Dispiroketals in synthesis. Part 24.[1] Preparation and use of chiral 2,2′-bis(triisopropylsilyloxymethyl)bi(dihydropyran)s as new protecting and resolving agents for 1,2-diols

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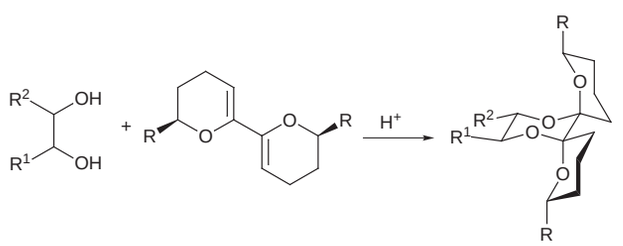
C_2 symmetric chiral 2,2′-bis(triisopropylsilyloxymethyl)bi(dihydropyran)s (*S*,*S*)-**1** and (*R*,*R*)-**1** were prepared from the corresponding glycidols and selectively reacted with 1,2-diols to give dispiroketals. The products of these reactions could be deprotected following treatment with fluoride, oxidation and reductive cleavage with samarium(II) iodide.

Introduction

Dispiroketals have proven to be useful intermediates in synthesis.[2] These architecturally rigid structures are formed from 1,2-diols by acid catalysed reaction with bi(dihydropyran)s. The controlling elements of these reactions are that the products obtained possess maximum anomeric stabilisation at the newly formed centres and that the pendant side chains prefer to adopt equatorial orientations (Scheme 1). These features combine to give stable and often crystalline products which permit predictive use of the chirality associated with the individual components in desymmetrisation reactions,[3] resolution,[4] or enantioselective protection.[5]

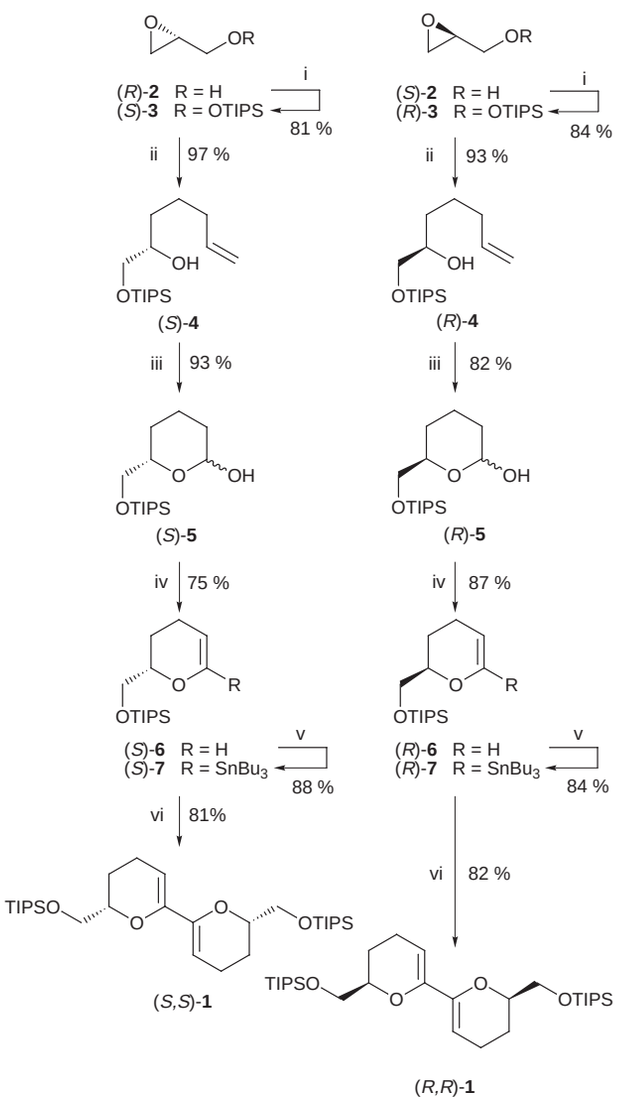


Scheme 1 Acid catalysed dispiroketal formation.

In an effort to expand the scope of the bi(dihydropyran)s in synthesis we have continued to develop novel methods and report here a new and efficient route to enantiopure 2,2′-bis(triisopropylsilyloxymethyl)bi(dihydropyran)s (*S*,*S*)-**1** and (*R*,*R*)-**1** and their use in the resolution and selective protection of 1,2-diols has been studied.

Results and discussion

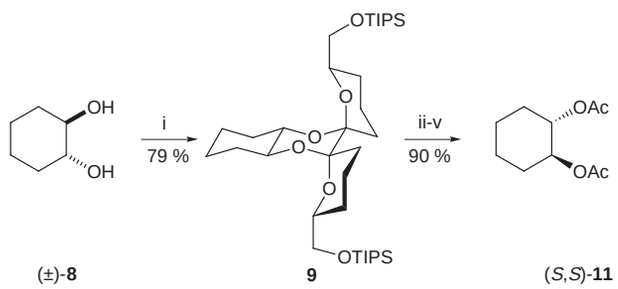
The routes to (*S*,*S*)-**1** and (*R*,*R*)-**1** were designed to be complementary to our previous methods for the synthesis of chiral bi(dihydropyran)s[6] and utilise commercially available enantiopure glycidols (*R*)-**2** and (*S*)-**2** as chiral starting materials (Scheme 2). Thus, straightforward protection of (*R*)-**2** as its triisopropylsilyl (TIPS) derivative (*S*)-**3** was followed by epoxide ring opening with but-3-enylmagnesium bromide and catalytic Li_2CuCl_4[7] to give the alkene (*S*)-**4** in 79% yield over the two steps. Subsequent ozonolysis of (*S*)-**4** provided lactol (*S*)-**5** which was dehydrated *via* its corresponding mesylate to afford the glycal derivative (*S*)-**6** in 70% overall yield. Compound (*S*)-**6** was oxidatively dimerised to (*S*,*S*)-**1** using Bu^nLi–$KOBu^t$–



Scheme 2 *Reagents and Conditions*: i,TIPS-Cl, Et_3N, DMAP, DCM, rt, 24 h; ii, but-3-enylmagnesium bromide, Li_2CuCl_4, THF, −30 °C, 30 min; iii, O_3, $NaHCO_3$, DCM, −78 °C, 1 h then PPh_3, −78 °C to rt, 12 h; iv, MsCl, Et_3N, DCM, 0 °C, 2 h then DBU, rt, 15 min; v, Bu^nLi–$KOBu^t$–TMEDA, pentane, −78 °C to −15 °C, 2 h then $ClSnBu_3$, −78 °C to rt, 12 h; vi, $Cu(NO_3)_2$, THF, rt, 30 min.

TMEDA[8] and then tributyltin chloride to give an intermediate stannane (*S*)-**7** which was oxidised with $Cu(NO_3)_2 \cdot 2.5H_2O$[9] to provide the desired diene (*S*,*S*)-**1** (71% yield over the two steps). Similarly, the other glycidol enantiomer (*R*)-**2** was processed following the same route to provide the diene (*R*,*R*)-**1** in an enantiopure form.

In order to evaluate (*R*,*R*)-**1** as a resolving agent we reacted this compound with the racemic (±)-*trans*-cyclohexane-1,2-diol **8** in toluene for 2 hours using camphorsulfonic acid (CSA) as a catalyst to give the dispiroketal **9** as a single product in 79% yield (Scheme 3). The selectivity in this reaction is derived from



Scheme 3 *Reagents and Conditions:* i, (*R*)-**1**, CSA, toluene, reflux, 2 h; ii, TBAF, THF, rt, 4 h; iii, $(COCl)_2$, DMSO, DCM, Et_3N; iv, SmI_2 (13 eq.), THF, rt, 30 min; v, Ac_2O, Et_3N, DMAP, THF, 24 h.

the chirality match of the configurated bi(dihydropyran) with only the enantiomer of the diol leading to the fully anomerically stabilised product with placement of the isopropylsilyloxymethyl side chains in equatorial environments. The other anomeric diol failed to react owing to a mis-match of the chiral components.

Next, conditions to remove the protecting auxiliary were devised. This was achieved by removing the TIPS group of the dispiroketal **9** using tetrabutylammonium fluoride (TBAF) in THF to give an intermediate alcohol **10** which was oxidised to the corresponding dialdehyde. Subsequent reductive cleavage was achieved by treatment with SmI_2[10] in THF and the resulting diol was worked-up as its diacetate (*S*,*S*)-**11** in 90% overall yield (Scheme 3). The enantiopurity of (*S*,*S*)-**11** was shown by chiral GC to be in excess of 95%. The same sequence of reactions was carried out with a series of diols using both (*S*,*S*)-**1** and (*R*,*R*)-**1** as the resolving agents (Table 1). In all these reactions the protection and the deprotection steps were found to occur in a very efficient manner to provide the corresponding acetates with ee greater than 95%.

