Synthesis of diospongin A, ent-diospongin A and C-5 epimer of diospongin B from tri-*O*-acetyl-D-glucal

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Abstract

We describe a new synthesis of diospogin A, its enantiomer ent-diospongin A and C-5 epimer of diospongin B from commercially available tri-O-acetyl-D-glucal, based on a copper catalyzed Michael addition of phenyllitium to the corresponding α,β-unsaturated ketone. The stereochemical course of the Michael addition was unambiguously established by X-ray crystallographic analysis.

Keywords: Diospongin, natural products, total synthesis, Michael addition, Mitsunobu reaction

Introduction

Diospongins A (**1**) and B (**2**) are a novel class of cyclic 1,7-diarylheptanoid natural products (Figure 1). They were isolated in 2004 by S. Kadota and co-workers, from the rhizomes of *Dioscorea spongiosa*.[1] While diospongin A (**1**) did not show any activity, diospongin B (**2**) exhibited a potent inhibitory activity on bone resorption induced by parathyroid hormone in a bone organ culture system and hence can be regarded as a lead compound for the development of antiosteoporotic drugs.[1]

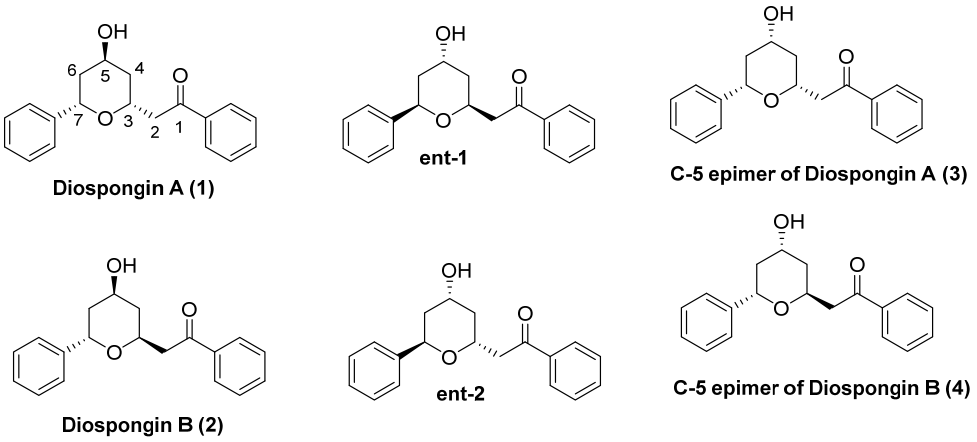
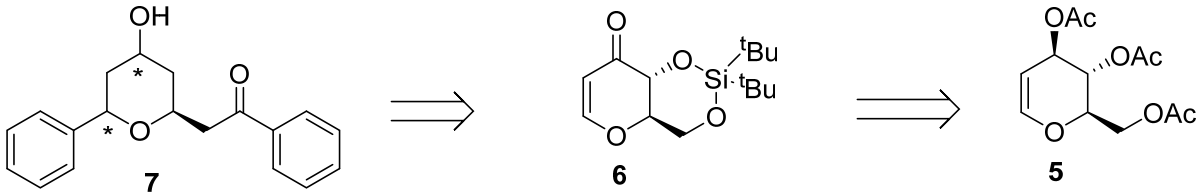


Figure 1. Structures of diospongins A and B and their enantiomers and C-5 epimers.

Because of their biological activities, diospongins have attracted much interest in the synthetic community. Since the first asymmetric total synthesis of diospongins A and B carried out in 2006 by Jennings and co-workers,[2] several total syntheses of **1** and **2** and their enantiomers have been developed.[3-20]

Results and Discussion

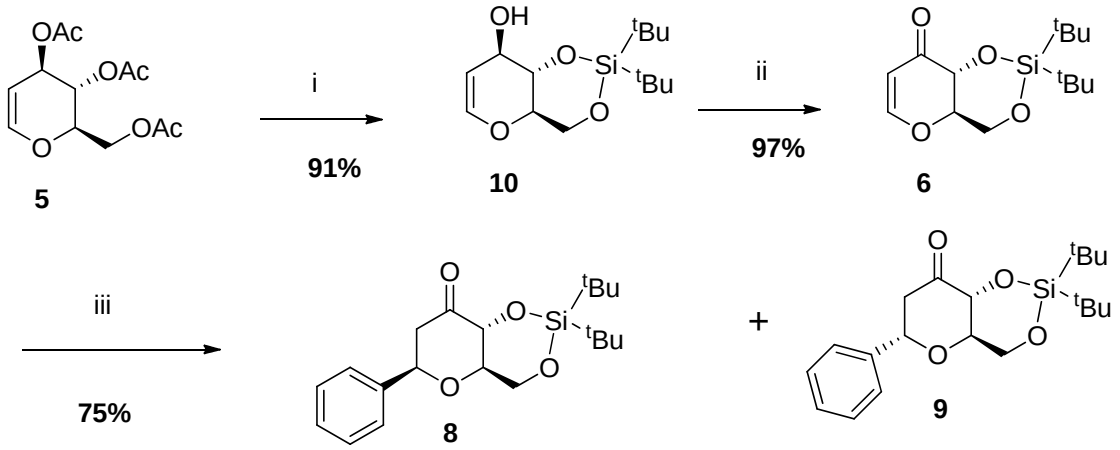
As part of our ongoing program focusing on the use of readily available chiral substrate tri-O-acetyl-D-glucal (**5**) for the synthesis of natural products,[21-25] we wish now to report the synthesis of diospongin A, ent-diospongin A and C-5 epimer of diospongin B, using this compound.
Our retrosynthetic basis is outlined in Scheme 1.



Scheme 1. Retrosynthetic analysis for diastereoisomers of diospongin B.

We anticipated that a Michael addition with diphenylcuprate on enone **6** would give diastereoisomers **8** and **9**, precursors of target compounds **7**. Accordingly, compound **10** was prepared in 2 steps from **5** in 91% yield, following the procedure described by Mori and Hayashi[26] (Scheme 2).

PDC oxidation of **10** afforded α,β-unsaturated ketone **6** in 97% yield which underwent copper catalyzed Michael addition of PhLi, giving a separable mixture of diastereomeric ketones **8** and **9** in a 1:1.2 ratio.



Scheme 2 *Reagents and conditions.* (i) (a) K_2CO_3, MeOH; (b) *t*-$Bu_2Si(OTf)_2$, DMF, Py, -30 ºC. (ii) PDC, DMF, rt (iii) PhLi, CuCN, BF_3OEt_2, Et_2O, -78 ºC to rt.

The structures of **8** and **9** were unambiguously established by X-ray crystallographic analysis of **9**[27] (Figure 2).

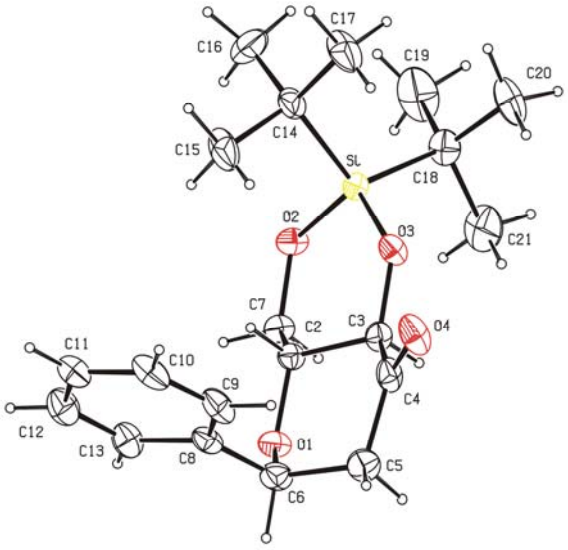
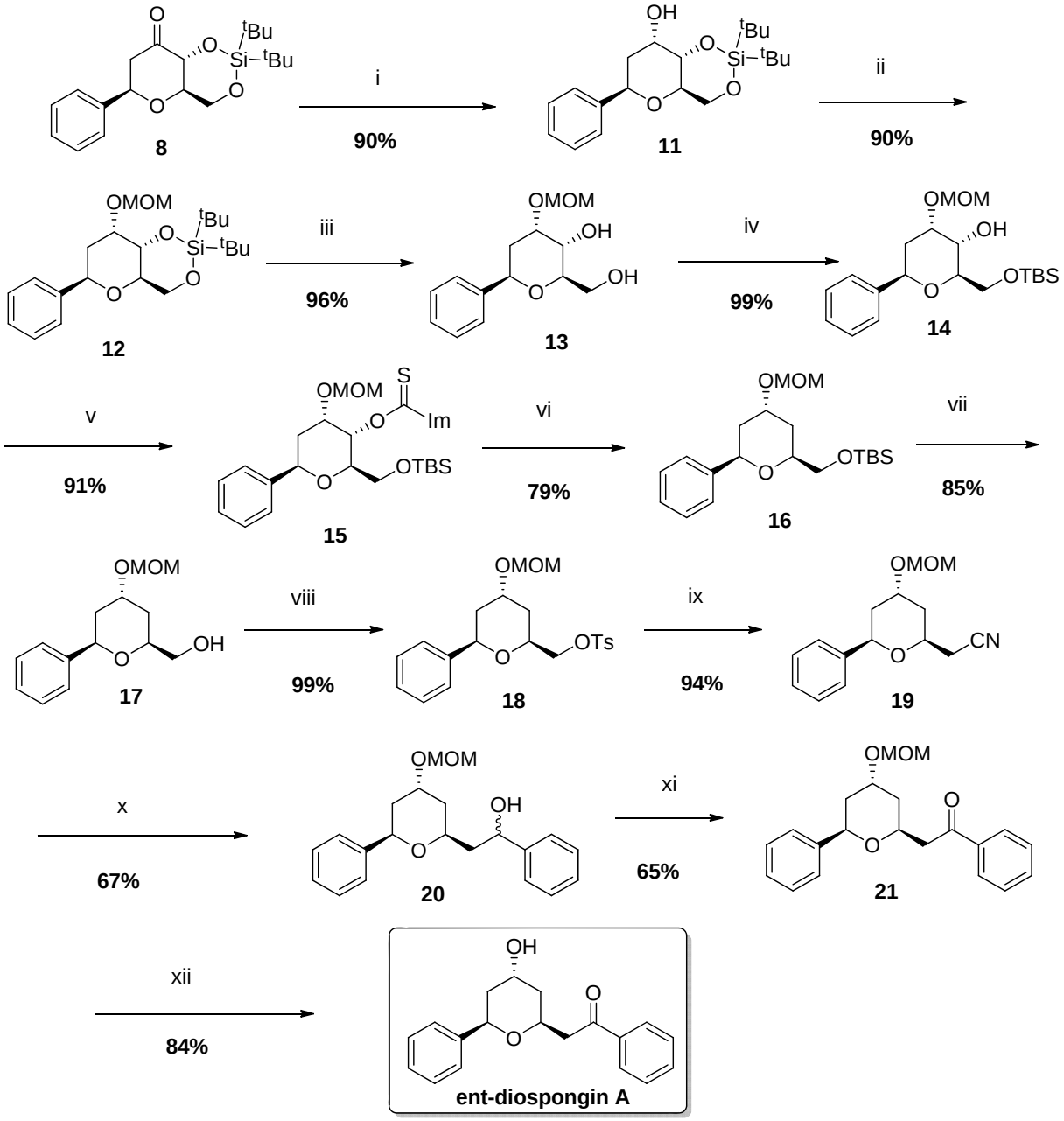
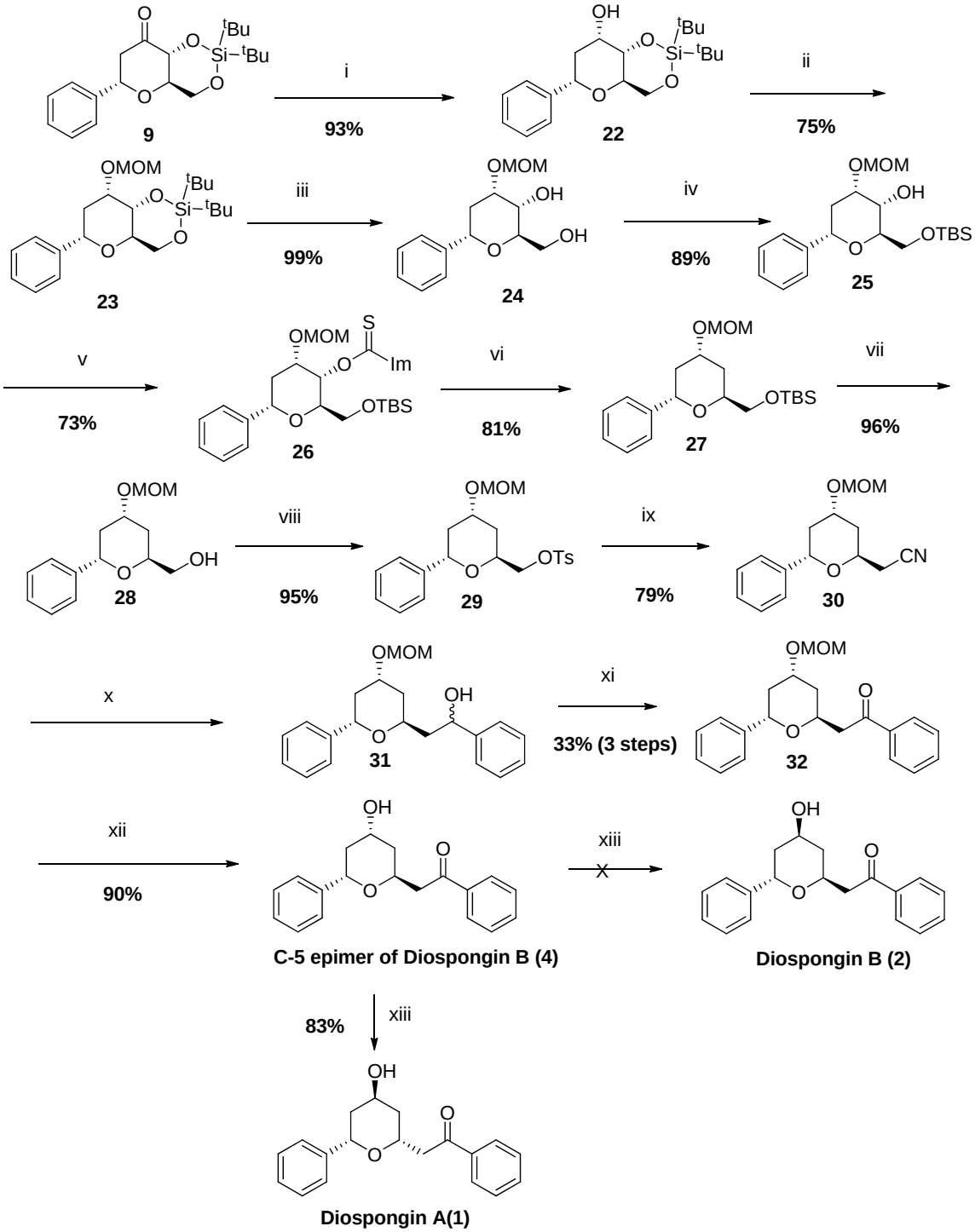


Figure 2. X-ray crystal structure (ORTEP) of ketone **9**.

We anticipated that stereoselective reduction of ketones **8** and **9** followed by side chain elaboration would lead to ent-diospongin A, in the case of ketone **8** and to diospongin B in the case of ketone **9**. Accordingly, ent-diospongin A was prepared as shown in Scheme 3.



Scheme 3 *Reagents and conditions.* (i) L-Selectride, THF, -38 ºC. (ii) ClMOM, CH_2Cl_2, DIEA. (iii) TBAF, THF, rt. (iv) TBSCl, DMAP, Imidazole, THF, rt. (v) Im_2CS, THF, 70 ºC. (vi) AIBN, Bu_3SnH, toluene, 120 ºC. (vii) TBAF, THF, rt. (viii) p-TsCl, Pyr, CH_2Cl_2. (ix) NaCN, DMSO, 90 ºC. (x) (a) DIBAL-H, CH_2Cl_2, -78 ºC; (b) PhLi, THF, -78 ºC. (xi) PDC, CH_2Cl_2, rt. (xii) HCl (37%), MeOH.

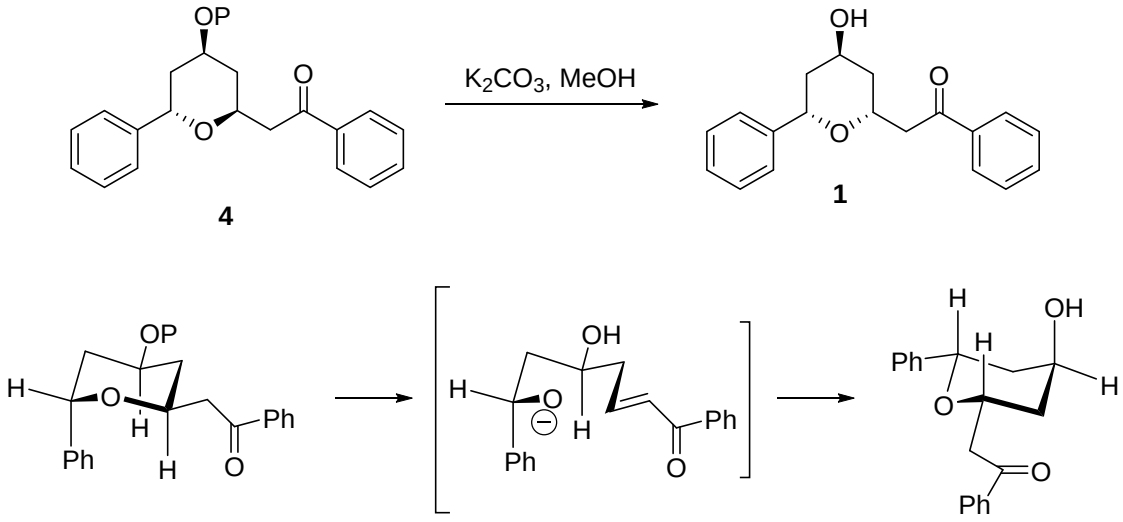


Scheme 4 *Reagents and conditions.* (i) L-Selectride, THF, -38 ºC. (ii) ClMOM, CH_2Cl_2, DIEA. (iii) TBAF, THF, rt. (iv) TBSCl, DMAP, Imidazole, THF, rt. (v) Im_2CS, THF, 70 ºC. (vi) AIBN, Bu_3SnH, toluene, 120 ºC. (vii) TBAF, THF, rt. (viii) p-TsCl, Pyr, CH_2Cl_2. (ix) NaCN, DMSO, 90 ºC. (x) (a) DIBAL-H, CH_2Cl_2, -78 ºC; (b) PhLi, THF, -78 ºC. (xi) TPAP, NMO, Molecular sieves, CH_2Cl_2, rt. (xii) HCl (37%), MeOH. (xiii) (a) PPh_3, *p*-NO_2PhCO_2H; (b) K_2CO_3, MeOH.

L-Selectride reduction of ketone **8** afforded stereoselectively 90% yield of alcohol **11** which was protected as MOM ether to give **12** in 90% yield. Removal of the silyl protecting group of compound **12** afforded the diol **13** (96%). The primary hydroxyl group of **13** was selectively protected giving almost quantitatively alcohol **14**. Radical deoxygenation[28] of alcohol **14** led to tert-butyldimethylsilylether **16** in 72% overall yield. Removal of the TBS protecting group of **16** afforded alcohol **17** in 85% yield. Alcohol **17** was uneventfully converted into nitrile **19** in 93% overall yield by tosylation followed by tosylate displacement with sodium cyanide. Reduction of nitrile **19** with DIBALH[29] gave an aldehyde which was subjected to a reaction with PhLi to obtain alcohol **20** in 67% overall yield. PDC oxidation of alcohol **20** afforded ketone **21** (65% yield). Removal of the MOM protecting group of **21** gave 84% yield of target ent-diospongin A.

Using a similar sequence of reactions to that used above, ketone **9** led to the synthesis of C-5-epimer of diospongin B (**4**) (Scheme 4).

Our intention was to synthesize diospongin B (**2**) from **4**, by means of a Mitsunobu reaction,[30] but instead of the expected compound we got diospongin A (**1**). The formation of **1** from **4** can be rationalized by first inversion of C-5 configuration, a retro-Michael reaction followed by an intramolecular Michael reaction which then leads to the thermodynamically more stable diospongin **1** (Scheme 5). This type of epimerization is not unprecedented as observed by Kumaraswamy and co-workers[10] while deprotecting a TBDPS group with excess of TBAF (10 equiv).



Scheme 5. Rationalization of the formation of **1** from **4.**

Conclusions

We have developed a new synthesis of diospongin A, its enantiomer and C-5-epimer of diospongin B, from a relatively cheap starting material. To the best of our knowledge this is so

far only the second synthesis described for ent-diospongin A. Our strategy could be used to generate a library of small molecules with varying substitutions in the aromatic rings. Work is now in progress for the synthesis of such diospongin analogues with a view to their biological evaluation.

Experimental Section

General. Solvents were purified and dried by standard procedures before use. Melting points are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded with a Bruker ARX-400 spectrometer (400 MHz for 1H NMR, 100.61 MHz for ^{13}C NMR) using TMS as internal standard (Chemical shifts in δ values, J in Hz). Flash chromatography (FC) was performed on silica gel (Merck 60, 230-400 mesh); analytical TLC was performed on plates precoated with silica gel (Merck 60 F254, 0.25mm); mass spectra (FAB, EI) were recorded using FISONS VG and electron spray ionization (ESI-MS) spectroscopy was recorded using Bruker FTMS APEXIII.

Due to some C signals overlapping the number of C signals in some spectra might be less. Also some hydroxy groups H might be missing.

(4a*R*,8a*R*)-2,2-Di-*tert*-butyl-4,4adihydropyrano[3,2-*d*][1,3,2]dioxasilin-8(8a*H*)-one (6). To a solution of **10** (1 g, 3.5 mmol) in DMF (33 mL) was added PDC (5.1 g, 13.9 mmol) and the mixture was stirred at room temperature for 1 hour, quenched with $NaHCO_3$ (10 mL) and extracted with AcOEt (30 ml), the organic phase was washed with H_2O (3x30 ml) and brine (3x30 mL). After drying with Na_2SO_4 and solvent evaporation the residue was chromatographed on silica using 15% AcOEt/ Hexane affording **6** (960 mg, 97%). **Compound 6**: colourless oil, $[\alpha]_D^{24}$ = +95.2 (c 1.09, $CHCl_3$), Rf: 0.37 (30% AcOEt). ^{1}H NMR ($CDCl_3$, δ): 7.18 (d, *J* 5.8 Hz, 1H, CH-6), 5.30 (d, *J* 5.8 Hz, 1H, CH-7), 4.49 (m, 1H, CH-8a), 4.20 (m, 2H, CH_2-4), 4.10 (m, 1H, CH-4a), 0.98 (s, 9H, CH_3-tBu), 0.91 (s, 9H, CH_3-tBu). ^{13}C NMR ($CDCl_3$, δ): 191.08 (CO), 160.84 (CH-6), 105.75 (CH-7), 77.36 (CH-8a), 74.68 (CH-4a), 65.45 (CH_2-4), 27.32 (CH_3-tBu), 26.85 (CH_3-^{t}Bu), 22.78 (C- ^{t}Bu), 20.02 (C- ^{t}Bu); MS (ESI) [*m/z*, (%)]: 285 ([M+1]+, 100), 331 (71). HRMS (ESI): 285.1444 calcd for $C_{14}H_{25}O_4Si$, found 285.1517.

