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Synthesis of the spiroacetal fragment of broussonetine H

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Abstract—(2*S*,6*S*)-2-(3-Bromopropyl)-1,7-dioxaspiro[5.5]undecane **3** was prepared by the addition of the acetylide derived from (4*S*)-4-benzyloxy-7-*tert*-butyldiphenylsilyloxyhep-1-yne **8** to δ-valerolactone **6** followed by treatment with hydrogen and palladium on charcoal which effected hydrogenation of the alkyne, hydrogenolysis of the benzyl ether and subsequent spiroacetal formation. The (4*S*)-stereochemistry in acetylene **8** was established by addition of trimethylsilylacetylene **10** to (2*S*)-epoxide **9**, which in turn is derived from L-glutamic acid **11**.

1. Introduction

The broussonetines and broussonetinines are a family of alkaloids characterized by a hydroxylated pyrrolidine moiety (Fig. 1(a)).[1] To-date, Kusano and co-workers have reported the isolation and structure determination of 30 congeners from the hot water extracts of the bark of *Broussonetia kazinoki* SIEB (Moraceae),[2] a deciduous tree distributed throughout Asia. The cortex is a raw material for handmade Japanese paper known as 'washi', and various parts of the tree have been used in Chinese folk medicine. The isolated compounds have demonstrated glycosidase inhibition properties, which is hardly surprising given the structural resemblance to 2,5-dideoxy-2,5-imino-D-mannitol (2,5-dihydroxy-methyl-3,4-dihydroxypyrrolidine, DMDP).[3] Most of the broussonetines have 2*R*,3*R*,4*R* and 5*R* configurations around the periphery of the pyrrolidine ring, although a subset have the 3*S* configuration. Diversity arises in the nature of the thirteen carbon 'side-chain' attached at C5. Biosynthetic studies have led to the proposal that C2, C3 and the CH_2OH group at C2 are derived from D-serine and the remaining carbons arise from palmitoyl-CoA[4] via a pathway akin to that involved in the assembly of sphingosine. One of the more exotic examples is broussonetine H (**1**)[2c] (Fig. 1(b)), which features a 1,6-dioxaspiro-[5.5]undecane unit. Given the individual importance of both spiroacetals[5] and hydroxylated pyrrolidines[6,7] we were attracted to broussonetine H (**1**) as a synthetic target.[8] We report herein, an enantioselective synthesis of the spiroacetal domain.

2. Results and discussion

We embarked upon a synthetic strategy that would lead to the rapid assembly of broussonetine H and be amenable to the synthesis of natural and novel analogues. Thus, our primary disconnection involved cleavage of the C6–C7 bond to yield a suitably protected prolinal derivative **2** (where P is an unspecified protecting group) and alkyl bromide **3** (Scheme 1). In a forward sense, it was envisaged that addition of the Grignard reagent derived from **3** to the aldehyde in compound **2**, would amalgamate the two fragments. The stereochemistry at C6 would be generated during this key step and we recognized that the inherent stereochemistry in the two fragments will influence this.

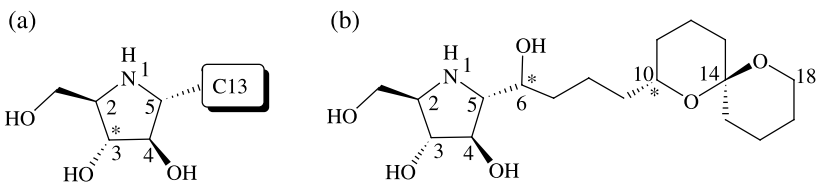

Figure 1. (a) General structure; (b) broussonetine H (**1**).

Keywords: broussonetines; spiroacetal fragment; glutamic acid.
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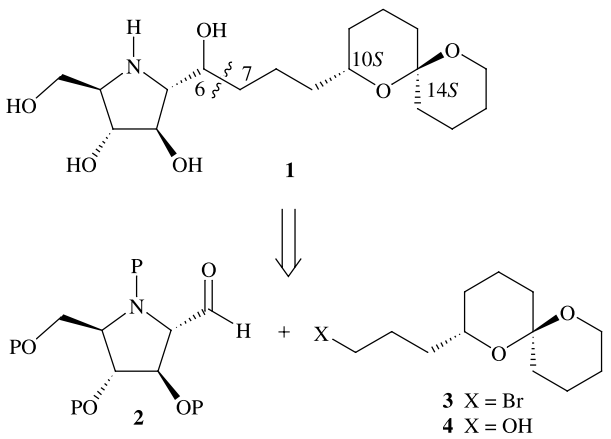


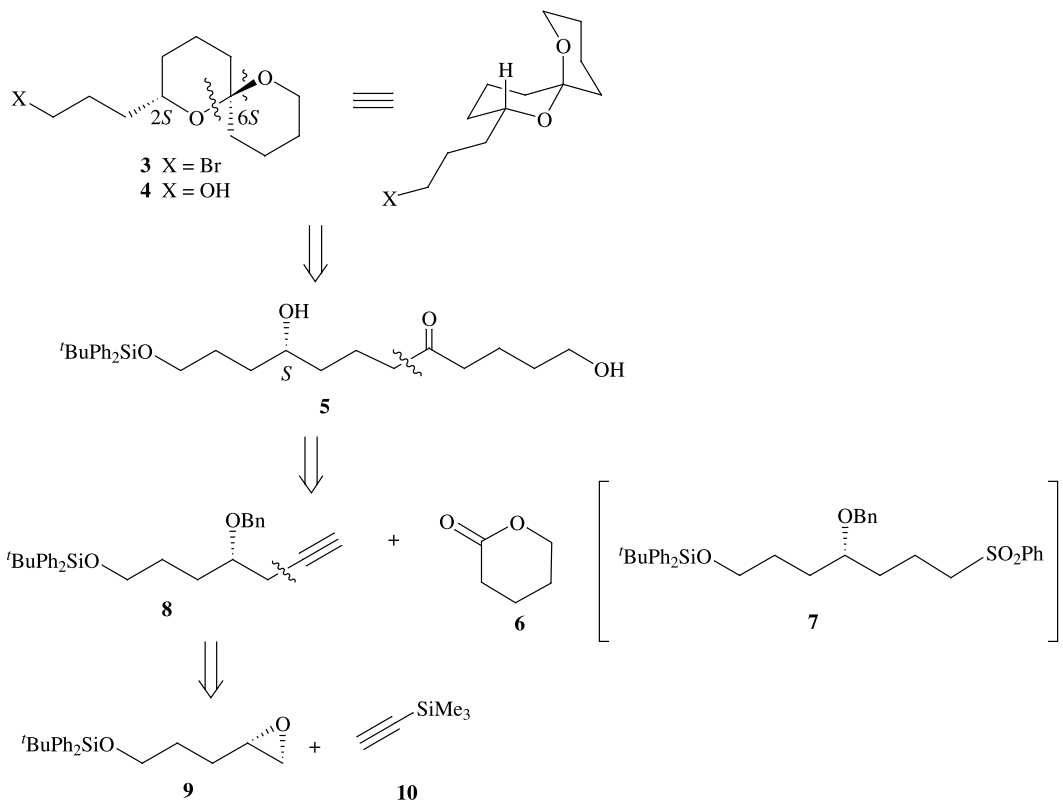
Scheme 1. Retrosynthetic analysis of broussonetine H (**1**).