In summary we have developed a new and shorter route to enantiopure 2,2′-bis(triisopropylsilyloxymethyl)bi(dihydropyran)s in six steps from the commercially available chiral glycidols. These reagents were successfully used as resolving agents for *trans*-1,2-diols *via* their corresponding dispiroketals. An efficient three-step deprotection protocol using samarium iodide was designed to release the diols in high yields and high enantiopurities.

Experimental

Proton NMR spectra were recorded on a Bruker DRX-600 (600 MHz) spectrometer as solutions in $CDCl_3$ using the residual $CHCl_3$ as an internal reference (7.26 ppm). The following abbreviations were used to explain the multiplicities: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet, br, broad. Coupling constants *J* are quoted in Hz. ^{13}C NMR spectra were recorded on a Bruker DRX-600 (150 MHz) or AM-400 (100 MHz) spectrometer as solutions in $CDCl_3$. Infra-red spectra were recorded on a Perkin-Elmer 1600 series FT-IR spectrometer. Mass spectra were recorded at the EPSRC mass spectrometry service, Swansea. Microanalyses were performed in the University of Cambridge microanalysis laboratory. Melting points were determined on a Reicher hot stage apparatus and are uncorrected. Optical rotations were measured using an Optical Activity AA-1000 polarimeter and are quoted as 10^{-1} deg cm^2 g^{-1}. Flash column chromatography was performed on Merck 9385 Kieselgel 60 silica (230–400 mesh) using hexane, 40–60 petroleum ether (petrol), diethyl ether (ether) or ethyl acetate as eluents. The reactions were monitored by thin layer chromatography and the plates were visualised with UV light (254 nm) and acidified ammonium molybdate(IV). GC analyses were carried out on a LIPODEX-E column (carrier gas He, 80 kPa) with a Hewlett-Packard 5890 series II chromatograph. HPLC analyses were carried out on a chiral CHIRACEL OP column with a Hewlett-Packard HP series 100 apparatus.

All reactions were carried out under an argon atmosphere with dry freshly distilled solvents, under anhydrous conditions. Tetrahydrofuran (THF), diethyl ether (ether) and pentane were distilled from sodium–benzophenone and dichloromethane (DCM), triethylamine (NEt_3), benzene and toluene were distilled from calcium hydride. Dimethylformamide (DMF) was dried over 4 Å molecular sieves.

(*S*)-3-Triisopropylsilyloxy-1,2-epoxypropane (*S*)-3

A mixture of (*R*)-glycidol (2.0 g, 27 mmol), triisopropylsilyl chloride (6.4 ml, 30 mmol), triethylamine (4.4 ml, 47 mmol) and 4-dimethylaminopyridine (DMAP) in dichloromethane (DCM) (100 ml) was stirred at 25 °C for 24 hours. The reaction mixture was then treated with 1.5 M HCl (36 ml) at 0 °C and the phases were separated. The aqueous layer was extracted with DCM (30 ml). The combined organic phases were washed with aq. saturated sodium bicarbonate (30 ml), dried over $MgSO_4$ and concentrated. The crude mixture was purified by column chromatography (petrol 95%, ether 5%) to give a colourless oil (5.0 g, 81%); $[a]_D^{31}$ −4.7 (*c* 1.17, $CHCl_3$); IR (thin film) ν_{max} 2942, 2866, 2727, 1454, 1384, 1367, 1343, 1254, 1161, 1137, 1102, 1090, 1032 cm^{-1}; δ_H (600 MHz; $CDCl_3$) 3.91 (1H, dd, *J* 11.6, 3.2, -C$H_a$$H_b$-OTIPS), 3.75 (1H, dd, *J* 11.6, 4.6, -C$H_a$$H_b$-OTIPS), 3.11 (1H, m, H-2), 2.77 (1H, dd, *J* 5.1, 4.3, H-1a), 2.67 (1H, dd, *J* 5.1, 2.6 H-1b), 1.14–1.00 (21H, m, Si(C*H*$(CH_3)_2)_3$ and Si(CH(CH_3)$_2$)$_3$); δ_C (150 MHz; $CDCl_3$) 63.9 (C-1), 52.6 (C-2), 44.4 (C-3), 17.9 (Si(CH(*C*H_3)$_2$)$_3$), 11.9 (Si(*C*H$(CH_3)_2)_3$); *m*/*z* (CI) 248 (MNH_4^+, 40%), 231 (MH^+, 9), 215 ([M − Me]$^+$, 15); HRMS (CI) Calc. for $C_{12}H_{30}NO_2Si$ (MNH_4^+): 248.2046; found 248.2042. Anal. calc. for $C_{12}H_{26}O_2Si$: C, 62.55; H, 11;37; found: C, 62.57; H, 11.30%.

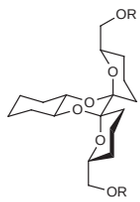
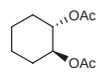
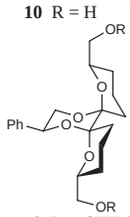
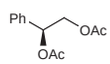
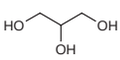
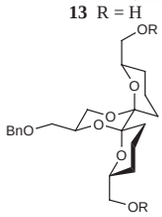
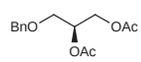
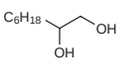
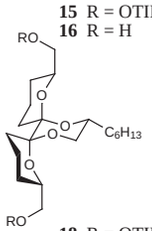
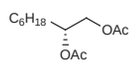
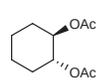
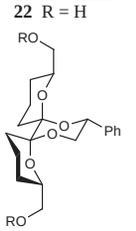
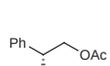
(*R*)-3-Triisopropylsilyloxy-1,2-epoxypropane (*R*)-3

(*R*)-**3** was obtained in 84% yield from (*S*)-glycidol using a similar procedure to above. All data were identical to compound (*S*)-**3** except $[a]_D^{31}$ +5.4 (*c* 1.09, $CHCl_3$).

(*S*)-6-Hydroxy-7-triisopropylsilyloxyhept-1-ene (*S*)-4

But-3-enylmagnesium bromide (31.2 ml (0.5 M in THF), 15.6 mmol) was added dropwise to a mixture of (*S*)-**3** (3.0 g, 13 mmol) and copper dilithium tetrachloride (Li_2CuCl_4) (13 ml of a 0.1 M sol. in THF) in THF (15 ml) at −40 °C. The reaction was stirred for 30 min at −40 °C then quenched with aq. saturated ammonium chloride (20 ml) and the mixture was allowed to warm to room temperature. The phases were separated and the aqueous layer was extracted with ether (20 ml). The organic phases were combined, dried over $MgSO_4$ and concentrated. Purification by flash chromatography (petrol 83%, ether 17%) yields a colourless oil (3.6 g, 97%); $[a]_D^{28}$ +2.8 (*c* 1.57, $CHCl_3$); IR (thin film) ν_{max} 3582, 3458 (br, OH), 2942, 2866, 1641, 1462, 1384, 1249, 1116, 1088 cm^{-1}; δ_H (600 MHz; $CDCl_3$) 5.81 (1H, m, -CH_2-C*H*=CH_2), 5.01 (1H, dd, *J* 17.1, 1.6, -CH_2-CH= CH_{trans}-H), 4.95 (1H, dd, *J* 10.1, 0.8, -CH_2-CH=CHH_{cis}), 3.71 (1H, dd, *J* 9.5, 3.3, -C$H_a$$H_b$-OTIPS), 3.69–3.64 (1H, m, -C*H*OH-), 3.48

Table 1 Resolution of diols using the chiral bi(dihydropyran)s (*S*,*S*)-**1** and (*R*,*R*)-**1**

Diol[a]	Diene	Dispiroketal adduct	Yield[b] (%)	Product after deprotection	Yield[c] (%)	ee[d] (%)
	(*R*,*R*)-**1**	 **9** R = OTIPS **10** R = H	79	 (*S*,*S*)-**11**	90	>95
	(*R*,*R*)-**1**	 **12** R = OTIPS **13** R = H	76	 (*S*)-**14**	92	>95
	(*R*,*R*)-**1**	 **15** R = OTIPS **16** R = H	86[e]	 (*S*)-**17**	85	>95[f]
	(*S*,*S*)-**1**	 **18** R = OTIPS **19** R = H	86	 (*R*)-**20**	85	>95
	(*S*,*S*)-**1**	 **21** R = OTIPS **22** R = H	79	 (*R*,*R*)-**11**	73	>95
	(*S*,*S*)-**1**	 **23** R = OTIPS **24** R = H	80	 (*R*)-**14**	85	>95

[a] All diol starting materials used were racemic mixtures. Cyclohexane-1,2-diol was used as its *trans* isomer as depicted above. [b] The yields refer to the initial dispiroketal formation. [c] The yields refer to the four-step deprotection sequence (removal of TIPS, oxidation, samarium(II) iodide reduction and acylation). [d] Determined by chiral GC on a LIPODEX-E column unless otherwise specified. [e] The initial dispiroketal adduct **25** was protected by benzylation (NaH, BnBr, THF) in quantitative yield to give **15** (see Experimental). [f] Determined by chiral HPLC on a CHIRACEL OP column.