(4a*R*,6*S*,8a*R*)-2,2-Di-*tert*-butyl-tetrahydro-6-phenylpyrano[3,2-*d*][1,3,2]dioxasilin-8(8a*H*)-one (8) and (4a*R*,6*R*,8a*R*)-2,2-di-*tert*-butyl-tetrahydro-6-phenylpyrano[3,2-*d*][1,3,2]-dioxasilin-8(8a*H*)-one (9). To a solution of CuCN (1.86, 20.84 mmol) in ether (20 mL) cooled to -78 ºC was slowly added PhLi (23.15 mL, 41.68 mmol). The mixture was stirred at 0 ºC for 10 minutes and then was cooled again at -78 ºC for 30 minutes. On the other hand, to a solution of compound **6** (2.96 g, 10.42 mmol) in ether (20), cooled to -78 ºC, was added $BF_3{\cdot}Et_2O$ (1.28 mL, 10.42 mmol) and was stirred in the same conditions for 5 minutes. After that this solution was added over the PhLi solution at -78 º C and was stirred for 1 hour. The reaction was quenched with NH_4Cl (30 mL) and was extracted with AcOEt (3x30 mL). The combined organic phases

were washed with H_2O (50 mL) and brine (50 mL) and were dried (Na_2SO_4) and the solvent evaporated under reduced pressure. The residue was chromatographed on silica gel using 1% AcOEt/Hexane affording **8** and **9** (75%, ratio 1:1.2). **Compound 8**: yellow oil, $[\alpha]_D^{24}$ =16.4 (c=1.13,$CHCl_3$), R_f: 0.5 (30% AcOEt).^{1}H NMR ($CDCl_3$,δ)**:**7.40-7.29 (m,5H,$CH_{o,m,p}$), 4.81-4.75 (m,1H, CH-6),4.59 (d,*J* 9.84 Hz,1H, CH-8a), 4.32 (dd,*J* 9.9,*J* 5.0 Hz,1H, CH_2-4), 4.11 (t,*J* 10.2 Hz,1H, CH_2-4), 3.77 (td,*J* 9.9,*J* 4.9 Hz,1H, CH-4a), 2.79-2.75 (m,2H, CH_2-7), 1.10 (s,9H, CH_3-^{t}Bu), 1.06 (s,9H, CH_3-^{t}Bu).^{13}C NMR ($CDCl_3$,δ):202.02 (CO), 139.57 (C-Ph), 128.76 (CH_m-Ph), 128.46 (CH_p-Ph), 125.67 (CH_o-Ph), 80.33 (CH-6), 80.19 (CH-8a), 77.54 (CH-4a), 66.89 (CH_2-4), 49.26 (CH_2-7), 27.37 (CH_3-^{t}Bu), 27.00 (CH_3-^{t}Bu), 22.76 (C-^{t}Bu), 20.18 (C-^{t}Bu).MS (ESI) [*m/z*, (%)**]:**361([M-H]$^+$, 100%),363 (39%),345 ([M-H_2O]$^+$,39%). HRMS (ESI): 363.19861 calculated for $C_{20}H_{31}O_4Si$, found 363.19821. **Compound 9**: colourless solid, mp 87°C, $[\alpha]_D^{24}$= 62.8 (c=2.93,$CHCl_3$), R_f: 0.45 (30% AcOEt) ^{1}H NMR ($CDCl_3$,δ): 7.40-7.27 (m,5H, $CH_{o,m,p}$-Ph),5.47-5.42 (m,1H, CH-6),4.56 (d,*J* 10.12 Hz,1H, CH-8a),4.07-3.98 (m,2H, CH_2-4),3.58-3.49 (m,1H, CH-4a),3.15-3.10 (m,2H, CH_2-7),1.06 (s,9H, CH_3-^{t}Bu),0.88 (s,9H, CH_3-^{t}Bu).^{13}C NMR ($CDCl_3$,δ): 203.05 (CO),138.22 (C-Ph),128.75 (C_m-Ph),128.50 (C_p-Ph),127.76 (C_o-Ph),80.41 (CH-8a),76.05 (CH-6),70.82 (CH-4a), 66.87 (CH_2-4),42.97 (CH_2-7),27.32 (CH_3-^{t}Bu),26.79 (CH_3-^{t}Bu),22.69 (C-^{t}Bu),20.03 (C-^{t}Bu). MS (ESI) [*m/z*, (%)]:361 ([M-H]$^+$, 100),363 (39),345([M-H_2O]$^+$, 39). HRMS (ESI): 363.19861 calcd for $C_{20}H_{31}O_4Si$, found 363.1987.

(4a*R*,6*R*,8*S*,8a*S*)-2,2-di-*tert*-butyl-6-phenylhexahydropyrano[3,2-*d*][1,3,2]dioxasilin-8-ol (11). To a solution of ketone **8** (0.362 g, 0.99 mmol) in THF (8 mL) cooled at -78ºC was slowly added L-selectride (2.5 mL, 2.5 mmol). After 1.5 hours the reaction was quenched with NH_4Cl (10 mL) and was stirred for 30 minutes. The aqueous layer was extracted with CH_2Cl_2 (4x15 mL).The combined organic phases were dried (Na_2SO_4) and the solvent evaporated under reduced pressure. The residue was chromatographed on silica gel using 2%→4% AcOEt/Hexane affording alcohol **11** (0.326 g, 90%). **Compound 11**: white solid, mp102°C. $[\alpha]_D^{24}$=14.6 (c=2.39,$CHCl_3$), R_f:0.3 (10% AcOEt). ^{1}H-NMR ($CDCl_3$,δ):7.30 (quasi d, *J* 1.9 Hz, 4H, $CH_{o,m}$-Ph), 7.25 (m, 1H, CH_p-Ph), 4.87 (dd,*J* 11.6,*J* 1.9 Hz, 1H, CH-6), 4.20 (dd,*J* 10.0,*J* 4.6 Hz, 1H, CH_2-4),4.17 (m, 1H, CH-8), 4.0-3.98 (m, 1H, CH-4a), 3.94 (m, 1H, CH-8a),3.91 (m, 1H, CH_2-4),2.54 (s, 1H, OH),2.20 (dt,*J* 14.1,*J* 3.0 Hz, 1H, CH_2-7),1.87 (t,*J* 12.8 Hz, 1H, CH_2-7),1.07 (s, 9H, CH_3-^{t}Bu),1.04 (s, 9H, CH_3-^{t}Bu). ^{13}C-NMR ($CDCl_3$,δ):141.48 (C-Ph),128.39 (CH_o-Ph),127.6 (CH_p-Ph),125.89 (CH_m-Ph),75.24 (CH-8a),73.78 (CH-6),70.85 (CH-4a),67.12 (CH_2-4,CH-8),38.86 (CH_2-7),27.46 (CH_3-^{t}Bu),27.26 (CH_3-^{t}Bu),22.71 (C-^{t}Bu),19.48 (C-^{t}Bu). MS (ESI) [*m/z*, (%)]:298 (100),385 ([M+Na-2H]$^+$, 94),345 (94), 363([M-H]$^+$, 34). HRMS (ESI): 363.19861 calcd for $C_{20}H_{31}O_4Si$, found 363.19869.

(4a*R*,6*R*,8*S*,8a*S*)-2,2-Di-*tert*-butyl-8-(methoxymethoxy)-6-phenylhexahydropyrano[3,2-*d*]-[1,3,2]dioxasiline (12). To a solution of **11** (1.05 g, 2.88 mmol) in CH_2Cl_2 (10 mL) cooled to 0 ºC was added DIPEA (2.51 mL, 14.41 mmol) dropwise at the same temperature. After 10 minutes the ClMOM (1.09 mL, 14.41 mmol) was added and the mixture was stirred for 16 hours to room temperature.The reaction was quenched with H_2O (20 mL) and was extracted with CH_2Cl_2 (2x15 mL) and the combined organic layers were washed with H_2O (20 mL) and brine

(20 mL) and were dried (Na_2SO_4) and the solvent evaporated under reduced pressure. The residue was chromatographed on silica gel using 2% AcOEt/Hexane affording **12** (1.06 g, 90%). **Compound 12**: white solid, mp 101°C, $[\alpha]_D^{27}$= -21.8 (c= 0.78, $CHCl_3$), R_f 0.66 (30% AcOEt/Hexane). ^{1}H NMR ($CDCl_3$,δ) 7.36 (quasi d, *J* 4.4, 4H, $CH_{o,m}$-Ph), 7.32 – 7.27 (m, 1H, CH_p-Ph), 5.03 (d, 2*J* 6.6, 1H, CH_2-MOM), 4.90 (dd, *J* 2.1, 11.7, 1H, CH-6), 4.82 (d, 2*J* 6.6, 1H, CH_2-MOM), 4.26 – 4.18 (m, 2H, CH_2-5, CH-8), 4.14 (td, *J* 4.9, 9.9, 1H, CH-4a), 4.01 – 3.94 (m, 1H, CH-8a), 3.92 (d, *J* 10.1, 1H, CH_2-4), 3.48 (s, 3H, CH_3-MOM), 2.14 (ddd, *J* 2.3, 3.6, 14.1, 1H, CH_2-7), 1.92 (ddd, *J* 2.4, 11.8, 14.1, 1H, CH_2-7), 1.11 (s, 9H, CH_3-^{t}Bu), 1.07 (s, 9H, CH_3-^{t}Bu). ^{13}C NMR ($CDCl_3$, δ) 141.59(C-Ph), 128.45(CH_o-Ph), 127.71(CH_p-Ph), 126.01(CH_m-Ph), 97.02 (CH_2-MOM), 76.24 (CH-8a), 74.30 (CH-6), 72.47 (CH-8), 71.20 (CH-4a), 67.18 (CH_2-4), 55.40 (CH_3-MOM), 39.43 (CH_2-7), 27.56(CH_3-^{t}Bu), 27.03(CH_3-^{t}Bu), 22.80(C-^{t}Bu), 20.24(C-^{t}Bu). MS (ESI) [*m/z*, (%)]: 432 ([M+H+Na]$^+$, 32), 431 ([M+Na]$^+$, 100), 301 (8), 255 (11). HRMS (ESI): 431.2224 calcd for $C_{22}H_{36}NaO_5Si$, found 431.2220.

(2*R*,3*S*,4*S*,6*R*)-2-(Hydroxymethyl)-4-(methoxymethoxy)-6-phenyltetrahydro-2*H*-pyran-3-ol (13). To a solution of **12** (1.04 g, 2.55 mmol) in THF (20 mL) was added a 1,0 M solution of TBAF (7.64 mL, 7.64 mmol) at r.t. and the mixture was stirred for 24 hours in the same conditions. The solvent was evaporated and the residue was chromatographed on silica gel using 50% AcOEt/Hexane affording diol **13** (656 mg, 96%). **Compound 13**: white solid, mp 140ºC, $[\alpha]_D^{27}$= 78.3 (c 1,65, $CHCl_3$), R_f 0.22 (100% AcOEt). ^{1}H NMR ($CDCl_3$, δ): 7.57 – 7.10 (m, 5H, $CH_{o,m,p}$-Ph), 4.84 (m, 3H, CH_2-MOM, CH-6), 4.08 (m, 1H, CH-4), 3.97 (M, 1H, CH_2-1´), 3.88 – 3.77 (m, 2H, CH_2-1´, CH-2), 3.66 – 3.57 (m, 1H, CH-3), 3.51 (s, 3H, CH_3-MOM), 2.30 – 2.16 (m, 1H, CH_2-5), 1.97 – 1.78 (m, 1H, CH_2-5). ^{13}C NMR ($CDCl_3$, δ): 141.53 (C-Ph), 128.44 (CH_o-Ph), 127.74 (CH_p-Ph), 125.94 (CH_m-Ph), 97.44 (CH_2-MOM), 77.27 (CH-4), 76.89 (CH-2), 73.69 (CH-6), 68.36 (CH-3), 63.67 (CH_2-1´), 56.04 (CH_3-MOM), 39.23 (CH_2-5). MS (ESI) [*m/z*, (%)]: 292 ([M+H+Na]$^+$, 17), 291 ([M+Na]$^+$, 100), 245 (2). HRMS (ESI): 291.1203 calcd for $C_{14}H_{20}NaO_5$, found 291.1204.

(2*R*,3*S*,4*S*,6*R*)-2-((*tert*-butyldimethylsilyloxy)methyl)-4-(methoxymethoxy)-6-phenyl-tetrahydro-2*H*-pyran-3-ol (14). To a solution of diol **13** (595 mg, 2.22 mmol) in THF (10 mL) were added imidazole (181 mg, 2.66 mmol), a catalytic amount of DMAP and TBSCl (399 mg, 2.66 mmol) and the mixture was stirred for 18 hours at r.t.. The solvent was evaporated, H_2O (10 mL) added and the product extracted with CH_2Cl_2 (4 × 10 mL).). The organic phase was dried over Na_2SO_4, filtered and the solvent evaporated under reduced pressure. The residue was purified by chromatography on silica gel (30% EtOAc/Hexane) affording **14** (848 mg, 99%). **Compound 14**: colourless oil, $[\alpha]_D^{27}$= 40.8 (c 4.45, $CHCl_3$), R_f 0.24 (30% EtOAc/Hexane). ^{1}H NMR ($CDCl_3$, δ): 7.48 – 7.22 (m, 5H, $CH_{o,m,p}$-Ph), 4.98 – 4.71 (m, 3H, CH_2-MOM, CH-6), 4.11 (s, 1H, CH-4), 4.04 – 3.88 (m, 2H, CH_2-1´), 3.87 – 3.76 (m, 1H, CH-2), 3.71 (dd, *J* 1.8, 9.8, 1H, CH-3), 3.50 (d, *J* 1.5, 3H, CH_3-MOM), 2.32 – 2.10 (m, 1H, CH_2-5), 1.81 (m, 1H, CH_2-5), 0.94 (s, 9H, ^{t}Bu-TBS), 0.13 (s, 3H, CH_3-TBS), 0.11 (s, 3H, CH_3-TBS). ^{13}C NMR ($CDCl_3$ δ): 142.12 (C-Ph), 128.29 (CH_o-Ph), 127.40 (CH_p-Ph), 125.87 (CH_m-Ph), 97.29 (CH_2-MOM), 76.40 (CH-2), 75.94 (CH-4), 73.53 (CH-6), 69.43 (CH-3), 64.88 (CH_2-1´), 55.82 (CH_3-MOM), 39.32 (CH_2-

5), 25.95 (CH_3-^{t}Bu(TBS)), 18.39 (C-^{t}Bu(TBS)), -5.25 (CH_3-Me(TBS)), -5.30 (CH_3-Me(TBS)). MS (ESI) [*m/z*, (%)]: 406 ([M+H+Na]$^+$, 29), 405 ([M+Na]$^+$, 100), 383 ([M+H]$^+$, 5). HRMS (ESI): 405.2068 calcd for $C_{20}H_{34}NaO_5Si$, found 405.2050.

***O*-(2*R*,3*S*,4*S*,6*R*)-2-((*tert*-butyldimethylsilyloxy)methyl)-4-(methoxymethoxy)-6-phenyltetrahydro-2*H*-pyran-3-yl 1*H*-imidazole-1-carbothioate (15).** To a solution of **14** (535 mg, 1.397 mmol) in THF (15 mL) was added Im_2CS (498 mg, 2.79 mmol) and the mixture was stirred for 23 hours at 70 ºC. The reaction was quenched with H_2O (10 mL) extracted with AcOEt (2x15 mL) and the combined organic layers were washed with H_2O (20 mL) and brine (20 mL) dried over Na_2SO_4, filtered and the solvent evaporated under reduced pressure. The residue was purified by chromatography on silica gel (20% EtOAc/Hexane) affording **15** (624 mg, 91%). **Compound 15**: colourless oil, $[\alpha]_D^{27}$= 52.4 (c 0.58, $CHCl_3$), R_f 0.17 (30% EtOAc/Hexane). ^{1}H NMR ($CDCl_3$, δ) 8.39 (s, 1H, H2-Im), 7.69 (s, 1H, H5-Im), 7.38 (m, 4H, $CH_{o,m}$-Ph), 7.34 – 7.26 (m, 1H, CH_P-Ph), 7.08 (s, 1H, H4-Im), 5.74 (dd, *J* 2.9, 10.0, 1H, CH-3´), 4.96 (d, *J* 10.6, 1H, CH-6´), 4.76 (d, *J* 6.9, 1H, CH_2-MOM), 4.67 (d, *J* 6.9, 1H, CH_2-MOM), 4.61 (s, 1H, CH-4´), 4.33 (d, *J* 9.8, 1H, CH-2´), 3.92 (d, *J* 9.9, 1H, CH_2-1´´), 3.83 (dd, *J* 3.5, 11.5, 1H, CH_2-1´´), 3.32 (s, 3H, CH_3-MOM), 2.23 (d, *J* 14.3, 1H, CH_2-5´), 1.93 (t, *J* 12.2, 1H, CH_2-5´), 0.88 (s, 9H, ^{t}Bu-TBS), 0.05 (s, 3H, CH_3-TBS), -0.01 (s, 3H, CH_3-TBS). ^{13}C NMR ($CDCl_3$, δ) 182.72 (CS), 141.40 (C-Ph), 136.76 (CH-Im), 130.94 (CH-Im), 128.41 (CH_o-Ph), 127.69 (CH_p-Ph), 125.86 (CH_m-Ph), 117.98 (CH-Im), 96.33 (CH_2-MOM), 77.97 (CH-3´), 74.38 (CH-2´), 74.14 (CH-6´), 70.63 (CH-4´), 63.08 (CH_2-1´´), 55.60 (CH_3-MOM), 38.98 (CH_2-5´), 25.86 (CH_3-tBu(TBS)), 18.28 (C-TBS), -5.32 (CH_3-TBS), -5.43 (CH_3-TBS). MS (ESI) [*m/z*, (%)]: 494 (46%), 493 ([M+H]$^+$, 100), 477 (55%). HRMS (ESI): 493.2187 calcd for $C_{24}H_{37}N_2O_5SSi$, found 493.2178.

***tert*-Butyl(((2*S*,4*S*,6*R*)-4-(methoxymethoxy)-6-phenyltetrahydro-2*H*-pyran-2-yl)methoxy) dimethylsilane (16).** A solution of **15** (219 mg, 0.445 mmol) in toluene (5 mL) in a sealed tube was desoxygenated the following way: first the solution was freezed in liquid N_2, then the sealed tube connected to vacuum to eliminated the oxygen and finally purged with argon. This process is repeated until the whole oxygen has been eliminated. To the solution was added at room temperature Bu_3SnH (0.144 mL, 0.534 mmol) and then AIBN (0.178 mL, 0.035 mmol), the tube was closed and the solution was stirred at 120 ºC for 5 hours. The solvent was evaporated under reduced pressure. The residue was purified by chromatography on silica gel (2% AcOEt/ Hexane) affording **16** (129 mg, 79%). **Compound 16**: colourless oil, $[\alpha]_D^{27}$= 15.6 (c 1.69, $CHCl_3$), R_f 0.58 (30% AcOEt/ Hexane). ^{1}H NMR ($CDCl_3$, δ): 7.42 – 7.33 (m, 4H, $CH_{o,m}$-Ph), 7.28 (m, 1H, CH_P-Ph), 4.86 (d, *J* 10.1, 1H, CH-6), 4.82 – 4.76 (m, 2H, CH_2-MOM), 4.21 – 4.16 (m, 1H, CH-4), 4.03 (dd, *J* 5.0, 10.4, 1H, CH-2), 3.81 (dd, *J* 5.0, 10.4, 1H, CH_2-2´), 3.65 (dd, *J* 5.8, 10.4, 1H, CH_2-2´), 3.46 (s, 3H, CH_3-MOM), 2.09 – 1.96 (m, 2H, CH_2-3, CH_2-5), 1.78 – 1.64 (m, 2H, CH_2-5), 1.64 – 1.53 (m, 1H, CH_2-3), 0.95 (d, *J* 10.3, 9H, ^{t}Bu-TBS), 0.11 (s, 3H, CH_3-TBS), 0.09 (s, 3H, CH_3-TBS). ^{13}C NMR ($CDCl_3$, δ):143.06 (C-Ph), 128.26 (CH_o-Ph), 127.23 (CH_p-Ph), 125.91 (CH_m-Ph), 95.19 (CH_2-MOM), 74.24 (CH-6), 73.41 (CH-2), 70.17 (CH-4), 66.64 (CH_2-2´), 55.44 (CH_3-MOM), 38.97 (CH_2-5), 32.71 (CH_2-3), 25.95 (CH_3- ^{t}Bu(TBS)),

18.38 (C-TBS), -5.18 (CH_3-TBS), -5.23 (CH_3-TBS). MS (ESI) [*m/z*, (%)]: 390 ($[M+Na+H]^+$, 39), 389 ($[M+Na]^+$, 100), 384 (19), 367 ($[M+H]^+$, 5). HRMS (ESI): 389.2119 calcd for $C_{20}H_{34}NaO_4Si$, found 389.2133.

((2*S*,4*S*,6*R*)-4-(Methoxymethoxy)-6-phenyltetrahydro-2*H*-pyran-2-yl)methanol(17). To a solution of **16** (330 mg, 0.9 mmol) in THF (10 mL) was added a 1,0 M solution of TBAF (1.35 mL, 1.35 mmol) at r.t. and stirred for 12 hours in the same conditions. The solvent was evaporated and the residue was chromatographed on silica gel using 50% AcOEt/Hexane affording **17** (194 mg, 85%). **Compound 17**: Colourless oil, $[\alpha]_D^{27}$= 35.3 (c 1.27, $CHCl_3$), R_f 0.13 (30% AcOEt/Hexane). ^{1}H NMR ($CDCl_3$, δ): 7.41 – 7.32 (m, 4H, $CH_{o,m}$-Ph), 7.31 – 7.26 (m, 1H, CH_P-Ph), 4.87 – 4.82 (m, 1H, CH-6), 4.77 – 4.72 (m, 2H, CH_2-MOM), 4.16 – 4.11 (m, 1H, CH-4), 4.10 – 4.02 (m, 1H, CH-2), 3.68 – 3.52 (m, 2H, CH_2-2´), 3.42 (s, 3H, CH_3-MOM), 2.76 (s, 1H, OH), 2.07 – 1.96 (m, 1H, CH_2-5), 1.79 – 1.66 (m, 2H, CH_2-5, CH_2-3), 1.64 – 1.49 (m, 1H, CH_2-3). ^{13}C NMR ($CDCl_3$, δ):142.61 (C-Ph), 128.37 (CH_o-Ph), 127.54 (CH_p-Ph), 126.08 (CH_m-Ph), 95.12 (CH_2-MOM), 74.31 (CH-6), 73.46 (CH-2), 69.90 (CH-4), 66.07 (CH_2-2´), 55.47 (CH_3-MOM), 38.48 (CH_2-5), 31.76 (CH_2-3). MS (ESI) [*m/z*, (%)]: 276 ($[M+Na+H]^+$, 17), 275 ($[M+Na]^+$, 100). HRMS (ESI): 275.1254 calcd for $C_{14}H_{20}NaO_4$, found 275.1260.

((2*S*,4*S*,6*R*)-4-(Methoxymethoxy)-6-phenyltetrahydro-2*H*-pyran-2-yl)methyl4-methylbenzenesulfonate (18). To a solution of **17** (115 mg, 0.456 mmol) in CH_2Cl_2 (5 mL) was added pyridine (0.5 mL) and p-TsCl (174 mg, 0.912 mmol) and was stirred at room temperature for 28 hours. The reaction was quenched with H_2O (10 mL) and was extracted with EtOAc (2x10 mL) and the combined organic layers were washed with Cu_2SO_4 (15 mL), H_2O (15 mL) and brine (15 mL), dried over Na_2SO_4, filtered and the solvent evaporated under reduced pressure. The residue was purified by chromatography on silica gel (20% EtOAc/Hexane) affording **18** (184 mg, 99%). **Compound 18**: colourless oil, $[\alpha]_D^{27}$= 25.1 (c 0.51, $CHCl_3$), R_f 0.67 (50% EtOAc/Hexane). ^{1}H NMR ($CDCl_3$, δ):7.84 – 7.78 (m, 2H, CH-Ts), 7.37 – 7.24 (m, 7H, CH-Ts, $CH_{o,m,p}$-Ph), 4.82 – 4.72 (m, 3H, CH_2-MOM, CH-6), 4.17 (m, 2H, CH-2, CH-4), 4.10 (m, 2H, CH_2-2´), 3.43 (s, 3H, CH_3-MOM), 2.44 (s, 3H, CH_3-Ts), 2.05 – 1.97 (m, 1H, CH_2-3), 1.87 – 1.80 (m, 1H, CH_2-3), 1.71 – 1.56 (m, 2H, CH_2-5). ^{13}C NMR ($CDCl_3$, δ): 144.69(C-Ts), 142.25 (C-Ph), 132.89(C-Ts), 129.78(CH-Ts), 128.28 (CH_o-Ph), 128.04(CH-Ts), 127.44 (CH_p-Ph), 125.78 (CH_m-Ph), 95.16(CH_2-MOM), 74.21(CH-6), 72.53(CH-2), 70.22(CH-4), 69.46(CH_2-2´), 55.57(CH_3-MOM), 38.24(CH_2-5), 31.98(CH_2-3), 21.69(CH_3-Ts). MS (ESI) [*m/z*, (%)]: 430 ($[M+Na+H]^+$, 32), 429 ($[M+Na]^+$, 100), 245 (29). HRMS (ESI): 429.1342 calcd for $C_{21}H_{26}NaO_6S$, found 429.1327.

2-((2*R*,4*R*,6*R*)-4-(methoxymethoxy)-6-phenyltetrahydro-2*H*-pyran-2-yl)acetonitrile (19). To a solution of **18** (173 mg, 0.426 mmol) in DMSO (8 mL) was added NaCN (64 mg, 1.28 mmol) and was stirred at 50 ^{o}C for 6 hours. The reaction was quenched with H_2O (5 mL) and was extracted with EtOAc (2x10mL) and the combined organic layers were washed with H_2O (15 mL) and brine (15 mL), dried over Na_2SO_4, filtered and the solvent evaporated under reduced pressure. The residue was purified by chromatography on silica gel (10% EtOAc/Hexane) affording **19** (104 mg, 94%). **Compound 19**: Colourless oil, $[\alpha]_D^{27}$= 22.6 (c

0.28, $CHCl_3$), R_f 0.5 (50% EtOAc/Hexane). ^{1}H NMR ($CDCl_3$, δ): 7.42 – 7.34 (m, 4H, $CH_{o,m}$-Ph), 7.33 – 7.26 (m, 1H, CH_P-Ph), 4.89 (dd, *J* 11.8, 2.2 Hz, 1H, CH-6), 4.77 (s, 2H, CH_2-MOM), 4.26 (dtd, *J* 11.6, 5.7, 2.1 Hz, 1H, CH-2), 4.20 (p, *J* 3.0 Hz, 1H CH-4), 3.45 (d, *J* 0.7 Hz, 3H, CH_3-MOM), 2.71 – 2.58 (m, 2H, CH_2-1′), 2.11 – 1.97 (m, 2H, CH_2-3, CH_2-5), 1.78 – 1.68 (m, 2H, CH_2-3, CH_2-5). ^{13}C NMR (CDCl3, δ):141.97 (C-Ph), 128.44 (C_o-Ph), 127.65 (C_p-Ph), 125.81 (C_m-Ph), 117.18 (CN), 95.32 (CH_2-MOM), 74.63 (CH-6), 69.65 (CH-4), 68.20 (CH-2), 55.62 (CH_3-MOM), 37.96 (CH_2-5), 35.25 (CH_2-3), 24.79 (CH_2-1′). MS (ESI) [*m/z*, (%)]: 285 ($[M+Na+H]^+$, 21), 284 (($[M+Na]^+$, 100), 279 (27). HRMS (ESI)**:**284.1257, calcd for $C_{15}H_{19}NNaO_3$, found 284.1247.

2-((2*S*,4*R*,6*R*)-4-(Methoxymethoxy)-6-phenyltetrahydro-2*H*-pyran-2-yl)-1-phenylethanone (21). To a solution of **19** (98.5 mg, 0.337 mmol) in CH_2Cl_2 (5 mL) was added dropwise at -78 ºC DIBAL-H (0.566 mL, 0.566 mmol) and was stirred at the same temperature for 5 hours. The reaction was quenched with NH_4Cl (6 mL) and was stirred for 30 min at room temperature. The mixture was extracted with CH_2Cl_2 (3 x 8 mL). The combined organic layers were dried over Na_2SO_4, filtered and the solvent evaporated under reduced pressure affording an aldehyde (99.5 mg, 99%), used in the next reaction without further purification. The crude aldehyde (99.5 mg, 0.377 mmol) was disolved in THF (5 mL) and was cooled to -78 ºC. PhLi (0.452 mmol, 0.251 mL) was added dropwise and the mixture stirred for 4 hours at -78 ºC. The reaction was quenched with H_2O (10 mL) and the mixture was extracted with EtOAc (2x10 mL) and the combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered and the solvent evaporated under reduced pressure. The residue was purified by chromatography on silica gel (5% EtOAc/Hexane) affording **20** (87 mg, 68%) as a mixture of diastereoisomeric alcohols. **Mixture of alcohols 20:** ^{1}H NMR ($CDCl_3$, δ): 7.43 – 7.25 (m, 20H, Ph), 5.13 – 5.07 (m, 1H, CH-6), 5.03 (dd, *J* 9.8, 2.7 Hz, 1H, CH-6), 4.95 (dd, *J* 11.8, 2.2 Hz, 1H, CH-2′), 4.83 (dd, *J* 11.8, 2.2 Hz, 1H, CH-2′), 4.78 (s, 2H, CH_2-MOM), 4.73 (s, 2H, CH_2-MOM), 4.35 (m, 1H, CH-2), 4.22 (m, 2H, CH-2, CH-4), 4.14 (m, 4H, CH-4), 3.45 (s, 3H, CH_3-MOM), 3.37 (s, 3H, CH_3-MOM), 2.12 – 1.99 (m, 4H, CH_2-1′, CH_2-3, CH_2-5), 1.90 – 1.69 (m, 8H, CH_2-1′, CH_2-3, CH_2-5). **^{13}C** NMR ($CDCl_3$, δ):144.74 (C-Ph), 144.54 (C-Ph), 142.58 (C-Ph), 142.28 (C-Ph), 128.52 (C_o-Ph), 128.49 (C_o-Ph), 128.33 (C_o-Ph), 128.32 (C_o-Ph), 127.60 (C_p-Ph), 127.54 (C_p-Ph), 127.24 (C_p-Ph), 127.00 (C_p-Ph), 125.78 ($2C_m$-Ph), 125.72 (C_m-Ph), 125.60 (C_m-Ph), 95.19 (CH_2-MOM), 95.16 (CH_2-MOM), 74.59 (CH-2, CH-6), 74.51 (CH-2′), 74.26 (CH-2′), 71.44 (CH-6), 70.68 (CH-2), 70.10 (CH-4), 69.86 (CH-4), 55.54 (CH_3-MOM), 55.45 (CH_3-MOM), 45.51 (CH_2-5), 43.96 (CH_2-5), 38.46 (CH_2-3), 38.30 (CH_2-3), 36.58 (CH_2-1′), 35.75 (CH_2-1′). To a solution of **20** (87 mg, 0.254 mmol) in CH_2Cl_2 (4 mL) was added PDC (287 mg, 0.763 mmol) and was stirred at room temperature for 30 hours. The reaction was quenched with Et_2O (5 mL) and a formation of a precipitate was observed and was filtered over celita and was washed with Et_2O (3x10 mL). The residue was purified by chromatography on silica gel (5% EtOAc/Hexane) affording ketone **21** (56 mg, 65%). **Compound 21**: Colourless oil, $[\alpha]_D^{27}$= 13.8 (c 1.13, $CHCl_3$), R_f 0.48 (50% EtOAc/Hexane). ^{1}H NMR ($CDCl_3$, δ): 8.06 – 7.97 (m, 2H, CH_o-Ph(C1)), 7.62 – 7.55 (m, 1H, CH_p-Ph(C1)), 7.48 (m, 2H, CH_m-Ph(C1)), 7.37 – 7.31 (m, 4H,

$CH_{o,m}$-Ph(C-6′)), 7.29 – 7.23 (m, 1H, CH_p-Ph(C-6′)), 4.91 (m, 1H, CH-6′), 4.84 – 4.75 (m, 2H, CH_2-MOM), 4.63 (m, 1H, CH-2′), 4.17 (m, 1H, CH-4′), 3.46 (s, 3H, CH_3-MOM), 3.42 (d, *J* 5.8 Hz, 1H, CH_2-2), 3.08 (dd, *J* 15.9, 6.6 Hz, 1H, CH_2-2), 2.16 – 2.03 (m, 2H, CH_2-5′, CH_2-3′), 1.81 – 1.68 (m, 1H, CH_2-5′), 1.61 (m, 1H, CH_2-3′). ^{13}C NMR ($CDCl_3$, δ):198.28 (CO), 142.77 (C-Ph(C6′)), 137.38 (C-Ph(C1)), 133.07 (CH_p-Ph(C6′)), 128.55 (CH_o-Ph(C1)), 128.36 (CH_o-Ph(C6)), 128.28 (CH_m-Ph(C6′)), 127.27 (CH_p-Ph(C6′)), 125.82 (CH_m-Ph(C1)), 95.15 (CH_2-MOM), 74.34 (CH-6′), 69.93 (CH-4′), 69.77 (CH-2′), 55.53 (CH_3-MOM), 45.26 (CH_2-2), 38.36 (CH_2-5′), 35.93 (CH_2-3′). MS (ESI) [*m/z*, (%)]: 364 ($[M+Na+H]^+$, 24), 363 ($[M+Na]^+$, 100), 341 ($[M+H]^+$, 10). HRMS (ESI): 363.1567 calcd for $C_{21}H_{24}NaO_4$, found 363.1564.

2-((2′*S*,4′*R*,6′*R*)-4′-hydroxy-6′-phenyltetrahydro-2*H*-pyran-2′-yl)-1-phenylethanone (ent-1). To a solution **21** (31 mg, 0.091 mmol) in MeOH (2 mL) was added dropwise HCl(37%, 34 drops) and the reaction was followed by TLC. The reaction was concentrated and the crude was purified by chromatography on silica gel (20% EtOAc/Hexane) affording **ent-Diospongin A** (22.7 mg, 84%). **Ent-Diospongin A:** white solid, mp 128 ºC, $[\alpha]_D^{28}$= 25.4 (c 1.07, $CHCl_3$), R_f 0.24 (50% EtOAc/Hexane). ^{1}H NMR (CDCl3, δ): 8.01 (m, 2H, CH_o-Ph(CH-1)), 7.62 – 7.54 (m, 1H, CH_p-Ph(CH-1)), 7.48 (m, 2H, CH_m-Ph(CH-1)), 7.37 – 7.22 (m, 5H, $CH_{o,m,p}$-Ph(CH-6′)), 4.97 (dd, *J* 11.7, 2.1 Hz, 1H, CH-6′), 4.68 (m, 1H, CH-2′), 4.44 – 4.33 (m, 1H, CH4′), 3.45 (dd, *J* 16.1, 5.7 Hz, 1H, CH_2-2), 3.10 (dd, *J* 16.1, 6.9 Hz, 1H, CH_2-2), 2.39 – 2.12 (m, 1H, OH), 2.07 – 1.92 (m, 2H, CH_2-3′,CH_2-5′), 1.74 (m, 2H, CH_2-3′,CH_2-5′). ^{13}C NMR (CDCl3, δ): 198.50 (CO), 142.71 (C-Ph(CH-6′)), 137.25 (C-Ph(CH-1), 133.18 (CH_p-Ph(CH-1)), 128.57(CH_m-Ph(CH-6′)), 128.36 (CH_o-Ph(CH-1)), 128.28 (CH_m-Ph(CH-1)), 127.27 (CH_p-Ph(CH-6′)), 125.86 (CH_o-Ph(CH-6′)), 73.84 (CH-6′), 69.07 (CH-2′), 64.63 (CH-4′), 45.18 (CH_2-2), 40.02 (CH_2-5′), 38.48 (CH_2-3′). MS (ESI) [*m/z*, (%)]: 320 ($[M+Na+H]^+$, 19), 319 ($[M+Na]^+$, 100), 297 ($[M+H]^+$, 14). HRMS (ESI): 319.1305 calcd for $C_{19}H_{20}NaO_3$, found 319.1300.

(4a*R*,6*S*,8*S*,8a*S*)-2,2-Di-*tert*-butyl-6-phenylhexahydropyrano[3,2-*d*][1,3,2]dioxasilin-8-ol (22). To a solution of ketone **9** (2.05 g, 5.65 mmol) in THF (20 mL) cooled at -78 ºC was added slowly L-selectride (14.14 mL, 14.14 mmol). After 2′5 hours the reaction was quenched with NH_4Cl (20 mL) and was stirred for 30 minutes. The aqueous layer was extracted with CH_2Cl_2 (4x25 mL).The combined organic phases were dried (Na_2SO_4) and the solvent evaporated under reduced pressure. The residue was chromatographed on silica gel using 2%→4% AcOEt/Hexane affording alcohol **22** (1.91 g, 93%). Compound **22**: colourless oil, $[\alpha]_D^{21}$= 31.1 (c 0.67, $CHCl_3$), R_f 0.42 (30% EtOAc/Hexane). ^{1}H-NMR ($CDCl_3$,δ): 7.54 (d, *J* 7.7 Hz, 2H, CH_o-Ph), 7.41 (t, *J* 7.7 Hz, 2H, CH_m-Ph), 7.36 – 7.23 (m, 1H, CH_p-Ph), 5.05 (d, *J* 6.8, 1H, CH-6), 4.26 (m, 1H, CH_2-4), 4.23 (m, 1H, CH-8), 4.01 (m, 1H, CH-4a), 3.95 (m, 2H, CH-8a, CH_2-4), 2.82 (m, 1H, CH_2-7), 2.32 (m, 1H, CH_2-7), 1.12 (s, 9H, CH_3-^{t}Bu), 0.97 (s, 9H, CH_3-^{t}Bu). ^{13}C-NMR ($CDCl_3$,δ): 141.05 (C-Ph), 128.12 (CH_o-Ph), 126.81 (CH_p-Ph), 126.23 (CH_m-Ph), 75.35 (CH-4a), 71.83 CH-6), 67.07 (CH_2-4), 66.38 (CH-8), 63.88 (CH-8a), 31.62 (CH_2-7), 27.55 (CH_3-^{t}Bu), 27.21 (CH_3-^{t}Bu), 22.79 (C-^{t}Bu), 20.18 (C-^{t}Bu). MS (ESI) [*m/z*, (%)]:363 (30), 345 (100). HRMS (ESI):363.19861 calcd for $C_{20}H_{31}O_4Si$, found 363.19874.

(4a*R*,6*S*,8*S*,8a*S*)-2,2-Di-*tert*-butyl-8-(methoxymethoxy)-6-phenylhexahydropyrano[3,2-*d*]-

[1,3,2]dioxasiline (23). To a solution of **22** (1.73 g, 4.75 mmol) in CH_2Cl_2 (8 mL) cooled to 0 ºC was added DIPEA (4.13 mL, 23.75 mmol) dropwise at the same temperature. after 10 minutes the ClMOM (1.80 mL, 23.75 mmol) was added and the mixture was stirred for 16 hours to room temperature.The reaction was quenched with H_2O (15 mL) and was extracted with CH_2Cl_2 (2x10 mL) and the combined organic layers were washed with H_2O (20 mL) and brine (20 mL), dried (Na_2SO_4) and the solvent evaporated under reduced pressure. The residue was chromatographed on silica gel using 2% AcOEt/Hexane affording **23** (1.45 g, 75%). **Compound 23**: colourless oil, $[\alpha]_D^{21}$= 5.9 (c 7.43, $CHCl_3$), R_f 0.61 (10% EtOAc/Hexane). ^{1}H NMR ($CDCl_3$, δ): 7.45 (m, 2H, CH_o-Ph), 7.37 (m, 2H, CH_m-Ph), 7.26 (m, 1H, CH_p-Ph), 5.05 (d, *J* 6.5, 1H, CH-6), 4.65 (d, *J* 6.7, 1H, CH_2-MOM), 4.52 (d, *J* 6.6, 1H, CH_2-MOM), 4.28 (m, 1H, CH_2-4), 4.14 (m, 2H, CH-8, CH-8a), 4.03 (m, 1H, CH-4a), 3.95 (m, 1H, CH_2-4), 3.32 (s, 3H, CH_3-MOM), 2.70 (m, 1H, CH_2-), 2.29 (m, 1H, CH_2-7), 1.07 (s, 9H, CH_3-^{t}Bu), 1.01 (s, 9H, CH_3-^{t}Bu). ^{13}C NMR ($CDCl_3$, δ): 141.62 (C-Ph), 127.98 (CH_o-Ph), 126.38 (CH_p-Ph), 125.48 (CH_m-Ph), 96.17 (CH_2-MOM), 76.04 (CH-4a), 71.70 (CH-6), 70.95 (CH-8), 67.08 (CH_2-4), 64.69 (CH-8a), 55.31 (CH_3-MOM), 32.25 (CH_2-7), 27.59 (CH_3-^{t}Bu), 26.90 (CH_3-^{t}Bu), 22.80 (C-^{t}Bu), 20.12 (C-^{t}Bu). MS (ESI) [*m/z*, (%)]:409 ($[M+H]^+$, 65), 408 ($[M]^+$, 44), 407 ($[M-H]^+$, 100), 377 (50), 345 (33). HRMS (ESI): 409.2405 calcd for $C_{22}H_{37}O_5Si$, found 409.2395.

(2*R*,3*S*,4*S*,6*S*)-2-(Hydroxymethyl)-4-(methoxymethoxy)-6-phenyltetrahydro-2*H*-pyran-3-ol (24). To a solution of **23** (1.45 g, 3.55 mmol) in THF (20 mL) was added a 1,0 M solution of TBAF (10.65 mL, 10.65mmol) at r.t. and stirred for 24 hours in the same conditions. The solvent was evaporated and the residue was chromatographed on silica gel using 50% AcOEt/Hexane affording diol **24** (948 mg,99%). **Compound 24:** white solid, mp 120ºC, $[\alpha]_D^{21}$= 34.7 (c 1.65, $CHCl_3$), R_f 0.76 (100% EtOAc). ^{1}H NMR ($CDCl_3$,δ): 7.42 (m, 2H, CH_o-Ph), 7.36 (m, 2H, CH_m-Ph), 7.29 (m, 1H, CH_p-Ph), 4.78 (dd, *J* 3.3, 9.8 Hz, 1H, CH-6), 4.72 (d, *J* 6.9 Hz, 1H, CH_2-MOM), 4.67 (d, *J* 6.9 Hz, 1H, CH_2-MOM), 4.25 – 4.15 (m, 1H, CH-2), 4.08 – 3.99 (m, 1H, CH-4), 3.95 (dd, *J* 8.3, 11.5 Hz, 1H, CH_2-1´), 3.89 (m, 1H, CH-3), 3.74 (dd, *J* 4.7, 11.6 Hz, 1H, CH-1´), 3.37 (s, 3H, CH_3-MOM), 2.23 (m, 1H, CH_2-5), 2.08 – 1.97 (m, 1H, CH_2-5). ^{13}C NMR ($CDCl_3$, δ): 141.46 (C-Ph), 128.39 (CH_o-Ph), 127.59 (CH_p-Ph), 125.95 (CH_m-Ph), 94.90 (CH_2-MOM), 77.37 (CH-2), 72.88 (CH-4), 71.95 (CH-6), 66.68 (CH-3), 60.69 (CH_2-1´), 55.74 (CH_3-MOM), 33.51 (CH_2-5). MS (ESI) [*m/z*, (%)]: 291 ($[M+Na]^+$, 100), 288 (33). HRMS (ESI): 291.1203 calcd for $C_{14}H_{20}NaO_5$, found 291.1201.

(2*R*,3*S*,4*S*,6*S*)-2-((*tert*-Butyldim**eth**ylsilyloxy)methyl)-4-(methoxymethoxy)-6-phenyltetrahydro-2*H*-pyran-3-ol (25).** To a solution of diol **24** (0.285 mg, 1.06 mmol) in THF (5 mL) were added imidazole (87 mg, 1.28 mmol), a catalytic amount of DMAP and TBSCl (192 mg, 1.28 mmol) and stirred for 18 hours at r.t.. The solvent was evaporated, H_2O (5 mL) added and the product extracted with CH_2Cl_2 (4 × 5 mL).). The organic phase was dried over Na_2SO_4, filtered and the solvent evaporated under reduced pressure. The residue was purified by chromatography on silica gel (30% EtOAc/Hexane) affording **25** (361 mg, 89%). **Compound 25:** colourless oil, $[\alpha]_D^{22}$= 7.8 (c 1.74, $CHCl_3$), R_f 0.77 (30% EtOAc/Hexane). ^{1}H NMR ($CDCl_3$, δ): 7.42 (d, *J* 7.4 Hz, 2H, CH_o-Ph), 7.35 (t, *J* 7.6 Hz, 2H, CH_m-Ph), 7.28 (m, 1H, CH_p-Ph), 4.91

(dd, *J* 2.6, 10.9 Hz, 1H, CH-6), 4.76 (d, *J* 6.8 Hz, 1H, CH_2-MOM), 4.72 (d, *J* 6.8 Hz, 1H, CH_2-MOM), 4.35 – 4.25 (m, 1H, CH-4), 4.21 – 4.13 (m, 1H, CH-2), 4.08 (d, *J* 2.2 Hz, 1H, CH-3), 4.01 (dd, *J* 5.5, 10.8 Hz, 1H, CH_2-1´), 3.90 (dd, *J* 4.7, 10.8 Hz, 1H, CH_2-1´), 3.40 (s, 3H, CH_3-MOM), 2.72 (d, *J* 2.9 Hz, 1H, OH), 2.21 – 2.03 (m, 1H, CH_2-5), 2.03 – 1.94 (m, 1H, CH_2-5), 0.96 (s, 9H, ^{t}Bu-TBS), 0.13 (s, 3H, CH_3-TBS), 0.12 (s, 3H, CH_3-TBS). ^{13}C NMR ($CDCl_3$ δ): 142.20 (C-Ph), 128.34 (CH_o-Ph), 127.49 (CH_p-Ph), 125.96 (CH_m-Ph), 94.61 (CH_2-MOM), 78.31 (CH-2), 73.70 (CH-6), 72.51 (CH-4), 67.05 (CH-3), 64.03 (CH_2-1´), 55.52 (CH_3-MOM), 33.65 (CH_2-5), 25.89 (CH_3-^{t}Bu(TBS)), 18.18 (C-^{t}Bu(TBS)), -5.47 (CH_3-Me(TBS)), -5.54 (CH_3-Me(TBS)). MS (ESI) [*m/z*, (%)]: 406 ($[M+Na+H]^+$, 37), 405 ($[M+Na]^+$, 100), 383 ($[M+H]^+$, 10), 351 (38), 303 (49). HRMS (ESI): 405.2068 calcd for $C_{20}H_{34}NaO_5Si$, found 405.2080.

***O*-(2*R*,3*S*,4*S*,6*S*)-2-((*tert*-Butyldimethylsilyloxy)methyl)-4-(methoxymethoxy)-6-phenyltetrahydro-2*H*-pyran-3-yl 1*H*-imidazole-1-carbothioate (26).** To a solution of alcohol **25** (895 mg, 2.34 mmol) in THF (15 mL) was added Im_2CS (570 mg, 4.68 mmol) and was stirred for 34 hours at 70ºC. The reaction was quenched with H_2O (10 mL) extracted with AcOEt (2x15 mL) and the combined organic layers were washed with H_2O (20 mL) and brine (20 mL) were dried over Na_2SO_4, filtered and the solvent evaporated under reduced pressure. The residue was purified by chromatography on silica gel (20% EtOAc/Hexane) affording **26** (835 mg, 73%). **Compound 26:** yellow oil, $[\alpha]_D^{22}$= 2.6 (c 2.27, $CHCl_3$), R_f 0.47 (50% EtOAc/Hexane). ^{1}H NMR ($CDCl_3$, δ): 8.45 (s, 1H, CH2-Im), 7.73 (s, 1H, CH5-Im), 7.39 (m, 4H, $CH_{o,m}$-Ph), 7.32 (m, 1H, CH_P-Ph), 7.08 (s, 1H, CH4-Im), 6.10 (s, 1H, CH-3´), 5.06 (m, 1H, CH-6´), 4.73 (d, *J* 7.0 Hz, 1H, CH_2-MOM), 4.68 (d, *J* 7.0 Hz, 1H, CH_2-MOM), 4.61 (m, 1H, CH-4´), 4.41 (m, 1H, CH-2´), 4.10 (dd, *J* 5.6, 11.0 Hz, 1H, CH_2-1´´), 4.00 (dd, *J* 4.5, 11.0 Hz, 1H, CH_2-1´´), 3.35 (s, 3H, CH_3-MOM), 2.16 (m, 1H, CH_2-5´), 2.10 (m, 1H, CH_2-5´), 0.99 (s, 9H, ^{t}Bu-TBS), 0.17 (s, 3H, CH_3-TBS), 0.16 (s, 3H, CH_3-TBS). ^{13}C NMR ($CDCl_3$, δ): 183.81 (CS), 141.57 (C-Ph), 136.87 (CH2-Im), 130.87 (CH4-Im), 128.64 (CH_o-Ph), 128.02 (CH_p-Ph), 125.81 (CH_m-Ph), 118.14 (CH5-Im), 94.86 (CH_2-MOM), 78.69 (CH-3´), 76.51 (CH-2´), 74.25 (CH-6´), 70.14 (CH-4´), 63.61 (CH_2-1´´), 55.62 (CH_3-MOM), 35.82 (CH_2-5´), 25.86 (CH_3- tBu(TBS)), 18.12 (C-TBS), -5.48 (CH_3-TBS), -5.59 (CH_3-TBS). MS (ESI) [*m/z*, (%)]: 405 (100), 351 (39), 303 (52). HRMS (ESI): 493.2187 calcd for $C_{24}H_{37}N_2O_5Ssi$, found 493.2190.

***tert*-Butyl(((2*S*,4*S*,6*S*)-4-(methoxymethoxy)-6-phenyltetrahydro-2*H*-pyran-2-yl)methoxy) dimethylsilane (27).** A solution of **26** (485 mg, 0.985 mmol) in toluene (5 mL) in a sealed tube was desoxygenate the following way: first the solution was freezed in liquid N_2, then the sealed tube connected to vacuum to remove the oxygen and finally purged with argon. This process is repeated until the whole oxygen has been eliminated. To the solution was added at room temperature Bu_3SnH (0.318 mL, 1.182 mmol) and then AIBN (0.394 mL, 0.078 mmol), the tube was closed and the solution was stirred at 120 ºC for 5 hours. The solvent was evaporated under reduced pressure. The residue was purified by chromatography on silica gel (2% AcOEt/ Hexane) affording **27** (292 mg, 81%). **Compound 27:** colourless oil, $[\alpha]_D^{22}$= 8.9 (c 3.16, $CHCl_3$), R_f 0.45 (30% EtOAc/Hexane). ^{1}H NMR ($CDCl_3$, δ): 7.43 – 7.33 (m, 4H, $CH_{o,m}$-Ph), 7.32 – 7.25 (m, 1H, CH_P-Ph), 4.78 (dd, *J* 11.4, 2.3 Hz, 1H, CH-6), 4.73 (q, *J* 6.9 Hz, 2H, CH_2-

MOM), 4.25 – 4.16 (m, 2H, CH-4, CH-2), 3.94 – 3.88 (m, 1H, CH_2-2′), 3.88 – 3.82 (m, 1H, CH_2-2′), 3.39 (s, 3H, CH_3-MOM), 2.27 – 2.16 (m, 2H, CH_2-3, CH_2-5), 1.82 – 1.73 (m, 1H, CH_2-5), 1.70 – 1.58 (m, 1H, CH_2-3), 0.95 (s, 9H, ^{t}Bu-TBS), 0.12 (s, 3H, CH_3-TBS), 0.11 (s, 3H, CH_3-TBS). ^{13}C NMR ($CDCl_3$, δ):142.51 (C-Ph), 128.39 (CH_o-Ph), 127.52 (CH_p-Ph), 126.03 (CH_m-Ph), 94.44 (CH_2-MOM), 73.91 (CH-2), 73.13 (CH-6), 69.91 (CH-4), 64.52 (CH_2-2′), 55.27 (CH_3-MOM), 40.12 (CH_2-5), 32.35 (CH_2-3), 25.92 (CH_3- tBu(TBS)), 18.25 (C-TBS), -5.37 (CH_3-TBS), -5.43 (CH_3-TBS). MS (ESI) [*m/z*, (%)]: 389 ([M+Na]$^+$, 100), 386 (45), 287 (76). HRMS (ESI): 389.2119 calcd for $C_{20}H_{34}NaO_4Si$, found 389.2106.

((2*S*,4*S*,6*S*)-4-(Methoxymethoxy)-6-phenyltetrahydro-2*H*-pyran-2-yl)methanol(28). To a solution of **27** (159 mg, 0.434 mmol) in THF (8 mL) was added a 1,0 M solution of TBAF (0.651 mL, 0.651mmol) at r.t. and stirred for 18 hours in the same conditions. The solvent was evaporated and the residue was chromatographed on silica gel using 50% AcOEt/Hexane affording **28** (106 mg, 96%). **Compound 28:** colourless oil, $[\alpha]_D^{22}$= 2.2 (c 2.61, $CHCl_3$), R_f 0.85 (50% EtOAc/Hexane). ^{1}H NMR ($CDCl_3$, δ): 7.41 – 7.34 (m, 4H, $CH_{o,m}$-Ph), 7.33 – 7.27 (m, 1H, CH_P-Ph), 4.72 – 4.63 (m, 3H, CH_2-MOM, CH-6), 4.33 – 4.26 (m, 1H, CH-2), 4.03 – 3.92 (m, 2H, CH_2-2′, CH-4), 3.59 – 3.50 (m, 1H, CH_2-2′), 3.36 (s, 3H, CH_3-MOM), 2.46 (d, *J* 5.9 Hz, 1H, OH), 2.25 – 2.18 (m, 1H, CH_2-5), 2.02 – 1.94 (m, 1H, CH_2-3), 1.88 – 1.78 (m, 1H, CH_2-3), 1.71 – 1.61 (m, 1H, CH_2-5). ^{13}C NMR ($CDCl_3$, δ):141.91 (C-Ph), 128.46 (CH_o-Ph), 127.73 (CH_p-Ph), 126.07 (CH_m-Ph), 94.56 (CH_2-MOM), 73.91 (CH-2), 71.50 (CH-6), 69.84 (CH-4), 61.73 (CH_2-2′), 55.39 (CH_3-MOM), 40.17 (CH_2-5), 32.30 (CH_2-3). MS (ESI) [*m/z*, (%)]: 279 (30), 276 ([M+Na+H]$^+$, 18), 275 ([M+Na]$^+$, 100), 272 (17). HRMS (ESI): 275.1254 calcd for $C_{14}H_{20}NaO_4$, found 275.1263.

((2*S*,4*S*,6*S*)-4-(Methoxymethoxy)-6-phenyltetrahydro-2*H*-pyran-2-yl)methyl4-methyl-benzenesulfonate (29). To a solution of alcohol **28** (154 mg, 0.611 mmol) in CH_2Cl_2 (6 mL) was added pyridine (1 mL) and p-TsCl (269 mg, 1.22 mmol) and was stirred at room temperature for 36 hours. The reaction was quenched with H_2O (10 mL) and was extracted with EtOAc (2x10 mL) and the combined organic layers were washed with Cu_2SO_4 (15 mL), H_2O (15 mL) and brine (15 mL) were dried over Na_2SO_4, filtered and the solvent evaporated under reduced pressure. The residue was purified by chromatography on silica gel (20% EtOAc/Hexane) affording tosylate **29** (235 mg, 95%). **Compound 29:** colourless oil, $[\alpha]_D^{22}$= 27.9 (c 0.86, $CHCl_3$), R_f 0.27 (50% EtOAc/Hexane). ^{1}H NMR ($CDCl_3$, δ): 7.82 – 7.77 (m, 2H, CH-Ts), 7.38 – 7.31 (m, 2H, CH-Ts), 7.31 – 7.24 (m, 5H, CH-Ph), 4.67 (q, *J* 6.9 Hz, 2H, CH_2-MOM), 4.50 (m, 1H, CH-6), 4.41 (m, 1H, CH-2), 4.35 (dd, *J* 10.1, 7.6 Hz, 1H, CH_2-2′), 4.14 (dd, *J* 10.2, 4.7 Hz, 1H, CH_2-2′), 3.94 (m, 1H, CH-4), 3.36 (s, 3H, CH_3-MOM), 2.42 (s, 3H, CH_3-Ts), 2.26 – 2.17 (m, 1H, CH_2-5), 2.06 – 1.98 (m, 1H, CH_2-3), 1.81 (m, 1H, CH_2-3), 1.69 – 1.55 (m, 1H, CH_2-5). ^{13}C NMR ($CDCl_3$, δ):144.98 (C-Ts), 141.55 (C-Ph), 132.76 (C-Ts), 129.96 (CH-Ts), 128.36 (CH_o-Ph), 127.92 (CH-Ts), 127.65 (CH_p-Ph), 125.95 (CH_m-Ph), 94.65 (CH_2-MOM), 72.20 (CH-6), 70.64 (CH-2), 69.44 (CH-4), 69.10 (CH_2-2′), 55.42 (CH_3-MOM), 39.76 (CH_2-5), 32.16 (CH_2-3), 21.67 (CH_3-Ts). MS (ESI) [*m/z*, (%)]: 430 (26), 429 ([M+Na]$^+$, 100), 345 (13). HRMS (ESI): 429.1342 calcd for $C_{21}H_{26}NaO_6S$, found 429.1334.

2-((2*R*,4*R*,6*S*)-4-(Methoxymethoxy)-6-phenyltetrahydro-2*H*-pyran-2-yl)acetonitrile (30). To a solution of tosylate **29** (148 mg, 0.364 mmol) in DMF (5 mL) was added NaCN (55 mg, 1.09 mmol) and was stirred at 65ºC for 46 hours. The reaction was quenched with H_2O (3 mL) and was extracted with EtOAc (2x8mL) and the combined organic layers were washed with H_2O (10 mL) and brine (10 mL) were dried over Na_2SO_4, filtered and the solvent evaporated under reduced pressure. The residue was purified by chromatography on silica gel (10% EtOAc/Hexane) affording nitrile **30** (75.3 mg, 79%). **Compound 30:** colourless oil, $[\alpha]_D^{22}$= 13.84 (c 0.25, $CHCl_3$), R_f 0.55 (50% EtOAc/Hexane). ^{1}H NMR ($CDCl_3$, δ): 7.42 – 7.35 (m, 4H, $CH_{o,m}$), 7.35 – 7.27 (m, 1H, CH_p), 4.75 – 4.65 (m, 3H, CH_2-MOM, CH-6), 4.58 (dd, *J* 5.4, 2.9 Hz, 1H, CH-2), 4.05 (dt, *J* 10.1, 5.4 Hz, 1H, CH-4), 3.38 (s, 3H, CH_3-MOM), 2.82 (dd, *J* 16.8, 7.5 Hz, 1H, CH_2-2′), 2.73 (dd, *J* 16.8, 7.2 Hz, 1H, CH_2-2′), 2.34 – 2.25 (m, 1H, CH_2-5), 2.14 – 2.06 (m, 1H, CH_2-3), 1.91 (m, 1H, CH_2-3), 1.84 – 1.70 (m, 1H, CH_2-5). ^{13}C NMR ($CDCl_3$, δ): 140.94 (C-Ph), 128.51 (CH_o), 127.85 (CH_p), 126.03 (CH_m), 117.24 (CN), 94.58 (CH_2-MOM), 72.02 (CH-6), 68.72 (CH-2), 68.56 (CH-4), 55.52 (CH_3-MOM), 38.70 (CH_2-5), 34.18 (CH_2-3), 21.48 (CH_2-2′). MS (ESI) [*m/z*, (%)]: 285 ($[M+Na+H]^+$, 20), 284 ($[M+Na]^+$, 100), 281 (36). HRMS (ESI): 284.1257 calcd for $C_{15}H_{19}NNaO_3$, found 284.1247.

2-((2*S*,4*R*,6*R*)-4-(Methoxymethoxy)-6-phenyltetrahydro-2*H*-pyran-2-yl)-1-phenylethanone (32). To a solution of **30** (41 mg, 0.156 mmol) in CH_2Cl_2 (5 mL) was added at -78ºC DIBAL-H dropwise (0.234 mL, 0.234 mmol) and was stirred at the same temperature for 6 hours. The reaction was quenched with NH_4Cl (8 mL) and was stirred for 30 min at room temperature. The mixture was extracted with CH_2Cl_2 (3x10 mL). The combined organic layers were dried over Na_2SO_4, filteredand the solvent evaporated under reduced pressure affording (42 mg). The residue (42 mg, 0.160 mmol) was disolved in THF (4 mL) and was cooled to -78ºC. PhLi (0.240 mmol, 0.133 mL) was added dropwise and was stirred for 5 hours at -78ºC. The reaction was quenched with H_2O (10 mL) and the mixture was extracted with EtOAc (2x10 mL) and the combined organic layers were washed with brine (10 mL), were dried over Na_2SO_4, filtered and the solvent evaporated under reduced pressure. The residue was solved in CH_2Cl_2 and was added molecular sieves (18 mg), NMO (29 mg, 0.250 mmol) and a catalitic amount of TPAP and was stirred at room temperature for 16 hours. The reaction was filtered under celite and the residue was purified by chromatography on silica gel (5% EtOAc/Hexane) affording ketone **32** (21 mg, 39% three steps). **Compound 32:**colourless oil, $[\alpha]_D^{24}$= 75.9(c 0.53, $CHCl_3$), R_f 0.66 (30% EtOAc/Hexane). ^{1}H NMR ($CDCl_3$, δ): 8.02 – 7.96 (m, 2H, CH_o-Ph(C1)), 7.63 – 7.57 (m, 1H, CH_p-Ph(C1)), 7.52 – 7.46 (m, 2H, CH_m-Ph(C1)), 7.38 – 7.32 (m, 4H, $CH_{o,m}$-Ph(C-6′)), 7.31 – 7.26 (s, 1H, CH_p-Ph(C-6′)), 4.99 – 4.89 (m, 1H, CH-6′), 4.79 – 4.68 (m, 3H, CH-2′, CH_2-MOM), 4.20 – 4.07 (m, 1H, CH-4′), 3.57 – 3.45 (m, 1H, CH_2-2), 3.41 – 3.30 (m, 4H, CH_2-2, CH_3-MOM), 2.35 – 2.24 (m, 1H, CH_2-3′), 2.15 – 2.04 (m, 1H, CH_2-5′), 1.97 – 1.86 (m, 1H, CH_2-5′), 1.75 – 1.65 (m, 1H, CH_2-3′). ^{13}C NMR ($CDCl_3$, δ): 197.86 (CO), 141.81 (C-Ph(C6′)), 136.83 (C-Ph(C1)), 133.33 (CH_p-Ph(C6′)), 128.75 (CH_o-Ph(C1)), 128.42 (CH_o-Ph(C6)), 128.22 (CH_m-Ph(C6′)), 127.65 (CH_p-Ph(C6′)), 126.11 (CH_m-Ph(C1)), 94.47 (CH_2-MOM), 71.98 (CH-2′), 70.19 (CH-6′), 69.47 (CH-4′), 55.43 (CH_3-MOM), 41.07 (CH_2-2), 40.04 (CH_2-3′), 35.06

(CH_2-5′). MS (ESI) [*m/z*, (%)]: 364 ([M+Na+H]$^+$, 24), 363 ([M+Na]$^+$, 100), 360 (35), 279 (17). HRMS (ESI): 363.1567 calcd for $C_{21}H_{24}NaO_4$, found 363.1570.

2-((2′*S*,4′*R*,6′*S*)-4′-Hydroxy-6′-phenyltetrahydro-2*H*-pyran-2′-yl)-1-phenylethanone (4). To a solution **32** (15 mg, 0.044 mmol) in MeOH (1 mL) was added dropwise HCl (37%, 30 drops) and the reaction was followed by TLC. The reaction was concentrated and the crude was purified by chromatography on silica gel (20% EtOAc/Hexane), affording **4** (11.7 mg, 90%). **Compound 4**: colourless oil,$[\alpha]_D^{21}$= 88.6 (c 0.26, $CHCl_3$), R_f 0.28 (50% EtOAc/Hexane). ^{1}H NMR ($CDCl_3$, δ):8.08 – 7.89 (m, 2H, CH_o-Ph(C1)), 7.66 – 7.54 (m, 1H, CH_p-Ph(C1)), 7.49 (dd, *J* 8.4, 6.9 Hz, 2H, CH_m-Ph(C1)), 7.40 – 7.26 (m, 5H, CH-Ph(C6′)), 4.98 – 4.87 (m, 1H, CH-6′), 4.76 (dd, *J* 10.8, 2.7 Hz, 1H, CH-2′), 4.24 (m, 1H, CH-4′), 3.50 (dd, *J* 15.4, 6.2 Hz, 1H, CH_2-2), 3.34 (dd, *J* 15.4, 8.0 Hz, 1H, CH_2-2), 2.31 – 2.22 (m, 1H, CH_2-3′), 2.13 – 2.06 (m, 1H, CH_2-5′), 1.84 (ddd, *J* 12.8, 10.6, 5.7 Hz, 1H, CH_2-5′), 1.69 (dd, *J* 12.8, 10.7 Hz, 1H, CH_2-3′). ^{13}C NMR ($CDCl_3$, δ): 197.92 (CO), 141.63 (C-Ph(C6′)), 136.81 (C-Ph(C1), 133.35 (CH_p-Ph(C1)), 128.76 (CH_m-Ph(C6′)), 128.48 (CH_o-Ph(C1)), 128.23 (CH_m-Ph(C1)), 127.67 (CH_p-Ph(C6′)), 126.10 (CH_o-Ph(C6′)), 71.90 (CH-′6), 69.77 (CH-2′), 64.72 (CH-4′), 41.99 (CH-2), 41.33 (CH_2-5′), 37.60 (CH_2-3′). MS (ESI) [*m/z*, (%)]:615 (100), 297 ([M+H]$^+$, 16). HRMS (ESI): 319.13047 calcd for $C_{19}H_{20}NaO_3$, found 319.13052.

2-((2*S*,4*R*,6*S*)-4-Hydroxy-6-phenyltetrahydro-2*H*-pyran-2-yl)-1-phenylethanone (1). To a solution of **4** (12mg, 0.04 mmol) in THF (3 mL) was added PPh_3 (42 mg, 0.16 mmol), p-nitrobenzene (27 mg, 0.16 mmol) and the resulting mixture was cooled to 0 ºC and DIAD (0.031 mL, 0.16 mmol) was added slowly. When the addition was finished the reaction was introduced in the Microwaves at 40ºC for 20 minutes. The reaction was concentrated and the crude was dissolved in MeOH and a catalytic amount of K_2CO_3 was added and was stirred at room temperature for 12 hours. The mixture was concentrated and the crude was purified by chromatography on silica gel (20% EtOAc/Hexane) affording **Diospongin A (1)** (10 mg, 83%). **Diospongin A:** Colourless oil, $[\alpha]_D^{28}$= -22.6 (c 0.66, $CHCl_3$), R_f 0.46 (50% EtOAc/Hexane). ^{1}H NMR ($CDCl_3$, δ): 8.01 – 7.95 (m, 2H, CH_o-Ph(C1)), 7.58 – 7.52 (m, 1H, CH_p-Ph(C1)), 7.45 (m, 2H, CH_m-Ph(C1)), 7.32 – 7.19 (m, 5H, CH-Ph(C6′)), 4.92 (dd, *J* 11.9, 2.2 Hz, 1H, CH-6′), 4.69 – 4.60 (m, 1H, CH-2′), 4.40 – 4.33 (m, 1H, CH-4′), 3.41 (dd, *J* 15.9, 5.8 Hz, 1H, CH_2-2), 3.06 (dd, *J* 16.0, 6.8 Hz, 1H, CH_2-2), 1.95 (dt, *J* 13.9, 2.4 Hz, 2H, CH_2-3′), 1.81 – 1.64 (m, 2H, CH_2-5′). ^{13}C NMR (CDCl3, δ): 198.26 (CO), 142.66 (C-Ph(C6′)), 137.30 (C-Ph(C1), 133.08 (CH_p-Ph(C1)), 128.53 (CH_m-Ph(C1)), 128.32 (CH_o-Ph(C1)), 128.25 (CH_m-Ph(C6′), 127.25 (CH_p-Ph(C6′), 125.80 (CH_o-Ph(C6′), 73.77 (CH-′6), 69.06 (CH-2′), 64.70 (CH-4′), 45.14 (CH_2-2), 40.04 (CH_2-5′), 38.51 (CH_2-3′). MS (ESI) [*m/z*, (%)]: 615 (100), 297 ([M+H]$^+$, 11). HRMS (ESI):297.14852 calcd for $C_{19}H_{21}O_3$, found 297.14857.

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