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Graphical Abstract

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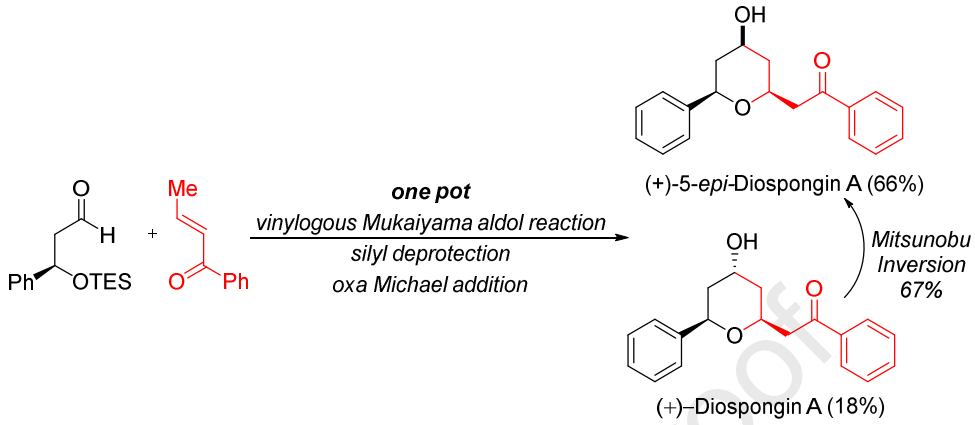

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Total Synthesis of (+)-Diospongin A

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ABSTRACT

Enantioselective total synthesis of 2,4,6-trisubstituted pyran natural product diospongin A is accomplished from benzaldehyde in 5 steps using a direct addition of vinylogous aryl methyl ketone to chiral β-alkoxy aldehyde and subsequent *oxa*-Michael addition.

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1. Introduction

Substituted pyrans are ubiquitous structural units present in a number of natural products displaying various bio-activities. Diospongin A and B (figure 1) are two simple 2,4,6-tri substituted pyran natural products isolated from the rhizhomes of *Dioscorea spongiosa* possessing potent anti-oesteoporotic activity.[1] Number of groups reported the total synthesis of both diospongins majority relying on *oxa*-Michael addition for the construction of the pyran ring while Prins cylization and intramolecular carbonylative arylation were also utilized to construct the pyran framework.[2(a-u)] While this manuscript was under preparation Mohapatra's group reported the synthesis of diospongin A using a Mukaiyama reaction on a functionalized lactol.[2x]

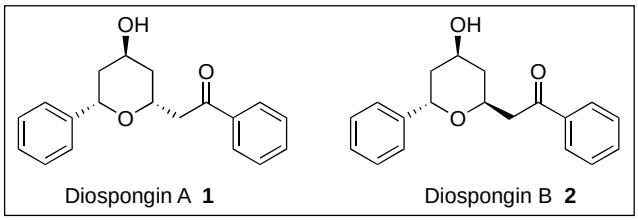
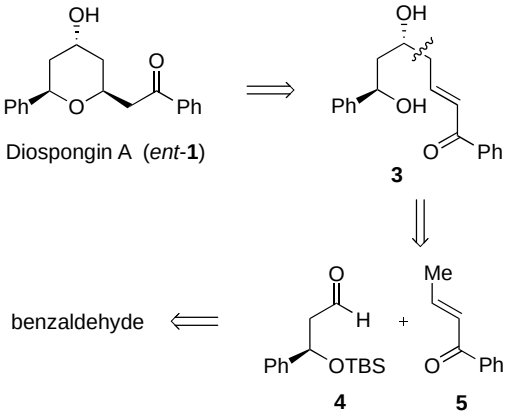


Figure 1: Structure of (–)-diospongin A **1** and B **2**.

Interestingly, most of the syntheses either relied on the *oxa*-Michael addition reaction or on Wacker type oxidation to install the required carbonyl group in the natural product, while a direct addition of the vinylogous aryl methyl ketone to the chiral aldehyde and subsequent *oxa*-Michael addition was never investigated. We reasoned that such stereocontrolled direct addition of unsaturated ketone **5** to the aldehyde **4**, leads to the formation of the 1,3-diol **3** possessing the unsaturated ketone which can *in situ* undergo the *oxa*-Michael addition yielding the product diospongin A **1** in a single step process (Scheme 1).



Scheme 1. Retrosynthesis for *ent*-diospongin A (*ent*-**1**).

2. Results and Discussion

With this proposal, the synthetic sequence commenced with the preparation of the required β-alkoxy aldehyde **4** from benzaldehyde involving the Nagao acetate aldol reaction[3] and subsequent conversion of the aldol product **7** to the aldehyde **4**. Mukaiyama aldol reaction of the aldehyde **4** with silylenol ether **9** (obtained from the unsaturated ketone **5)** afforded the mono silyloxy protected diol **10** in 71% yield, as an inseparable mixture of diastereomers (77:23) and the diol **3** in 14% yield (79:21) as an inseparable diastereomeric mixture, 1,3-*trans* diol being the major diastereomer in both cases. Formation of the major 1,3-*trans* diastereomer in the addition of **9** to **4** can be rationalized based on the model proposed by Evans[5] for similar reactions. Reaction of the alcohol **10** with either camphorsulphonic acid or