(1H, dd, *J* 9.5, 7.7, -CH_aH_b-OTIPS), 2.53 (1H, d, *J* 2.5, OH), 2.10–2.06 (2H, m, -CH_2-CH=CH_2), 1.60–1.55 (1H, m, H-4a), 1.48–1.39 (3H, m, H-4a, H-5a, H-5b), 1.15–1.00 (21H, m, Si(C*H*-$(CH_3)_2)_3$ and Si($CH(CH_3)_2)_3$); δ_C (150 MHz, $CDCl_3$) 138.6 (C-6), 114.6 (C-7), 71.8 (C-2), 67.6 (C-1), 33.7 (C-3), 32.2 (C-5), 24.9 (C-4), 17.9 (Si($CH(CH_3)_2)_3$), 11.9 (Si($CH(CH_3)_2)_3$); *m*/*z* (CI) 304 (MNH_4^+, 26%), 287 (MH^+, 38), 248 (100); HRMS (CI) Calc. for $C_{16}H_{35}O_2Si$: 287.2406; found 287.2403. Anal. calc. for $C_{16}H_{34}O_2Si$: C, 67.07; H, 11.96; found: C, 67.20; H, 11.82%.

(*R*)-6-Hydroxy-7-triisopropylsilyloxyhept-1-ene (*R*)-4

Compound (*R*)-**4** was obtained in 93% yield from (*R*)-**3** using a similar procedure to above. All data identical to compound (*S*)-**4** except $[a]_D^{31}$ −4.2 (*c* 0.98, $CHCl_3$).

(*S*)-6-Hydroxy-2-triisopropylsilyloxymethyl-3,4,5,6-tetrahydro-2*H*-pyran (*S*)-5

Ozone was passed through a mixture of (*S*)-**4** (1.5 g, 5.2 mmol) and sodium bicarbonate (500 mg) in DCM (50 ml) at −78 °C until a blue colour appeared in the flask. Oxygen was then bubbled through until the mixture became colourless. After stirring at −78 °C for 1 hour, triphenylphosphine (2.3 g, 10.4 mmol) was added and the resulting mixture was allowed to warm-up to room temperature over 12 hours. The solid was filtered off and the filtrate was concentrated to give a crude oil. Purification by flash chromatography (petrol 80%, ether 20%) afforded a colourless oil (1.4 g, 93%). ^{1}H NMR analysis revealed that the compound was present as a mixture of the open chain aldehyde (6%, referred to below as *ald*), and the two anomers of the cyclic aldol form (mixture: 41% for the minor one (*min*) and 53% the major one (*maj*)); $[\alpha]_D^{31}$ +7.4 (*c* 0.62, $CHCl_3$); IR (thin film) ν_{max} 3414 (br, OH), 2942, 2866, 1463, 1442, 1383, 1366, 1261, 1195, 1126, 1102, 1064, 1042, 1014 cm^{-1}; δ_H (600 MHz; $CDCl_3$) 9.78 (0.06H, t, *J* 1.5, -CHO), 5.26 (0.41H, br s, H-6$_{min}$), 4.75–4.72 (0.53H, m, H-6$_{maj}$), 4.05–4.00 (0.41H, m, H-2$_{min}$), 3.85–3.79 (0.59H, m, includes at 3.81 (0.53H, dd, *J* 9.7, 5.0, -CH_aH$_b$-OTIPS$_{maj}$), -CH_aH$_b$-OTIPS$_{ald}$), 3.71 (0.41H, dd, *J* 10.0, 5.3, -CH_aH$_b$-OTIPS$_{min}$), 3.61 (0.53H, dd, *J* 9.7, 6.7, -CH$_a$$H_b$-OTIPS$_{maj}$), 3.58–3.53 (0.94H, m, includes at 3.56 (0.41H, dd, *J* 9.9, 5.9, -CH$_a$$H_b$-OTIPS$_{min}$), H-2$_{maj}$), 3.48 (0.06H, dd, *J* 8.6, 7.14, -C*H*OH-$_{ald}$), 3.07 (0.53H, d, *J* 6.2, OH$_{maj}$), 2.59 (0.12 H, dt, *J* 7.2, 1.4, -CH_2-CHO$_{ald}$), 1.94–0.94 (27H, m, 3 × -CH$_2$-, Si(C*H*(CH$_3$)$_2$)$_3$ and Si(CH(C*H*$_3$)$_2$)$_3$ of all three isomers); δ_C (150 MHz; $CDCl_3$) 96.3 (C-6$_{maj}$), 91.8 (C-6$_{min}$), 77.0 (C-2$_{maj}$), 69.7 (C-2$_{min}$), 67.0 (-*C*H$_2$-OTIPS$_{min}$), 66.6 (-*C*H$_2$-OTIPS$_{maj}$), 32.9, 29.8, 28.0, 27.5, 21.6 and 16.9 (-CH$_2$-$_{maj}$ and -CH$_2$-$_{min}$), 17.9 (Si(CH(*C*H$_3$)$_2$)$_3$), 11.9 (Si(*C*H(CH$_3$)$_2$)$_3$); *m*/*z* (CI) 306 (MNH_4^+, 15%), 288 (M^+, 45), 271 ($[M - OH]^+$, 75), 75 (100); HRMS (CI) Calc. for $C_{15}H_{36}NO_3Si$ (MNH_4): 306.2464; found 306.2461.

(*R*)-6-Hydroxy-2-triisopropylsilyloxymethyl-3,4,5,6-tetrahydro-2*H*-pyran (*R*)-5

(*R*)-**5** was obtained in 82% yield from (*R*)-**4** using a similar procedure to above. All data identical to compound (*S*)-**5** except $[\alpha]_D^{31}$ −7.9 (*c* 1.4, $CHCl_3$).

(*S*)-2-Triisopropylsilyloxymethyl-3,4-dihydro-2*H*-pyran (*S*)-6

Methanesulfonyl chloride (0.16 ml, 2.1 mmol) was added to a mixture of (*S*)-**5** (0.2 g, 0.7 mmol) and triethylamine (0.34 ml, 2.4 mmol) in DCM (5 ml). After 3 hours of stirring at room temperature, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (0.29 ml, 2.1 mmol) was added and the resulting yellow mixture stirred at room temperature for 1 hour then concentrated to give a crude residue. Purification by flash chromatography (petrol 98%, ether 1%, NEt_3 1%) gave a colourless oil (140 mg, 75%); $[\alpha]_D^{28}$ +32.3 (*c* 1.06, $CHCl_3$); IR (thin film) ν_{max} 2943, 2866, 1651, 1464, 1383, 1241, 1140, 1072, 1004 cm^{-1}; δ_H (600 MHz; $CDCl_3$) 6.36 (1H, d, *J* 6.2, H-6), 4.67–4.64 (1H, m, H-5), 3.90–3.85 (1H, m, H-2), 3.84 (1H, dd, *J* 9.9, 5.1, -CH_aH$_b$-OTIPS), 3.69 (1H, dd, *J* 9.9, 6.1, -CH$_a$$H_b$-OTIPS), 2.12–2.05 (1H, m, H-4a), 2.01–1.94 (2H, m, H-4b, H-3a), 1.70–1.64 (1H, m, H-3b), 1.15–1.05 (21H, m, Si(C*H*(CH$_3$)$_2$)$_3$ and Si(CH(C*H*$_3$)$_2$)$_3$); δ_C (150 MHz; $CDCl_3$) 143.6 (C-6), 100.4 (C-5), 75.6 (C-2), 65.7 (-*C*H$_2$-OTIPS), 24.5 (C-3), 19.2 (C-4), 17.9 (Si(CH(*C*H$_3$)$_2$)$_3$), 11.9 (Si(*C*H(CH$_3$)$_2$)$_3$); *m*/*z* (CI) 288 (MNH_4^+, 63%), 271 (MH^+, 100); HRMS (CI) Calc. for $C_{15}H_{31}O_2Si$ (MH): 271.2093; found 271.2095. Anal. calc. for $C_{15}H_{30}O_2Si$: C, 66.61; H, 11.18; found: C, 66.75; H, 11.08%.