While the absolute configuration at C6 in broussonetine H has not been reported, the corresponding stereogenic centre in broussonetines K and L,[2e] and in broussonetines R, S and T,[2h] has been determined to be *R*, using a modification of the Mosher method.

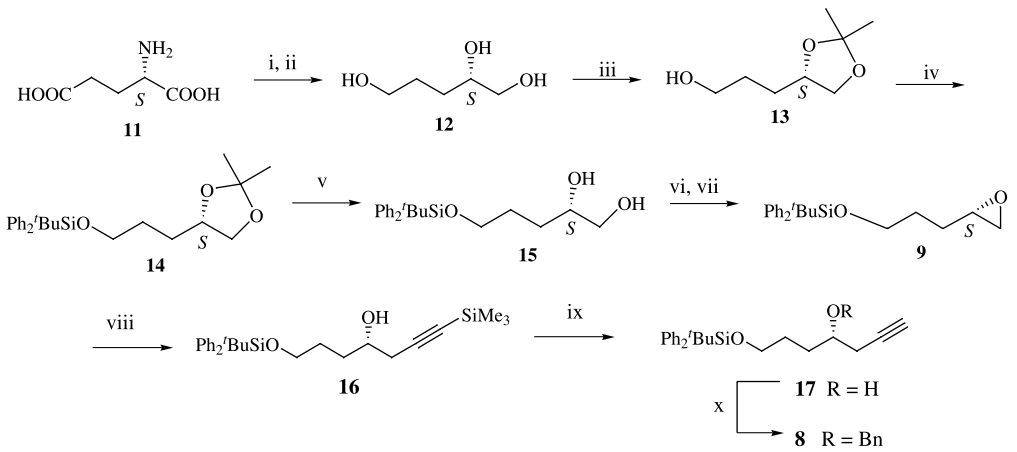
Further retrosynthetic analysis of the spiroacetal fragment is illustrated in Scheme 2. The absolute configuration is not known, but it is reasonable to assume that there will be a favoured conformation in which there is a lone pair of electrons antiperiplanar to each C–O bond, thereby gaining maximum stability from the anomeric effect.[9] The 2*S*,6*S* configuration (depicted in Scheme 2) permits this, although the natural configuration might equally well correspond to the enantiomer (2*R*,6*R*). We have arbitrarily pursued a synthesis of the 2*S*,6*S* isomer, based on the relative availability of starting materials (L-glutamic acid vs D-glutamic acid, vide supra). Disconnection of the spiroacetal functionality leads to acyclic precursor **5**. It was anticipated that the existing stereogenic centre in **5** would govern the formation of the new stereogenic centre at C6, resulting in the 2*S*,6*S* stereochemistry of the target molecule. Addition of an anion derived from either sulfone **7** or acetylene **8**[10] to δ-valerolactone was expected to assemble the carbon skeleton.

The racemic sulfone (±)-**7** was prepared and the anion generated, as evidenced by successful incorporation of deuterium, upon quenching with D_2O. Unfortunately, addition of the anion derived from (±)-**7** to δ-valerolactone, and other electrophiles, was unsuccessful.[11]

Our attention therefore quickly turned to the formation of acetylene **8**. Initial studies with racemic material[11,12] were encouraging and so **8** was prepared in optically active form via epoxide **9**[13] (Scheme 2). Epoxide **9** has been prepared on a number of occasions and the route we adopted is detailed in Scheme 3. Diazotization of L-glutamic acid **11** affords a γ-lactone carboxylic acid[14] which can be reduced to triol **12**.[15] The availability of triol **12** in our laboratory encouraged us to utilize this intermediate in the preparation of epoxide **9**. The 1,2-diol could be protected as an acetonide to give compound **13**.[16] The primary alcohol was protected as its *tert*-butyldiphenylsilyl ether (compound **14**) then hydrolysis of the acetonide gave diol **15**.[16b–d] The diol was converted to epoxide **9** in a two-step procedure, following the conditions reported by Yuasa et al.[16b,c] The lithium acetylide generated from trimethylsilylacetylene **10** reacted with epoxide **9**, under Yamaguchi conditions,[17] to



Scheme 2. Retrosynthetic analysis of the spiroacetal fragment **3**.