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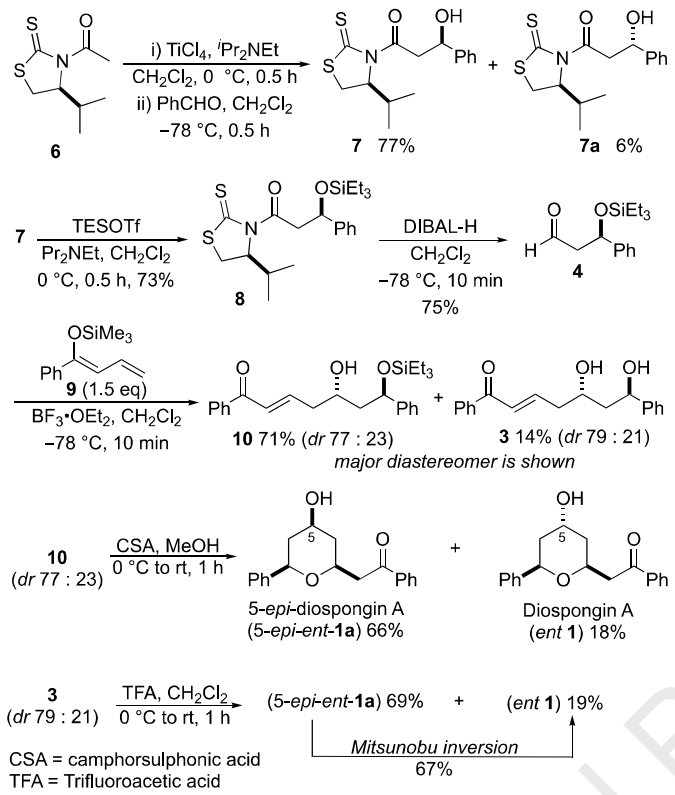
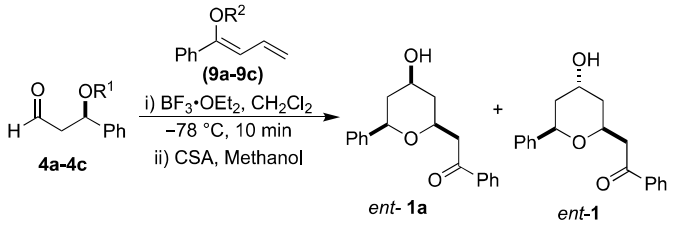
followed by *oxa*-Michael reaction[2w] affording diospongin A (*ent*-**1)** in 18% yield and 5-*epi*-diospongin A (*ent*-**1a)** in 66% yield. Mitsunobu inversion of *ent*-**1a** afforded *ent*-diospongin A (*ent*-**1**) in 67% yield (Scheme 2).



Scheme 2. Total synthesis of (+)-diospongin A (*ent*-**1**).

Formation of the 2,6 *cis*-tetrahydropyrans (*ent*-**1a** and *ent*-**1)** can be explained on the basis of the proposal of Fuwa *et al.*[6] and also by the recent theoretical and experimental observations of oxa-Michael addition reactions on structurally similar substrates containing unsaturated thioesters (instead of unsaturated ketones) using trifluoroacetic acid reported by Clarke's group.[2w]

In an effort to improve the diastereomeric ratio of the product diospongins (**1a** and **1**) as well as to decrease the number of steps in the synthesis, structurally diverse silyl enol ethers **9a-c** were treated with the siloxy aldehyde with varied silyl substitutions **(4a-c)**. The intermediate products **10** and **3** were treated with CSA in one pot to afford directly (+)-diospongin A (*ent*-**1**) and its 5-epimer (*ent*-**1a**) (Scheme 3).



Scheme 3. One pot vinylogous Mukaiyama aldol reaction/silyl deprotection/*oxa* Michael addition.

Table 1: Reaction conditions for vinylogous Mukaiyama aldol reaction of siloxy aldehyeds (4a-4c) with silyloxydienes (9a-9c).[a]

Entry	R^1	R^2	Time	(**1a**:**1**)[b]	**1a** yield[c]	**1** yield[c]
1	-TMS **4a**	-TMS **9**	0.5 h	90:10	61%	3%
2	-TBS **4b**	-TMS **9**	1 h	87:13	48%	6%
3	-TES **4**	-TMS **9**	2 h	76:24	36%	8%
4	-TIPS **4c**	-TMS **9**	12 h	64:36	27%	14%
5	-TBS **4b**	-TBS **9a**	2 h	84:16	36%	6%
6	-TES **4**	-TES **9b**	1 h	76:24	40%	8%
7	-TIPS **4c**	-TIPS **9c**	12 h	57:43	26%	13%

[a]Condition: reaction was performed at −78 °C for 10 min and then slowly warmed to room temperature and stirred at room temperature for the time specified in table.
[b]Ratio of the products **1a:1** (was determined by crude ^{1}H NMR spectroscopy). [c]Isolated yield.

As evident from table-1, reaction of the trimethylsiloxy aldehyde **4a** with the trimethylsilyl enol ether **9** afforded the products *ent*-**1a** and *ent*-**1** in 90:10 ratio and the major product *ent*-**1a** was isolated in 61% yield. No improvement in the ratio towards the formation of required *ent*-diospongin (*ent*-**1)** was observed when the trimethylsilyl group in **4** was replaced with other bulky silyl groups such as *tert*-butyldimethylsilyl or triethylsilyl groups (entries 2-4). It is observed that the less bulky trimethylsiloxy aldehyde **4a** offered better diastereoselectivity in the reaction for the formation of *ent*-**1a**. The reaction of **9** with TIPS protected aldehyde **4c** afforded the product in 3:2 diastereomeric ratio, while the reaction of the triisopropylsilyloxy aldehyde **4c** with the triisopropylsilyloxy diene **9c** furnished the products *ent*-**1a** and *ent*-**1** in 57:43 ratio. These experimental observations (table 1) suggest that the steric bulk in the β-substituent of the aldehyde plays a crucial role in the outcome of the diastereoselectivity of the vinylogous Mukaiyama aldol reaction.

3. Conclusions

In conclusion, synthesis of (+)-diospongin A (*ent*-**1**) is accomplished from β-siloxy aldehyde **4a** involving a single pot operation of vinylogous Mukaiyama aldol reaction, silyldeprotection and *oxa*-Michael addition reactions. The total synthesis involves 5 linear steps, starting from commercially available benzaldehyde with 25% overall yield.