(*R*)-2-Triisopropylsilyloxymethyl-3,4-dihydro-2*H*-pyran (*R*)-6

(*R*)-**6** was obtained in 87% yield from (*R*)-**5** using a similar procedure to above. All data identical to compound (*S*)-**6** except $[\alpha]_D^{31}$ −30.9 (*c* 0.96, $CHCl_3$).

(*S*)-2-Triisopropylsilyloxymethyl-3,4-dihydro-2*H*-pyran-6-yl-tributylstannane (*S*)-7

To a suspension of potassium *tert*-butoxide (1.75 g, 15.5 mmol) in pentane (25 ml) was added Bu^{n}Li (10.9 ml of a 1.6 M solution in hexane, 15.6 mmol) and tetramethylethylenediamine (TMEDA) (3.1 ml, 20.8 mmol) at −78 °C. The resulting mixture was allowed to warm up to −15 °C until it became a clear yellow solution. After recooling to −78 °C, a solution of (*S*)-**6** in pentane (2 ml) was added and the mixture was allowed to warm up to −15 °C over 2 hours. A precipitate was observed in the dark yellow–orange solution. The mixture was cooled back to −78 °C and the potassium anion was intercepted with tributyltin chloride (6.0 ml, 22.3 mmol). After warming up to room temperature, the white opaque mixture was quenched with water (5 ml). The phases were separated and the aqueous layer was extracted with ether (2 × 10 ml). The organic layers were combined, dried over $MgSO_4$ and concentrated to give a residue which was purified by flash column chromatography (silica neutralised with NEt_3, hexane) to afford (*S*)-**7** as a colourless oil (5.10 g, 88%); $[\alpha]_D^{31}$ +16.3 (*c* 0.91, $CHCl_3$); IR (thin film) ν_{max} 2955, 2922, 2866, 1607, 1463, 1376, 1270, 1218, 1183, 1139, 1108, 1057 cm^{-1}; δ_H (600 MHz; $CDCl_3$) 4.74–4.67 (1H, m, H-5), 3.81–3.76 (2H, m, H-2, -CH_aH$_b$OTIPS), 3.67–3.63 (1H, m, -CH$_a$$H_b$OTIPS), 2.14–2.06 (1H, m, H-4a), 2.07–1.88 (2H, m, H-4b, H-5a), 1.70–1.62 (1H, m, H-3b), 1.53–1.48 (6H, m, 3 × -CH$_2$- of $SnBu_3$), 1.34–1.28 (6H, m, 3 × -CH$_2$- of $SnBu_3$), 1.12–1.05 (21H, m, Si(C*H*(CH$_3$)$_2$)$_3$ and Si(CH(C*H*$_3$)$_2$)$_3$), 0.92–0.88 (15H, m, 3 × n-CH$_2$- and 3 × -CH$_3$ of $SnBu_3$); δ_C (150 MHz; $CDCl_3$) 162.0 (C-6), 111.8 (C-5), 75.6 (C-2), 66.0 (*C*H$_2$OTIPS), 28.9, 27.1, 24.7 (C-3), 20.9 (C-4), 17.9 (Si(CH(*C*H$_3$)$_2$)$_3$), 13.6, 11.9 (Si(*C*H(CH$_3$)$_2$)$_3$), 9.4; *m*/*z* (CI) 561 (MH^+, 100%), 520 (10), 308 (12), 271 (20); HRMS (CI) calc. for $C_{27}H_{57}O_2SiSn$ (MH): 561.3149; found 561.3170. Anal. calc. for $C_{27}H_{56}O_2SiSn$: C, 57.96; H, 10.09; found: C, 57.97; H, 10.17%.

(*R*)-2-Triisopropylsilyloxymethyl-3,4-dihydro-2*H*-pyran-6-yl-tributylstannane (*R*)-7

(*R*)-**7** was obtained in 84% yield from (*R*)-**6** using a similar procedure to above. All data identical to compound (*S*)-**7** except $[\alpha]_D^{31}$ −16.9 (*c* 1.15, $CHCl_3$).

(2*S*,2*S*′)-2,2′-Bis(triisopropylsilyloxymethyl)-3,3′,4,4′-tetrahydro-6,6′-bi-2*H*-pyran (*S*,*S*)-1

To the stannane (*S*)-**7** (228 mg, 0.41 mmol) in THF (10 ml) was added copper(II) nitrate hemipentahydrate (106 mg, 0.44 mmol) in a single portion. After stirring for 30 min at room temperature, the reaction mixture was diluted with ethyl acetate (50 ml) and washed with 5% aq. ammonia (20 ml), water (20 ml) and brine (20 ml). The organic layer was dried over Na_2SO_4, and evaporated to give a green residue. Purification by flash column chromatography (80 g of silica previously neutralized with NEt_3, hexane with 1% of NEt_3) gave in order of elution the desilylated product (*S*)-**6** as a colourless oil (2 mg, 1.5%), then the diene (*S*,*S*)-**1** (89 mg, 81%) as a white amorphous powder; $[\alpha]_D^{31}$ +33.8 (*c* 0.94, $CHCl_3$); IR (thin film) ν_{max} 2940, 2864, 1631 (C=C), 1463, 1380, 1337, 1277, 1220, 1139, 1097; δ_H (600 MHz; $CDCl_3$) 5.22 (2H, br t, H-5, H-5′), 3.93–3.86 (4H, m, 2 × -CH_a-H$_b$OTIPS, H-2, H-2′), 3.74–3.68 (2H, m, 2 × -CH$_a$$H_b$OTIPS), 2.22–2.09 (4H, m, 2 × H-4, 2 × H-4′), 2.04–1.94 (2H, m, H-3a, H-3′a), 1.66–1.54 (2H, m, H-3b, H-3′b), 1.15–1.02 (42H, m, 2 × Si(C*H*(CH$_3$)$_2$)$_3$ and 2 × Si(CH(C*H*$_3$)$_2$)$_3$); δ_C (150 MHz; $CDCl_3$) 147.1 (C-6, C-6′), 96.71 (C-5, C-5′), 76.1 (C-2, C-2′), 65.8 (*C*H$_2$OTIPS), 24.4 and 19.9 (C-3, C-3′, C-4, C-4′), 17.9 (Si(CH(*C*H$_3$)$_2$)$_3$, 11.92 (Si(*C*H(CH$_3$)$_2$)$_3$); *m*/*z* (CI) 539 (MH^+, 100%), 52 (32); HRMS (CI) calc. for $C_{30}H_{59}O_4Si_2$ (MH): 539.3952; found 539.3950. Anal. calc. for $C_{30}H_{58}O_4Si_2$: C, 66.86; H, 10.85; found C, 66.31; H, 10.73%.

(2*R*,2*R*′)-2,2′-Bis(triisopropylsilyloxymethyl)-3,3′,4,4′-tetrahydro-6,6′-bi-2*H*-pyran (*R*,*R*)-1

(*R*,*R*)-**1** was obtained in 82% yield from (*R*)-**7** using a similar procedure to above. All data identical to compound (*S*,*S*)-**1** except $[\alpha]_D^{31}$ −34.9 (*c* 1.17, $CHCl_3$).

General procedure A: Formation of the dispiroketals

To a solution of the diol (9.0 mmol, 3 eq.) and CSA (0.8 mmol, 0.25 eq.) in chloroform (30 ml) was added the bi(dihydropyran) (3.0 mmol, 1 eq.). The resulting mixture was heated at reflux for 2 hours, then diluted with DCM (30 ml) and washed with water (20 ml). The layers were separated and the aqueous layer was extracted with DCM (2 × 20 ml). The combined organic phases were dried over $MgSO_4$, and the solvents were concentrated to give an oily residue. Purification by flash column chromatography (0 to 10% ether in petrol) afforded the dispiroketal.

