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PAPER

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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

†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. ¹H and ¹³C NMR spectra of all new compounds. See DOI: 10.1039/c2ob06802h [‡]This article is part of the Organic & Biomolecular Chemistry 10th Anniversary issue.

ÇH₃ Bistramide A analogue 1 - anti-tumour activity 85% inhibition of non small cell lung cancer cells at 2.5 mM concentration TBDMSO ŌAc SPIKET-P 2 Protein phosphate inhibitor 3 - derived from spongistatin 1 - IC₅₀ 6 mM against VHR anti-mitotic activity phosphatases H₃C BnO Apoptosis inducing agent 4 - derived from okadaic acid and tautomycin - LC₅₀ 14 mM against T-cell leukemia Jurkat cells Fig. 1 Biologically privileged spiroacetal analogues.⁸

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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Bioisosteric triazole analogues.¹⁰ Fig. 2

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

Lev 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 spiroacetalcarbamate 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·NEt₃ 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 spiroacetaltriazoles 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. Acetvlenic spiroacetal 11 can be prepared by the Lewis acid mediated C-glycosidation¹⁴ of ethoxy-spiroacetal **12**, which in turn can be prepared from δ -valerolactone 13 using procedures previously reported by our group (Scheme 2).^{12a}



First generation retrosynthesis of C-linked spiroacetal-tria-Scheme 2 zoles 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 silvl-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.



Scheme 3 First generation synthesis of acetylenic spiroacetal 16. *Reagents and conditions*: (a) CSA, aq. THF, 40 °C, 18 h; (b) Ac₂O, DMAP (cat.), NEt₃, CH₂Cl₂, RT, 4 h, 44% over 2 steps; (c) TMSOTf, 15, CH₂Cl₂, -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 CH₂Cl₂ 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·HN(CH₃)OCH₃) followed by protection using TBDMSCl to give silvl-protected Weinreb amide 19.^{12a} Reaction of 19 with the Grignard reagent prepared from 5-bromo-1-pentene¹⁸ 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 NEt₃, (+)-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 (3S, 11S) 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-NO₂^{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 BH₃·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 (3S,11S)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·HN(CH₃)OCH₃, Al(CH₃)₃, CH₂Cl₂, 0 °C to RT, 3 h; (b) TBDMSCl, DMAP, imidazole, CH₂,Cl₂, 40 °C, 24 h, 78% over two steps; (c) 5-bromo-1-pentene, Mg, I₂, Et₂O, 0 °C, 3 h, 79%; (d) ethylene glycol, Bi(OTf)₃, (EtO)₃CH, RT, 1.25 h; (e) O₃, NaHCO₃, Sudan III, CH₂Cl₂, -78 °C, NEt₃, 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) K₂CO₃, CH₃OH, 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.) ^{<i>b,c</i>}
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 ·S(CH ₃) ₂	THF	RT, 10 min	Decomposition
5	(S)-CBS-Me, BH ₃ ·S(CH ₃) ₂	THF	0 °C, 40 min	Decomposition
6	(S)-CBS-Me, BH ₃ ·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 ·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 ·S(CH ₃) ₂	EtNO ₂	-78 °C 1 h, then RT, overnight	32 (20)
11	(S)-CBS-Me, BH ₃ ·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 $\delta_{\rm H}$ 4.53 ppm for the anomeric proton, 8–H (dt, ${}^{3}J_{8,9ax}$ 11.4, ${}^{3}J_{8,9eq}$ 2.6, and ${}^{4}J_{8,2'}$ 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 bisanomerically 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(1) salt, CuI·P(OEt)₃²⁷ 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



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 (S



Table 2(Contd.)



^{*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.

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(1) 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·NEt₃),^{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·NEt₃ (48 h), the reagent proved reliable. Furthermore, the lower toxicity of 3HF·NEt₃ 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 airand/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