4. Experimental section

General Procedures: Column chromatography was performed on silica gel, Acme grade 100-200 mesh. TLC plates were visualized either with UV, in an iodine chamber, or with phosphomolybdic acid spray, unless noted otherwise. Unless stated otherwise, all reagents were purchased from commercial sources and used without additional purification. THF was freshly distilled over Na-benzophenone ketyl. Melting points were uncorrected. Unless stated otherwise, ^{1}H NMR and ^{13}C NMR spectra were recorded on 400 MHz machine in $CDCl_3$ as solvent with TMS as reference unless otherwise indicated. Unless stated otherwise, all the reactions were performed under inert atmosphere. All the specific rotations were determined at 24 °C.

Pre **-3-thioxothiazolidin-3-yl)-3-phenylpropan-1-one (7):** To a pre-cooled (−15 °C) solution of **6** (0.4 g, 2 mmol) in freshly distilled dry CH_2Cl_2 (8 mL) was added diisopropylethylamine (0.45 mL, 2.6 mmol) under inert atmosphere. $TiCl_4$ (0.24 mL, 2.2 mmol) was introduced into the reaction mixture and the resulting dark brown solution was stirred for 30 min at −15 °C. The reaction mixture was cooled to −78 °C and a solution of benzaldehyde (0.2 mL, 2.1 mmol) in CH_2Cl_2 (4 mL) was added dropwise and was stirred at −78 °C. After completion of the reaction (~30 min), it was quenched by addition of saturated NH_4Cl solution (10 mL). The reaction mixture was extracted with CH_2Cl_2 (2 x 10 mL). The combined organic layers were washed with brine (10 mL) and dried over anhydrous Na_2SO_4. Evaporation of the solvent followed by silica gel column chromatography of the resultant residue with petroleum ether/EtOAc (8:2) as eluent furnished **7** (0.47 g, 77%) as yellow colour oil and **7a** (0.036 g, 6%) as yellow colour solid; **Major diastereomer 7:** $[\alpha]^{24}_D$ +353.5 (*c* 1.1, $CHCl_3$), [lit[3] $[\alpha]^{24}_D$ +386.7 (*c* 1.0, $CHCl_3$)]; IR (neat) 3419, 2921, 1694, 1514, 1161 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.43-7.25 (m, 5H), 5.27 (dd, *J* = 9.2, 2.8 Hz, 1H), 5.13 (t, *J* = 7.2 Hz, 1H), 3.79 (dd, *J* = 17.2, 2.4 Hz, 1H), 3.59 (dd, *J* = 17.2, 9.2 Hz, 1H), 3.48 (dd, *J* = 11.6, 8 Hz, 1H), 3.02 (d, *J* = 11.6 Hz, 1H), 2.37 (*sext*, *J* = 6.8 Hz, 1H), 1.06 (d, *J* = 6.8 Hz, 3H), 0.99 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.0, 172.6, 142.4, 128.5 (2C), 127.7, 125.8 (2C), 71.5, 70.2, 46.8, 30.8, 30.7, 19.1, 17.8; HRMS for $C_{15}H_{19}NO_2S_2$+Na calcd 332.0755; found 332.0765.

Minor diastereomer 7a: (*S*)-3-hydroxy-1-((*S*)-4-isopropyl-2-thioxothiazolidin-3-yl)-3-phenylpropan-1-one: M.P: 86–90 °C, [lit.[3] M.P: 88–95 °C]; $[\alpha]^{24}_D$ +271.7 (*c* 1.1, $CHCl_3$), [lit[3] $[\alpha]^{24}_D$ +279.2 (*c* 1.0, $CHCl_3$)].; IR (KBr) 3423, 2962, 1689, 1493, 1159 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.45-7.20 (m, 5H), 5.21-5.11 (m, 2H), 3.83 (dd, *J* = 17.2, 9.6 Hz, 1H), 3.59 (dd, *J* = 17.2, 3.2 Hz, 1H), 3.48 (dd, *J* = 11.6, 8.0 Hz, 1H), 3.02 (d, *J* = 11.2 Hz, 1H), 2.36 (sext, *J* = 6.8 Hz, 1H), 1.06 (d, *J* = 6.8 Hz, 3H), 0.98 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.0, 172.9, 142.4, 128.5 (2C), 127.7, 125.9 (2C), 71.4, 70.7, 46.7, 30.7, 30.6, 19.0, 17.7; HRMS for $C_{15}H_{19}NO_2S_2$+Na calcd 332.0755; found 332.0757.

Procedure A: Preparation of (*R*)-1-((*S*)-4-isopropyl-2-thioxothiazolidin-3-yl)-3-phenyl-3-((triethylsilyl)oxy)propan-1-one (8): To a pre-cooled (−20 °C) solution of **7** (0.35 g, 1.1 mmol) in CH_2Cl_2 (10 mL) were added diisopropylamine (0.3 mL, 1.7 mmol) and triethylsilyltriflate (0.28 mL, 1.2 mmol). The reaction mixture was allowed to stir at −20 °C for 0.5 h. After completion of the reaction (TLC) it was quenched by addition of water (10 mL) and the reaction mixture was extracted with EtOAc (2 × 10 mL). The organic layer was washed with brine (20 mL) dried over anhydrous Na_2SO_4 and the solvent was evaporated under reduced pressure to give a crude residue, which on purification by silica gel column chromatography petroleum ether/EtOAc (9:1) as eluent furnished the compound **8** (0.35 g, 73%) as a yellow oil; $[\alpha]^{24}_D$ +280.9 (*c* 1.1, $CHCl_3$); IR (neat) 2959, 2854, 1697, 1252, 1151 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.38-7.21 (m, 5H), 5.31 (dd, *J* = 8.8, 3.6 Hz, 1H), 5.02 (t, *J* = 6.8 Hz, 1H), 3.96 (dd, *J* = 16.4, 8.8 Hz, 1H), 3.47 (dd, *J* = 11.6, 8.0 Hz, 1H), 3.21 (dd, *J* = 16.4, 3.6 Hz, 1H), 3.02 (d, *J* = 11.6 Hz, 1H), 2.34 (sextet, *J* = 13.6, 6.8 Hz, 1H), 1.02 (d, *J* = 6.8 Hz, 3H), 0.94 (d, *J* = 7.2 Hz, 3H), 0.84 (t, *J* = 8.0 Hz, 9H), 0.56-0.44 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.8, 171.2, 144.1, 128.2 (2C), 127.5, 126.1 (2C), 71.8, 71.7, 48.5, 30.9, 30.8, 19.1, 17.8, 6.7 (3C), 4.7 (3C). HRMS for $C_{21}H_{33}NO_2SiS_2$+Na calcd 446.1620; found 446.1620.