(1*S*,2*S*,2′*R*,2″*R*,6′*R*,6″*R*)-1,2-*O*-[6′,6″-Bis(triisopropylsilyloxymethyl)-3′,3″,4′,4″,5′,5″,6′,6″-octahydro-2′,2″-bi(2*H*-pyran-2′,2″-diyl)]cyclohexane-1,2-diol 9. Compound **9** was obtained as a white amorphous solid in 79% yield following general procedure A and using *trans*-cyclohexane-1,2-diol as the diol and (*R*,*R*)-**1** as the bi(dihydropyran); $[\alpha]_D^{25}$ −40.6 (*c* 0.34, $CHCl_3$); IR (thin film) ν_{max} 2939, 2865, 1463, 1382, 1277, 1204, 1172, 1098, 1070, 1044, 1012 cm^{-1}; δ_H (600 MHz; $CDCl_3$) 3.77 (2H, dd, *J* 9.2, 5.5, 2 × C$H_a$$H_b$OTIPS), 3.76–3.71 (2H, m, H-6′, H-6″), 3.59–3.54 (2H, m, H-1, H-2), 3.51 (2H, dd, *J* 9.2, 5.8, 2 × CH_a-H_bOTIPS), 1.83 (2H, tq, *J* 13.3, 4.0, H-4′ax, H-4″ax), 1.81–1.67 (8H, m, H-4eq, H-5eq, H-3′eq, H-3″eq, H-3eq, H-6eq, H-5′eq, H-5″eq), 1.57 (2H, br d, *J* 13.0, H-4′eq, H-4″eq), 1.44 (2H, dt, *J* 13.5, 4.7, H-3′ax, H-3″ax), 1.37–1.27 (2H, m, H-3ax, H-6ax), 1.27–1.20 (2H, m, H-4ax, H-5ax), 1.12–1.02 (44H, m, H-5′ax, H-5″ax, 2 × Si(CH(CH_3)$_2$)$_3$ and 2 × Si(CH(CH_3)$_2$)$_3$); δ_C (150 MHz, $CDCl_3$) 97.2 (C-2′, C-2″), 70.6 (C-1, C-2, C-6′, C-6″), 67.3 (2 × CH_2OTIPS), 29.7 (C-3, C-6), 28.5 (C-3′, C-3″), 27.8 (C-5′, C-5″), 24.3 (C-4, C-5), 18.1 (C-4′, C-4″), 18.0 and 17.9 (2 × Si(CH(CH_3)$_2$)$_3$), 11.9 (2 × Si(CH(CH_3)$_2$)$_3$); *m*/*z* (CI) 672.7 (MNH_4^+, 100%), 655.8 (MH^+, 28), 539.6 (34), 304.3 (32); HMRS (CI) calc. for $C_{36}H_{71}O_6Si_2$ (MH): 655.4789; found (CI) 655.4790. Anal. calc. for $C_{36}H_{70}O_6Si_2$: C, 66.01; H, 10.77; found C, 66.52; H, 10.80%.

(1*R*,2*R*,2′*S*,2″*S*,6′*S*,6″*S*)-1,2-*O*-[6′,6″-Bis(triisopropylsilyloxymethyl)-3′,3″,4′,4″,5′,5″,6′,6″-octahydro-2′,2″-bi(2*H*-pyran-2′,2″-diyl)]cyclohexane-1,2-diol 21. Compound **21** was obtained as a white amorphous solid in 79% yield following the general procedure A for dispiroketal formation and using *trans*-cyclohexane-1,2-diol as the diol and (*S*,*S*)-**1** as the bi(dihydropyran). All data identical to compound **9** except $[\alpha]_D^{31}$ +48.0 (*c* 0.71, $CHCl_3$).

(2*R*,6*S*,7*S*,9*R*,14*S*)-14-Hydroxymethyl-2,9-bis(triisopropylsilyloxymethyl)-1,8,13,16-tetraoxadispiro[5.0.5.4]hexadecane 25. The title compound **25** was obtained as a colourless oil in 86% yield following general procedure A and using glyerol as the diol and (*R*,*R*)-**1** as the bi(dihydropyran); $[\alpha]_D^{23}$ −36.9 (*c* 1.15, $CHCl_3$); IR (thin film) ν_{max} 3540 (OH), 2942, 2865, 1599, 1463, 1382, 1205, 1112, 1043, 1014 cm^{-1}; δ_H (600 MHz; $CDCl_3$) 4.10–4.07 (1H, m, H-14), 3.82 (1H, t, *J* 11.1, H-15$_{ax}$), 3.79–3.75 (4H, m, 2 × C$H_a$$H_b$OTIPS, H-2, H-9), 3.64–3.61 (1H, m, -C$H_a$$H_b$-OH), 3.57–3.52 (3H, m, 2 × -$CH_a$$H_b$OTIPS, -$CH_a$$H_b$OH), 3.41 (1H, dd, *J* 11.1, 2.9, H-15$_{eq}$), 1.90 (1H, t, *J* 6.4, OH), 1.83–1.73 (5H, m), 1.70–1.65 (1H, m), 1.66–1.64 (2H, m), 1.48–1.42 (2H, m), 1.19–1.14 (2H, m), 1.12–1.04 (42H, m, 2 × Si(CH(CH_3)$_2$)$_3$, 2 × Si(CH(CH_3)$_2$)$_3$; δ_C (150 MHz; $CDCl_3$) 96.9 and 95.8 (C-6, C-7), 71.0 and 70.8 (C-2, C-9), 67.1 and 67.0 (2 × CH_2OTIPS, C-14), 62.5 (CH_2OH), 59.3 (C-15), 28.3, 28.2, 27.6, 27.4, 18.1 and 18.0 (C-1, C-4, C-5, C-10, C-11, C-12), 18.0 (Si(CH-(CH_3)$_2$)$_3$), 11.9 (Si(CH(CH_3)$_2$)$_3$); *m*/*z* (CI) 648.7 (MNH_4^+, 100%), 540 (51), 304 (100); HRMS (CI) calc. for $C_{33}H_{70}O_7NSi_2$ (MNH_4): 648.4691; found 648.4690.

(2*S*,6*R*,7*R*,9*S*,14*R*)-14-Hexyl-2,9-bis(triisopropylsilyloxymethyl)-1,8,13,16-tetraoxadispiro[5.0.5.4]hexadecane 18. The title compound **18** was obtained as a colourless oil in 85% yield following general procedure A and using octane-1,2-diol as the diol and (*S*,*S*)-**1** as the bi(dihydropyran); $[\alpha]_D^{31}$ +33.9 (*c* 0.62, $CHCl_3$); IR (thin film) ν_{max} 2941, 2865, 1463, 1382, 1966, 1278, 1256, 1205, 1173, 1108, 1043, 1014 cm^{-1}; δ_H (600 MHz; $CDCl_3$) 3.94–3.89 (1H, m, H-14), 3.80–3.77 (2H, m), 3.75–3.69 (2H, m), 3.60 (1H, t, *J* 10.9. H-15ax), 3.51 (2H, dd, *J* 9.5, 6.7), 3.36 (1H, dd, *J* 10.9, 2.7, H-15eq), 1.85–1.70 (6H, m), 1.62–1.58 (2H, m), 1.52–1.39 (4H, m), 1.34–1.24 (8H, m), 1.16–1.00 (44H, m, including 2 × Si(CH(CH_3)$_2$)$_3$ and 2 × Si(CH(CH_3)$_2$)$_3$); δ_C (150 MHz, $CDCl_3$) 96.7, 95.7, 70.7, 70.6, 67.2, 67.1, 66.5 (C-14), 63.0 (C-15), 31.7, 31.1, 29.3, 28.6, 28.4, 28.0, 25.3, 22.5, 18.1, 18.04, 18.0, 17.9, 17.9, 14.0, 11.93, 11.91; *m*/*z* (CI) 702.8 (MNH_4^+, 100%), 539.7 (95); HMRS (CI) calc. for $C_{38}H_{77}O_6Si_2$ (MH): 685.5259; found 685.5222. Anal. calc. for $C_{38}H_{76}O_6Si_2$: C, 66.61; H, 11.18; found C, 66.83; H, 11.02%.

(2*R*,6*R*,7*S*,9*R*,14*S*)-14-Phenyl-2,9-bis(triisopropylsilyloxymethyl)-1,8,13,16-tetraoxadispiro[5.0.5.4]hexadecane 12. The title compound **12** was obtained as a colourless oil in 78% yield following general procedure A and using benzene-1,2-diol as the diol and (*R*,*R*)-**1** as the bi(dihydropyran); $[\alpha]_D^{27}$ −16.5 (c 0.57, $CHCl_3$); IR (thin film) ν_{max} 2942, 2865, 1606, 1496, 1463, 1383, 1365, 1277, 1256, 1205, 1174, 1112, 1069, 1040, 1013 cm^{-1}; δ_H (600 MHz; $CDCl_3$) 7.39 (2H, d, *J* 7.4, aromatics), 7.33 (2H, t, *J* 7.6, aromatics), 7.28 (1H, t, *J* 7.3, aromatic), 5.02 (1H, dd, *J* 10.8, 2.7, H-14), 3.84 (1H, t, *J* 10.7, H-2a), 3.82 (1H, t, *J* 4.7), 3.79–3.72 (3H, m), 3.61–3.53 (3H, m), 1.91 (1H, br d, *J* 15.3), 1.88–1.78 (3H, m), 1.71 (1H, br d, *J* 13.0), 1.68–1.58 (3H, m), 1.54–1.47 (2H, m), 1.20–1.02 (44H, m, includes 2 × Si(CH-(CH_3)$_2$)$_3$ and 2 × Si(CH(CH_3)$_2$)$_3$); δ_C (150 MHz, $CDCl_3$) 128.1, 127.6 and 126.5 (aromatics), 97.8 and 95.7 (C-6, C-7), 71.0 (C-2, C-9), 68.7 (C-14), 67.2 and 67.1 (2 × -CH_2-OTIPS), 63.8 (C-15), 28.5, 28.2, 27.8, 27.3, 18.2, 18.0, 11.9; *m*/*z* (CI) 694.6 (MNH_4^+, 52%), 539.6 (35), 304.3 (70), 243.2 (50), 148.1 (62), 104.1 (70), 72.2 (100); HMRS (CI) calc. for $C_{38}H_{72}NO_6Si_2$ (MNH_4): 694.4898; found 694.4900. Anal. calc. for $C_{38}H_{68}$-O_6Si_2: C, 67.41; H, 10.12; found C, 67.82; H, 10.21%.

(2*S*,6*S*,7*R*,9*S*,14*R*)-14-Phenyl-2,9-bis(triisopropylsilyloxymethyl)-1,8,13,16-tetraoxadispiro[5.0.5.4]hexadecane 23. The title compound **23** was obtained as a colourless oil in 80% yield following general procedure A and using benzene-1,2-diol as the diol and (*S*,*S*)-**1** as the bi(dihydropyran). All data identical to compound **12** except $[\alpha]_D^{31}$ +17.4 (*c* 0.55, $CHCl_3$).

General procedure B: Removal of the triisopropylsilyloxy (TIPS) group

A mixture of the triisopropylsilyloxy protected dispiroketal (3 mmol, 1 eq.) and TBAF (10.9 ml (1.1 M in THF), 12 mmol, 4 eq.) in THF (28 ml) was stirred at room temperature for 12 hours. The solvent was removed *in vacuo* and the residue was purified by flash column chromatography (petrol 50%, ethyl acetate 50%) to give the deprotected dispiroketal diol.

(1*S*,2*S*,2′*R*,2″*R*,6′*R*,6″*R*)-1,2-*O*-[6′,6″-Bis(hydroxymethyl)-3′,3″,4′,4″,5′,5″,6′,6″-octahydro-2′,2″-bi(2*H*-pyran-2′,2″diyl)]-cyclohexane-1,2-diol 10. Compound **10** was obtained as a white amorphous solid in 96% yield following procedure B and using **9** as the starting material; $[\alpha]_D^{25}$ −80.0 (*c* 0.40, $CHCl_3$); IR (thin film) ν_{max} 3427 (br OH), 2935, 2856, 1627 (br), 1554, 1275, 1205, 1173 cm^{-1}; δ_H (600 MHz; $CDCl_3$) 3.78–3.70 (2H, m, H-6′, H-6″), 3.56–3.46 (6H, m, includes at 3.54 (2H, dd, *J* 11.3, 3.3), H-1, H-2, 2 × -CH_2OH), 1.85 (2H, qt, *J* 13.1, 3.8, H-4′ax,

H-4″ax), 1.80–1.71 (6H, m, H-3′eq, H-3″eq, H-4eq, H-5eq, H-3eq, H-6eq), 1.59 (2H, br d, *J* 13.0, H-4′eq, H-4″eq), 1.51–1.43 (2H, m, H-5′eq, H-5″eq), 1.44 (2H, dd, *J* 13.6, 4.6, H-3′ax, H-3″ax), 1.36–1.20 (4H, m, H-4ax, H-5ax, H-3ax, H-6ax), 1.21 (2H, qd, *J* 12.7, 3.6, H-5′ax, H-5″ax); δ_C (150 MHz, $CDCl_3$) 97.1 (C-2′, C-2″), 70.9 (C-1, C-2), 70.4 (C-6′, C-6″), 66.0 (2 × -*C*H_2OH), 29.7 (C-3, C-6), 28.4 (C-3′, C-3″), 26.3 (C-5′, C-5″), 24.2 (C-4, C-5), 17.8 (C-4′, C-4″); *m*/*z* (CI) 360 (MNH_4^+, 73%), 244 (90), 227 (100), 148 (25), 134 (14); HMRS (CI) Calc. for $C_{18}H_{34}NO_6$ (MNH_4): 360.2386; found 360.2386.

(1*R*,2*R*,2′*S*,2″*S*,6′*S*,6″*S*)-1,2-*O*-[6′,6″-Bis(hydroxymethyl)-3′,3″,4′,4″,5′,5″,6′,6″-octahydro-2′,2″-bi(2*H*-pyran-2′,2″-diyl)]-cyclohexane-1,2 diol 22. Compound **22** was obtained as a white amorphous solid in 100% yield following procedure B and using **21** as the starting material. All data identical to compound **10** except $[\alpha]_D^{31}$ +82.0 (*c* 0.71, $CHCl_3$).

(2*R*,6*R*,7*S*,9*R*,14*S*)-14-Benzyloxymethyl-2,9-bis(hydroxymethyl)-1,8,13,16-tetraoxadispiro[5.0.5.4]hexadecane 16. Compound **16** was obtained as a colourless oil in 100% yield following procedure B and using **15** as the starting material; $[\alpha]_D^{28}$ −55.6 (*c* 1.24, $CHCl_3$); IR (thin film) ν_{max} 3449, 2932, 1612, 1454, 1366, 1206, 1098, 1047 cm^{-1}; δ_H (600 MHz; $CDCl_3$) 7.35–7.26 (5H, m, aromatics), 4.55 (1H, d, *J* 12.1, Ph-C$H_a$$H_b$), 4.54 (1H, d, *J* 12.1, Ph-C$H_a$$H_b$), 4.19–4.15 (1H, m), 3.83–3.77 (3H, m), 3.63–3.59 (2H, m), 3.55–3.46 (5H, m), 2.47 (1H, br, OH), 2.32 (1H, br, OH), 1.90–1.24 (12H, m); δ_C (100 MHz; $CDCl_3$) 137.9, 128.4, 127.7 and 127.7 (aromatics), 96.9 and 95.8 (C-6, C-7), 73.5, 70.8 and 70.7 (C-2, C-9), 69.8, 66.1, 65.9, 66.0 (C-14), 60.5, 28.2, 28.1, 26.1, 26.1, 17.8 and 17.7 (C-3, C-4, C-5, C-10, C-11, C-12); *m*/*z* (CI) 426 (MNH_{4+}, 100%), 244 (31), 227 (47), 148 (20); HRMS (CI) calc. for $C_{22}H_{36}O_7N$ (MNH_4): 426.2492; found 426.2492.

(2*S*,6*S*,7*R*,9*S*,14*R*)-14-Hexyl-2,9-bis(hydroxymethyl)-1,8,13,16-tetraoxadispiro[5.0.5.4]hexadecane 19. Compound **19** was obtained as a colourless oil in 100% yield following procedure B and using **18** as the starting material; $[\alpha]_D^{28}$ +76.2 (*c* 1.55, $CHCl_3$); IR (thin film) ν_{max} 3449 (br OH), 2931, 2870, 2241, 1456, 1440, 1379, 1358, 1278, 1236, 1205, 1177, 1103, 1047, 1012 cm^{-1}; δ_H (600 MHz; $CDCl_3$) 3.92–3.87 (1H, m, H-14), 3.82–3.75 (2H, m, H-9, H-2), 3.65–3.55 (3H, m, 2 × -C$H_a$$H_b$-OH, H-15ax), 3.54–3.45 (2H, m, 2 × -C$H_a$$H_b$-OH), 3.41 (1H, dd, *J* 11.2, 2.8, H-15eq), 2.11 (2H, br s, 2 × OH), 1.90–1.72 (4H, m), 1.68–1.62 (2H, m), 1.54–1.39 (6H, m), 1.35–1.24 (11H, m), 0.88 (3H, t, *J* 6.8, -CH_3); δ_C (150 MHz; $CDCl_3$) 95.6 and 95.7 (C-6, C-7), 70.6 (C-2, C-9), 66.6 (C-14), 66.1 and 66.0 (2 × -*C*H_2-OH), 63.0 (C-15), 31.7, 31.1, 29.3, 28.4, 28.2, 26.3, 26.2, 25.2, 22.6, 17.8, 17.7, 14.0; *m*/*z* (CI) 390 (MNH_4^+, 100%), 244 (90), 227 (100), 148 (62); HMRS (CI) calc. for $C_{20}H_{40}NO_6$ (MNH_4): 390.2856; found 390.2850.

(2*S*,6*S*,7*R*,9*S*,14*R*)-2,9-Bis(hydroxymethyl)-14-phenyl-1,8,13,16-tetraoxadispiro[5.0.5.4]hexadecane 13. Compound **13** was obtained as a white amorphous solid in 93% yield following procedure B and using **12** as the starting material; $[\alpha]_D^{28}$ +35.1 (*c* 0.94, $CHCl_3$); IR (thin film) ν_{max} 3424 (br OH), 2946, 1496, 1453, 1358, 1276, 1204, 1174, 1102, 1042 cm^{-1}; δ_H (600 MHz; $CDCl_3$) 7.39–7.27 (5H, m, aromatics), 4.99 (1H, dd, *J* 10.9, 3.0, H-14), 3.87–3.79 (3H, m, includes at 3.81 (1H, t, *J* 11.2, H-15ax), H-2, H-9), 3.68–3.61 (3H, m, H-15eq, 2 × -C$H_a$$H_b$-OH), 3.57–3.52 (2H, m, 2 × -C$H_a$$H_b$-OH), 2.11 (1H, dd, *J* 7.7, 5.3, OH), 2.05 (1H, dd, *J* 8.2, 4.8, OH), 1.93–1.81 (4H, m, 2 × -CH_2-), 1.71–1.60 (2H, m, -CH_2-), 1.60–1.46 (4H, m, 2 × -CH_2-), 1.35–1.27 (2H, m, -CH_2-); δ_C (150 MHz; $CDCl_3$) 137.9, 128.4, 128.0 and 126.4 (aromatics), 97.1 and 95.5 (C-6, C-7), 70.7 and 70.5 (C-2, C-9), 68.7 (C-14), 66.1 (2 × -CH_2-OH), 63.7 (C-15), 28.4, 28.2, 26.1, 26.1, 17.8 and 17.7 (all -CH_2-); *m*/*z* (CI) 384 (MNH_4^+, 31%), 244 (25), 227 (32), 148 (100), 138 (45), 132 (32), 122 (35), 120 (40), 118 (38); HMRS (CI) calc. for $C_{20}H_{32}NO_6$ (MNH_4): 382.2230; found 382.2233.

(2*R*,6*R*,7*S*,9*R*,14*S*)-2,9-Bis(hydroxymethyl)-14-phenyl-1,8,13,16-tetraoxadispiro[5.0.5.4]hexadecane 24. Compound **24** was obtained as a white solid in 94% yield following procedure B and using **23** as the starting material. All data identical to compound **13** except $[\alpha]_D^{28}$ −36.4 (*c* 1.00, $CHCl_3$).

(2*R*,6*S*,7*S*,9*R*,14*S*)-14-Benzyloxymethyl-2,9-bis(triisopropylsilyloxymethyl)-1,8,13,16-tetraoxadispiro[5.0.5.4]hexadecane 15. To a stirred solution of **25** (170.6 mg, 0.27 mmol) in a solvent mixture of THF (3.0 ml) and DMF (1.0 ml) were added sodium hydride (20 mg, 0.50 mmol, 60% in mineral oil) at 0 °C followed by benzyl bromide (71 μl, 0.60 mmol). The resulting mixture was allowed to warm up to room temperature and stirred for 6 h. The reaction mixture was quenched with a saturated aq. solution of ammonium chloride. The phases were separated and the aqueous layer was extracted with ether (3 × 5 ml). The combined organic extracts were washed with brine, dried over $MgSO_4$ and concentrated to give an oily residue. Purification by flash chromatography (ether 10%, petrol 90%) afforded the title compound **15** (198.5 mg, 100%); $[\alpha]_D^{27}$ −23.7 (*c* 0.76, $CHCl_3$); IR (thin film) ν_{max} 2942, 2865, 1605, 1462, 1106, 1043, 1014 cm^{-1}; δ_H (600 MHz; $CDCl_3$) 7.39–7.26 (5H, m, aromatics), 4.57 (1H, d, *J* 12.1, Ph-C$H_a$$H_b$-), 4.55 (1H, d, *J* 12.1, Ph-C$H_a$$H_b$-), 4.23–4.21 (1H, m), 3.82–3.72 (5H, m), 3.55–3.42 (5H, m), 1.85–1.57 (8H, m), 1.48–1.41 (2H, m), 1.20–1.04 (44H, m); δ_C (100 MHz; $CDCl_3$) 138.4, 128.3, 127.5 (aromatics), 96.9 and 95.9 (C-6, C-7), 73.4, 70.9 and 70.7 (C-2, C-9), 70.2, 67.2 and 67.1 (-*C*H_2-OTIPS), 65.9 (C-14), 60.7, 28.4, 28.3, 27.8, 27.7, 18.1 and 18.0 (C-3, C-4, C-5, C-10, C-11, C-12), 18.0 (Si(CH(*C*H_3)$_2$)$_3$), 12.0 (Si(*C*H(CH$_3$)$_2$)$_3$); *m*/*z* (CI) 738 (MNH_4^+, 100%), 540 (33), 304 (28); HRMS (CI) calc. for $C_{40}H_{76}O_7NSi_2$ (MNH_4): 738.5160; found 738.5160.

General procedure C: Deprotection of the dispiroketal

The deprotection was achieved in a three-step protocol: Swern oxidation,[11] treatment with samarium iodide and acylation with acetic anhydride. Dimethyl sulfoxide (0.23 ml, 3.20 mmol) was added to a solution of oxalyl dichloride (0.13 ml, 1.54 mmol) in DCM (4 ml) at −78 °C. After stirring at −78 °C for 45 min, a solution of the diol (0.31 mmol) in DCM (1.5 ml) was added. After stirring for 45 min at −78 °C, triethylamine (0.47 ml, 3.38 mmol) was added and the resulting mixture was warmed, whilst stirring, from −78 °C to room temperature over 12 hours. The mixture was then treated with brine (3 ml) and diluted with DCM (20 ml). The phases were separated and the aqueous phase was extracted with DCM (4 × 20 ml). The organic phases were dried over $MgSO_4$ and concentrated. The crude aldehyde was used without purification for the next step. To a solution of freshly prepared samarium iodide (4.3 mmol) in THF (150 ml) and methanol (30 ml) was added a solution of the crude aldehyde in THF (5 ml) and methanol (1 ml). After complete disappearance of the initial blue colour (5–15 min), the solvents were concentrated *in vacuo* to afford a crude residue containing the diol. This residue was dried under vacuum then treated with a mixture of acetic anhydride (1.5 ml, 15.4 ml), triethylamine (4.3 ml) and DMAP in THF (10 ml). After 24 hours of stirring at room temperature, the residue was diluted with ether (100 ml) and washed with aq. HCl (70 ml (0.5 M solution)). The phases were separated and the aqueous layer was extracted with ether (4 × 50 ml). The organic phases were combined, dried over $MgSO_4$ and concentrated to afford the crude diacetate. The product was purified by flash chromatography (petrol 90%, ether 10%).

(1*R*,2*R*)-*trans*-1,2-Diacetoxycyclohexane (*R*,*R*)-11. The title compound (*R*,*R*)-**11** was obtained as a colourless oil in 73%

yield from **22** following procedure C; $[a]_D^{33}$ −10.7 (*c* 0.58, $CHCl_3$); IR (thin film) ν_{max} 3458, 2943, 2866, 1738 (CO), 1452, 1368, 1231, 1158, 1042 cm^{-1}; δ_H (600 MHz; $CDCl_3$) 4.82–4.78 (2H, m, H-1, H-2), 2.07–2.00 (8H, m, H-3a, H-6a, 2 × $COCH_3$), 1.75–1.68 (2H, m, H-4a, H-5a), 1.45–1.32 (4H, m, H-3b, H-4b, H-5b, H-6b); δ_C (150 MHz, $CDCl_3$) 170.4 (2 × *C*O), 73.7 (C-1, C-2), 30.1 (C-3, C-6), 23.4 (C-4, C-5), 21.1 (2 × CO*C*H_3); *m*/*z* (CI) 218 (MNH_4^+, 100%), 77 (18); HMRS (CI) calc. for $C_{10}H_{20}NO_4$ (MNH_4): 218.1392; found 218.1394. Anal. calc. for $C_{10}H_{16}O_4$: C, 59.98; H, 8.05; found C, 60.86; H, 8.19%.

GC anal. (90 °C): A racemic sample showed two peaks after 24.6 and 25.7 min. Compound (*R*,*R*)-**11** showed two peaks after 24.6 (98%) and 25.7 (2%) min: ee = 96%.

(1*S*,2*S*)-*trans*-1,2-Diacetoxycyclohexane (*S*,*S*)-11. The title compound (*S*,*S*)-**11** was obtained as a colourless oil in 94% yield from **10** following procedure C. All data identical to compound (*R*,*R*)-**11** except $[a]_D^{31}$ +12.0 (*c* 0.96, $CHCl_3$).

GC anal. (90 °C): A racemic sample showed two peaks after 24.6 and 25.7 min. Compound (*S*,*S*)-**11** showed two peaks after 24.6 (1.3%) and 25.9 (98.7%) min: ee = 97%.

(*R*)-1,2-Diacetoxy-1-phenylethane (*R*)-14. The title compound (*R*)-**14** was obtained as a colourless oil in 91% yield from **24** following procedure C; $[a]_D^{31}$ −69.4 (*c* 1.03, $CHCl_3$); IR (thin film) ν_{max} 2955, 1744 (CO), 1496, 1455, 1372, 1113, 1045 cm^{-1} δ_H (600 MHz; $CDCl_3$) 7.39–7.31 (5H, m, aromatics), 6.02 (1H, dd, *J* 8.0, 3.8, H-1), 4.34 (1H, dd, *J* 11.9, 3.8, H-2a), 4.29 (1H, dd, *J* 11.9, 8.1, H-2b), 2.12 (3H, s, CO*C*H_3), 2.06 (3H, s, CO*C*H_3); δ_C (150 MHz, $CDCl_3$) 170.6 and 170.0 (*C*O), 136.5, 128.6 and 126.7 (aromatics), 73.30 (C-1), 66.1 (C-2), 21.05 and 20.72 (CO*C*H_3); *m*/*z* (CI) 240 (M^+, 100%), 163 ($[M - Ph]^+$, 36), 77 (15); HMRS (CI) calc. for $C_{12}H_{18}NO_4$ (MNH_4): 240.1236; found 240.1233. Anal. calc. for $C_{12}H_{14}O_4$: C, 64.85; H, 6.35; found C, 64.50; H, 6.41%.

GC anal. (95 °C): A racemic sample showed two peaks after 51.3 and 52.9 min. Compound (*R*)-**14** showed one peak after 53.2 min: ee > 95%.

(*S*)-1,2-Diacetoxy-1-phenylethane (*S*)-14. The title compound (*S*)-**14** was obtained as a colourless oil in 100% yield from **13** following procedure C. All data identical to compound (*R*)-**14** except $[a]_D^{31}$ +69.0 (*c* 1.17, $CHCl_3$).

GC anal. (95 °C): A racemic sample showed two peaks after 51.3 and 52.9 min. Compound (*S*)-**14** showed two peaks after 51.3 (97.5%) and 52.6 (2.5%) min: ee = 95%.

(*R*)-1,2-Diacetoxyoctane (*R*)-20. The title compound (*R*)-**20** was obtained as a colourless oil in 94% yield from **19** following procedure C; $[a]_D^{31}$ +2.4 (*c* 0.41, $CHCl_3$); IR (thin film) ν_{max} 2931, 2859, 1744 (CO), 1458, 1371, 1228, 1126, 1047 cm^{-1}; δ_H (600 MHz; $CDCl_3$) 5.09–5.04 (1H, m, H-2), 4.22 (1H, dd, *J* 11.9, 3.2, H-1a), 4.03 (1H, dd, *J* 11.9, 6.6, H-1b), 2.07 (3H, s, CO*C*H_3), 2.07 (3H, s, CO*C*H_3), 1.60–1.54 (2H, m, -CH_2-), 1.35–1.24 (8H, m, 4 × -CH_2-), 0.88 (3H, t, *J* 6.8, CH_3); δ_C (150 MHz; $CDCl_3$) 170.8 and 170.7 (*C*O), 71.6 (C-2), 65.1 (C-1), 31.65, 30.7, 29.0, 25.0 and 22.5 (all -CH_2-), 21.0 and 20.7 (CO*C*H_3), 14.0 (CH_3); *m*/*z* (CI) 248 (M^+, 100%), 77 (61); HMRS (CI) calc. for $C_{12}H_{26}NO_4$ (MNH_4): 248.1862; found 248.1861. Anal. calc. for $C_{12}H_{22}O_4$: C, 62.58; H, 9.63; found C, 62.68; H, 9.54%.

GC anal. (105 °C): A racemic sample showed two peaks after 39.1 and 40.2 min. Compound (*R*)-**20** showed one peak after 39.1 min: ee > 95%.

(*S*)-3-Benzyloxy-1,2-diacetoxypropane (*S*)-17. The title compound (*S*)-**17** was obtained as a colourless oil in 93% yield from **16** following procedure C; $[a]_D^{31}$ +16.2 (*c* 1.01, $CHCl_3$); IR (thin film) ν_{max} 3063, 2953, 2866, 1744 (CO), 1496, 1454, 1372, 1225, 1090, 1048, 1020 cm^{-1}; δ_H (600 MHz; $CDCl_3$) 7.37–7.27 (5H, m, aromatics), 5.24–5.19 (1H, m, H-2), 4.56 (1H, d, *J* 12.1, Ph-C$H_a$$H_b$), 4.52 (1H, d, *J* 12.1, Ph-C$H_a$$H_b$), 4.34 (1H, dd, *J* 11.9, 3.8, H-1a), 4.19 (1H, dd, *J* 6.4, H-1b), 3.62–3.57 (2H, m, H-3), 2.08 (3H, s, CO-CH_3), 2.04 (3H, s, COCH_3); δ_C (150 MHz, $CDCl_3$) 170.6 and 170.3 (2 × *C*O), 137.6, 128.4, 127.8 and 127.6 (all aromatics), 73.3 (Ph-CH_2-O), 70.2 (C-2), 68.1, (C-3), 62.8 (C-1), 21.0 and 20.7 (2 × CO*C*H_3); *m*/*z* (CI) 284 (MNH_4^+, 100%), 106 (37), 77 (100); HMRS (EI) calc. for $C_{14}H_{18}O_5$ (M): 266.1154; found 266.1155. Anal. calc. for $C_{14}H_{18}O_5$: C, 63.15; H, 6.81; found C, 63.08; H, 6.88%.

HPLC anal.: A racemic sample showed two peaks after 22.0 and 23.8 min. Compound (*S*)-**17** showed two peaks after 22.0 (98.5%) and 23.7 min (1.5%): ee = 97%.

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References

1 Dispiroketals in Synthesis. Part 23: J. E. Innes, P. J. Edwards and S. V. Ley, *J. Chem. Soc.*, *Perkin Trans 1*, 1997, 795.
2 For a comprehensive review of dispiroketal chemistry see: S. V. Ley, R. Downham, P. J. Edwards, J. E. Innes and M. Woods, *Contemp. Org. Synth.*, 1995, **2**, 365.
3 P. J. Edwards, D. A. Entwistle, C. Genicot, K. S. Kim and S. V. Ley, *Tetrahedron Lett.*, 1994, **35**, 7443.
4 P. J. Edwards, D. A. Entwistle, S. V. Ley, D. Owen and E. J. Perry, *Tetrahedron*: *Asymmetry*, 1994, **5**, 553.
5 P. J. Ewards, D. A. Entwistle, C. Genicot, S. V. Ley and G. Visentin, *Tetrahedron*: *Asymmetry*, 1994, **5**, 2609.
6 S. V. Ley, S. Mio and B. Meseguer, *Synlett*, 1996, 787.
7 D. J. Dixon, S. V. Ley and E. W. Tate, *J. Chem. Soc.*, *Perkin Trans 1*, 1998, 3125; R. J. K. Taylor, *Organocopper Regents*, Oxford University Press, Oxford, 1994, and references cited therein.
8 M. Schlosser and S. Stunk, *Tetrahedron Lett.*, 1984, **25**, 741; L. Lochmann, J. Pospil and D. Lim, *Tetrahedron Lett.*, 1966, 257.
9 S. Ghosal, G.P. Luke and K.S. Kyler, *J. Org. Chem.*, 1987, **52**, 429.
10 For similar samarium(II) iodide induced cleavage of α-alkoxy carbonyl cleavage see: G. Molander, *Reactions with samarium(II) iodide*, Organic Reactions, Wiley, 1994, **46**, 211 and H. B. Kagan and J. L. Namy, *Tetrahedron*, 1986, **42**, 6573.
11 K. Omura and D. Swern, *Tetrahedron*, 1978, **34**, 1651; A. J. Mancuso and D. Swern, *Synthesis*, 1981, 165.

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