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 cm² 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 $(v, \text{ cm}^{-1})$. NMR spectra were recorded on either a Bruker DRX 300 spectrophotometer operating at 300 MHz for ¹H nuclei and 75 MHz for ¹³C nuclei, or a Bruker DRX400 or a Bruker UltraShield Plus 400 spectrophotometer operating at 400 MHz for ¹H nuclei and 100 MHz for ¹³C nuclei at ambient temperature. ¹H NMR chemical shifts are reported in parts per million (ppm) relative to the chloroform peak (δ 7.26). ¹H 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. ¹³C NMR chemical shifts are reported in ppm relative to the chloroform peak (δ 77.0). ¹³C 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 Et₂O (2 mL) and a single crystal of I₂. 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 Et₂O (4 mL, then 2×2 mL) were added by cannula. The resulting dark grey suspension was stirred at 0 °C for 3 h. Saturated NH₄Cl (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 \times 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 MgSO₄ 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%). $[\alpha]_{\rm D}^{20}$ -12.0 (*c* 1.02 in CHCl₃); IR (film) $v_{\rm max}$ /cm⁻¹ 2929 (C-H), 2857 (C-H), 1715 (C=O), 1641 (C=C), 1428, 1253, 1111, 824, 774, 701; $\delta_{\rm H}$ (400 MHz, CDCl₃) -0.08 (3H, s, OSi(CH₃)₂^tBu), 0.00 (3H, s, OSi(CH₃)₂^tBu), 0.84 (9H, s, OSi(CH₃)₂^tBu), 1.04 (9H, s, OSiPh2^tBu), 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 ${}^{3}J_{11A,10}$ 6.9, 11–H_A), 3.57 (1H, dd, ${}^{2}J_{AB}$ 10.1 and ${}^{3}J_{11B,10}$ 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, CDCl₃) -4.8 (CH₃, OSi(CH₃)₂^tBu), -4.5 (CH₃, OSi(CH₃)₂^tBu), 18.0 (C, OSi(CH₃)₂^tBu), 19.2 (C, OSiPh2^tBu), 19.6 (CH2, C-8), 22.8 (CH2, C-4), 25.8 (CH3, OSi(CH₃)₂^tBu), 26.9 (CH₃, OSiPh₂^tBu), 33.1 (CH₂, C-3), 33.9 (CH₂, C-9), 41.8 (CH₂, C-5), 43.2 (CH₂, C-7), 67.5 (CH₂, 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. C₃₃H₅₃O₃Si₂⁺ 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 $(3 \times 1 \text{ mL})$. 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 NaHCO₃ (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 Na₂SO₄ and concentrated in vacuo to afford an opaque yellow oil. Purification by flash chromatography (0%, 5% EtOAc/nhexane) gave the title compound 18 as a pale yellow oil (871 mg, 86%). $[\alpha]_{\rm D}^{23}$ -15.5 (c 1.08 in CHCl₃); IR (film) $v_{\rm max}$ cm⁻¹ 2930 (C–H), 2857 (C–H), 1641 (C=C), 1428 (=C–H), 1253, 1112 (C–O–C), 824, 774, 702; $\delta_{\rm H}$ (400 MHz, CDCl₃) -0.06 (3H, s, OSi(CH₃)₂^tBu), 0.01 (3H, s, OSi(CH₃)₂^tBu), 0.84 (9H, s, OSi(CH₃)₂^tBu), 1.05 (9H, s, OSiPh₂^tBu), 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, ${}^{2}J_{AB}$ 10.0 and ${}^{3}J_{11A,10}$ 6.7, 11–H_A), 3.58 (1H, dd, ${}^{2}J_{AB}$ 10.0 and ${}^{3}J_{11B,10}$ 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); $\delta_{\rm C}$ (100 MHz, CDCl₃) -4.8 (CH₃, OSi(CH₃)₂^tBu), -4.4 (CH₃, $OSi(CH_3)_2{}^tBu)$, 18.1 (C, $OSi(CH_3)_2{}^tBu)$, 19.2 (C, $OSiPh_2{}^tBu)$, 19.5 (CH₂, C–8), 23.1 (CH₂, C–4), 25.9 (CH₃, OSi(CH₃)₂^tBu), 26.9 (CH₃, OSiPh₂^tBu), 33.9 (CH₂, C-3), 34.7 (CH₂, C-9), 36.7 (CH₂, C-5), 37.5 (CH₂, C-7), 64.9 (2 × CH₂, C-1' and C-2'), 67.8 (CH₂, C-11), 72.9 (CH, C-10), 111.7 (C, C-6), 114.6 (CH₂, 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.

(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 CH₂Cl₂ (46 mL) was added a few drops of Sudan III indicator $(0.1\% \text{ in CH}_2\text{Cl}_2)$. The bright red solution was cooled to $-78 \text{ }^\circ\text{C}$ and O_3 was bubbled through the solution for 1 h (O_3 generator settings, flow rate: 50 L h^{-1} , discharge: 100 V, O₂ 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 Na₂SO₄, 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%). $[\alpha]_{\rm D}^{22}$ -13.5 (c 1.04 in CHCl₃); IR (film) $v_{\rm max}$ cm⁻¹ 2929 (C-H), 2857 (C-H), 1726 (C=O), 1428 (C-H), 1389, 1111 (C–O–C), 701; $\delta_{\rm H}$ (300 MHz, CDCl₃) –0.06 (3H, s, OSi(CH₃)₂^tBu), 0.01 (3H, s, OSi(CH₃)₂^tBu), 0.84 (9H, s, OSi(-CH₃)₂^tBu), 1.05 (9H, s, OSiPh₂^tBu), 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, ${}^{2}J_{AB}$ 10.0 and ${}^{3}J_{10A,9}$ 6.7, 10–H_A), 3.58 (1H, dd, ${}^{2}J_{AB}$ 10.0 and ${}^{3}J_{10B,9}$ 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); $\delta_{\rm C}$ (75 MHz, CDCl₃) –4.8 (CH₃, OSi(CH₃)₂^tBu), -4.4 (CH₃, OSi(CH₃)₂^tBu), 16.5 (CH₂, C-3), 18.1 (C, OSi(-CH₃)₂^tBu), 19.2 (C, OSiPh₂^tBu), 19.5 (CH₂, C-7), 25.8 (CH₃, OSi(CH₃)₂^tBu), 26.9 (CH₃, OSiPh₂^tBu), 34.7 (CH₂, C–8), 36.4 (CH₂, C–4), 37.5 (CH₂, C–6), 43.9 (CH₂, C–2), 65.0 (2 × CH₂, C-1' and C-2'), 67.8 (CH₂, 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 $([M + Na]^+, 68), 599 ([M + H]^+, 4), (7); HRMS (ESI+): [M + 100)$ 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 NH₄Cl (10 mL) and distilled H₂O (5 mL) were added and the mixture stirred vigourously. The phases were separated and the aqueous phase extracted with EtOAc (3 \times 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 Na2SO4 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-3one (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 ($3 \times 900 \mu$ L) 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 Na₂S₂O₃ (3 mL) and EtOAc (3 mL) were added. The aqueous phase was extracted with EtOAc (4 \times 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 Na2SO4 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 CHCl₃); IR (film) $v_{\text{max}}/\text{cm}^{-1}$ 3309 (=C–H), 2929 (C–H), 2858 (C–H), 2091 (C=C), 1734 (C=O), 1683, 1472, 1187, 1106 (C-O-C), 835, 701; $\delta_{\rm H}$ (400 MHz, CDCl₃) -0.07 (3H, s, OSi(CH₃)₂^tBu), 0.00 (3H, s, OSi(CH₃)₂^tBu), 0.84 (9H, s, OSi(CH₃)₂^tBu), 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, ${}^{2}J_{AB}$ 10.0 and ${}^{3}J_{12A,11}$ 6.7, 12–H_A), 3.57 (1H, dd, ${}^{2}J_{AB}$ 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); $\delta_{\rm C}$ (100 MHz, CDCl₃) -4.8 (CH₃, OSi(CH₃)₂^tBu), -4.4 (CH₃, OSi(CH₃)₂^tBu), 18.1 (C, OSi(CH₃)₂^tBu), 18.1 (CH₂, C–5), 19.2 (C, OSiPh₂^tBu), 19.4 (CH₂, C-9), 25.9 (CH₃, OSi(CH₃)₂^tBu), 26.9 (CH₃, OSiPh₂^tBu), 34.7 (CH₂, C–8), 36.1 (CH₂, C–10), 37.5 (CH₂, C-6), 45.4 (CH₂, C-4), 65.0 (2 × CH₂, C-1' and C-2'), 67.8 (CH₂, 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 $([M + K]^+, 6\%)$ $H_2O^{+}_{1}$, 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 μ L, 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,