((triethylsilyl)oxy)propanal (4): To a solution of the compound **8** (0.28 g, 0.6 mmol) in CH_2Cl_2 (7 mL) was added DIBAL-H (1.3 mL, 1.3 mmol) at −78 °C and was stirred at the same temperature for 10 min. After the reaction was complete (TLC), it as quenched by addition of aqueous saturated solution of sodium potassium tartrate (10 mL) and allowed to stir at room temperature for 1 h. The reaction mixture was then extracted with EtOAc (2 × 20 mL) and the combined organic extract was washed with brine (10 mL), dried over anhydrous Na_2SO_4. Evaporation of the solvent gave the crude residue which on purification using silica gel column chromatography, petroleum ether/EtOAc (9:1) as eluent afforded the aldehyde **4** (0.13 g, 75%) as a colourless oil; $[\alpha]^{24}_D$ +74.4 (*c* 2.2, $CHCl_3$); IR (neat) 2954, 2877, 2724, 1721, 1666 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.78 (t, *J* = 2.4 Hz, 1H), 7.37-7.22 (m, 5H), 5.22 (dd, *J* = 8.0, 4.4 Hz, 1H), 2.87 (ddd, *J* = 15.6, 8.0, 2.4 Hz, 1H), 2.64 (ddd, *J* = 15.6, 4.0, 2.0 Hz, 1H), 0.86 (t, *J* = 8.0 Hz, 9H), 0.53 (ddd, *J* = 15.2, 7.6, 2.0 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) 201.4, 143.8, 128.4 (2C), 127.6, 125.6 (2C), 70.5, 53.9, 6.6 (3C), 4.7 (3C); HRMS for $C_{15}H_{24}O_2Si$+Na calcd 287.1443; found 287.1445.

Preparation of (*R*)-1-((*S*)-4-isopropyl-2-thioxothiazolidin-3-yl)-3-phenyl-3-((trimethylsilyl)oxy)propan-1-one (8a): TMS-ether **8a** was prepared from the alcohol **7** (0.09 g, 0.32 mmol) with diisopropylethylamine (0.08 mL, 0.5 mmol) in presence of trimethylsilyltriflate (0.06 mL, 0.36 mmol) using the procedure A described above in (0.09 g, 81%) as a yellow oil; $[\alpha]^{24}_D$ +350.7 (*c* 1.0, $CHCl_3$); IR (neat) 2960, 2736, 1697, 1598, 1460 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.39-7.21 (m, 5H), 5.32 (dd, *J* = 9.2, 3.2 Hz, 1H), 5.04 (t, *J* = 7.2 Hz, 1H), 3.86 (dd, *J* = 16.4, 9.2 Hz, 1H), 3.49 (dd, *J* = 11.6, 8.0 Hz, 1H), 3.30 (dd, *J* = 16.4, 3.2 Hz, 1H), 3.02 (d, *J* = 11.2 Hz, 1H), 2.35 (sext, *J* = 6.8 Hz, 1H), 1.03 (d, *J* = 6.8 Hz, 3H), 0.96 (d, *J* = 7.2 Hz, 3H), 0.02 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.7, 171.1, 143.9, 128.3 (2C), 127.4, 126.0 (2C), 71.7 (2C), 48.4, 30.9, 30.8, 19.1, 17.7, 0.1 (3C); HRMS for $C_{18}H_{27}NO_2SiS_2$+Na calcd 404.1150; found 404.1151.

Preparation of (*R*)-3-phenyl-3-((trimethylsilyl)oxy)propanal 4a: aldehyde **4a** was prepared from silyl ether **8a** (0.09 g, 0.24mmol) in presence of DIBAL-H (0.5 mL, 0.49 mmol) using the procedure B described above in (0.051 g, 98%) as a colorless oil. $[\alpha]^{24}_D$ +88.4 (*c* 0.45, $CHCl_3$); IR (neat) 2960, 2872, 2723, 1724, 1494 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.78 (t, *J* = 2.0 Hz, 1H), 7.37-7.24 (m, 5H), 5.22 (dd, *J* = 8.4, 4.0 Hz, 1H), 2.88 (ddd, *J* = 16.0, 8.8, 2.8 Hz, 1H), 2.63 (ddd, *J* = 16.0, 4.0, 1.6 Hz, 1H), 0.04 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.3, 143.6, 128.5 (2C), 127.6, 125.6 (2C), 70.3, 53.8, –0.01 (3C). HRMS for $C_{12}H_{18}O_2Si$+Na calcd 245.0974; found 245.0977.

