

Truncated synthetic spiroacetals derived from complex natural products have also received considerable interest. These truncated spiroacetals retain the basic spiroacetal pharmacophore and other essential elements required for biological activity, while reducing structural complexity for simpler and faster synthesis. Examples of truncated analogues include the bistramide A analogue **1**, SPIKET-P **2**, and the simple 6,6-spiroacetals **3** and **4** (Fig. 1).[8]

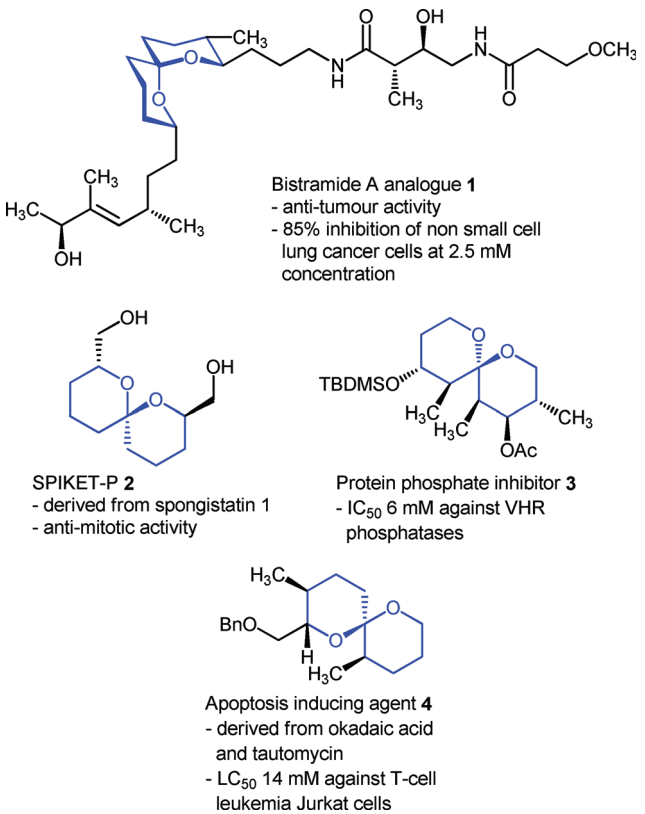

Fig. 1 Biologically privileged spiroacetal analogues.[8]

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†Electronic supplementary information (ESI) available: Experimental details and characterisation data for compounds **11**, **17–19**, **23–26**, azides **27a–h**, and spiroacetal-triazoles **28a–h** and **10a–h**. ^{1}H and ^{13}C NMR spectra of all new compounds. See DOI: 10.1039/c2ob06802h

‡This article is part of the *Organic & Biomolecular Chemistry* 10th Anniversary issue.

1,4-Disubstituted 1,2,3-triazoles have been used as bioisosteres of *trans*-peptide bonds as both moieties have planar geometries and share similar dipole moments. A key difference is that triazoles are more stable towards enzymatic and chemical modification than the corresponding parent peptide bonds.[9] The 2,3-diethanthioribonucleoside analogues **5a,b**[10a] and the dimeric nucleoside analogue **6**[10b] feature triazole linkers and were found

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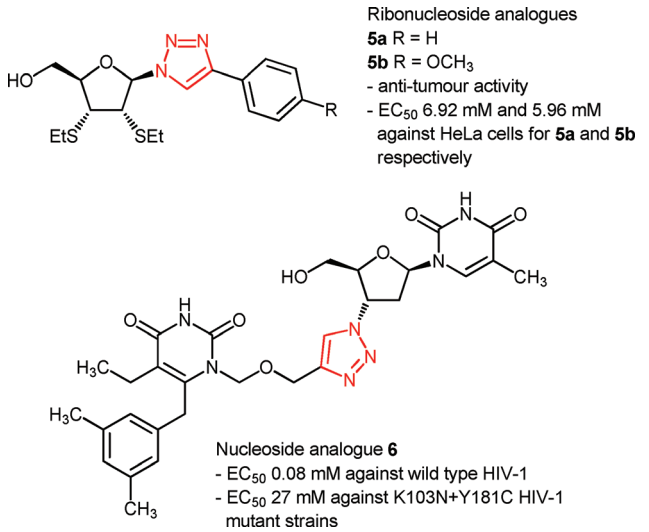
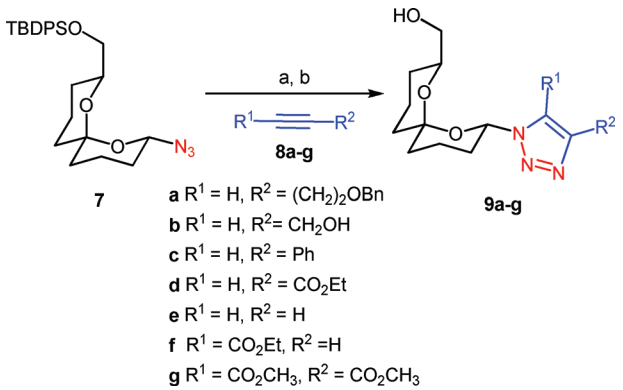


Fig. 2 Bioisosteric triazole analogues.[10]

to exhibit activity against HeLa tumour cells and HIV-1 respectively (Fig. 2).

Ley *et al.*[11] recently reported the synthesis of a library of structurally related spiroacetal hybrids that bear triazole, amino acid and carbamate moieties. Subsequent biological evaluation of these hybrid compounds revealed that the spiroacetal-carbamate hybrids had high *in vitro* apoptotic activity against chronic lymphocytic leukemia (CLL) cells.[11b]

Our research group has a long-standing interest in the synthesis of spiroacetals present in a wide range of biologically active compounds.[12] Recent efforts culminated in the synthesis of racemic *N*-linked hydroxymethyl spiroacetal-triazole analogues **9**[12a] *via* the Copper-Catalysed Azide–Alkyne Cycloaddition (CuAAC)[13] or the Huisgen 1,3-dipolar cycloaddition of azido-spiroacetal **7** and substituted alkynes **8** (Scheme 1).



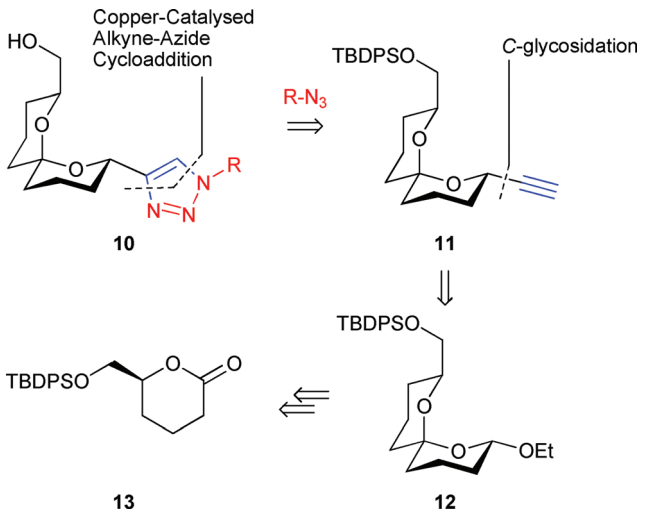
Scheme 1 Synthesis of *N*-linked spiroacetal-triazoles by Brimble *et al.*[12a] *Reagents and conditions*: (a) **8a–d**, CuI·P(OEt)$_3$ (cat.), toluene, reflux, 83–98% or **8e–g**, toluene, reflux, 64–84%; (b) then 3HF·NEt$_3$ or HF·pyridine or TBAF, 69–99%.

As part of our on-going studies to increase chemical diversity utilizing spiroacetal and triazole moieties, we decided to embark on the enantioselective synthesis of *C*-linked hydroxymethyl spiroacetal-triazoles **10**, wherein the anomeric *C*-linkage is anticipated to provide increased stability towards hydrolytic cleavage over the *N*-linked spiroacetal-triazole series.[14] By combining the biologically privileged 6,6-spiroacetal scaffold with triazole moieties, novel hybrid molecules can then be probed for biological activity.

Results and discussion

Initial synthetic strategy

Our initial retrosynthetic strategy for the *C*-linked spiroacetal-triazoles **10** is based on the CuAAC of acetylenic spiroacetal **11** with various azides. This late stage diversification is envisaged to enable facile access to a broad range of novel structures. Acetylenic spiroacetal **11** can be prepared by the Lewis acid mediated *C*-glycosidation[14] of ethoxy-spiroacetal **12**, which in turn can be prepared from δ-valerolactone **13** using procedures previously reported by our group (Scheme 2).[12a]



Scheme 2 First generation retrosynthesis of *C*-linked spiroacetal-triazoles **10**.