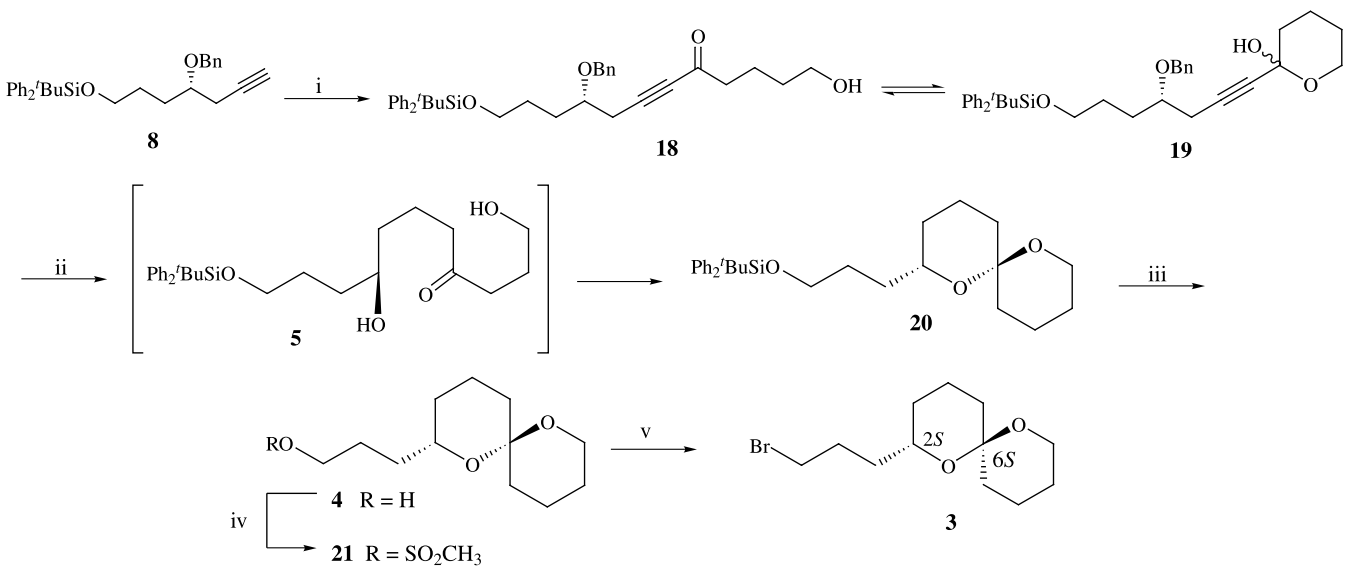
Scheme 3. *Reagents, conditions and yields*. (i) $NaNO_2$, HCl, H_2O, 0°C, 54%; (ii) $LiAlH_4$, THF, reflux, 47%; (iii) *p*-toluenesulfonic acid, acetone, 85%; (iv) $^tBuPh_2SiCl$, imidazole, CH_2Cl_2, 87%; (v) PPTS, MeOH, 72%; (vi) TsCl, DMAP, NEt_3, CH_2Cl_2, 95%; (vii) NaH, 18-crown-6, THF, 86%; (viii) $HCCSiMe_3$, ^{n}BuLi, $BF_3{\cdot}OEt_2$, THF, −78°C; (ix) NaOMe, MeOH, 94%; (x) NaH, BnBr, $^nBu_4NI$, DMF, 88%.

give alcohol **16**. The trimethylsilyl group in acetylene **16** was then removed to give **17**, and the hydroxyl group protected as a benzyl ether, to afford compound **8**.

The elaboration of acetylide **8** to the spiroacetal target **3** is illustrated in Scheme 4. The acetylide anion derived from compound **8** was reacted with δ-valerolactone (**6**) to afford a mixture of keto-alcohol **18** and hemiacetal **19** in good yield. This mixture was treated with hydrogen in the presence of 10% palladium on charcoal. This was expected to simultaneously hydrogenate the triple bond and effect hydrogenolysis of the benzyl ether to give compound **5**. A single product was obtained from the hydrogenation in 86% yield, which, to our initial disappointment, was not compound **5**. Under the reaction conditions, compound **5** had spontaneously assembled into spiroacetal **20**. It appears that a trace of HCl present in the catalyst is sufficient to promote the cyclization. We had anticipated that a second, acid-catalyzed step would be required for this transformation. The silyl ether protecting group was removed to afford alcohol **4**. Direct conversion of the primary alcohol **4** to the corresponding alkyl bromide **3** proved low yielding (PPh_3, CBr_4, CH_2Cl_2, 10% yield),[11] however, the two-step procedure (Scheme 4) proved more efficient.

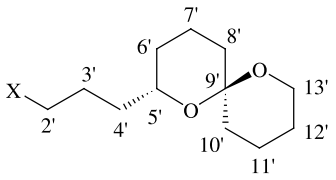
Comparison of the NMR data of compound **3** with that reported by Shibano et al. for broussonetine H[2c] supports the successful formation of the 1,6-dioxaspiro[5.5]undecane ring system, as summarized in Table 1, where the numbering system of the broussonetines has been adopted for clarity.[18]

The Mosher ester derivative of compound **4** was prepared[19] and ^{19}F NMR analysis established that the enantiomeric excess was only 70%. This forced us to look back over the synthesis to ascertain where the stereochemical integrity had been lost. Comparison of $[\alpha]_D$ values with those reported previously in the literature (see Section 4) for compounds **9** and **13** suggested that their e.e.'s were in the order of 80%, i.e. considerable racemization had taken place during the conversion of L-Glu **11** to compound **13**. Herdeis has reported that the lactone acid (intermediate in the

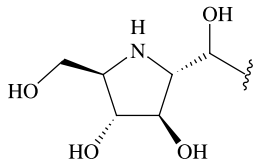


Scheme 4. *Reagents, conditions and yields*. (i) ^{n}BuLi, $BF_3{\cdot}OEt_2$, THF, −78°C, then δ-valerolactone **6**, 86%; (ii) H_2, Pd/C, EtOAc, 86%; (iii) $^nBu_4NF$, THF, 96%; (iv) MsCl, DMAP, pyridine, 78%; (v) LiBr, acetone, reflux, 85%.

Table 1. ^{13}C NMR chemical shifts



1 X =



3 X = Br

Carbon	Broussonetine H (**1**) δ (pyridine-d_5) 125 MHz	Compound **3** δ ($CDCl_3$) 100 MHz
C2′	35.27	35.0
C3′	23.10	25.4
C4′	37.22	34.1
C5′	69.21	68.4
C6′	31.61	31.1
C7′	19.36	18.6
C8′	35.88	35.8
C9′	95.36	95.4
C10′	36.27	35.3
C11′	19.10	18.7
C12′	25.82	29.4
C13′	60.22	60.4

conversion of **11→12**) is susceptible to racemization.[14b] However, we suspect that epimerization at C-2 is taking place during the formation of acetonide **13** from triol **12**, as proposed by Sugai et al.[20] Indeed, Mori et al. have reported poor optical purity of (+)-ipsdienol prepared via the analogous derivatization of 2*R*-butane-1,2,4-triol.[21] Syntheses which converted L-glutamic acid **11** to acetonide **13**, via a slightly different series of reactions,[16a] appear to give compounds with established optical activity. We therefore, concur with the opinion of others that triol **12** is an epimerizable intermediate that should be avoided.

3. Conclusion

(2*S*,6*S*)-2-(3-Bromopropyl)-1,7-dioxaspiro[5.5]undecane **3** has been prepared in enantioenriched form in eight steps starting from (2*S*)-epoxide **9**, trimethylsilylacetylene **10** and δ-valerolactone **6**. Spiroacetal **3** is a potentially useful intermediate for the construction of broussonetine H and analogues thereof.