Preparation of (*R*)-3-((tert-butyldimethylsilyl)oxy)-1-((S)-4-isopropyl-2-thioxothiazolidin-3-yl)-3-phenylpropan-1-one (8b): TBS-ether **8b** was prepared from the alcohol **7** (0.106 g, 0.25 mmol) with diisopropylethylamine (0.08 mL, 0.5 mmol) in presence of tertiarybutyldimethylsilyltriflate (0.08 mL, 0.35 mmol) using the procedure A described above in (0.106 g, 77%) as a yellow oil. $[\alpha]^{24}_D$ +318.3 (*c* 2.3, $CHCl_3$); IR (neat) 2927, 2855, 2314, 1695, 1582 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.38-7.20 (m, 5H), 5.29 (dd, *J* = 9.2, 3.6 Hz, 1H), 5.01 (t, *J* = 6.8 Hz, 1H), 3.99 (dd, *J* = 16.4, 9.2 Hz, 1H), 3.47 (dd, *J* = 11.2, 8.0 Hz, 1H), 3.16 (dd, *J* = 16.4, 3.6 Hz, 1H), 3.02 (d, *J* = 11.2 Hz, 1H), 2.35 (sext, *J* = 6.8 Hz, 1H), 1.03 (d, *J* = 6.4 Hz, 3H), 0.95 (d, *J* = 7.2 Hz, 3H), 0.83 (s, 9H), 0.03 (s, 3H), –0.18 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.8, 171.3, 144.0, 128.2 (2C),

12 was 18.0, 17.8, −4.7, −5.1; HRMS for $C_{21}H_{33}NO_2SiS_2$+Na calcd 446.1620; found 446.1625.

Preparation of (*R*)-3-((tert-butyldimethylsilyl)oxy)-3-phenylpropanal (4b): aldehyde **4b** was prepared from silyl ether **8b** (0.106 g, 0.25 mmol) in presence of DIBAL-H (0.53 mL, 0.53 mmol) using the procedure B described above **4b** in (0.06 g, 91%) as a colourless oil. $[\alpha]^{24}_D$ +70.9 (*c* 1.0, $CHCl_3$), [lit.[7] $[\alpha]^{24}_D$ +70.0 (*c* 1.0, $CHCl_3$)]; IR (neat) 3432, 2856, 2718, 1727, 1644 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.79 (t, *J* = 2.4 Hz, 1H), 7.34-7.22 (m, 5H), 5.21 (dd, *J* = 8.0, 4.0 Hz, 1H), 2.85 (ddd, *J* = 15.6, 8.0, 2.4 Hz, 1H), 2.63 (ddd, *J* = 16.0, 4.0, 2.0 Hz, 1H), 0.87 (s, 9H), 0.04 (s, 3H) −0.14 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.3, 143.7, 128.4 (2C), 127.6, 125.7 (2C), 70.7, 54.0, 25.7 (3C), 18.1, −4.7, −5.2; HRMS for $C_{15}H_{24}O_2Si$+Na calcd 287.1443; found 287.1443.

Preparation of (*R*)-1-((S)-4-isopropyl-2-thioxothiazolidin-3-yl)-3-phenyl-3-((triisopropylsilyl)oxy)propan-1-one (8c): TIPS-ether **8c** was prepared from the alcohol **7** (0.11 g, 0.37 mmol) with diisopropylethylamine (0.08 mL, 0.5 mmol) in presence of triisopropylsilyltriflate (0.11 mL, 0.41 mmol) using the procedure A described above in (0.14 g, 81%) as a yellow oil. $[\alpha]^{24}_D$ +216.3 (*c* 1.08, $CHCl_3$); IR (neat) 2937, 2864, 1696, 1587, 1461 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (*J* = 7.2 Hz, 2H), 7.30 (t, *J* = 7.2 Hz, 2H), 7.27-7.19 (m, 1H), 5.40 (dd, *J* = 7.2, 5.2 Hz, 1H), 4.98 (t, *J* = 7.2 Hz, 1H), 4.03 (dd, *J* = 16.8, 7.6 Hz, 1H), 3.46 – 3.35 (m, 2H), 2.98 (d, *J* = 11.2 Hz, 1H), 2.23 (sext, *J* = 6.8 Hz, 1H), 1.05 – 0.85 (m, 27H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.7, 171.3, 144.2, 128.1 (2C), 127.5, 126.5 (2C), 72.1, 71.7, 48.9, 30.7, 30.6, 19.0, 18.0 (3C), 17.9 (3C), 17.6, 12.4 (3C); HRMS for $C_{24}H_{39}NO_2SiS_2$+Na calcd 488.2089; found 488.2083.

Preparation of (*R*)-3-phenyl-3-((triisopropylsilyl)oxy)propanal (4c): Aldehyde **4c** was prepared from silyl ether **8c** (0.14 g, 0.3 mmol) in presence of DIBAL-H (0.6 mL, 0.6 mmol) using the procedure B described above in (0.08 g, 88%) as a colourless oil. $[\alpha]^{24}_D$ +59.8 (*c* 2.35, $CHCl_3$); IR (neat) 2957, 2893, 2721, 1722, 1500 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.77 (t, *J* = 2.4 Hz, 1H), 7.40-7.21 (m 5 H), 5.31 (t, *J* = 6.0 Hz, 1H), 2.86 (ddd, *J* = 15.6, 6.0, 2.4 Hz, 1H), 2.76 (ddd, *J* = 15.6, 5.6, 2.4 Hz, 1H), 1.11 – 0.93 (m, 21H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.3, 143.9, 128.4 (2C), 127.6, 125.8 (2C), 71.0, 54.2, 17.9 (3C), 17.8 (3C), 12.2.(3C); HRMS for $C_{18}H_{30}O_2Si$+Na calcd 329.1913; found 329.1913.

Procedure C: (Z)-trimethyl((1-phenylbuta-1,3-dien-1-yl)oxy)silane (9): To a pre-cooled solution of (E)-1-phenylbut-2-en-1-one **5** (0.1 g, 0.67 mmol) in CH_2Cl_2 (7 mL), were added diisopropylethylamine (0.3 mL, 1.7 mmol) followed by trimethylsilyltriflate (0.14 mL, 0.75 mmol) dropwise at −10 °C. The reaction mixture was stirred at −10 °C for 0.5 h. After completion of the reaction (TLC) it was quenched by addition of water (10 mL) and the mixture was extracted with petroleum ether (2 × 10 mL). The combined organic layer was washed with brine (20 mL) dried over anhydrous Na_2SO_4 and the solvent was evaporated under reduced pressure to give a crude product **9**, which was used to next step without any purification. Same procedure was utilised to synthesize other silyl enol ethers with the corresponding triflates.