First generation synthesis

To test the favourable prospect of *C*-glycosidation, racemic δ-valerolactone **13** was prepared from commercially available ethyl 2-oxocyclopentanecarboxylate in 57% yield over five steps using procedures adapted from Taylor *et al.*[15] δ-Valerolactone **13** was then converted to ethoxy-spiroacetal **12** in 26% yield over four steps employing procedures recently reported by our research group (Scheme 3).[12a] With ethoxy-spiroacetal **12** in hand, attention turned to the installation of the alkyne moiety by *C*-glycosidation of the anomeric ethoxy group.[14] Disappointingly, only trace quantities of the desired silyl-protected acetylenic spiroacetal **16** were obtained upon treatment of a mixture of ethoxy-spiroacetal **12** and silyl-protected ethynyltributylstannane **15** with trimethylsilyl trifluoromethanesulfonate (TMSOTf) in CH_2Cl_2 at −78 °C.[16] It was possible that the poor leaving group ability of the ethoxy group hindered installation of the alkyne moiety. Based on this idea, ethoxy-spiroacetal **12** was treated with camphorsulfonic acid (CSA) and the resulting lactol was acetylated[12b] to afford the more reactive acetoxy-spiroacetal **14**.

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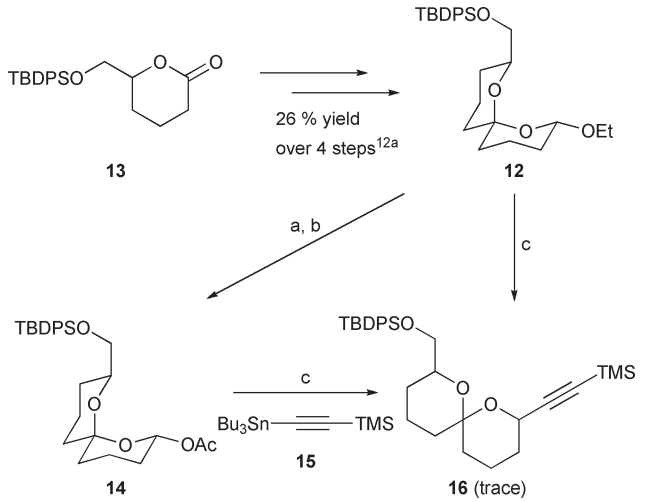


Scheme 3 First generation synthesis of acetylenic spiroacetal **16**. *Reagents and conditions*: (a) CSA, aq. THF, 40 °C, 18 h; (b) Ac_2O, DMAP (cat.), NEt_3, CH_2Cl_2, RT, 4 h, 44% over 2 steps; (c) TMSOTf, **15**, CH_2Cl_2, −78 °C, 3.5 h, trace.

Unfortunately, despite screening various Lewis acids and reaction conditions,[16] only trace quantities of protected acetylenic spiroacetal **16** were obtained upon treatment of acetoxy-spiroacetal **14** with TMSOTf and silyl-protected ethynyltributylstannane **15** in CH_2Cl_2 at −78 °C.

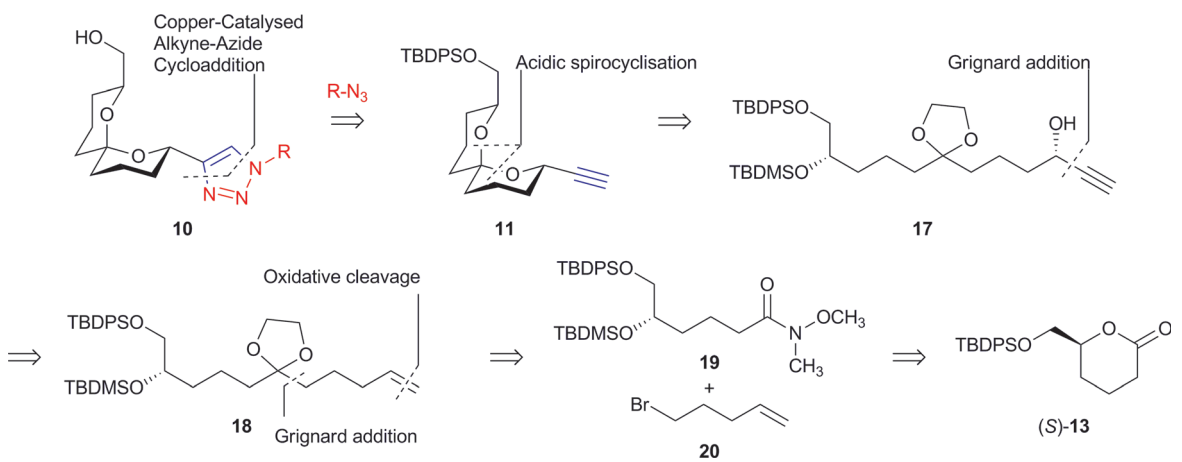
Second generation synthesis

With the first generation synthesis proving unsuccessful, the synthesis was revised such that the alkyne moiety was installed prior to spirocyclisation (Scheme 4). Acetylenic spiroacetal **11** could be formed *via* acid-catalysed spirocyclisation of linear alkynol **17** which is obtained by oxidative cleavage of alkene **18** and addition of ethynylmagnesium bromide to the resulting aldehyde. Alkene **18** in turn is obtained by addition of the Grignard reagent formed from bromide **20** to Weinreb amide **19**. Finally, **19** is available from known chiral δ-valerolactone **13**.[17]

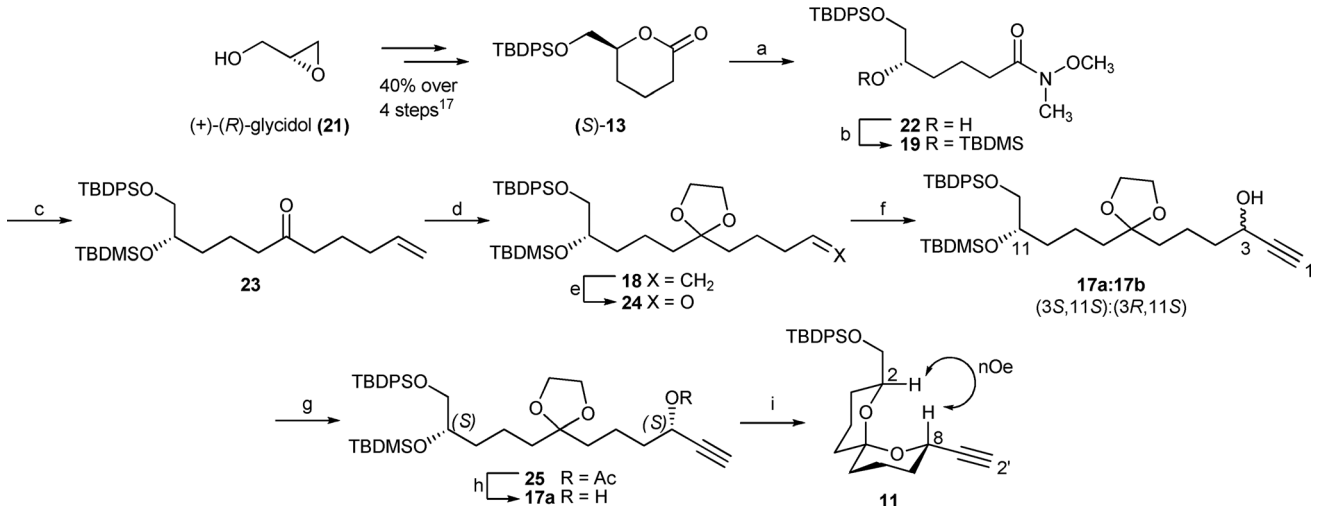
Preparation of acetylenic spiroacetal 11

The synthesis of acetylenic spiroacetal **11** is outlined in Scheme 5. Commerically available (*R*)-(+)-glycidol (**21**) was converted to (*S*)-valerolactone **13** by literature procedures in 40% yield over four steps.[17] (*S*)-Valerolactone **13** was then converted to Weinreb amide **22** employing *N*,*O*-dimethylhydroxylamine hydrochloride ($HCl{\cdot}HN(CH_3)OCH_3$) followed by protection using TBDMSCl to give silyl-protected Weinreb amide **19**.[12a] Reaction of **19** with the Grignard reagent prepared from 5-bromo-1-pentene[18] afforded ketone **23** in 79% yield. Subsequent protection of ketone **23** *via* bismuth(III) catalysed acetalisation with ethylene glycol,[19] followed by ozonolysis of the resultant alkene **18**[20] afforded aldehyde **24** in 59% yield over 2 steps. Attempts at the direct asymmetric alkynylation of aldehyde **24** with trimethylsilylacetylene in the presence of stoichiometric quantities of NEt_3, (+)-*N*-methylephedrine, and $Zn(OTf)_2$,[21] proved unsuccessful with only starting material being recovered. Nonetheless, addition of ethynyl magnesium bromide to aldehyde **24** furnished alkynol **17a** : **17b** as an inseparable, 1 : 1 mixture of diastereomers.

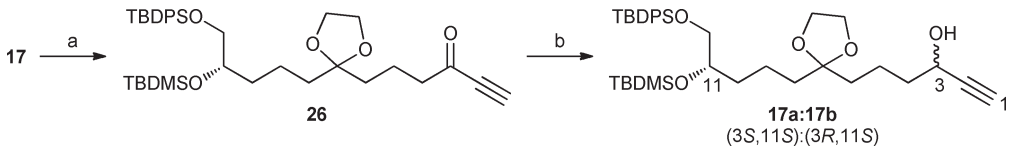
An oxidation/asymmetric reduction sequence was then investigated to obtain the desired (3*S*,11*S*) stereochemistry in alkynol **17a** from the mixture of alkynols **17a** : **17b**. Heating alkynols **17a** : **17b** with 2-iodoxybenzoic acid (IBX) in DMSO at 40 °C furnished ynone **26** in 96% yield.[22] A range of asymmetric reducing agents and reaction conditions were then evaluated as summarised in Table 1.[23] The use of alpine borane,[23a] CBS catalysts,[23b] and TarB-NO_2[23c] only afforded alkynol **17** in low diastereomeric excess or resulted in decomposition of the starting material. After much investigation, it was revealed that the (*S*)-CBS-Me catalyst and BH_3·diethylaniline in THF at 0 °C gave the best overall result with alkynol **17a** : **17b** obtained in 88% yield and 67% d.e.[23b,24] Treating the diastereo-enriched mixture of **17a** : **17b** with CSA furnished acetylenic spiroacetal as a mixture of isomers that were difficult to separate by flash chromatography, thus indicating that 67% d.e. was insufficient to direct spirocyclisation of alkynols **17a** : **17b** to access exclusively the desired bis-anomerically stabilised acetylenic spiroacetal **11**. Gratifyingly, Novozyme-435 promoted enzymatic kinetic resolution converted a mixture of alkynols **17a** : **17b** to (3*S*,11*S*)-acetate **25** and the unreacted alkynol **17b** (Scheme 5).[25] Facile



Scheme 4 Retrosynthesis of *C*-linked spiroacetal-triazoles **10**.



Scheme 5 Synthesis of acetylenic spiroacetal **11**. *Reagents and conditions*: (a) $HCl{\cdot}HN(CH_3)OCH_3$, $Al(CH_3)_3$, CH_2Cl_2, 0 °C to RT, 3 h; (b) TBDMSCl, DMAP, imidazole, CH_2,Cl_2, 40 °C, 24 h, 78% over two steps; (c) 5-bromo-1-pentene, Mg, I_2, Et_2O, 0 °C, 3 h, 79%; (d) ethylene glycol, $Bi(OTf)_3$, $(EtO)_3CH$, RT, 1.25 h; (e) O_3, $NaHCO_3$, Sudan III, CH_2Cl_2, −78 °C, NEt_3, 0.5 h, 59% over 2 steps; (f) ethynylmagnesium bromide, THF, 0 °C, 2 h, 73%; (g) lipase acrylic resin (Novozyme 435), vinyl acetate, hexanes, microwave reactor (50 W), 50 °C, 1 h; (h) K_2CO_3, CH_3OH, RT, 20 min, 30% (90–96% d.e.) over 2 steps; (i) CSA, aq. EtOH, RT, 3 h, 75%.



Scheme 6 Asymmetric reduction of ynone **26** to alkynol **17a** : **17b**. *Reagents and conditions*: (a) IBX, DMSO, 40 °C, 2.5 h, 96%; (b) See Table 1 for results.

Table 1 Summary of reagents and conditions for the asymmetric reductions of ynone **26** (Scheme 6)

Entry	Reductant[a]	Solvent	Reaction conditions	% Yield of **17**[b] (% d.e.)[b,c]
1	(*S*)-Alpine Borane	THF	−78 °C to RT, 7.5 h	Decomposition
2	D-TarB-NO_2, $NaBH_4$	THF	−78 °C to RT, overnight	Decomposition
3	D-TarB-NO_2, $LiBH_4$	THF	0 °C to RT, 2.5 h	Decomposition
4	(*S*)-CBS-Me, $BH_3{\cdot}S(CH_3)_2$	THF	RT, 10 min	Decomposition
5	(*S*)-CBS-Me, $BH_3{\cdot}S(CH_3)_2$	THF	0 °C, 40 min	Decomposition
6	(*S*)-CBS-Me, $BH_3{\cdot}S(CH_3)_2$	THF	−30 °C, 20 min	70 (69)
7	(*S*)-CBS-Me, catecholborane	THF	−78 °C to 0 °C, 6 h, then RT, overnight	Decomposition
8	(*S*)-CBS-*o*-tolyl, $BH_3{\cdot}S(CH_3)_2$	Toluene/THF	−40 °C, 3 h	56 (2)
9	(*S*)-CBS-Me, catecholborane	$EtNO_2$	−78 °C to 0 °C, 6 h, then RT, overnight	Decomposition
10	(*S*)-CBS-Me, $BH_3{\cdot}S(CH_3)_2$	$EtNO_2$	−78 °C 1 h, then RT, overnight	32 (20)
11	(*S*)-CBS-Me, $BH_3{\cdot}$diethylaniline	THF	0 °C, 2.5 h	88 (67)

[a] Reactions were performed with 1.0–2.0 equiv. of catalyst and reductant. [b] Yields of alkynol **17** isolated after flash chromatography. [c] % d.e. were obtained by Mosher ester analysis. No attempt was made to establish the absolute stereochemistry of **17**.

basic hydrolysis of acetate **25** gave **17a** in 90–96% d.e.,[24] and acidic spirocyclisation with CSA[12a] furnished the required acetylenic spiroacetal **11** in 75% yield.

The stereochemistry of acetylenic spiroacetal **11** was confirmed by NMR analysis. A distinct resonance at δ_H 4.53 ppm for the anomeric proton, 8–H (dt, $^3J_{8,9ax}$ 11.4, $^3J_{8,9eq}$ 2.6, and $^4J_{8,2'}$ 2.3 Hz), established that the alkyne substituent adopted an equatorial position. In addition, an nOe correlation observed between 2–H and 8–H, confirmed formation of the bis-anomerically stabilised spiroacetal system.

Preparation of spiroacetal-triazoles 26

With acetylenic spiroacetal **11** in hand, attention turned to the CuAAC with various azides.[12a,26] A mixture of acetylenic spiroacetal **11**, azide and catalytic quantities of the copper(I) salt, $CuI{\cdot}P(OEt)_3$[27] were heated to reflux in toluene for one hour to afford the triazole analogues **28** as single regioisomers (Table 2). Moderate to good yields were obtained for the CuAAC of spiroacetal **11** with aliphatic azides **27a–e** (entries 1–5). CuAAC of spiroacetal **11** with aryl azides **27f–h** also gave the

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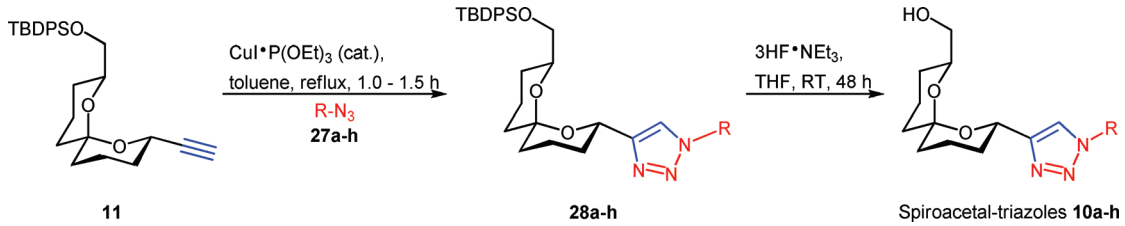


Scheme 7 CuAAC of acetylenic spiroacetal **11** to azides **27** followed by desilylation of TBDPS-protected spiroacetal-triazoles **28**. See Table 2 for results.

Table 2 Summary of CuAAC and desilylation of *C*-Linked Spiroacetal-Triazole Analogues (Scheme 7)

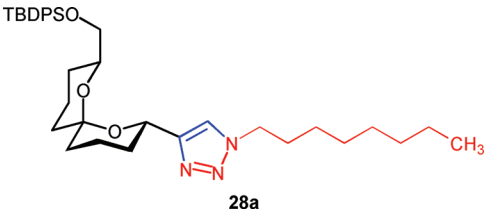
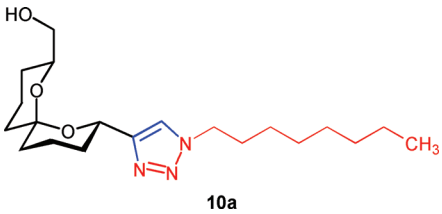
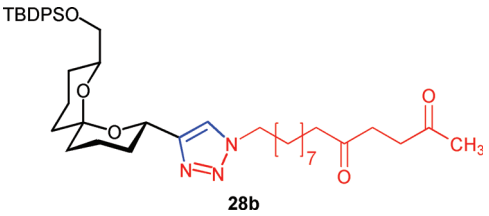
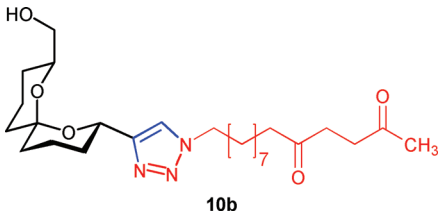
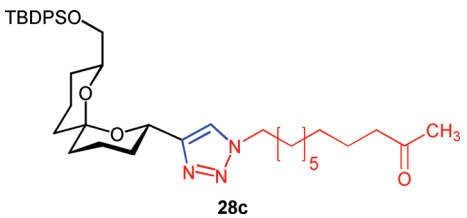
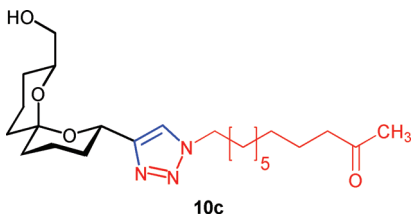
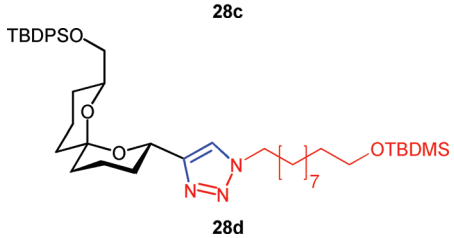
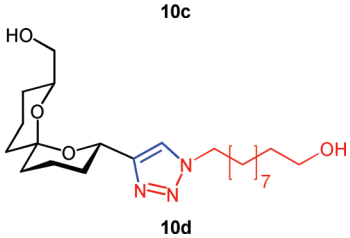
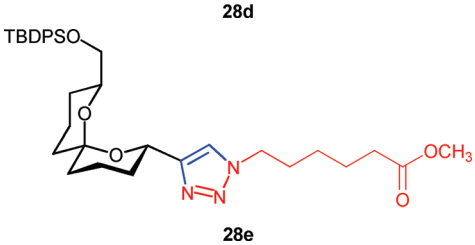
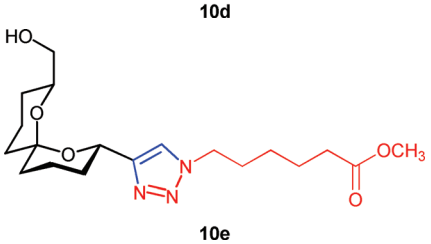
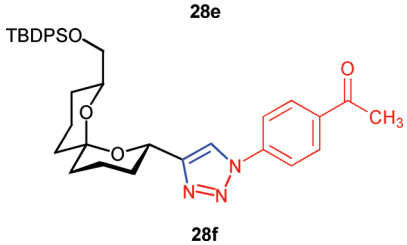
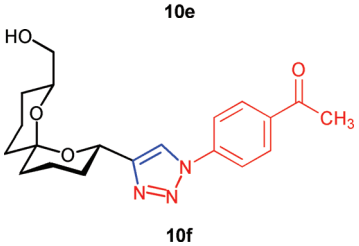
Entry	CuAAC product[a]	CuAAC yield **28a–h**	Desilylation product	Desilylation yield **10a–h**
1	 **28a**	99	 **10a**	85
2	 **28b**	58	 **10b**	54
3	 **28c**	55	 **10c**	52[b]
4	 **28d**	57	 **10d**	63
5	 **28e**	78	 **10e**	38
6	 **28f**	81	 **10f**	59

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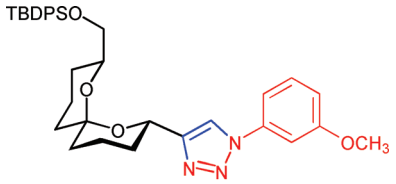
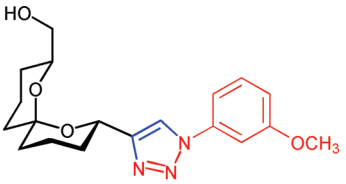
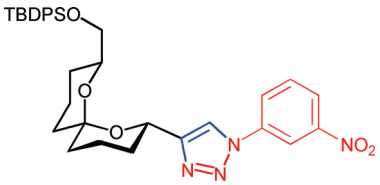
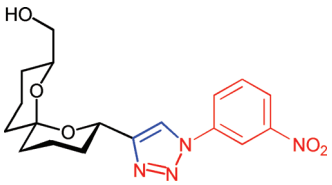
Table 2 *(Contd.)*

Entry	CuAAC product[a]	CuAAC yield **28a–h**	Desilylation product	Desilylation yield **10a–h**
7	 **28g**	65	 **10g**	99
8	 **28h**	75	 **10h**	67

[a] Azides **27a**, **b**, **e–h** were prepared by literature procedures.[26] Azide **27c** was prepared from 11-bromoundec-1-ene by Wacker oxidation and subsequent azide substitution. Azide **27d** was prepared by tosylation and azide displacement of the corresponding silyl protected alcohol using standard procedures.[26a] [b] Alternatively, desilylation of **28c** using TBAF, 3 Å mol. sieves, THF, RT, 2 h gave **10c** in 14% yield.

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corresponding triazole analogues in moderate yields (entries 6–8). Further attempts were made to extend the scope of the CuAAC of **11** to free acids, alcohols and simple amino acids. However, the reaction of **11** with 4-azidobutyric acid, 6-azidohexanoic acid, 2-azidobenzoic acid and 2-azidophenol using the CuAAC conditions developed gave only trace quantities of the desired triazole products (not shown), whereas no reaction was observed between **11** and *N*-Fmoc-protected azido alanine with a catalytic quantity of CuI·P(OEt)$_3$ after one hour of reflux in a *t*-BuOH–toluene solvent mixture.[28] It was possible that Cu(I) complexed with the free acid and alcohol groups of the respective azides, thus preventing the formation of the requisite copper acetylide, a key intermediate in the proposed CuAAC mechanism.[29] In addition, it was postulated that steric hindrance caused by the close proximity of the azide moiety to the acid or alcohol groups was preventing 2-azidobenzoic acid and 2-azidophenol from participating in CuAAC with **11**.

Deprotection of the silyl ether group in spiroacetal-triazoles 26

With several spiroacetal-triazoles prepared, the final step involved cleavage of the silyl ether group. Desilylation of spiroacetal-triazoles **28a–h** with trihydrogen fluoride-triethylamine complex (3HF·NEt$_3$),[12a,30] furnished the *C*-linked hydroxymethyl spiroacetal-triazole analogues **10a–h** in satisfactory yields (38–99%). Although a long reaction time was required to effect desilylation using 3HF·NEt$_3$ (48 h), the reagent proved reliable. Furthermore, the lower toxicity of 3HF·NEt$_3$ made it more desirable to use than the related reagent, HF·pyridine.[12a,31] TBAF was briefly investigated as an alternative desilylating reagent, however, treatment of **28c** with TBAF,[12a] gave desilylated triazole **10c** after 2 h but in only 14% yield.

Conclusion

In conclusion, an enantioselective synthesis of novel bis-anomerically stabilised 6,6-spiroacetal-triazoles bearing a hydroxymethyl group has been completed. CuAAC of acetylenic spiroacetal **11** with various azides allows access to a chemically diverse set of analogues that can be probed for bioactivity in broad phenotypic assays. Incorporation of the triazole moiety at the anomeric position of the spiroacetal ring system *via* a chemically stable carbon–carbon bond, along with the inherent bioisosteric property of triazoles as hydrolytically-resistant peptide bond mimetics, could confer desirable biological properties to these spiroacetal hybrids. The methodology developed in this study also provides the platform for future research involving the incorporation of other bioactive motifs to the 6,6-spiroacetal scaffold.

Experimental

General

Experiments requiring anhydrous conditions were performed under a dry nitrogen or argon atmosphere using apparatus heated and dried under vacuum and standard techniques in handling air- and/or moisture-sensitive materials unless otherwise stated. Solvents used for reactions and chromatographic purifications were distilled, unless otherwise stated. Commercial reagents were analytical grade or were purified by standard procedures prior to use.[32] Reactions were monitored by thin layer chromatography (TLC) carried out on 0.2 mm Kieselgel F254 (Merck) silica gel plates using UV light as a visualising agent and then stained and developed with heat using either vanillin in ethanolic sulfuric acid, ammonium heptamolybdate and cerium sulfate in aqueous sulfuric acid or potassium permanganate and potassium

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carbonate in aqueous sodium hydroxide. Separation of mixtures was performed by flash chromatography using 0.063–0.1 mm silica gel with the indicated eluent. Melting points were determined on a Kofler hot stage apparatus and are uncorrected. Optical rotations were measured using a Perkin–Elmer 341 polarimeter at a wavelength of 598 nm and are reported in 10^{-1} °C cm^2 g^{-1}. Infrared spectra were obtained using a Perkin Elmer Spectrum 100 Fourier Transform Infrared spectrometer on a film ATR sampling accessory. Absorption peaks are reported as wavenumbers (ν, cm^{-1}). NMR spectra were recorded on either a Bruker DRX 300 spectrophotometer operating at 300 MHz for ^{1}H nuclei and 75 MHz for ^{13}C nuclei, or a Bruker DRX400 or a Bruker UltraShield Plus 400 spectrophotometer operating at 400 MHz for ^{1}H nuclei and 100 MHz for ^{13}C nuclei at ambient temperature. ^{1}H NMR chemical shifts are reported in parts per million (ppm) relative to the chloroform peak (δ 7.26). ^{1}H NMR values are reported as chemical shifts δ, relative integral, multiplicity (s, singlet; d, doublet; t, triplet; dd, doublet of doublets; dt, doublet of triplets; td, triplet of doublets; 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). ^{13}C NMR values are reported as chemical shifts δ and assignment. Assignments were made with the aid of DEPT, COSY, HSQC, HMBC and NOESY experiments. Mass spectra were recorded on a VG-70SE mass spectrometer at a nominal accelerating voltage of 70 eV or on a Bruker micrOTOF-Q II mass spectrophotometer by electrospray ionisation in positive mode. 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%). High-resolution mass spectra (HRMS) were obtained with a nominal resolution of 5000 to 10 000.

(10*S*)-10-(*tert*-Butyldimethylsilyloxy)-11-(*tert*-butyldiphenylsilyloxy)undec-1-en-6-one (23)

Magnesium turnings (467 mg, 19.21 mmol) were stirred vigorously under an argon atmosphere overnight. To this was added dry Et_2O (2 mL) and a single crystal of I_2. The mixture was heated gently and stirred until the orange colour faded. 5-Bromo-1-pentene (1.1 mL, 9.30 mmol) was added dropwise with gentle heating whereupon the reaction was initiated. The reaction mixture turned bright opaque yellow with evolution of gas that changed to a white cloudy suspension. Upon cessation of gaseous evolution (0.5 h), the Grignard reagent was cooled to 0 °C and a solution of Weinreb amide **19** (2.09 g, 3.84 mmol) in dry Et_2O (4 mL, then 2 × 2 mL) were added by cannula. The resulting dark grey suspension was stirred at 0 °C for 3 h. Saturated NH_4Cl (6 mL) was carefully added at 0 °C and the mixture allowed to warm to RT with vigourous stirring. The organic layer was separated and the aqueous phase extracted with EtOAc (4 × 30 mL). The combined organic extracts were washed with saturated NaCl (50 mL), and the aqueous washing extracted with EtOAc (30 mL). The organic extracts were dried over $MgSO_4$ and concentrated *in vacuo* to give a yellow oil. Purification by flash chromatography (0%, 5% EtOAc/*n*-hexane) gave the *title compound* **23** as a pale yellow oil (1.67 g, 79%). $[\alpha]_D^{20}$ −12.0 (*c* 1.02 in $CHCl_3$); IR (film) ν_{max}/cm^{-1} 2929 (C–H), 2857 (C–H), 1715 (C=O), 1641 (C=C), 1428, 1253, 1111, 824, 774, 701; δ_H (400 MHz, $CDCl_3$) −0.08 (3H, s, OSi(C*H*$_3$)$_2$^{t}Bu), 0.00 (3H, s, OSi(C*H*$_3$)$_2$^{t}Bu), 0.84 (9H, s, OSi(CH$_3$)$_2$^{t}*Bu*), 1.04 (9H, s, OSiPh$_2$^{t}*Bu*), 1.40–1.46 (2H, m, 8–H$_A$ and 9–H$_A$), 1.55–1.72 (4H, m, 4–H, 8–H$_B$ and 9–H$_B$), 2.03–2.08 (2H, m, 3–H), 2.37–2.42 (4H, m, 5–H and 7–H), 3.45 (1H, dd, $^2J_{AB}$ 10.1 and $^3J_{11A,10}$ 6.9, 11–H$_A$), 3.57 (1H, dd, $^2J_{AB}$ 10.1 and $^3J_{11B,10}$ 5.0, 11–H$_B$), 3.66–3.72 (1H, m, 10–H), 4.92–5.04 (2H, m, 1–H), 5.72–5.83 (1H, m, 2–H), 7.36–7.45 (6H, m, Ph), 7.65–7.68 (4H, m, Ph); δ_C (100 MHz, $CDCl_3$) −4.8 (CH$_3$, OSi(C*H*$_3$)$_2$^{t}Bu), −4.5 (CH$_3$, OSi(C*H*$_3$)$_2$^{t}Bu), 18.0 (C, OSi(CH$_3$)$_2$^{t}*Bu*), 19.2 (C, OSiPh$_2$^{t}*Bu*), 19.6 (CH$_2$, C–8), 22.8 (CH$_2$, C–4), 25.8 (CH$_3$, OSi(CH$_3$)$_2$^{t}*Bu*), 26.9 (CH$_3$, OSiPh$_2$^{t}*Bu*), 33.1 (CH$_2$, C–3), 33.9 (CH$_2$, C–9), 41.8 (CH$_2$, C–5), 43.2 (CH$_2$, C–7), 67.5 (CH$_2$, C–11), 72.5 (CH, C–10), 115.2 (CH, C–1), 127.6 (CH, Ph), 129.6 (CH, Ph), 133.6 (C, Ph), 133.6 (C, Ph) 135.6 (CH, Ph), 138.0 (CH, C–2) 210.9 (C, C–6); MS m/z (ESI+) 575 ([M + Na]$^+$, 100%), 553 (M + H$^+$, 12), 475 (4), 421 (15); HRMS (ESI+): [M + H]$^+$, found 553.3535. $C_{33}H_{53}O_3Si_2^+$ requires 553.3528.

(10*S*)-10-(*tert*-Butyldimethylsilyloxy)-11-(*tert*-butyldiphenylsilyloxy)-6-(1,3-dioxolan-2-yl)undec-1-ene (18)

A mixture of ketone **23** (932 mg, 1.69 mmol) and ethylene glycol (190 μL, 3.41 mmol) were azeotrophically dried with toluene (3 × 1 mL). Triethyl orthoformate (820 μL, 4.93 mmol) and $Bi(OTf)_3$ (39 mg, 0.059 mmol) were then added at RT. After stirring at RT for 1.75 h, the mixture turned homogeneous. Saturated $NaHCO_3$ (20 mL) and a few drops of aqueous NaOH (1 M) were added at RT and the aqueous phase extracted with EtOAc (3 × 20 mL). The organic extracts were washed with saturated NaCl (20 mL) and the aqueous washing extracted with EtOAc (20 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo* to afford an opaque yellow oil. Purification by flash chromatography (0%, 5% EtOAc/*n*-hexane) gave the *title compound* **18** as a pale yellow oil (871 mg, 86%). $[\alpha]_D^{23}$ −15.5 (*c* 1.08 in $CHCl_3$); IR (film) ν_{max}/cm^{-1} 2930 (C–H), 2857 (C–H), 1641 (C=C), 1428 (=C–H), 1253, 1112 (C–O–C), 824, 774, 702; δ_H (400 MHz, $CDCl_3$) −0.06 (3H, s, OSi(C*H*$_3$)$_2$^{t}Bu), 0.01 (3H, s, OSi(C*H*$_3$)$_2$^{t}Bu), 0.84 (9H, s, OSi(CH$_3$)$_2$^{t}*Bu*), 1.05 (9H, s, OSiPh$_2$^{t}*Bu*), 1.20–1.52 (6H, m, 4–H$_A$, 5–H$_A$, H–7$_A$, 8–H, and 9–H$_A$) 1.55–1.70 (4H, m, 4–H$_B$, 5–H$_B$, H–7$_B$, and 9–H$_B$), 2.03–2.08 (2H, m, 3–H), 3.46 (1H, dd, $^2J_{AB}$ 10.0 and $^3J_{11A,10}$ 6.7, 11–H$_A$), 3.58 (1H, dd, $^2J_{AB}$ 10.0 and $^3J_{11B,10}$ 5.0, 11–H$_B$), 3.67–3.71 (1H, m, 10–H), 3.92 (4H, s, 1′–H and 2′–H), 4.93–5.03 (2H, m, 1–H), 5.75–5.85 (1H, m, 2–H), 7.35–7.44 (6H, m, Ph), 7.66–7.69 (4H, m, Ph); δ_C (100 MHz, $CDCl_3$) −4.8 (CH$_3$, OSi(C*H*$_3$)$_2$^{t}Bu), −4.4 (CH$_3$, OSi(C*H*$_3$)$_2$^{t}Bu), 18.1 (C, OSi(CH$_3$)$_2$^{t}*Bu*), 19.2 (C, OSiPh$_2$^{t}*Bu*), 19.5 (CH$_2$, C–8), 23.1 (CH$_2$, C–4), 25.9 (CH$_3$, OSi(CH$_3$)$_2$^{t}*Bu*), 26.9 (CH$_3$, OSiPh$_2$^{t}*Bu*), 33.9 (CH$_2$, C–3), 34.7 (CH$_2$, C–9), 36.7 (CH$_2$, C–5), 37.5 (CH$_2$, C–7), 64.9 (2 × CH$_2$, C–1′ and C–2′), 67.8 (CH$_2$, C–11), 72.9 (CH, C–10), 111.7 (C, C–6), 114.6 (CH$_2$, C–1) 127.6 (CH, Ph), 129.6 (CH, Ph), 133.7 (C, Ph), 133.7 (C, Ph), 135.6 (CH, Ph), 138.7 (CH, C–2); MS m/z (ESI+, MS_2+ (597)) 597 ([M + H]$^+$ 17%), 519 ([M – Ph]$^+$, 23), 465 ([M – OTBDMS]$^+$, 69), 403 (36), 383 (100), 329 (57), 279 (21); HRMS (ESI+): [M + H]$^+$, found 597.3791. $C_{35}H_{57}O_4Si_2$ requires 597.3790.

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(9*S*)-9-(*tert*-Butyldimethylsilyloxy)-10-(*tert*-butyldiphenylsilyloxy)-5-(1,3-dioxolan-2-yl)decanal (24)

To a solution of acetal **18** (738 mg, 1.24 mmol) in anhydrous CH_2Cl_2 (46 mL) was added a few drops of Sudan III indicator (0.1% in CH_2Cl_2). The bright red solution was cooled to −78 °C and O_3 was bubbled through the solution for 1 h (O_3 generator settings, flow rate: 50 L h^{-1}, discharge: 100 V, O_2 pressure: 15 psi) until complete discolouration was observed. While maintaining the reaction mixture at −78 °C, the reaction vessel was flushed with nitrogen for 0.5 h whereupon the reaction mixture turned pale orange. Triethylamine (860 μL, 1.65 mmol) was slowly added at −78 °C, stirred for 5 min, then warmed to RT. The organic phase was dried over Na_2SO_4, passed through a glass sinter and the filtrate concentrated *in vacuo* to obtain a pale red oil. Purification by flash chromatography (0%, 20% EtOAc/*n*-hexane) afforded the *title compound* **24** as a yellow oil (518 mg, 69%). $[\alpha]_D^{22}$ −13.5 (*c* 1.04 in $CHCl_3$); IR (film) ν_{max}/cm^{-1} 2929 (C–H), 2857 (C–H), 1726 (C═O), 1428 (C–H), 1389, 1111 (C–O–C), 701; δ_H (300 MHz, $CDCl_3$) −0.06 (3H, s, OSi(CH_3)$_2$^{t}Bu), 0.01 (3H, s, OSi(CH_3)$_2$^{t}Bu), 0.84 (9H, s, OSi(-CH$_3$)$_2$^{t}*Bu*), 1.05 (9H, s, OSiPh$_2$^{t}Bu), 1.32–1.55 (3H, m, 7–H, and 8–H_A), 1.58–1.75 (7H, m, 3–H, 4–H, 6–H, and 8–H_B), 2.44 (2H, td, $J_{2,1}$ 1.7 and $J_{2,3}$ 7.2, 2–H), 3.46 (1H, dd, $^2J_{AB}$ 10.0 and $^3J_{10A,9}$ 6.7, 10–H_A), 3.58 (1H, dd, $^2J_{AB}$ 10.0 and $^3J_{10B,9}$ 5.0, 10–H_B), 3.66–3.71 (1H, m, 9–H), 3.92 (4H, s, 1′–H and 2′–H), 7.34–7.45 (6H, m, Ph), 7.65–7.70 (4H, m, Ph), 9.76 (1H, t, $J_{1,2}$ 1.7, 1–H); δ_C (75 MHz, $CDCl_3$) −4.8 (CH_3, OSi(*C*H$_3$)$_2$^{t}Bu), −4.4 (CH_3, OSi(*C*H$_3$)$_2$^{t}Bu), 16.5 (CH_2, C–3), 18.1 (C, OSi(-CH$_3$)$_2$^{t}*Bu*), 19.2 (C, OSiPh$_2$^{t}*Bu*), 19.5 (CH_2, C–7), 25.8 (CH_3, OSi(CH$_3$)$_2$^{t}*Bu*), 26.9 (CH_3, OSiPh$_2$^{t}*Bu*), 34.7 (CH_2, C–8), 36.4 (CH_2, C–4), 37.5 (CH_2, C–6), 43.9 (CH_2, C–2), 65.0 (2 × CH_2, C–1′ and C–2′), 67.8 (CH_2, C–10), 72.8 (CH, C–9), 111.3 (C, C–5), 127.6 (CH, Ph), 129.6 (CH, Ph), 129.6 (CH, Ph), 133.7 (C, Ph), 133.7 (C, Ph), 135.6 (CH, Ph), 135.6 (CH, Ph), 202.3 (CH, C–1); MS *m*/*z* (ESI+) 669 (19%), 653 (100), 637 (26), 621 ([M + Na]$^+$, 68), 599 ([M + H]$^+$, 4), (7); HRMS (ESI+): [M + H]$^+$, found 599.3583. $C_{34}H_{55}O_5Si_2^+$ requires 599.3583.

(3*S*,11*S*)- and (3*R*,11*S*)-11-(*tert*-Butyldimethylsilyloxy)-12-(*tert*-butyldiphenylsilyloxy)-7-(1,3-dioxolan-2-yl)-dodec-1-yn-3-ol (17a : 17b)

To a solution of aldehyde **24** (1.27 g, 2.12 mmol) in anhydrous THF (20 mL) at 0 °C under an argon atmosphere was added a solution of ethynylmagnesium bromide (0.5 M in THF, 34 mL, 17 mmol). After stirring at 0 °C for 3 h, saturated NH_4Cl (10 mL) and distilled H_2O (5 mL) were added and the mixture stirred vigourously. The phases were separated and the aqueous phase extracted with EtOAc (3 × 20 mL). The organic extracts were washed with saturated NaCl (50 mL) and the aqueous washing extracted with EtOAc (40 mL). The combined organic extracts were then dried over Na_2SO_4 and the solvent removed *in vacuo*. The resulting dark brown oil was purified by flash chromatography (0%, 20% to 33% EtOAc/*n*-hexane) to afford an inseparable diastereomeric mixture of the *title compound* **17a** : **17b** as a thick golden oil (963 mg, 73%). The characterisation data of compound **17** is provided in the procedure describing the hydrolysis of acetate **25** to alkynol **17a**.

(11*S*)-11-(*tert*-Butyldimethylsilyloxy)-12-(*tert*-butyldiphenylsilyloxy)-7-(1,3-dioxolan-2-yl)dodec-1-yn-3-one (26)

IBX (87.3 mg, 0.312 mmol) was dissolved in DMSO (600 μL) and stirred at RT for 15 min. A solution of alkynol **17a** : **17b** (83 mg, 0.133 mmol) in dry DMSO (3 × 900 μL) was added and the reaction mixture heated to 40 °C. After 2.5 h, the reaction mixture was allowed to cool to RT and saturated $Na_2S_2O_3$ (3 mL) and EtOAc (3 mL) were added. The aqueous phase was extracted with EtOAc (4 × 15 mL) and the organic extracts washed with saturated NaCl (50 mL). The aqueous washing was back extracted with EtOAc (50 mL) and the combined organic extracts dried over Na_2SO_4 and the EtOAc removed *in vacuo* to give an orange solution. Purification by flash chromatography (0%, 17% EtOAc/*n*-hexane) afforded the *title compound* **26** as a pale yellow oil. (80 mg, 96%). $[\alpha]_D^{22}$ −11.8 (*c* 1.07 in $CHCl_3$); IR (film) ν_{max}/cm^{-1} 3309 (≡C–H), 2929 (C–H), 2858 (C–H), 2091 (C≡C), 1734 (C═O), 1683, 1472, 1187, 1106 (C–O–C), 835, 701;δ_H (400 MHz, $CDCl_3$) −0.07 (3H, s, OSi(CH_3)$_2$^{t}Bu), 0.00 (3H, s, OSi(CH_3)$_2$^{t}Bu), 0.84 (9H, s, OSi(CH$_3$)$_2$^{t}*Bu*), 1.04 (9H, s, OSiPh$_2$^{t}*Bu*), 1.29–1.52 (4H, m, 8–H, 9–H_A and 10–H_A), 1.54–1.69 (4H, m, 6–H, 9–H_B, and 10–H_B), 1.72–1.80 (2H, m, 5–H), 2.60 (2H, t, $^3J_{4,5}$ 7.3, 4–H), 3.18 (1H, s, 1–H), 3.46 (1H, dd, $^2J_{AB}$ 10.0 and $^3J_{12A,11}$ 6.7, 12–H_A), 3.57 (1H, dd, $^2J_{AB}$ 10.0 and $^3J_{12B,11}$ 5.0, 12–H_B), 3.66–3.72 (1H, m, 11–H), 3.92 (4H, s, 1′–H and 2′–H), 7.35–7.44 (6H, m, Ph), 7.65–7.69 (4H, m, Ph); δ_C (100 MHz, $CDCl_3$) −4.8 (CH_3, OSi(*C*H$_3$)$_2$^{t}Bu), −4.4 (CH_3, OSi(*C*H$_3$)$_2$^{t}Bu), 18.1 (C, OSi(CH$_3$)$_2$^{t}*Bu*), 18.1 (CH_2, C–5), 19.2 (C, OSiPh$_2$^{t}*Bu*), 19.4 (CH_2, C–9), 25.9 (CH_3, OSi(CH$_3$)$_2$^{t}*Bu*), 26.9 (CH_3, OSiPh$_2$^{t}*Bu*), 34.7 (CH_2, C–8), 36.1 (CH_2, C–10), 37.5 (CH_2, C–6), 45.4 (CH_2, C–4), 65.0 (2 × CH_2, C–1′ and C–2′), 67.8 (CH_2, C–12), 72.8 (CH, C–11), 78.3 (CH, C–1), 81.4 (C, C–2) 111.3 (C, C–7), 127.6 (CH, Ph), 129.6 (CH, Ph), 133.7 (C, Ph), 133.7 (C, Ph), 135.6 (CH, Ph), 187.1 (C, C–3); MS *m*/*z* (ESI+) 661 ([M + K]$^+$, 6%), 645 ([M + Na]$^+$, 24), 640 ([M + H_2O]$^+$, 100), 623 ([M + H]$^+$, 14), 605 (30), 545 (15), 527 (7), 491 (16); HRMS (ESI+): [M + H]$^+$, found 623.3571. $C_{36}H_{55}O_5Si_2^+$ requires 623.3583.

(3*S*,11*S*)-11-(*tert*-Butyldimethylsilyloxy)-12-(*tert*-butyldiphenylsilyloxy)-7-(1,3-dioxolan-2-yl)dodec-1-yn-3-yl acetate (25)

To a solution of alkynol **17a** : **17b** (1.12 g, 1.79 mmol) in distilled hexanes (48 mL) in a 80 mL microwave reaction tube, was added vinyl acetate (300 μL, 3.25 mmol) and Novozyme 435 lipase acrylic resin (252 mg, derived from *Candida antarctica*, 141 mg $mmol^{-1}$). The mixture was heated in a microwave reactor (CEM Discover, 50 W) to a maximum of 50 °C for 1 h. The reaction mixture was filtered through a glass sinter, washed with EtOAc (20 mL) and concentrated *in vacuo* to obtain a pale yellow oil. Purification by flash chromatography (0%, 14% to 25% EtOAc/*n*-hexane) gave the *title compound* **25** as a pale yellow oil (214 mg, 18%) and alkynols **17a** : **17b** as a yellow oil (799 mg, 72%). The alkynol fractions were concentrated and resubjected to the enzymatic kinetic resolution as described above to afford a second portion of the *title compound* **25** as a pale yellow oil (155 mg, 13%) and alkynols **17a** : **17b** (617 mg,

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55%). $[\alpha]_D^{20}$ −28.4 (*c* 1.07 in $CHCl_3$); IR (film) ν_{max}/cm^{-1} 3293 (≡C–H), 2956 (C–H), 2859 (C–H), 1744 (C═O), 1473, 1429, 1372 (≡C–H), 1233 (C–C(═O)–O), 1112 (C–O–C), 703; δ_H (400 MHz, $CDCl_3$) −0.07 (3H, s, OSi(CH_3)$_2$^{t}Bu), 0.00 (3H, s, OSi(CH_3)$_2$^{t}Bu), 0.84 (9H, s, OSi(CH_3)$_2$^{t}*Bu*), 1.04 (9H, s, OSiPh$_2$^{t}*Bu*), 1.30–1.69 (10H, m, 5–H, 6–H, 8–H, 9–H and 10–H), 1.75–1.80 (2H, m, 4–H), 2.08 (3H, s, COCH_3), 2.44 (1H, d, $^4J_{1,3}$ 2.0, 1–H), 3.46 (1H, dd, $^2J_{AB}$ 10.0 and $^3J_{12A,11}$ 6.5, 12–H_A), 3.57 (1H, dd, $^2J_{AB}$ 10.0 and $^3J_{12B,11}$ 5.0, 12–H_B), 3.66–3.70 (1H, m, 11–H), 3.90–3.94 (4H, m, 1′–H and 2′–H), 5.34 (1H, td, $^3J_{3,4}$ 6.5 and $^4J_{3,1}$ 2.0, 3–H), 7.35–7.44 (6H, m, Ph), 7.65–7.68 (4H, m, Ph); δ_C (100 MHz, $CDCl_3$) –4.8 (CH_3, OSi(*C*H_3)$_2$^{t}Bu), –4.4 (CH_3, OSi(*C*H_3)$_2$^{t}Bu), 18.1 (C, OSi(-CH_3)$_2$^{t}*Bu*), 19.2 (C, OSiPh$_2$^{t}*Bu*), 19.3 (CH_2, C–5), 19.5 (CH_2, C–9), 21.0 (CH_3, CO*C*H_3), 25.8 (CH_3, OSi(CH_3)$_2$^{t}*Bu*), 26.8 (CH_3, OSiPh$_2$^{t}*Bu*), 34.7 (2 × CH_2, C–4 and C–10), 36.7 (CH_2, C–6), 37.5 (CH_2, C–8), 63.7 (CH_2, C–3), 65.0 (2 × CH_2, C–1′ and C–2′), 67.8 (CH_2, C–12), 72.8 (CH, C–11), 73.6 (CH, C–1), 81.1 (C, C–2) 111.4 (C, C–7), 127.6 (CH, Ph), 129.6 (CH, Ph), 133.6 (C, Ph), 133.7 (C, Ph), 135.6 (CH, Ph), 169.9 (C, *C*OCH$_3$); MS *m*/*z* (ESI+) 705 ([M + K]$^+$, 7%), 689 ([M + Na]$^+$, 100), 684 ([M + H_2O]$^+$, 26), 667 ([M + H]$^+$, 6), 645 (25), 589 (13), 535 (7); HRMS (ESI+): [M + H]$^+$, found 667.3846. $C_{38}H_{59}O_6Si_2^+$ requires 667.3845.

Hydrolysis of (3*S*,11*S*)-11-(*tert*-butyldimethylsilyloxy)-12-(*tert*-butyldiphenylsilyloxy)-7-(1,3-dioxolan-2-yl)dodec-1-yn-3-yl acetate (25) to (3*S*,11*S*)-11-(*tert*-butyldimethylsilyloxy)-12-(*tert*-butyldiphenylsilyloxy)-7-(1,3-dioxolan-2-yl)dodec-1-yn-3-ol (17a)

To a solution of acetate **25** (369 mg, 0.553 mmol) in CH_3OH (11 mL) at RT was added solid K_2CO_3 (160 mg, 1.16 mmol). After stirring for 20 min the mixture was filtered and washed with EtOAc (20 mL). The filtrate was concentrated *in vacuo* to afford a thick yellow oil. Purification by flash chromatography (0%, 20% to 25% EtOAc/*n*-hexane) gave (3*S*,11*S*)-alkynol **17a** as a colourless oil (337 mg, 97%, 90–96% d.e.).[24] $[\alpha]_D^{21}$ −14.0 (*c* 1.03 in $CHCl_3$); IR (film) ν_{max}/cm^{-1} 3411 (br, O–H), 3309 (≡C–H), 2929 (C–H), 2857 (C–H), 1472, 1428 (C–H), 1253, 1111 (C–O–C), 824, 775, 701; δ_H (400 MHz, $CDCl_3$) –0.06 (3H, s, OSi(*C*H_3)$_2$^{t}Bu), 0.00 (3H, s, OSi(*C*H_3)$_2$^{t}Bu), 0.84 (9H, s, OSi(CH_3)$_2$^{t}*Bu*), 1.05 (9H, s, OSiPh$_2$^{t}*Bu*), 1.33–1.49 (3H, m, 5–H_A, 9–H_A and 10–H_A), 1.51–1.87 (9H, m, 4–H, 5–H_B, 6–H, 8–H, 9–H_B and 10–H_B), 2.45 (1H, d, $^4J_{1,3}$ 2.0, 1–H), 3.46 (1H, dd, $^2J_{AB}$ 10.0 and $^3J_{12A,11}$ 6.6, 12–H_A), 3.58 (1H, dd, $^2J_{AB}$ 10.0 and $^3J_{12B,11}$ 5.0, 12–H_B), 3.66–3.73 (1H, m, 11–H), 3.90–3.95 (4H, m, 1′–H and 2′–H), 4.33–4.39 (1H, m, 3–H), 7.35–7.45 (6H, m, Ph), 7.66–7.68 (4H, m, Ph); δ_C (100 MHz, $CDCl_3$) −4.8 (CH_3, OSi(*C*H_3)$_2$^{t}Bu), −4.4 (CH_3, OSi(*C*H_3)$_2$^{t}Bu), 18.1 (C, OSi(CH_3)$_2$^{t}*Bu*), 19.2 (C, OSiPh$_2$^{t}*Bu*), 19.4 (CH_2, C–5), 19.5 (CH_2, C–9), 25.8 (CH_3, OSi(CH_3)$_2$^{t}*Bu*), 26.8 (CH_3, OSiPh$_2$^{t}*Bu*), 34.7 (CH_2, C–10), 36.7 (CH_2, C–6), 37.5 (CH_2, C–8), 37.8 (CH_2, C–4) 62.2 (CH, C–3), 65.0 (2 × CH_2, C–1′ and C–2′), 67.8 (CH_2, C–12), 72.8 (CH, C–11), 72.9 (CH, C–1), 84.9 (C, C–2) 111.6 (C, C–7), 127.6 (CH, Ph), 129.6 (CH, Ph), 129.6 (CH, Ph), 133.7 (C, Ph), 133.7 (C, Ph), 135.6 (CH, Ph); MS *m*/*z* (ESI+) 647 ([M + Na]$^+$, 48%), 563 (100), 431 (4), 307 (10); HRMS (ESI+): [M + Na]$^+$, found 647.3574. $C_{36}H_{56}NaO_5Si_2^+$ requires 647.3558.

8-Ethynyl-2-(*tert*-butyldiphenylsilyloxymethyl)-1,7-dioxaspiro[5.5]undecane (11)

To a stirred solution of alkynol **17a** (337 mg, 0.539 mmol) in EtOH : H_2O (99 : 1 mixture, 5.8 mL) was added (+)-CSA (272 mg, 1.17 mmol) in three equal portions at RT. After stirring for 3 h, solid $NaHCO_3$ (104 mg, 0.33 mmol) was added directly and the solvent was removed *in vacuo* to afford a yellow oil. The yellow oil was dissolved in saturated $NaHCO_3$ (10 mL) and the aqueous phase extracted with EtOAc (3 × 20 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo* to afford an orange oil. Purification by flash chromatography (0%, 9% EtOAc/*n*-hexane) gave the *title compound* **11** as a yellow oil (181 mg, 75%). $[\alpha]_D^{21}$ −9.3 (*c* 1.05 in $CHCl_3$); IR (film) ν_{max}/cm^{-1} 3292 (≡C–H), 2932 (C–H), 2858 (C–H), 1473 (CH_2), 1428 (C–H), 1219, 1112 (C–O–C), 1072 (C–O–C), 980; δ_H (300 MHz, $CDCl_3$) 1.06 (9H, s, OSiPh$_2$^{t}*Bu*), 1.14–1.28 (1H, m, 3–H_A), 1.34–1.64 (6H, m, 3–H_B, 4–H, 5–H_A, 9–H_A, and 10–H_A), 1.66–1.81 (3H, m, 9–H_B and 11–H), 1.88–2.03 (2H, m, 5–H_B and 10–H_B), 2.43 (1H, d, $^4J_{2',8}$ 2.3, 2′–H), 3.58 (1H, dd, $^3J_{AB}$ 10.3 and $^3J_{2\text{-}CH2,2}$ 4.4, 2–C$H_A$$H_B$O), 3.68 (1H, dd, $^3J_{AB}$ 10.3 and $^3J_{2\text{-}CH2,2}$ 6.5, 2–C$H_A$$H_B$O), 3.77–3.87 (1H, m, 2–H), 4.53 (1H, dt, $^3J_{8,9ax}$ 11.4, $^3J_{8,9eq}$ 2.6, and $^4J_{8,2'}$ 2.3, 8–H), 7.35–7.45 (6H, m, Ph), 7.68–7.76 (4H, m, Ph); δ_C (75 MHz, $CDCl_3$) 18.35, 18.4 (2 × CH_2, C–4 and C–10), 19.2 (C, OSiPh$_2$-^{t}*Bu*), 26.75 (CH_3, OSiPh$_2$^{t}*Bu*), 26.8 (CH_2, C–3), 31.8 (CH_2, C–9), 34.7, 35.0 (2 × CH_2, C–5 and C–11), 59.8 (CH, C–8), 67.3 (CH_2, 2–*C*H_2O), 70.6 (CH, C–2), 71.7 (CH, C–2′), 84.1 (C, C–1′), 96.6 (C, C–6), 127.6 (CH, Ph), 127.6 (CH, Ph) 129.5 (CH, Ph), 129.6 (CH, Ph), 133.8 (C, Ph), 135.7 (C, Ph); MS *m*/*z* (ESI+) 487 ([M + K]$^+$, 100%), 471 ([M + Na]$^+$, 11), 429 (22), 371 ([M – Ph]$^+$, 12); HRMS (ESI+): [M + K]$^+$, found 487.2084. $C_{28}H_{36}KO_3Si^+$ requires 487.2065.

General Procedure for the Copper-Catalysed Azide–Alkyne Cycloaddition (CuAAC) of Acetylenic Spiroacetal 11 to Azides 27

To a mixture of acetylenic spiroacetal **11** (1.0 equiv.) and azide **27** (1.1–1.4 equiv.) in anhydrous toluene (0.050–0.086 M) under an argon atmosphere was added a catalytic quantity (a single crystal) of CuI·P(OEt)$_3$ and the reaction mixture heated to reflux for 1.0–1.5 h. Upon reaction completion by TLC analysis, the product was purified directly by flash chromatography (14% to 25% EtOAc/*n*-hexane) to yield the desired spiroacetal-triazole analogue **28** (Table 2).

General Procedure for Deprotection of Silyl Protected Spiroacetal-Triazole Analogues 28

To a solution of silyl-protected spiroacetal-triazole **28** (1.0 equiv.) in anhydrous THF (0.042–0.078 M) under an argon atmosphere was added 3HF·NEt$_3$ (2.4–2.8 μL per μmol of spiroacetal-triazole) and the mixture stirred at RT for 24 h. A second portion of 3HF·NEt$_3$ (2.1–2.8 μL per μmol of spiroacetal-triazole) was added and the mixture was stirred at RT for an additional 24 h. Saturated $NaHCO_3$ was added dropwise (2 mL) and the aqueous phase extracted with EtOAc (4 × 5–10 mL). The combined organic extracts were dried over Na_2SO_4 and

concentrated *in vacuo*. Purification by flash chromatography (17% *n*-hexane/EtOAc to 100% EtOAc) afforded the desired hydroxymethyl spiroacetal-triazole analogue **10** (Table 2).

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