4. Experimental

4.1. General details

All reactions were conducted in flame-dried or oven-dried glassware under a dry nitrogen atmosphere unless otherwise noted. Tetrahydrofuran was dried over sodium/benzophenone and distilled prior to use. Flash chromatography was performed using Merck Kieselgel 60 (230–400 mesh) with the indicated solvents. Thin layer chromatography (TLC) was carried out on precoated silica plates (Merck Kieselgel $60F_{254}$) and compounds were visualized by UV fluorescence or by staining with vanillin in methanolic sulfuric acid and heating. Infrared spectra were recorded with a Perkin–Elmer 1600 series Fourier-transform infrared spectrometer as thin films between sodium chloride plates. Absorption maxima are expressed in wavenumbers (cm^{-1}) with the following abbreviations: s=strong, m=medium, w=weak and br=broad. ^1H and ^{13}C NMR spectra were obtained using a Bruker DRX-400 or a Bruker AM 200 spectrometer. All chemical shifts are given in parts per million (ppm) downfield from tetramethylsilane as internal standard (^1H) or relative to $CDCl_3$ (^{13}C) and *J* values are given in Hz. ^1H NMR data are tabulated as s, singlet; d, doublet; t, triplet; q, quartet, m, multiplet, br, broad. High resolution mass spectra were recorded using a VG7070 mass spectrometer operating at nominal accelerating voltage of 70 eV. Chemical ionisation (CI) mass spectra were obtained with ammonia as the reagent gas. Optical rotations were measured on a Perkin–Elmer 341 polarimeter. Samples were prepared at the concentration indicated (measured in g/100 cm^3) in the solvent stated.

4.1.1. (4*S*)-3-(2,2-Dimethyl-1,3-dioxolan-4-yl)propan-1-ol (13). A solution of (2*S*)-pentane-1,2,5-triol **12** (6.02 g, 50.2 mmol) and *p*-toluenesulfonic acid (0.19 g, 2.01 mmol) in acetone (60 mL) was stirred at room temperature under nitrogen for 3 days. The reaction mixture was diluted with ethyl acetate, washed with sat. aq. $NaHCO_3$, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography, eluting with 1:3 ethyl acetate–hexane to give (4*S*)-3-(2,2-dimethyl-1,3-dioxolan-4-yl)propan-1-ol **13** (7.22 g, 90%) as a pale yellow oil. $[\alpha]_D^{20}=+12.2$ ($c=1.03$, CH_2Cl_2) lit.[16a] $[\alpha]_D^{20}=+15.3$ ($c=2.45$, CH_2Cl_2); lit.[20] $[\alpha]_D^{22}=+12.0°$ ($c=1.05$, CH_2Cl_2); ^1H and ^{13}C NMR spectra were in agreement with those reported in the literature.[16a,21]

4.1.2. (4*S*)-*tert*-Butyl-[3-(2,2-dimethyl-1,3-dioxolan-4-yl)propoxy]diphenylsilane (14). A solution of (4*S*)-3-(2,2-dimethyl-1,3-dioxolan-4-yl)-propan-1-ol **13** (0.82 g, 5.0 mmol), *tert*-butyldiphenylsilyl chloride (1.43 mL, 5.5 mmol) and imidazole (0.68 g, 10.0 mmol) in CH_2Cl_2 (30 mL) was stirred at room temperature under nitrogen for 16 h. The reaction mixture was diluted with CH_2Cl_2 (50 mL), washed with brine (2×50 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography, eluting with 1:20 ethyl acetate–hexane to give (4*S*)-*tert*-butyl-[3-(2,2-dimethyl-1,3-dioxolan-4-yl)propoxy]diphenylsilane **14** (1.73 g, 87%) as a pale yellow oil. $[\alpha]_D^{20}=+6.9$ ($c=1.02$, CH_2Cl_2) lit.[16d] $[\alpha]_D^{20}=-8.6$ ($c=1.07$, $CHCl_3$) for the enantiomer. ^1H and ^{13}C NMR spectra were in agreement with the data reported for the *R*-enantiomer.[16d]

4.1.3. (2*S*)-5-(*tert*-Butyldiphenylsilyloxy)pentane-1,2-diol (15). A solution of (4*S*)-*tert*-butyl-[3-(2,2-dimethyl-1,3-dioxolan-4-yl)propoxy]diphenylsilane **14** (0.51 g) and pyridinium *p*-toluenesulfonate (51 mg, 10% w/w) in methanol (20 mL) was stirred at room temperature under nitrogen for 5 h. The reaction mixture was concentrated under reduced

pressure. The residue was purified by flash column chromatography, eluting with 1:3 ethyl acetate–hexane to give (2*S*)-5-(*tert*-butyldiphenyl-silyloxy)pentane-1,2*S*-diol **15** (0.31 g, 72%) as a pale yellow oil. $[\alpha]_D^{20}=-1.0°$ (c=1.03, CH_2Cl_2) lit.[16c] $[\alpha]_D^{20}=-1.27$ (c=1.73, CH_2Cl_2) and lit.[16d] $[\alpha]_D^{19}=+1.0$ (c=0.39, $CHCl_3$) for the *R*-enantiomer. ^1H and ^{13}C NMR spectra were in agreement with those reported in the literature.[16c,d]

4.1.4. (2*S*)-5-*tert*-Butyldiphenylsilyloxy-1,2-epoxypentane (9). *p*-Toluenesulfonyl chloride (0.13 g, 0.68 mmol), 4-(dimethylamino)pyridine (83 mg, 0.68 mmol) and triethylamine (95 μL, 0.68 mmol) were added to a solution of (2*S*)-5-(*tert*-butyldiphenylsilyloxy)pentane-1,2-diol **15** (0.22 g, 0.62 mmol) in CH_2Cl_2 (10 mL). The reaction mixture was stirred at room temperature under nitrogen for 16 h. The reaction mixture was diluted with CH_2Cl_2 (40 mL), washed with brine (2×30 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude *p*-toluenesulfonate ester (0.21 g, 0.41 mmol), sodium hydride (12 mg, 0.49 mmol) and 18-crown-6 (5 mg, 0.02 mmol) were dissolved in THF (5 mL). The reaction mixture was stirred at room temperature under nitrogen for 16 h. The reaction mixture was diluted with EtOAc (20 mL), washed with brine (2×10 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography, eluting with 1:10 ethyl acetate–hexane to give (2*S*)-5-*tert*-butyldiphenylsilyloxy-1,2-epoxypentane **9** (0.12 g, 86%) as a pale yellow oil. $[\alpha]_D^{20}=-2.71$ (c=1.1, $CHCl_3$) lit.[16c] $[\alpha]_D^{20}=-3.41$ (c=1.12, $CHCl_3$), lit.[22] $[\alpha]_D=-1.6$ (c=1.35), ^1H and ^{13}C NMR spectra were in agreement with those reported in the literature.[16c]

4.1.5. (4*S*)-7-(*tert*-Butyldiphenylsilyloxy)-1-trimethylsilylhept-1-yn-4-ol (16). ^{n}Butyllithium (5.65 mL, 1.6 M in hexane, 11.3 mmol) was added to a solution of trimethylsilylacetylene **10** (1.60 mL, 11.3 mmol) in THF (30 mL) at −78°C under nitrogen. After 10 min, boron trifluoride diethyl etherate (1.43 mL, 11.3 mmol) was added dropwise to the reaction mixture. After 10 min, a solution of (4*S*)-1-*tert*-butyldiphenylsilyloxy-4,5-epoxypentane **9** (1.28 g, 3.76 mmol) in THF (20 mL) was added dropwise. The mixture was stirred at the same temperature for 20 min following completion of the addition. Excess ^{n}BuLi was quenched with sat. aq. NH_4Cl and the reaction mixture diluted with EtOAc (100 mL), washed with brine (100 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography, eluting with 1:10 ethyl acetate–hexane to give (4*S*)-7-(*tert*-butyldiphenylsilyloxy)-1-trimethylsilylhept-1-yn-4-ol **16** (1.65 g, 92%) as a colourless oil; R_f: 0.63 (1:5 ethyl acetate–hexane); $[\alpha]_D^{20}=-4.03$ (c=0.98, $CHCl_3$). Found: C, 71.38; H, 8.44. $C_{26}H_{38}O_2Si_2$ requires C, 71.17; H, 8.73%. (Found (CI): MH^+, 439.2485. $C_{26}H_{39}O_2Si_2$, requires *MH*, 439.2489); ν_{max} (film)/cm^{-1} 3430 (O–H), 3301 (≡C–H), 2173 (C≡C), 1111 (Si–O–C), 703 (–C≡CH); δ_H (400 MHz, $CDCl_3$) 0.16 (9H, s, CH_3Si), 1.05 (9H, s, ^{t}Bu), 1.50–1.77 (4H, m, H-5, H-6), 2.37 (1H, dd, J=3.0, 11.5 Hz, H-3A), 2.45 (1H, dd, J=3.0, 11.5 Hz, H-3B), 2.51 (1H, br, OH), 3.69 (2H, t, J=5.6 Hz, OCH_2), 3.75–3.79 (1H, m, C*H*OH), 7.34–7.44 (6H, m, Ph), 7.64–7.68 (4H, m, Ph); δ_C (100 MHz, $CDCl_3$) 0.1 (CH_3, CH_3Si), 19.1 (quat, ^{t}Bu), 26.8 (CH_3, ^{t}Bu), 28.7 (CH_2, C-6), 28.8 (CH_2, C-3), 33.1 (CH_2, C-5), 64.0 (CH_2, OCH_2), 69.8 (CH CHOH), 87.3 (quat, C-1), 103.4 (quat, C-2), 127.6 (CH, Ph), 129.6 (CH, Ph), 133.6 (quat, Ph), 135.5 (CH, Ph); *m/z* (CI) 439 (MH^+, 100%), 381 (M−^{t}Bu, 7%), 361 (M−Ph, 5%), 199 (M−SiPh$_2^t$Bu, 17%).

4.1.6. (4*S*)-7-(*tert*-Butyldiphenylsilyloxy)hept-1-yn-4-ol (17). A solution of (4*S*)-7-(*tert*-butyldiphenylsilyloxy)-1-trimethylsilylhept-1-yn-4-ol **16** (1.01 g, 2.31 mmol) and sodium methoxide (0.25 g, 4.62 mmol) in methanol (10 mL) was stirred at room temperature under nitrogen for 5 h. The reaction mixture was concentrated under reduced pressure, diluted with EtOAc (100 mL), washed with brine (100 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography, eluting with 10:1 hexane-ethyl acetate to give (4*S*)-7-(*tert*-butyldiphenylsilyloxy)hept-1-yn-4-ol **17** (0.79 g, 94%) as a colourless oil; $[\alpha]_D^{20}=-2.25$ (c=1.20, $CHCl_3$); R_f: 0.44 (1:5 ethyl acetate–hexane). Found: C, 75.35; H, 8.42. $C_{23}H_{30}O_2Si$ requires C, 75.36; H, 8.25%. Found (CI): MH^+, 367.2098. $C_{23}H_{31}O_2Si$, requires *MH*, 367.2093; ν_{max} (film)/cm^{-1} 3430 (O–H), 3301 (≡C–H), 2110 (C≡C), 1110 (Si–O–C), 703 (–C≡CH); δ_H (400 MHz, $CDCl_3$) 1.05 (9H, s, ^{t}Bu), 1.57–1.84 (4H, m, H-5, H-6), 2.04 (1H, t, J=2.6 Hz, C≡CH), 2.36–2.40 (2H, m, H-3), 2.56 (1H, d, J=4.8 Hz, OH), 3.70 (2H, t, J=5.6 Hz, OCH_2), 3.76–3.83 (1H, m, C*H*OH), 7.36–7.45 (6H, m, Ph), 7.66–7.67 (4H, m, Ph); δ_C (100 MHz, $CDCl_3$) 19.1 (quat, ^{t}Bu), 26.8 (CH_3, ^{t}Bu), 27.3 (CH_2, C-6), 28.7 (CH_2, C-3), 33.1 (CH_2, C-5), 64.0 (CH_2, OCH_2), 69.7 (CH, C=*C*H), 70.6 (CH, CHOH), 81.0 (quat, *C*≡CH), 127.7 (CH, Ph), 129.6 (CH, Ph), 133.6 (quat, Ph), 135.6 (CH, Ph); *m/z* (CI) 367 (MH^+, 28%), 309 (M−^{t}Bu, 21%), 289 (M−Ph, 11%), 199 (OSiHPh$_2$, 100%).

4.1.7. (4*S*)-4-Benzyloxy-7-*tert*-butyldiphenylsilyloxyhep-1-yne (8). Benzyl bromide (0.38 mL, 3.29 mmol) and tetrabutylammonium iodide (1.21 g, 1.63 mmol) were added to a suspension of (4*S*)-7-(*tert*-butyldiphenylsilyloxy)hept-1-yn-4-ol **17** (1.43 g, 3.27 mmol) and sodium hydride (78 mg, 3.29 mmol) in DMF (40 mL). The reaction mixture was stirred at room temperature under nitrogen for 16 h. Excess hydride was quenched with sat. aq. NH_4Cl, the reaction mixture washed with brine (2×40 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography, eluting with 98:2 hexane-ethyl acetate to give (4*S*)-4-benzyloxy-7-*tert*-butyldiphenylsilyloxyhep-1-yne **8** (1.52 g, 88%) as a colourless oil; $[\alpha]_D^{20}=-11.1$ (c=1.02, $CHCl_3$); R_f: 0.43 (1:20 ethyl acetate–hexane). (Found: C, 78.63; H, 7.69. $C_{30}H_{36}O_2Si$ requires C, 78.90; H, 7.95%). Found (CI): MH^+, 457.2563. $C_{30}H_{37}O_2Si$, requires *MH*, 457.2556; ν_{max} (film)/cm^{-1} 3307 (≡C–H), 2110 (C≡C), 1111 (Si–O–C), 702 (–C≡CH); δ_H (400 MHz, $CDCl_3$) 1.05 (9H, s, ^{t}Bu), 1.58–1.86 (4H, m, H-5, H-6), 1.98 (1H, t, J=2.7 Hz, HC≡C), 2.39 (1H, ddd, J=2.7, 6.5, 16.9 Hz, H-3A), 2.46 (1H, ddd, J=2.7, 5.1, 16.9 Hz, H-3B), 3.52–3.58 (1H, m, CHO), 3.67 (2H, t, J=6.1 Hz, CH_2O), 4.53 (1H, d, J=11.7 Hz, CH_AH$_B$Ph), 4.55 (1H, d, J=11.7 Hz, CH$_A$H$_B$-Ph), 7.21–7.42 (10H, m, Ph), 7.45–7.72 (5H, m, Ph); δ_C (100 MHz, $CDCl_3$) 19.2 (quat, ^{t}Bu), 23.8 (CH_2, C-3), 26.9

(CH_3, ^{t}Bu), 28.2 (CH_2, C-6), 30.1 (CH_2 C-5), 63.7 (CH_2, CH_2O), 69.9 (CH, C≡CH), 71.2 (CH_2, CH_2Ph), 76.9 (CH, CHO), 81.2 (quat, HC≡*C*–C), 127.6 (CH, Ph), 127.7 (CH, Ph), 128.3 (CH, Ph), 129.5 (CH, Ph), 133.9 (quat, Ph), 135.6 (CH, Ph), 138.4 (quat, Ph); *m/z* (CI) 457 (MH^+, 26%), 349 (M−$PhCH_2OH$, 18%), 269 ($CH_2OSiPh_2^tBu$, 11%), 91 ($PhCH_2$, 100%).

4.1.8. (9*S*)-9-Benzyloxy-12-(*tert*-butyldiphenylsilyloxy)-5-oxododec-6-yn-1-ol (18, 19). ^{n}Butyllithium (50 μL, 1.6 M in hexane, 1.04 mmol) was added to a solution of (4*S*)-4-benzyloxy-7-*tert*-butyldiphenylsilyloxyhep-1-yne **18** (0.49 g, 0.87 mmol) in THF (20 mL) at −78°C under nitrogen. The reaction mixture was stirred at this temperature for 15 min then δ-valerolactone **6** (96 μL, 1.04 mmol) was added dropwise. The reaction mixture was stirred at this temperature for 1 h. Excess ^{n}BuLi was quenched with sat. aq. NH_4Cl and the reaction mixture washed with brine (2×10 mL). The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography, eluting with 3:1 hexane-ethyl acetate to give (9*S*)-9-benzyloxy-12-(*tert*-butyldiphenylsilyloxy)-5-oxododec-6-yn-1-ol **19** as an inseparable mixture with hemiacetal **20** (0.50 g, 86%) and as a colourless oil; R_f: 0.27 (1:3 ethyl acetate–hexane). Found (CI): MH^+, 557.3087. $C_{35}H_{44}O_4Si$, requires *MH*, 557.3092; ν_{max} (film)/cm^{-1} 3412 (O–H), 2211 (C≡C), 1671 (C=O), 1111 (Si–O–C); δ_H (400 MHz, $CDCl_3$) (mixture of compounds) 1.05 (9H, s), 1.29–1.35 (2H, m), 1.48–1.78 (7H, 2.41–2.63 (4H, m), 3.57–3.69 (3H, m, OCH_2, OCH), 3.67 (2H, t, *J*=6.0 Hz, OCH_2), 4.53 (1H, d, *J*=11.6 Hz, CH_AH_BPh), 4.55 (1H, d, *J*=11.6 Hz, CH_AH_BPh), 7.26–7.44 (10H, m, Ph), 7.60–7.71 (5H, m, Ph); δ_C (100 MHz, $CDCl_3$) (mixture of compounds) 13.8 (CH_3), 19.2 (quat), 19.7 (CH_2), 20.1 (CH_2), 22.3 (CH_2), 24.4 (CH_2), 25.9 (CH_2), 26.8 (CH_3), 28.1 (CH_3), 30.4 (CH_2), 31.8 (CH_2), 32.1 (CH_2), 42.2 (CH_2), 42.5 (CH_2), 45.0 (CH_2), 62.1 (CH_2), 62.2 (CH_2), 63.5 (CH_2), 71.4 (CH_2), 76.4 (CH), 82.0 (quat), 91.0 (quat), 127.6 (CH), 127.7 (CH), 128.4 (CH), 129.6 (CH), 133.8 (quat), 135.5 (CH), 138.0 (quat), 187.8 (quat); *m/z* (DCI) 557 (MH^+, 1%), 539 (M−H_2O, 5%), 269 ($CH_2OSiPh_2^tBu$, 11%), 141 (100%), 91 ($PhCH_2$, 46%).

4.1.9. (2*S*)-2-[3-(*tert*-Butyldiphenylsilyloxy)prop-1-yl]-1,7-dioxaspiro[5.5]undecane (20). 10% palladium on charcoal (0.21 g) was added to a solution of (9*S*)-9-benzyloxy-12-(*tert*-butyldiphenylsilyloxy)-5-oxo-dodec-6-yn-1-ol **18**,**19** (0.43 g, 3.27 mmol) in ethyl acetate (20 mL). The flask was evacuated then flushed with hydrogen and stirred under a balloon of hydrogen for 2 h. The reaction mixture was filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography, eluting with 20:1 hexane-ethyl acetate to give (2*S*)-2-[3-(*tert*-butyldiphenylsilyloxy)prop-1-yl]-1,7-dioxaspiro[5.5]undecane **20** (0.37 g, 86%) as a colourless oil; $[\alpha]_D^{20}$=−53.2 (*c*=0.97, $CHCl_3$); R_f: 0.27 (1:20 ethyl acetate–hexane). Found: C, 74.50; H, 8.93. $C_{28}H_{40}O_3Si$ requires C, 74.29; H, 8.91%. Found (CI): MH^+, 453.2825. $C_{28}H_{41}O_3Si$, requires *MH*, 453.2826; ν_{max} (film)/cm^{-1} 1110 (Si–O–C), 1107 (C–O–C); δ_H (400 MHz, $CDCl_3$) 1.05 (9H, s, ^{t}Bu), 1.09–1.69 (13H, m, H-2′, H-1′, H-3, H-4, H-9, H-10, H-11A), 1.76–1.87 (3H, m, H-5, H-11B), 3.51–3.62 (3H, m, H-2, H-8), 3.65–3.75 (2H, m, CH_2OSi), 7.35–7.45 (6H, m, Ph), 7.66–7.69 (4H, m, Ph); δ_C (100 MHz, $CDCl_3$) 18.6 (CH_2, C-4), 18.8 (CH_2, C-10), 19.2 (quat, ^{t}Bu), 25.4 (CH_2, C-2′), 26.9 (CH_3, ^{t}Bu), 29.0 (CH_2, C-9), 31.2 (CH_2, C-1′), 32.6 (CH_2, C-3), 35.4 (CH_2, C-11), 35.9 (CH_2, C-5), 60.3 (CH_2, C-8), 64.1 (CH_2, OCH_2), 68.9 (CH, C-2), 95.4 (quat, C-6), 127.6 (CH, Ph), 129.5 (CH, Ph), 134.1 (quat, Ph), 135.6 (CH, Ph); *m/z* (CI) 453 (MH^+, 97%), 395 (M−^{t}Bu, 100%), 375 (M−Ph, 12%), 199 ($OSiHPh_2$, 49%).

4.1.10. (2′*S*)-3-(1,7-Dioxaspiro[5.5]undec-2-yl)propan-1-ol (4). Tetrabutylammonium fluoride (2.84 mL, 1 M in THF, 2.84 mmol) was added to a solution of (2*S*)-2-[3-(*tert*-butyldiphenylsilyloxy)prop-1-yl]-1,7-dioxaspiro[5.5]undecane **21** (0.64 g, 1.42 mmol) in THF (30 mL). The reaction mixture was stirred under nitrogen for 16 h. Excess fluoride was quenched with sat. aq. NH_4Cl and the reaction mixture diluted with EtOAc (50 mL) then washed with brine (2×50 mL). The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography, eluting with 3:1 hexane-ethyl acetate to give (4*S*)-3-(1,7-dioxaspiro[5.5]undec-2-yl)propan-1-ol **4** (0.29 g, 96%) as a colourless oil; $[\alpha]_D^{20}$=−64.9° (*c*=1.04, $CHCl_3$); R_f: 0.23 (1:3 ethyl acetate–hexane). Found: C, 66.92; H, 10.47. $C_{12}H_{22}O_3$ requires C, 67.01; H, 10.35%. Found (EI): M^+, 214.1564. $C_{12}H_{22}O_3$, requires *M*, 214.1569; ν_{max} (film)/cm^{-1} 3369 (O–H), 977 (C–O–C); δ_H (400 MHz, $CDCl_3$) 1.19–1.92 (16H, m, H-3′, H-4′, H-5′, H-9′, H-10′, H-11′, H-2, H-3), 2.17 (1H, br, OH), 3.57–3.69 (5H, m, C-2′, C-8′, HOCH_2); δ_C (100 MHz, $CDCl_3$) 18.5 (CH_2, C-4′), 18.7 (CH_2, C-10′), 25.3 (CH_2, C-2), 29.0 (CH_2, C-9′), 31.0 (CH_2, C-3), 32.8 (CH_2, C-3′), 35.4 (CH_2, C-5′), 35.7 (CH_2, C-11′), 60.4 (CH_2, C-8′), 63.1 (CH_2, CH_2O), 69.1 (CH, C-2′), 95.7 (quat, C-6′); *m/z* (CI) 214 (M^+, 4%), 196 (M−H_2O, 6%), 101 (100%), 155 (M−$(CH_2)_3OH$, 15%), 141 (M−$(CH_2)_4OH$, 20%).

4.1.11. (2′*S*)-3-(1,7-Dioxaspiro[5.5]undec-2-yl)prop-1-yl methanesulfonate (21). Methanesulfonyl chloride (48 μL, 0.63 mmol) was added to a solution of 4-(dimethylamino)-pyridine (18 mg, 0.16 mmol) in pyridine (5 mL). The reaction mixture was stirred under nitrogen for 5 min. A solution of (4*S*)-3-(1,7-dioxaspiro[5.5]undec-2-yl)propan-1-ol **4** (67 mg, 0.31 mmol) in pyridine (5 mL) was added to the mixture dropwise and the reaction stirred for 16 h. The reaction mixture was diluted with CH_2Cl_2 (40 mL) and then washed with 10% HCl (2×40 mL), sat. aq. $NaHCO_3$ (40 mL) and brine (40 mL). The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography, eluting with 5:1 hexane-ethyl acetate to give (2*S*)-3-(1,7-dioxaspiro[5.5]undec-2-yl)prop-1-yl methanesulfonate **22** (71 mg, 78%) as a colourless oil; $[\alpha]_D^{20}$=−41.4 (*c*=1.00, $CHCl_3$); R_f: 0.32 (1:5 ethyl acetate–hexane). Found: C, 53.43; H, 8.13. $C_{13}H_{24}O_5S$ requires C, 53.40; H, 8.27%. Found (EI): M^+, 292.1341. $C_{13}H_{24}O_5S$, requires *M*, 292.1345; ν_{max} (film)/cm^{-1} 1354, 1175 (O=S=O), 983 (C–O–C); δ_H (400 MHz, $CDCl_3$) 1.14–1.63 (12H, m, H-1′, H-4′, H-9′, H-10′, H-2, H-3), 1.77–1.89 (3H, m, H-5′B, H-11′), 1.99–2.10 (1H, m, H-5′A), 3.01 (3H, s, SO_2CH_3), 3.59 (3H, m, CHO, H-8′), 4.23–4.35 (2H, m, OCH_2); δ_C (100 MHz, $CDCl_3$) 18.6 (CH_2, C-4′), 18.7 (CH_2, C-10′),

25.3 (CH_2, C-2), 25.9 (CH_2, C-9′), 31.1 (CH_2, C-3), 32.1 (CH_2, C-3′), 35.3 (CH_2, C-11′), 35.8 (CH_2, C-5′), 37.4 (CH_3, SO_2CH_3), 60.4 (CH_2, C-8′), 68.5 (CH, C-2′), 70.4 (CH_2, C-1), 85.5 (quat, C-6′); *m/z* (EI) 292 (M^+, 5%), 196 ($M-HOSO_2CH_3$, 10%), 155 {M-$(CH_2)_3OSO_2CH_3$, 19%}, 98 ($CH_3SO_3H_3$, 100%).

4.1.12. (2*S*)-(3-Bromopropyl)-1,7-dioxaspiro[5.5]undecane (3). Lithium bromide (46 mg, 0.52 mmol) was added to a solution of (2*S*)-3-(1,7-dioxaspiro[5.5]undec-2-yl)prop-1-yl methanesulfonate 22 (51 mg, 0.18 mmol) in acetone (10 mL). The reaction mixture was heated under reflux under nitrogen for 16 h then cooled to room temperature, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography, eluting with 98:2 hexane-ethyl acetate to give (2*S*)-(3-bromopropyl)-1,7-dioxaspiro[5.5]undecane 3 (41 mg, 85%) as colourless oil; $[\alpha]_D^{20}=-44.7$ (c=0.85, $CHCl_3$); R_f: 0.47 (1:20 ethyl acetate–hexane). Found: C, 52.04; H, 7.69. $C_{12}H_{21}O_2Br$ requires C, 51.99; H, 7.64%. Found (EI): M^+, 276.0722. $C_{12}H_{21}O_2^{79}Br$, requires *M*, 276.0725, M^+, 278.0701. $C_{12}H_{21}O_2^{81}Br$, requires *M*, 278.0705; ν_{max} (film)/cm^{-1} 1354, 1107 (C–O–C), 510 (C–Br); δ_H (400 MHz, $CDCl_3$) 1.14–1.69 (12H, m, H-3, H-4, H-9, H-10, H-1′, H-2′), 1.78–1.96 (3H, m, H-11, H-5B), 2.12–2.19 (1H, m, H-5A), 3.40–3.53 (2H, m, H-8), 3.58–3.63 (3H, m, CHO, CH_2Br); δ_C (100 MHz, $CDCl_3$) 18.6 (CH_2, C-4), 18.7 (CH_2, C-10), 25.4 (CH_2, C-2′), 29.4 (CH_2, C-9), 31.1 (CH_2, C-3), 34.1 (CH_2, C-1′), 35.0 (CH_2, C-3′), 35.3 (CH_2, C-11), 35.8 (CH_2, C-5), 60.4 (CH_2, C-8), 68.4 (CH, C-2), 95.4 (quat, C-6); *m/z* (EI) 276, 278 (M^+, 5%), 197, (M−Br, 13%), 155, $(M-(CH_2)_3^{79}$ Br, 14%), 101 (100%).

4.1.13. (2*R*)-3,3,3-Trifluoro-2-methoxy-2-phenylpropionic acid (4*S*)-3-(1,7-dioxaspiro[5.5]undec-2-yl)propyl ester (Mosher ester derivative of 4). A solution of (4*S*)-3-(1,7-dioxaspiro[5.5]undec-2-yl)propan-1-ol 4 (9 mg, 0.05 mmol) in CH_2Cl_2 was treated with triethylamine (10 μL, 0.06 mmol), (*S*)-α-methoxy-α-trifluoromethylphenylacetyl chloride (25 μL, 0.09 mmol) and 4-(dimethylamino)pyridine (23 mg, 0.2 mmol) and the mixture stirred at room temperature under nitrogen for 16 h. The reaction mixture was diluted with CH_2Cl_2 (10 mL) and washed with brine (2×10 mL). The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The resultant residue was purified by flash column chromatography, eluting with 5:1 hexane-ethyl acetate to give (2*S*)-3,3,3-trifluoro-2-methoxy-2-phenylpropionic acid 3-(1,7-dioxaspiro[5.5]undec-2-yl)propyl ester (15 mg, 81%) as a colourless oil; $[\alpha]_D^{20}=7.01$ (c=0.51, $CHCl_3$) δ_H (400 MHz, $CDCl_3$) 1.09–1.97 (16H, m, H-2, H-3, H-3′, H-4′, H-5′, H-9′, H-10′, H-11′), 3.54–3.58 (6H, m, CHO, OCH_3, H-8′), 4.37 (2H, t J=8.8 Hz, H-1), 7.38–7.43 (3H, m, Ph), 7.51–7.54 (2H, m, Ph); δ_C (100 MHz, $CDCl_3$) 18.6 (CH_2, C-4′), 18.7 (CH_2, C-10′), 25.0 (CH_2, C-2), 25.4 (CH_2, C-9′), 31.1 (CH_2, C-3), 32.4 (CH_2, C-3′), 35.4 (CH_2, C-5′), 35.8 (CH_2, C-11′), 55.4 (CH_3, OCH_3), 60.4 (CH_2, C-8′), 66.7 (CH_2, CH_2O), 68.5 (CH, CHO), 95.4 (quat, O–C–O), 127.3 (CH, Ph), 128.4 (CH, Ph), 129.6 (CH, Ph), 133.7 (quat, Ph), 165.4 (quat, C=O); δ_F (332 MHz, $CDCl_3$) -72.70 (15%, CF_3, *R* enantiomer), -72.73 (85%, CF_3, *S* enantiomer); *m/z* (EI) 430 (M^+, 19%), 189 (M−OC(O)CPh(CF_3)(OMe), 89%), 101 (100%).

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