(Z)-tert-butyldimethyl((1-phenylbuta-1,3-dien-1-yl)oxy)silane (9a): TBS enol ether **9a** was synthesised from enone **5** (0.05g, 0.34 mmol) with diisopropylethylamine (0.15 mL, 0.86 mmol), in the presence of TBSOTf (0.1 mL, 0.38 mmol) following used to next step without purification.

(Z)-triethyl((1-phenylbuta-1,3-dien-1-yl)oxy)silane (9b): TES enol ether **9b** was synthesised from enone **5** (0.05 g, 0.34 mmol) with diisopropylethylamine (0.15 mL, 0.86 mmol), in the presence of TESOTf (0.1 mL, 0.38 mmol) following procedure C above in 0.09 g (crude) and the crude product was used to next step without purification.

(Z)-triisopropyl((1-phenylbuta-1,3-dien-1-yl)oxy)silane (9c): TIPS enol ether **9c** was synthesised from enone **5** (0.05 g, 0.34 mmol) with diisopropylethylamine (0.15 mL, 0.86 mmol) in the presence of TIPSOTf (0.1 mL, 0.38 mmol) following procedure C above 0.11 g (crude) and the crude product was used to next step without purification.

Preparation of (7*R*,*E*)-5-hydroxy-1,7-diphenyl-7-((triethylsilyl)oxy)hept-2-en-1-one (10): To a stirred solution of the aldehyde **4** (0.105 g, 0.4 mmol) and silyl enol ether **9** (0.104 g, 0.48 mmol) in CH_2Cl_2 (8 mL) at −78 °C, was added $BF_3{\cdot}OEt_2$ (0.04 mL, 0,4 mmol) dropwise. After stirring at −78 °C for 10 min. the reaction was quenched by the addition of water (10 mL) and extracted with CH_2Cl_2 (2 × 5 mL). The combined organic layers were washed with brine (5 mL) and dried over anhydrous Na_2SO_4. Silica gel column chromatography of the residue obtained after evaporation of the solvent, using petroleum ether:EtOAc (9:1) as eluent gave the diastereomeric silyl alcohol **10** (0.166 g, 71%) as a colourless oil and diol **3** (10 mg, 14%) as a colourless oil. Alcohol **10**: $[\alpha]^{24}_D$ +44.0 (*c* 0.55, $CHCl_3$); IR (neat) 3440, 2954, 2876, 1669, 1549 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93-7.85 (m, 2H), 7.53 (t, *J* = 7.6 Hz, 1H), 7.44 (t, *J* = 7.6 Hz, 2H), 7.37-7.22 (m, 5H), 7.10-6.83 (m, 2H), 5.13 (dd, *J* = 5.2, 4.0 Hz, 0.75H), 4.91 (dd, *J* = 10.0, 4.0 Hz, 0.22H), 4.10-4.03 (m, 0.24H), 4.02-3.95 (m, 0.75H), 3.90 (s, 0.21H), 3.57 (s, 0.72H), 2.55-2.32 (m, 2H), 1.99-1.72 (m, 2H), 0.96-0.81 (m, 9H), 0.65-0.42 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.6_{maj}, 190.4_{min}, 145.7_{maj}, 145.4_{min}, 144.3_{min}, 143.7_{maj}, $137.7_{(maj+min)}$, 132.61_{min}, 132.56_{maj}, $128.5\ (2C)_{(maj+min)}$, $128.43\ (2C)_{min}$, $128.41\ (2C)_{maj}$, $128.3\ (2C)_{min}$, $128.2\ (2C)_{maj}$, 128.0_{min}, 127.9_{maj}, 127.7_{min}, 127.2_{maj}, $125.9\ (2C)_{min}$, $125.6\ (2C)_{maj}$, 76.4_{min}, 73.3_{maj}, 70.4_{min}, 67.0_{maj}, $45.4_{(maj+min)}$, $40.9_{(maj+min)}$, $6.7\ (3C)_{maj}$, $6.5\ (3C)_{min}$, $4.7\ (3C)_{min}$, $4.6\ (3C)_{maj}$; HRMS for $C_{25}H_{34}O_3Si$+Na calcd 433.2175; found 433.2178.

Diol: (7*R*,*E*)-5,7-dihydroxy-1,7-diphenylhept-2-en-1-one (3): $[\alpha]^{24}_D$ +10.5 (*c* 0.25, $CHCl_3$); IR (neat) 3409, 2923, 1665, 1618 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, *J* = 7.2 Hz, 0.4H), 7.90 (d, *J* = 7.2 Hz, 1.6H), 7.55 (t, *J* = 7.2 Hz, 1H), 7.45 (t, *J* = 7.6 Hz, 1H), 7.38-7.20 (m, 5.3H), 7.09-6.90 (m, 1.7H), 5.12-5.03 (m, 0.74H), 4.94 (dd, *J* = 10.0, 2.8 Hz, 0.2H), 4.22-3.98 (m, 1H), 3.46 (dd, *J* = 16.0, 5.6 Hz, 0.2 H), 3.25-3.13 (m, 1.2H), 2.58-2.45 (m, 1.6H), 2.25-2.17 (m, 0.4H), 1.96-1.90 (m, 1.6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ $190.7_{(maj+min)}$, $145.4_{(maj+min)}$, $144.2_{(maj+min)}$, $137.6_{(maj+min)}$, $132.9_{(maj+min)}$, 128.59 $(2C)_{maj+min}$, 128.57 $(2C)_{min}$, 128.54 $(2C)_{(maj+min)}$, 128.50 $(2C)_{maj}$, $128.3_{(maj+min)}$, 127.5_{maj}, 125.9_{min}, 125.6 $(2C)_{min}$, 125.5 $(2C)_{maj}$, 74.6_{min}, 71.5_{maj}, $67.7_{(maj+min)}$, $44.5_{(maj+min)}$, $40.8_{(maj+min)}$; HRMS for $C_{19}H_{20}O_3$+Na calcd 319.1310; found 319.1315.