55%). $[\alpha]_{D}^{20}$ –28.4 (c 1.07 in CHCl₃); IR (film) v_{max}/cm^{-1} 3293 (≡C-H), 2956 (C-H), 2859 (C-H), 1744 (C=O), 1473, 1429, 1372 (\equiv C–H), 1233 (C–C(\equiv O)–O), 1112 (C–O–C), 703; $\delta_{\rm H}$ (400 MHz, CDCl₃) -0.07 (3H, s, OSi(CH₃)₂^tBu), 0.00 (3H, s, $OSi(CH_3)_2^{t}Bu)$, 0.84 (9H, s, $OSi(CH_3)_2^{t}Bu)$, 1.04 (9H, s, OSiPh2^tBu), 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, COCH₃), 2.44 (1H, d, ${}^{4}J_{1,3}$ 2.0, 1–H), 3.46 (1H, dd, ${}^{2}J_{AB}$ 10.0 and ${}^{3}J_{12A,11}$ 6.5, 12– H_A), 3.57 (1H, dd, ${}^{2}J_{AB}$ 10.0 and ${}^{3}J_{12B,11}$ 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, ${}^{3}J_{3,4}$ 6.5 and ${}^{4}J_{3,1}$ 2.0, 3–H), 7.35–7.44 (6H, m, Ph), 7.65–7.68 (4H, m, Ph); δ_C (100 MHz, CDCl₃) –4.8 (CH₃, OSi(CH₃)₂^tBu), -4.4 (CH₃, OSi(CH₃)₂^tBu), 18.1 (C, OSi(- $(CH_3)_2 Bu$, 19.2 (C, OSiPh₂ Bu), 19.3 (CH₂, C-5), 19.5 (CH₂, C-9), 21.0 (CH₃, COCH₃), 25.8 (CH₃, OSi(CH₃)₂^tBu), 26.8 (CH₃, OSiPh₂^tBu), 34.7 (2 × CH₂, C–4 and C–10), 36.7 (CH₂, C-6), 37.5 (CH₂, C-8), 63.7 (CH₂, C-3), 65.0 (2 × CH₂, C-1' and C-2'), 67.8 (CH2, 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, COCH₃); MS m/z (ESI+) 705 ([M + K]⁺, 7%), 689 ([M + Na^{+}_{1} , 100), 684 ($[M + H_2O]^{+}_{1}$, 26), 667 ($[M + H]^{+}_{1}$, 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 CH₃OH (11 mL) at RT was added solid K₂CO₃ (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 (3S,11S)-alkynol 17a as a colourless oil (337 mg, 97%, 90–96% d.e.).²⁴ $[\alpha]_{\rm D}^{21}$ –14.0 (c 1.03 in CHCl₃); IR (film) $v_{\text{max}}/\text{cm}^{-1}$ 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; $\delta_{\rm H}$ (400 MHz, CDCl₃) –0.06 (3H, s, OSi(CH₃)₂^tBu), 0.00 (3H, s, OSi(CH₃)₂^tBu), 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, ${}^{2}J_{AB}$ 10.0 and ${}^{3}J_{12A,11}$ 6.6, 12–H_A), 3.58 (1H, dd, ${}^{2}J_{AB}$ 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, CDCl₃) –4.8 $(CH_3, OSi(CH_3)_2^{t}Bu), -4.4 (CH_3, OSi(CH_3)_2^{t}Bu), 18.1 (C, CH_3)_2^{t}Bu)$ OSi(CH₃)₂^tBu), 19.2 (C, OSiPh₂^tBu), 19.4 (CH₂, C-5), 19.5 (CH₂, C–9), 25.8 (CH₃, OSi(CH₃)₂^tBu), 26.8 (CH₃, OSiPh₂^tBu), 34.7 (CH₂, C-10), 36.7 (CH₂, C-6), 37.5 (CH₂, C-8), 37.8 (CH₂, C–4) 62.2 (CH, C–3), 65.0 ($2 \times$ CH₂, C–1' and C–2'), 67.8 (CH₂, 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: H₂O (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 NaHCO₃ (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 NaHCO3 (10 mL) and the aqueous phase extracted with EtOAc (3 \times 20 mL). The combined organic extracts were dried over MgSO₄ 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 CHCl₃); IR (film) v_{max} /cm⁻¹ 3292 (\equiv C–H), 2932 (C–H), 2858 (C–H), 1473 (CH₂), 1428 (C-H), 1219, 1112 (C-O-C), 1072 (C-O-C), 980; $\delta_{\rm H}$ (300 MHz, CDCl₃) 1.06 (9H, s, OSiPh₂^tBu), 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, ${}^{3}J_{AB}$ 10.3 and ${}^{3}J_{2-CH2,2}$ 4.4, 2–CH_AH_BO), 3.68 (1H, dd, ${}^{3}J_{AB}$ 10.3 and ${}^{3}J_{2-CH2,2}$ 6.5, 2–CH_AH_BO), 3.77–3.87 (1H, m, 2–H), 4.53 (1H, dt, ${}^{3}J_{8,9ax}$ 11.4, ${}^{3}J_{8,9eq}$ 2.6, and ${}^{4}J_{8,2'}$ 2.3, 8–H), 7.35–7.45 (6H, m, Ph), 7.68–7.76 (4H, m, Ph); δ_C (75 MHz, CDCl₃) 18.35, 18.4 (2 × CH₂, C-4 and C-10), 19.2 (C, OSiPh₂-^{tBu), 26.75 (CH}₃, OSiPh₂^tBu), 26.8 (CH₂, C-3), 31.8 (CH₂, C-9), 34.7, 35.0 (2 × CH₂, C-5 and C-11), 59.8 (CH, C-8), 67.3 (CH₂, 2-CH₂O), 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), $371 ([M - Ph]^+, 12); HRMS (ESI+): [M + K]^+, found 487.2084.$ $C_{28}H_{36}KO_{3}Si^{+}$ 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·NEt₃ (2.4–2.8 μ L per μ mol of spiroacetal-triazole) and the mixture stirred at RT for 24 h. A second portion of 3HF·NEt₃ (2.1–2.8 μ L per μ mol of spiroacetal-triazole) was added and the mixture was stirred at RT for an additional 24 h. Saturated NaHCO₃ was added dropwise (2 mL) and the aqueous phase extracted with EtOAc (4 × 5–10 mL). The combined organic extracts were dried over Na₂SO₄ 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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