Preparation of 2-((2*S*,4*S*,6*R*)-4-hydroxy-6-phenyltetrahydro-2H-pyran-2-yl)-1-phenylethan-1-one (5-*epi*-diospongin A (1a): A solution of the enone **10** (0.085 g, 0.21 mmol) in methanol (4 mL) was cooled to 0 °C, and camphor sulphonic acid (48 mg, 0.21 mmol) was added at the same temperature. The reaction mixture was then slowly warmed to room temperature

and **le-1**).

solvent was removed under reduced pressure, to give the crude residue, which was diluted with saturated $NaHCO_3$ solution and extracted with EtOAc (2 × 20 mL) and the combined organic extracts was washed with brine (10 mL), dried over anhydrous Na_2SO_4. Evaporation of the solvent gave the crude residue which on purification through silica gel column chromatography, petroleum ether/EtOAc (7:3) as eluent gave the 5-*epi*-diospongin (***ent*-1a**) (40 mg, 66%) as a colourless oil; $[\alpha]^{24}_D$ +14.7 (*c* 1.1, $CHCl_3$), [lit.[2g] *enantiomer* $[\alpha]^{24}_D$ −11.6 (*c* 0.54, $CHCl_3$)]; IR (neat) 3415, 2922, 2856, 1679, 1588 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.98 (d, *J* = 7.6 Hz, 2H), 7.56 (t, *J* = 7.2 Hz, 1H), 7.46 (t, *J* = 8.0 Hz, 2H), 7.35-7.21 (m, 5H), 4.44 (d, *J* = 10.4 Hz, 1H), 4.25-4.15 (m, 1H), 4.05 (*sept*, J = 10.0 Hz 1H), 3.48 (dd, *J* = 16.4, 6.0 Hz, 1H), 3.10 (dd, *J* = 16.4, 6.4 Hz, 1H), 2.23 (dd, *J* = 12.8, 3.6 Hz, 2H), 1.64 (brs, 1H), 1.51 (*q*, *J* = 11.6 Hz, 1H), 1.37 (*q*, *J* = 11.6 Hz, 1H; ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.0, 141.7, 137.2, 133.2, 128.6 (2C), 128.3 (2C), 128.3 (2C), 127.5, 125.7 (2C), 77.5, 72.5, 68.2, 44.8, 42.5, 40.9; HRMS for $C_{19}H_{20}O_3$+Na calcd 319.1310; found 319.1312.

(+)-diospongin A: 2-((2*S*,4*R*,6*R*)-4-hydroxy-6-phenyltetrahydro-2H-pyran-2-yl)-1-phenylethan-1-one (*ent*-1): (11 mg, 18%) as a white solid. M.P: 97-101 °C, [lit.[2m] M.P: 98-100 °C]; $[\alpha]^{24}_D$ +20.8 (*c* 1.6, $CHCl_3$), [lit.[2m] $[\alpha]^{24}_D$ +19.2 (*c* 1.0, $CHCl_3$)]; IR (neat) 3411, 2917, 2884, 1678, 1593,1054 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.98 (d, *J* = 8.0 Hz, 2H), 7.56 (t, *J* = 7.2 Hz, 1H), 7.45 (t, *J* = 7.6 Hz, 2H), 7.32-7.20 (m, 5H), 4.93 (d, *J* = 10.8 Hz, 1H), 4.70-4.60 (m, 1H), 4.39-4.33 (m, 1H), 3.42 (dd, *J* = 16.0, 5.6 Hz, 1H), 3.07 (dd, *J* = 16.0, 7.2 Hz, 1H), 1.96 (d, *J* = 13.2 Hz, 2H), 1.80-1.63 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.3, 142.7, 137.3, 133.1, 128.5 (2C), 128.3 (2C), 128.2 (2C), 127.2, 125.8 (2C), 73.8, 69.0, 64.7, 45.1, 40.0, 38.5; HRMS for $C_{19}H_{20}O_3$+Na calcd 319.1310; found 319.1310.

Preparation of 2-((2*S*,4*S*,6*R*)-4-hydroxy-6-phenyltetrahydro-2H-pyran-2-yl)-1-phenylethan-1-one (*ent*-1a) and diospongin A (*ent*-1) from 3: To a pre-cooled (0 °C) solution of the diol **3** (0.016 g, 0.05 mmol) in dichloromethane (2 mL), TFA (0.04 mL, 0.54 mmol) was added at the same temperature. After stirring at 0 °C for 10 min. the reaction mixture was quenched by the addition of saturated $NaHCO_3$ solution (10 mL) and extracted with CH_2Cl_2 (2 × 5 mL). The combined organic layer was washed with brine (5 mL) and dried over anhydrous Na_2SO_4. Silica gel column chromatography of the residue obtained after evaporation of the solvent, using petroleum ether:EtOAc (7:3) as eluent furnished 4-*epi*-diospongin (*ent*-**1a**) (11 mg, 69%) as a colourless oil and diospongin A (*ent*-**1**) (3 mg, 19%) as a white solid. Both physical and spectral properties of (*ent*-**1a**) and (*ent*-**1**) were identical with that obtained from **10** with the previous step synthesis.

General procedure for Mukaiyama aldol reaction and subsequent *oxa* Michael addition (procedure D): To a pre-cooled solution of aldehyde **(4a-4c)** (1 eq) and silyl enol ether **(9a-9c)** (1.3 eq-1.5 eq) in CH_2Cl_2 (8 mL) at −78 °C, was added $BF_3{\cdot}OEt_2$ (1 eq) dropwise. After stirring at −78 °C for 10 min. was added camphor sulphonicacid (2 eq in 1 mL of MeOH) in dropwise and then slowly warmed to at room temperature, stir for 1 h to 12 h. After completion of the reaction (indicated by TLC), the mixture was quenched with saturated $NaHCO_3$ solution (10 mL) and extracted with CH_2Cl_2 (2 × 5 mL). The combined organic layers were washed with brine (5 mL) and dried over anhydrous Na_2SO_4. Silica gel column chromatography of the residue obtained after evaporation of the solvent, using petroleum ether:EtOAc (7:3) as eluent gave (+)-diospongin A and its 5-

Preparation of 5-*epi*-diospongin A and diospongin A from 4a: Using a general procedure D aldehyde **4a** (25 mg, 0.11 mmol), silyl enol ether **9** (37 mg, 0.17 mmol), $BF_3{\cdot}OEt_2$ (0.012 mL, 0.1 mmol) and CSA (52 mg, 0.22 mmol) afforded 5-epidiospongin A (*ent*-**1a)** (20 mg, 61%) and diospongin A (*ent*-**1**) (1 mg, 3%).

Preparation of 5-*epi*-diospongin A and diospongin A from 4b: Using a general procedure D aldehyde **4b** (30 mg, 0.1 mmol), silyl enol ether **9** (37 mg, 0.17 mmol), $BF_3{\cdot}OEt_2$ (0.012 mL, 0.1 mmol) and CSA (52 mg, 0.22 mmol) afforded 5-epidiospongin A (*ent*-**1a)** (16 mg, 48%) and diospongin A (*ent*-**1**) (2 mg, 6%).

Preparation of 5-*epi*-diospongin A and diospongin A from 4: Using a general procedure D aldehyde **4** (30 mg, 0.1 mmol), silyl enol ether **9** (37 mg, 0.17 mmol), $BF_3{\cdot}OEt_2$ (0.012 mL, 0.1 mmol) and CSA (52 mg, 0.22 mmol) afforded 5-epidiospongin A (*ent*-**1a**) (12 mg, 36%) and diospongin A (*ent*-**1**) (3 mg, 6%).

Preparation of 5-*epi*-diospongin A and diospongin A from 4c: Using a general procedure D aldehyde **4c** (38 mg, 0.12 mmol), silyl enol ether **9** (34 mg, 0.15 mmol), $BF_3{\cdot}OEt_2$ (0.012 mL, 0.1 mmol) and CSA (58 mg, 0.22 mmol) afforded 5-epidiospongin A (*ent*-**1a**) (10 mg, 27%) and diospongin A (*ent*-**1**) (5 mg, 14%).

Preparation of 5-*epi*-diospongin A and diospongin A from 4b: Using a general procedure D aldehyde **4b** (30 mg, 0.11 mmol), silyl enol ether **9a** (44 mg, 0.17 mmol), $BF_3{\cdot}OEt_2$ (0.012 mL, 0.1 mmol) and CSA (53 mg, 0.22 mmol) afforded 5-epidiospongin A (*ent*-**1a**) (12 mg, 36%) and diospongin A (*ent*-**1**) (2 mg, 6%).

Preparation of 5-*epi*-diospongin A and diospongin A from 4: Using a general procedure D aldehyde **4** (20 mg, 0.08 mmol), silyl enol ether **9b** (35 mg, 0.11 mmol), $BF_3{\cdot}OEt_2$ (0.008 mL, 0.08 mmol) and CSA (35 mg, 0.15 mmol) afforded 5-epidiospongin A (*ent*-**1a**) (10 mg, 40%) and diospongin A (*ent*-**1**) (2 mg, 8%).

Preparation of 5-*epi*-diospongin A and diospongin A from 4c: Using a general procedure D aldehyde **4c** (40 mg, 0.13 mmol), silyl enol ether **9c** (59 mg, 0.19 mmol), $BF_3{\cdot}OEt_2$ (0.01 mL, 0.13 mmol) and CSA (61 mg, 0.26 mmol) afforded 5-epidiospongin A (*ent*-**1a**) (10 mg, 26%) and diospongin A (*ent*-**1**) (5 mg, 13%).

Preparation of 2-((2*S*,4*R*,6*R*)-4-hydroxy-6-phenyltetrahydro-2H-pyran-2-yl)-1-phenylethan-1-one (diospongin A, *ent*-1): To a pre cooled (0 °C) solution of triphenylphosphine (138 mg, 0.53 mmol), DIAD (0.1 mL, 0.53 mmol) in toluene (4 mL) was added a solution of *ent*-**1a** (52 mg, 0.18 mmol) in toluene (2 mL) was added and stirred for 10 min at the same temperature. *p*-Nitrobenzoic acid (88 mg, 0.53 mmol) was added at once to the reaction mixture and it was stirred at room temperature for 1 h. After completion of the reaction (monitored by TLC) most of the solvent was evaporated under vacuum and the residue thus obtained was purified by silica gel column chromatography using petroleum ether: EtOAc (9:1) as eluent furnish the corresponding *p*-Nitro benzoate (80 mg) as colourless oil, which was proceeded to next step without further purification.

To a stirred solution of the *p*-Nitrobenzoate (obtained above) in ethanol was added K_2CO_3 (74 mg, 0.53 mmol) and was stirred for 2 h at room temperature. After completion of the reaction (monitored by TLC) the solvent was evaporated off, under vacuum and the residue thus obtained was diluted with water (10 mL) and extracted with EtOAc (2 x 10 mL). The combined

anhydrous Na_2SO_4. Evaporation of solvent gave the crude residue which was purified by silica gel column chromatography using petroleum ether: EtOAc (6:4) as eluent furnished (*ent*-**1**) (35 mg, 67%) as a white solid.

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Supplementary Material

^{1}H NMR and ^{13}C NMR spectra for all the new compounds synthesized are provided.

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Highlights

- Short one-pot reaction conditions for the synthesis of diospongin A
- Involves the vinylogous Mukaiyama Aldol reaction, Silyl deprotection and Oxa-Michael reaction in one-pot.
- 25% overall yield from benzaldehyde

Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: