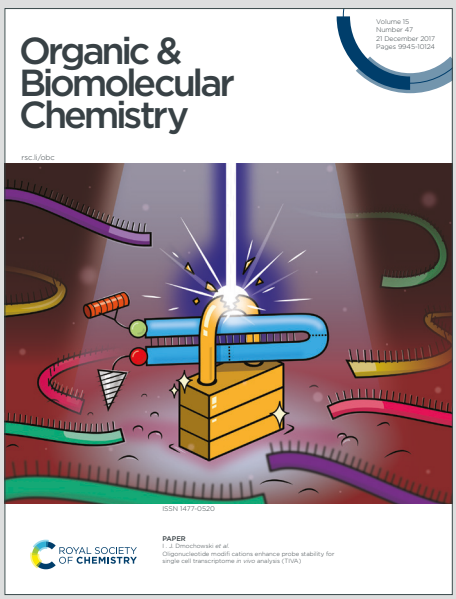
Organic & Biomolecular Chemistry

Accepted Manuscript

This article can be cited before page numbers have been issued, to do this please use: S. Nanda, J. Chakraborty and A. Ghosh, *Org. Biomol. Chem.*, 2020, DOI: 10.1039/D0OB00237B.



ROYAL SOCIETY OF CHEMISTRY

rsc.li/obc

DOI: 10.1039/D0OB00237B

Asymmetric total syntheses of naturally occurring α,β-enone-containing RALs, L-783290 and L-783277 through intramolecular base-mediated macrolactonization reaction

Joy Chakraborty,[1] Ankan Ghosh [1,2] and Samik Nanda*[1]

[1] Department of Chemistry, Indian Institute of Technology Kharagpur, Kharagpur.

[2] Department of Chemistry, University of Texas at Austin, Austin, TX, USA

Abstract: Asymmetric total synthesis of two naturally occurring α,β-enone containing RALs, L-783290 and L-783277 is described in this article. An *E*-selective Horner-Wadsworth-Emmons (HWE) olefination was used as a key reaction to construct the $C_{7'}$-$C_{8'}$ olefinic unsaturation in L-783290. An enantiopure alkyne addition to the aldehyde followed by *Z*-selective partial reduction was employed to construct the $C_{7'}$-$C_{8'}$ olefinic unsaturation in L-783277. Biomimetic lactonization reaction was used to construct the macrlactone core in both the target molecules.

Introduction: Resorcylic acid lactones (RALs)[1] are a unique class of fungal secondary metabolites defined by the presence of a β-resorcylic acid ring and a 14-membered lactone macrocycle with a methyl substituent at the $C_{10'}$-position in its core structure.[1] RALs have received considerable attention, due to their diversified biological properties, which include antifungal, cytotoxic, antimalarial, antiviral, antiparasitic, estrogenic, nematicidal, protein tyrosine kinase, and ATPase inhibition activities.[2] RALs containing an "α,β-enone" moiety in its structure is susceptible to Michael addition reactions with the cysteine residue present in the kinase nucleotide-binding site and thus serve as potent inhibitors of several protein kinases and they, therefore, represent a unique pharmacophore.[3] Some members of this family are LL-Z1640-2 (**3**), which was first isolated as an anti protozoan from unidentified fungi by Ellestad *et al.* [4] in 1978. L-783277 (**1**) was isolated from a Phoma sp (ATCC 74403) which came from the fruit body of *Helvella acetabulum*, is a potent and specific inhibitor of MEK.[5] L-783290 (**2**), the *trans*-isomer of L-783277 (**1**), was isolated from the same culture but RALs bearing the *cis*-enone moiety such as hypothemycin (**4**), LL-Z1640-2 and L-783277 are more potent than the *trans*-enone L-783290 (Figure 1).[6] Pochonin C (**5**) and D (**6**) are also "α,β-enone" containing RALs and isolated from the cultures of the clavicipitaceous hyphomycete *Pochonia chlamydosporia* var. *catenulata* strain P 0297 in 2003 and found to possess antiviral activity against HSV (Herpes Simplex Virus).[7] The first example of a naturally occurring RAL,

radicicol (**8**), was isolated from *Monocillium nordinii* in 1953 happened to contain an "α,β-enone" moiety (*E*-enone) in its structure.[8] Structurally similar to radicicol, another RAL monocillin I (**7**) was also isolated from the same species and showed to exhibit moderate antifungal and antibacterial activities. Cryptosporiopsin A (**9**) isolated from *Cryptosporiopsis* sp, an endophytic fungus from healthy leaves, stems and branches of *Zanthoxylum leprieurii*, having an *E*-enone functionality and a carbonyl group at $C_{6'}$ position.[9] Due to the broad spectrum of bioactivity and the architecturally complex structure of these molecules, synthetic organic chemist community has targeted these molecules for total synthesis and biosynthetic study. The first synthesis of L-783277 was achieved by Altmann *et al.* in the year 2008, through the successful exploration of Suzuki coupling and a late-stage macrolactonization reaction.[10] Whereas Banwell's group reported the first synthesis of L-783290 (the *E*-counterpart of L-783277) through the exploitation of Heck coupling and intramolecular Weinreb ketone synthesis followed by other synthetic manipulation.[11] Subsequently, few other total syntheses for the above two target molecules were reported in the literature.[12] Our previous endeavor in the asymmetric synthesis of several naturally occurring RALs, lead us to the total synthesis of paecilomycin C, cochliomycin A, cochliomycin C, paecilomycin E, zeaenol etc. by the successful exploration of several strategically important reactions such as ME-DKR (metal enzyme combined dynamic kinetic resolution), Keck asymmetric allylation, *E*-selective Julia-Kocienski olefination, RCM reaction, lactonization through intramolecular ring opening of an epoxide and macrolactonization (Yamaguchi and Mitsunobu) protocol.[13] Recent investigation has revealed that biosynthesis [14] of RALs involves a late-stage macrolactonization protocol. Hence we argue that late-stage macrolactonization protocol for synthesizing RALs mimic the biogenesis in true sense. Henceforth we would like to focus on the late-stage macrocyclization protocol (-CO_2H activation or -OH activation method) at the penultimate stage for the total synthesis of RALs.

View Article Online
DOI: 10.1039/D0OB00237B

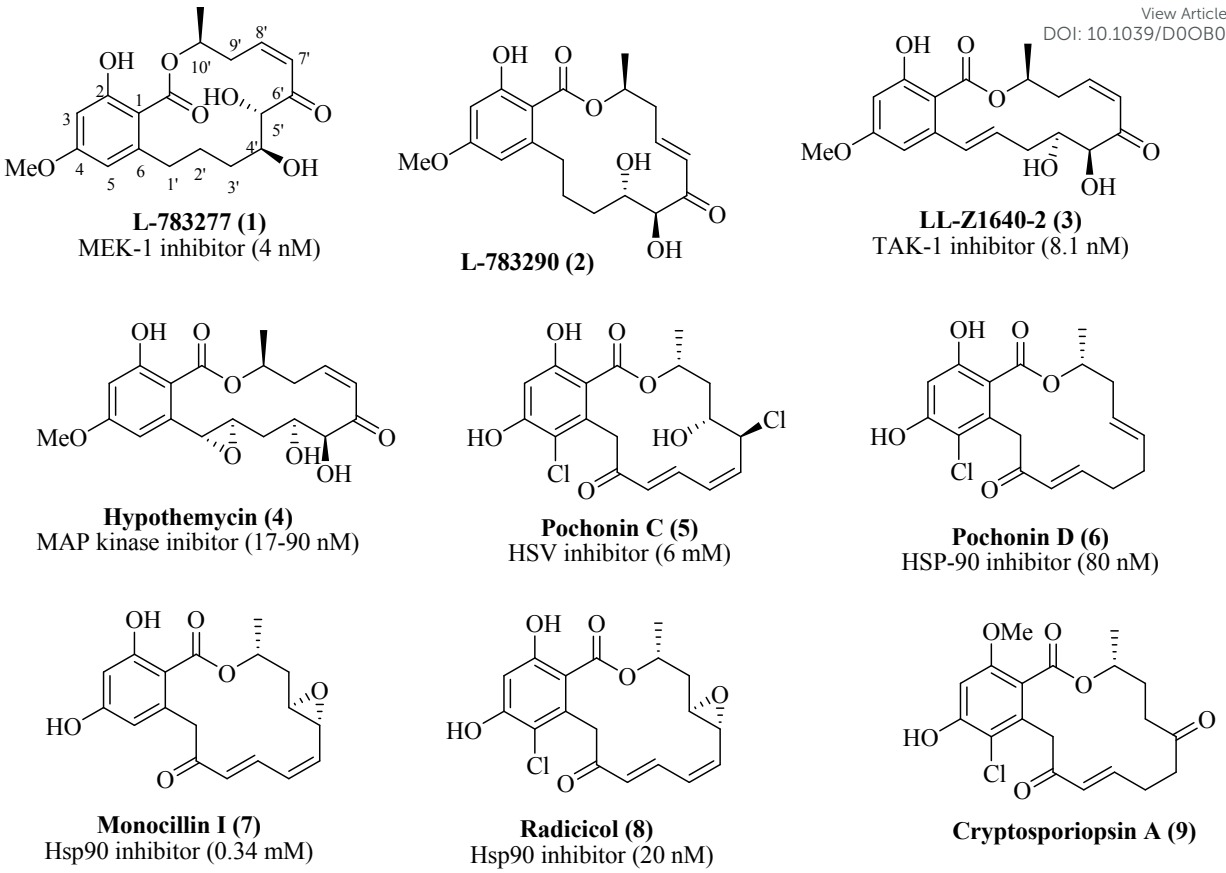


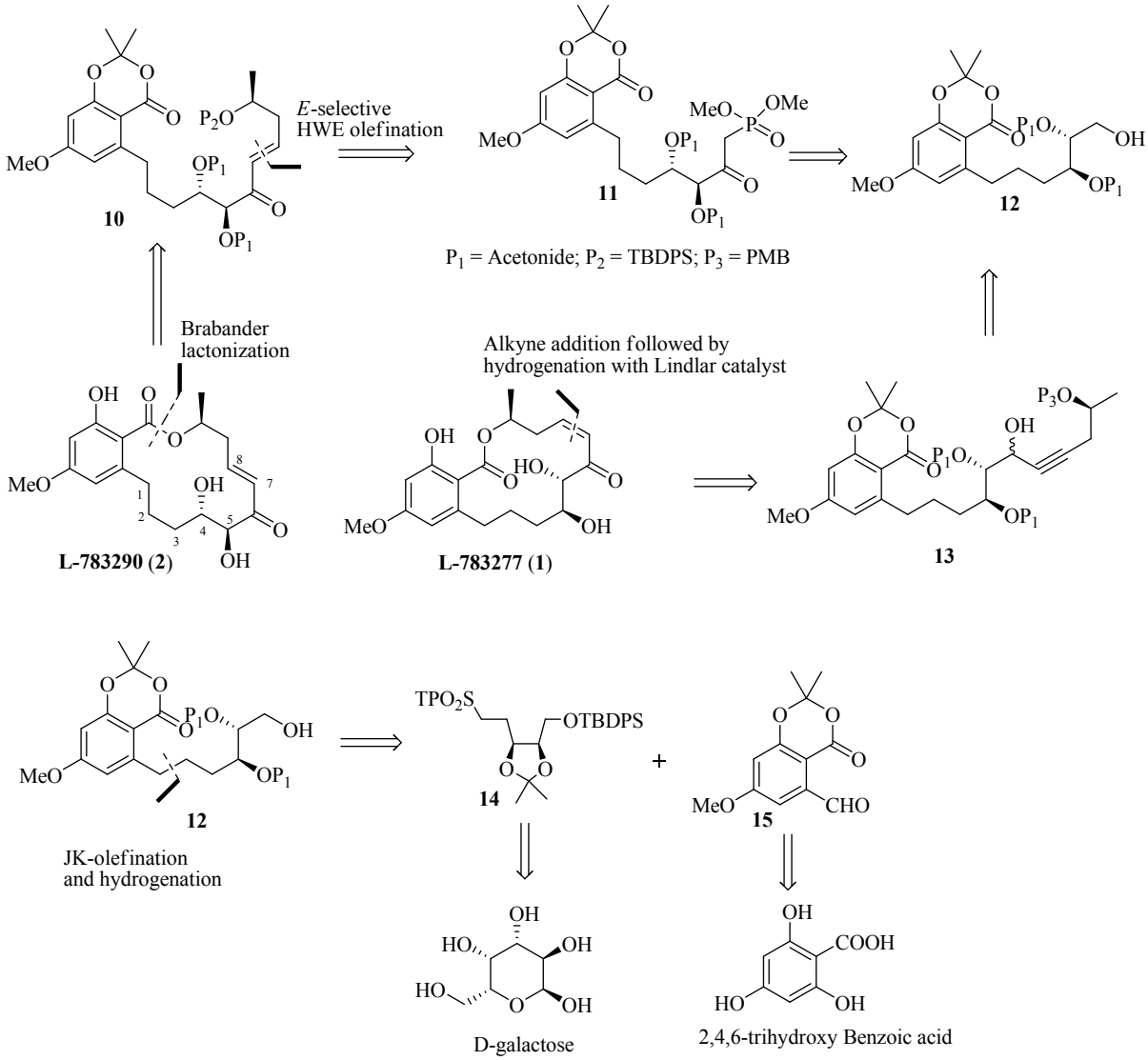
Figure 1: RALs containing *α,β*-unsaturated ketone moiety and their bioactivities

Retrosynthetic analysis of target molecules L-783290 and L-783277:

In this current scenario, we fixed our objective is to describe a general and flexible synthetic strategy for the asymmetric total synthesis of naturally occurring "α,β-enone" containing RALs, L-783290 (**2**) and L-783277 (**1**). A careful structural investigation reveals that the $C_{7'}$-$C_{8'}$olefinic unsaturation is "*E*" in the case of L-783290 (**2**) and "*Z*" for L-783277 (**1**). A common intermediate **12** was visualized as a key precursor for accessing both the target RAL molecules. The internal double bond ($C_{7'}$-$C_{8'}$) could be achieved by *E*-selective HWE olefination of a properly substituted *β*-ketophosphonate (**11**) and an aldehyde for L-783290. Such strategical disconnection by the execution of HWE olefination was never tried before for RAL synthesis. The required *β*-ketophosphonate (required for HWE olefination) could be achieved from an aldehyde and dimethyl methylphosphonate by aldol reaction followed by oxidation of the aldol product. The "*Z*" internal olefinic unsaturation ($C_{7'}$-$C_{8'}$) for L-783277, is proposed to be accessed through partial reduction of an alkyne functionality by hydrogenation with Lindlar catalyst. The alkyne can be constructed from compound **12** as depicted in scheme 1. The key intermediate **12** could be accessed by JK (Julia-Kocienski) olefination between sulfone **14** and aromatic aldehyde **15**. Sulfone **14** and aromatic aldehyde **15** could be prepared

View Article Online
DOI: 10.1039/D0OB00237B

from D-galactose and 2,4,6-trihydroxy benzoic acid respectively. De Brabander's intramolecular lactonization reaction [15] was used in the late stage for the construction of the core macrolactones in both the cases (Scheme 1).



Scheme 1: Retrosynthetic disconnection for L-783290 and L-783277

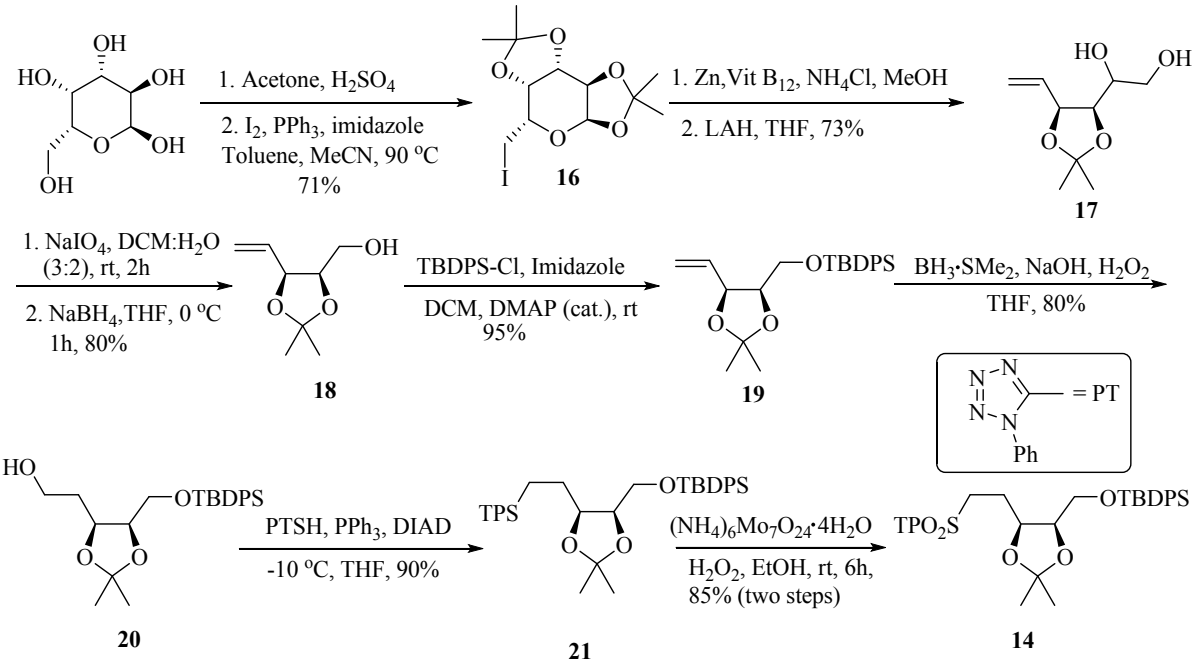
Results and discussion:

Synthesis of Sulfone 14:

The synthesis was initiated with D-galactose, which on di-acetonide protection and subsequent Appel reaction afforded the iodo compound **16** in 71% yield (in two steps).[16] Reductive ring-opening of compound **16** with Zn and ammonium chloride in the presence of Vitamin B_{12}, followed by LAH reduction, furnished the diol **17** in 73% yield (in two steps). Oxidative cleavage of the diol **17** with $NaIO_4$, followed by $NaBH_4$ reduction in THF at 0 ˚C, afforded the alcohol **18** in 80% yield (in two steps). Primary alcohol functionality in compound **18** was then converted to its TBDPS (tert-butyl diphenylsilyl) ether by treatment of TBDPS-Cl and

View Article Online
DOI: 10.1039/D0OB00237B

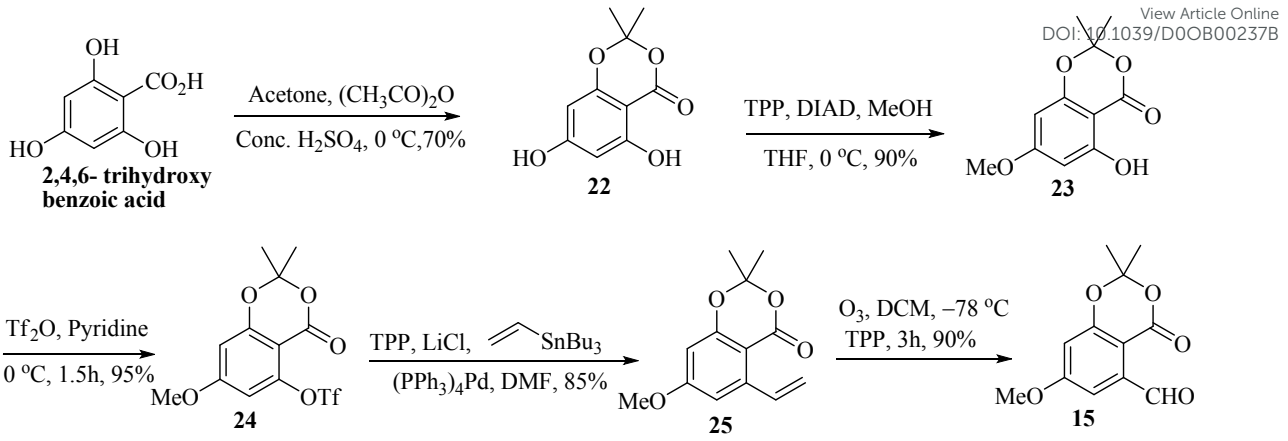
imidazole to afford compound **19** in 95% yield, which was then subjected to hydroboration with $BH_3.SMe_2$ and oxidation by NaOH and H_2O_2 to afford alcohol **20** in 80% yield. Compound **20** was then transformed into the corresponding 1-phenyl-1*H*-tetrazol-5-yl sulfide (**21**) through a Mitsunobu reaction, and subsequent Mo(IV)-catalyzed oxidation of sulfide produced the desired sulfone **14** in a yield of 85% over two steps (Scheme 2).



Scheme 2: Synthesis of sulfone **14** required for JK-olefination

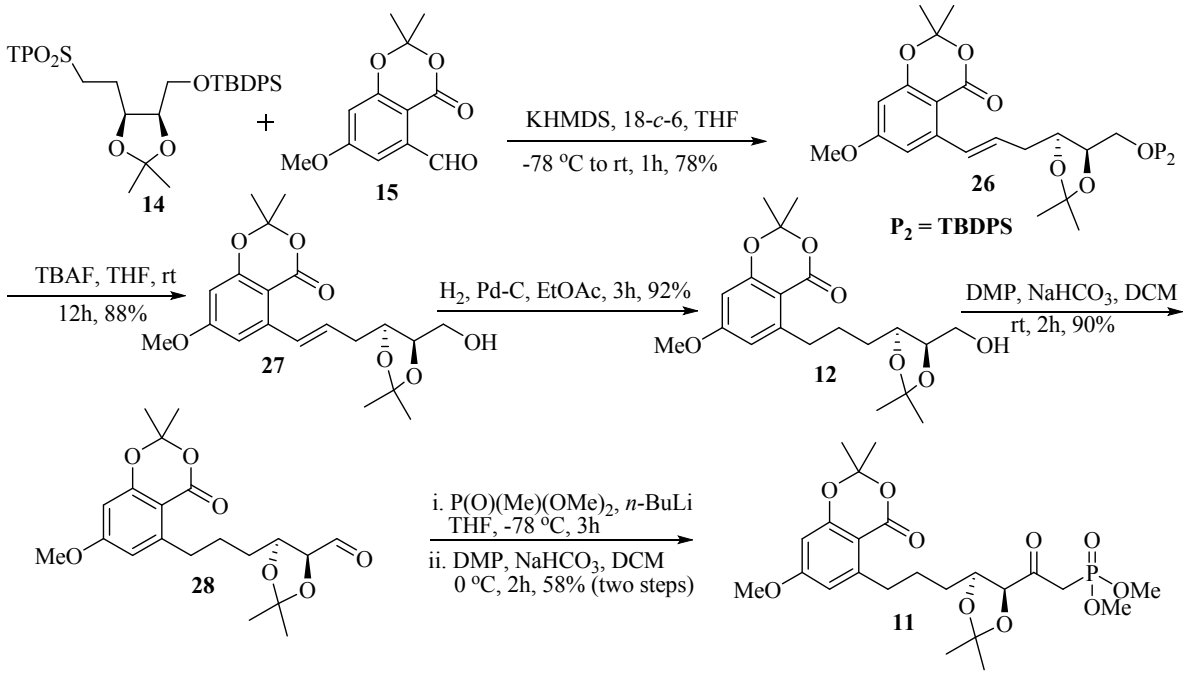
Synthesis of aromatic aldehyde 15:

The aromatic fragment **15** can be prepared in 4 steps starting from 2,4,6- trihydroxy benzoic acid as starting material.[17] At first, one of the hydroxyl groups and the carboxylic acid group of 2,4,6- trihydroxy benzoic acid has been protected to its acetonide by using acetone and acetic anhydride in the presence of conc. H_2SO_4 to provide compound **22** in 70 % yield. Regioselective monomethylation of one of the hydroxyl groups under the Mitsunobu condition furnished compound **23** in 90% yield. Compound **23** was then converted to its triflate in the presence of Tf_2O and pyridine to provide compound **24** in 95% yield. Stille coupling [18] of triflate **24** and tributyl vinyltin in the presence of $Pd(Ph_3)_4$ furnished aromatic compound **25** in 85% yield. Oxidative cleavage of **25** under ozonolytic condition then furnished the aldehyde **15** in 90% yield (Scheme 3).



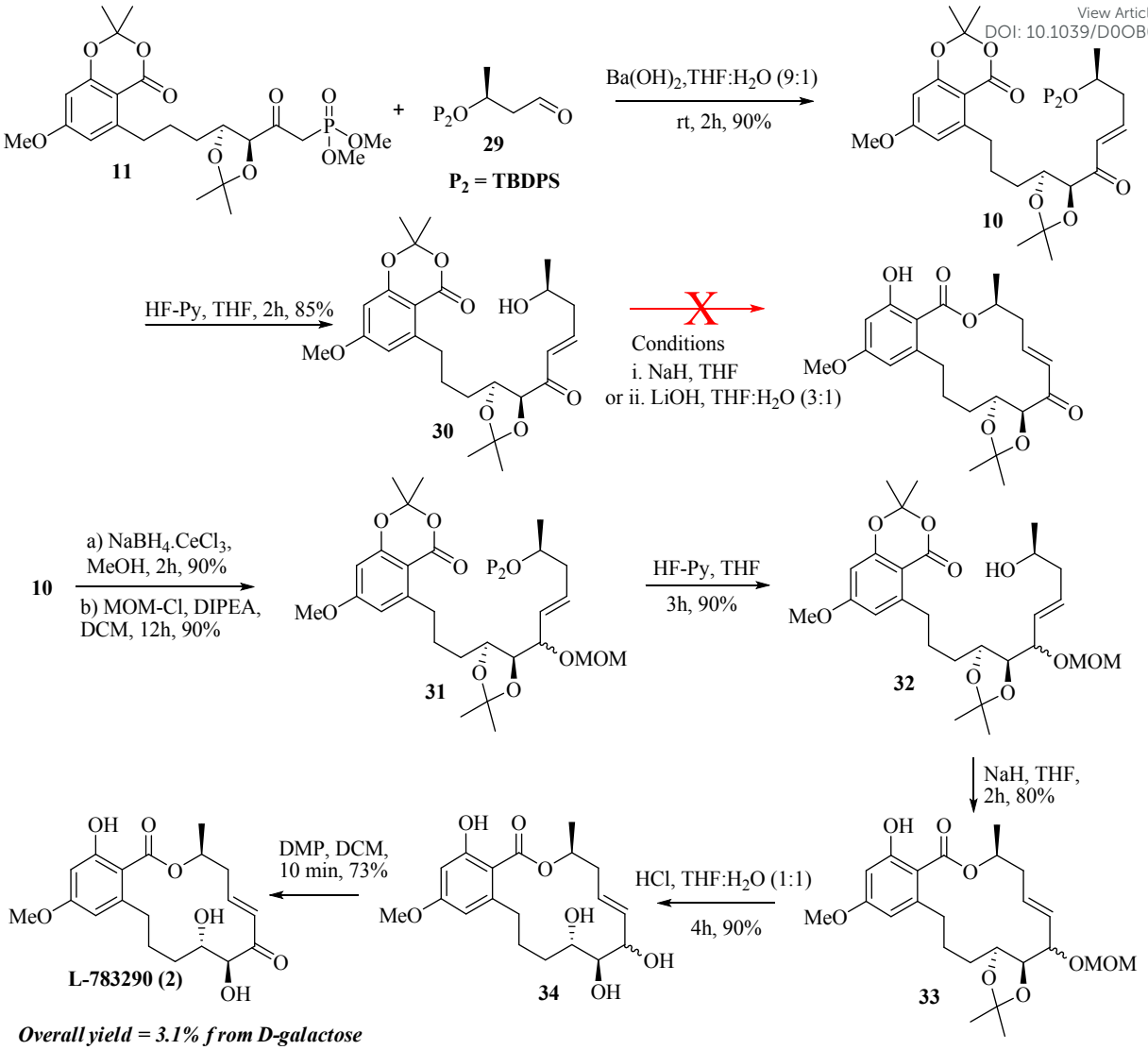
Scheme 3: Synthesis of aromatic aldehyde **15**

Synthesis of keto phosphonate 11 required for HWE olefination (for L-783290): Sulfone **14** and aromatic aldehyde **15** was then subjected to JK-olefination [19] in the presence of KHMDS and 18-*c*-6 ether in THF to furnish the '*E*'- olefin **26** in 78% yield. Compound **26** was then allowed to react with TBAF in THF to furnish alcohol **27** in 88% yield. Alcohol **27** was then subjected to hydrogenation with H_2 in the presence of Pd-C in ethyl acetate solvent to afford the corresponding hydrogenated alcohol **12** in 92% yield. The alcohol **12** on oxidation with DMP in DCM furnished aldehyde **28** in 90% yield. Aldehyde **28** was then reacted with diethyl methylphosphonate in the presence of *n*-BuLi in THF to give a diastereomeric mixture which was then subjected to DMP oxidation in DCM at 0 °C to afford the β-ketophosphonate **11** in 58% yield in two steps (Scheme 4).[20]



Scheme 4: Synthesis of the β-keto phosphonate **11**

Synthesis of L-783290: Ketophosphonate **11** and known enantiopure aldehyde **29** [21] was then subjected to HWE olefination in the presence of $Ba(OH)_2$ in THF: H_2O (9:1) to afford the *E* olefin **10** in 90% yield.[22] The TBDPS group deprotection was then carried out by using HF-Py in THF to furnish the lactone precursor **30** in 85% yield. Lactonization under Brabander condition with NaH in THF was attempted, but unfortunately, we did not observe the desired product and the starting material also got decomposed. Attempted hydrolysis of **10** with LiOH as a base also failed. Such base mediated hydrolysis was earlier attempted on similar systems,[13c] and found to be incompatible mainly due to depleted electrophilicity of the carbonyl carbon of the ester functionality (due to presence of electron releasing 4-OMe group). Then we also speculate that due to the presence of *α,β*-unsaturated ketone moiety in the system, side reactions may have taken place (base can act as a nucleophile in Michael fashion). Forcefully we had to reduce the *α,β*-unsaturated ketone functionality in **10** under Luche condition [23] and subsequent MOM protection affords compound **31** in 81% yield (two steps). TBDPS group deprotection was then done by using HF-Py in THF to afford the lactone precursor **32** in 90% yield. Lactonization under Brabander condition using NaH in THF now proceeded smoothly this time and furnished lactone **33** in 80% yield. Treatment of **33** with 2M HCl, deprotects the acetonide as well as MOM ether group to afford the triol **34** in 90 % yield. Selective allylic oxidation with Dess-Martin reagent [24] was then employed to furnish L-783290 in 73% yield as a white solid (overall yield = 3.1% from D-galactose; Scheme 5). The characteristic spectral data (^{1}H and ^{13}C-NMR) of our synthesized L-783290 matches well with that reported in the literature.[11]

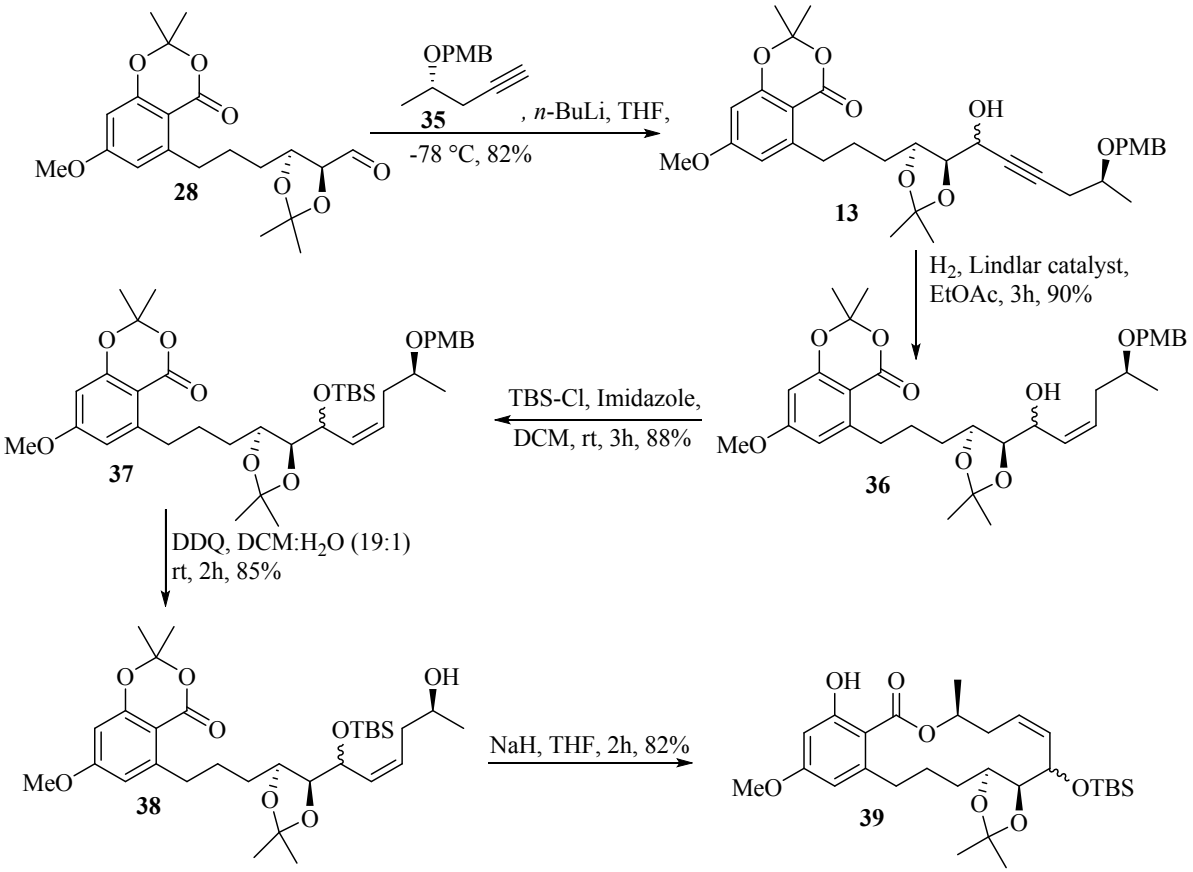


Scheme 5: Completion of the synthesis of L-783290 (**2**)

Synthesis of L-783277: We have started the journey for the synthesis of L-783277 (**1**) with the common intermediate aldehyde **28** which undergoes a nucleophilic addition reaction with alkyne **35** (alkyne **35** was synthesized from '*S*'- propylene oxide in two steps [25]) in presence of *n*-BuLi and afforded compound **13** (inseparable diastereomer) in 82% yield. Alkyne **13** was then converted to its corresponding '*Z*'-alkene **36** on restricted hydrogenation in the presence of Lindlar catalyst in 90% yield. The free hydroxyl functionality in compound **36** was then protected as its TBS-ether in the presence of TBS-Cl and imidazole to afford compound **37** in 88% yield. PMB group deprotection of compound **37** in the presence of DDQ in DCM: H_2O (19:1) afforded lactone precursor **38** in 85% yield. Compound **38** then underwent lactonization under De Brabander condition with NaH in THF to furnish lactone **39** in 82% yield. The diastereomers were then separated by column chromatography after lactonization. However,

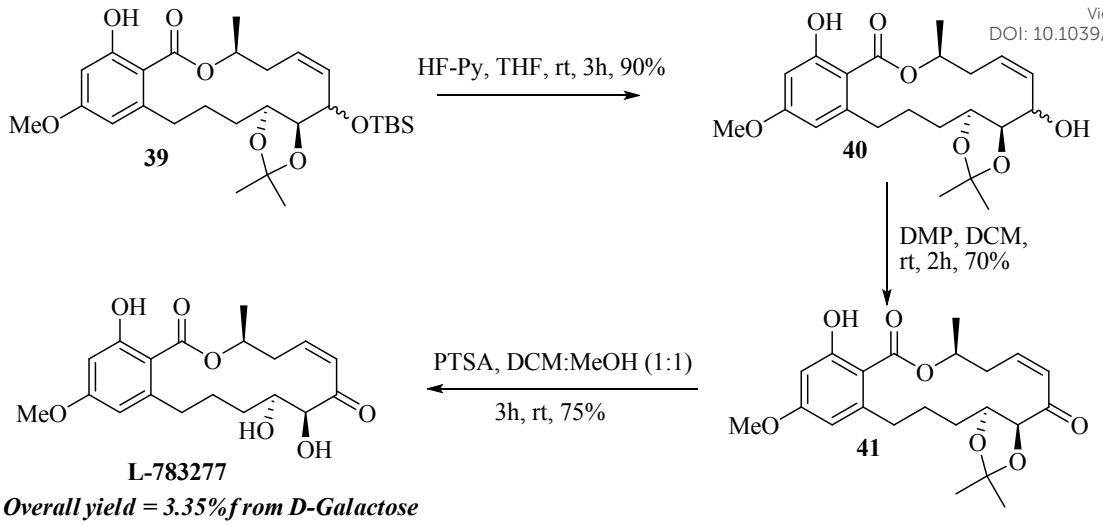
View Article Online
DOI: 10.1039/D0OB00237B

the determination of stereocenter at $C_{6'}$- position was not necessary since this stereocenter was going to be destroyed by the formation of an enone in the final natural product (Scheme 6).



Scheme 6: Synthesis of macrolactone core of L-783277

Completion of the synthesis of L-783277: Lactone **39** was then reacted with HF-Py in THF and underwent TBS deprotection to afford compound **40** in 90% yield. Oxidation with Dess-Martin periodinane in DCM availed compound **41** in 70% yield. Then deprotection of acetonide group was successfully carried out with PTSA in DCM: MeOH (1:1) to furnish the desired L-783277 (**1**) in 75% yield as a white solid (overall yield = 3.35% from D-galactose; Scheme 7). The characteristic spectral data (^{1}H and ^{13}C-NMR) of our synthesized L-783277 matches well with that reported in the literature.[5a]



Scheme 7: Completion of the synthesis of L-783277

Conclusion: In conclusion, we have successfully synthesized L-783290 in a convergent way with 3.1% overall yield from D-galactose as a chiral pool material (in 23 linear steps). The success of our strategy depends on an "*E*"-selective HWE olefination (for creation of $C_{7'}$-$C_{8'}$ olefinic unsaturation) and a late-stage De Brabender type lactonization reaction. We have also accomplished the total synthesis of another naturally occurring RAL, L-783277 from an advanced intermediate used in the synthesis of L-783290 in 3.35% overall yield from D-galactose (in 22 linear steps). Alkyne addition on an aldehyde followed by *Z*-selective partial reduction and nucleophilic macrolactonization under De Brabender condition is the main highlight of the current synthesis for L-783277.

Experimental procedures and characterization data:

General procedures: All oxygen and/or moisture-sensitive reactions were carried out under N_2 atmosphere in glassware that had been flame-dried under vacuum (ca. 0.5 Torr) and purged with N_2 prior to use. Unless otherwise stated, materials were obtained from commercial suppliers and used without further purification. THF, diethyl ether were distilled from sodium benzophenone ketyl. Dichloromethane (DCM), hexane were distilled from calcium hydride. Reactions were stirred magnetically using Teflon-coated magnetic stirring bars. Teflon-coated magnetic stirring bars and syringe needles were dried in an oven at 120 °C for at least 12 h prior to use then cooled in a desiccator cabinet over Drierite. Reactions were monitored by thin-layer chromatography (TLC) carried out on 0.25 mm silica gel plates with UV light, ethanolic anisaldehyde, and phosphomolybdic acid/heat as developing agents. Silica gel 100-200 mesh was used for column chromatography. Yields refer to chromatographically and

spectroscopically homogeneous materials unless otherwise stated. NMR spectra were recorded on 600, 400 and 200 MHz spectrometers at 25 ˚C in $CDCl_3$ using TMS as the internal standard. Chemical shifts are shown in δ. ^{13}C NMR spectra were recorded with a complete proton decoupling environment. Coupling constants (*J*) are reported in hertz (Hz), and the resonance multiplicity abbreviations used are s, singlet; d, doublet; dd, doublet of doublet; t, triplet; q, quartet; m, multiplet; overlapping multiplets of magnetically non-equivalent protons. The mass spectrometric analysis was performed in the CRF, IIT-Kharagpur (TOF analyzer).

(3a*R*,5*S*,5a*R*,8a*S*,8b*R*)-5-(iodomethyl)-2,2,7,7-tetramethyltetrahydro-5*H*-bis([1,3]dioxolo)[4,5-b:4',5'-*d*]pyran (16):

Two batches of D-(+)-galactose (7 g, 38.85 mmol) in acetone (250 mL) were treated in parallel with conc. H_2SO_4 (7.7 mL) at 0 °C. The reaction mixtures were stirred at room temperature for 3−5 h and then neutralized by the addition of a saturated solution of Na_2CO_3 until pH = 7.0. The precipitate was then removed by filtration through a pad of Celite. The filtrates were combined and concentrated under reduced pressure. The crude diacetonide protected D-(+)-galactose (19 g, 98%) was used without further purification.

To an ice-cooled solution of crude isopropylidene galactose (18.8 g, 72.36 mmol) in toluene (145 mL) and MeCN (70 mL) were added imidazole (9.85 g, 144.7 mmol), Ph_3P (28.47 g, 108.6 mmol) and iodine (27.55 g, 108.6 mmol). The reaction mixture was then heated to 90 °C and stirred for 2 h. The solution was subsequently cooled to 0 °C, and then Et_2O (200 mL) was added. The resultant precipitate was removed by filtration through a pad of Celite. The filtrate was concentrated under reduced pressure and purified by flash chromatography (ethyl acetate/hexane = 1:50) to provide iodide **16** (18.9 g, 71%) as a white solid. R_f = 0.6 (ethyl acetate/hexane = 1:20). $[\alpha]_D^{25}$ = -45 (*c* 1, $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$): δ 5.54 (d, *J* = 5.0 Hz, 1H), 4.61 (dd, *J* = 7.8, 2.4 Hz, 1H), 4.40 (dd, *J* = 7.9, 1.8 Hz, 1H), 4.30 (dd, *J* = 5.0, 2.5 Hz, 1H), 3.94 (td, *J* = 7.0, 1.7 Hz, 1H), 3.26 (ddd, *J* = 24.0, 9.9, 7.0 Hz, 2H), 1.54 (s, 3H), 1.44 (s, 3H), 1.35 (s, 3H), 1.33 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 109.5, 108.8, 96.6, 71.5, 71.1, 70.5, 68.9, 26.0, 25.9, 24.9, 24.4, 2.3. HRMS (ESI) for $C_{12}H_{19}O_5INa$ $[M+Na]^+$, calculated: 393.0175, found: 393.0187.

(*S*)-1-((4*R*,5*S*)-2,2-dimethyl-5-vinyl-1,3-dioxolan-4-yl)ethane-1,2-diol (17):

A suspension of NH_4Cl (9.74 g, 182.34 mmol) and zinc dust (11.9 g, 182.34 mmol) in MeOH (55 mL) was treated with vitamin B_{12} (99 mg, 0.07 mmol, 0.2 mol%) at room temperature. The reaction mixture was then stirred at ambient temperature for 15 min. Meanwhile, the

suspension lost its red color. Afterward, a solution of iodide **16** (13.5 g, 36.5 mmol) in MeOH (18 mL) was added at 15 °C, and the red color reappeared. The suspension was then stirred at ambient temperature for an additional 5 min, the red color got faded, and then ethyl acetate was added to the reaction solution. After being stirred for several minutes at room temperature, the resultant precipitate was removed by filtration through a pad of Celite. The filtrate was then washed with water and brine solution (2×15 mL). The combined aqueous phases were subsequently extracted with ethyl acetate (4×100 mL). The combined organic part were dried over $MgSO_4$ and concentrated under reduced pressure.

To an ice-cooled solution of the crude elimination product in THF (100 mL) was added LAH (2.77 g, 73 mmol) in portions. The reaction mixture was stirred at 0 °C for 1.5 h and then quenched by the addition of a saturated solution of Na_2SO_4. The resultant precipitate was removed by filtration through a pad of Celite, and the precipitate was washed with ethyl acetate (200 mL). The combined organic phases were dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash chromatography (ethyl acetate/hexane = 1:1) afforded the diol **17** (5.0 g, 73%) as a clear oil. R_f = 0.45 (ethyl acetate). $[\alpha]_D^{25}$ = +28.7 (*c* 1, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ 5.99 (td, *J* = 5.2, 4.2 Hz, 1H), 5.38 – 5.28 (m, 2H), 4.60 (t, *J* = 3.7 Hz, 1H), 4.17 (dd, *J* = 3.4, 2.4 Hz, 1H), 3.69 – 3.64 (m, 1H), 3.62 – 3.55 (m, 2H), 1.51 (s, 3H), 1.37 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 133.6, 119.7, 108.8, 78.9, 77.6, 69.8, 63.9, 27.2, 24.9. HRMS (ESI) for $C_9H_{16}O_4Na$ $[M+Na]^+$, calculated: 211.0946, found: 211.0972.

***tert*-Butyl(((4*R*,5*S*)-2,2-dimethyl-5-vinyl-1,3-dioxolan-4-yl)methoxy)diphenyl silane (19):**

To a stirring solution of the diol **17** (4.5 g, 23.75 mmol) in DCM: H_2O = 3:1 (90 mL) at room temperature was added $NaIO_4$ (1.12 g, 47.5 mmol). The mixture was then stirred vigorously at room temperature for 2 h. The reaction solution was then quenched by the addition of saturated aq. Na_2SO_3 solution (18 mL) and further stirred for 20 min at room temperature. The reaction mixture is then filtered through a Celite pad and washed with CH_2Cl_2 (150 mL). The organic layer was separated, and the aqueous part was washed with CH_2Cl_2 (2×50 mL). The combined organic layers were successively washed with 5% aq $NaHCO_3$ solution, saturated aq Na_2SO_3, and brine solution. The total organic solution was then dried over anhydrous $MgSO_4$ and concentrated under reduced pressure to furnish the crude aldehyde, which was used for the next reaction without further purification. $NaBH_4$ (550 mg, 14 mmol) was added to a stirring solution the crude aldehyde in THF (65 mL) at 0 °C. After stirring for the next 40 minutes at this temperature, the reaction mixture was quenched with the addition of a saturated solution of NH_4Cl (10 mL). THF was evaporated under reduced pressure, and the reaction mixture was

diluted with the addition of ethyl acetate (100 mL). The layer was separated, and the aqueous part was washed with ethyl acetate (2×100 mL). The combined organic phases were dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash chromatography (ethyl acetate/hexane = 1:3) afforded alcohol **18** (3.0 g, 80% in two steps) as a clear oil. R_f = 0.45 (ethyl acetate/hexane = 1:1).

To a cooled (0 ºC) solution of alcohol **18** (3.0 g, 19 mmol) in dry CH_2Cl_2 (60 mL) was added imidazole (1.94 g, 28.5 mmol), TBDPSCl (5.83 mL, 22.8 mmol) and catalytic amount of DMAP. The mixture was stirred for 6 h at room temperature and then quenched with 10 mL of water. The organic layer was separated and the aqueous part was extracted with CH_2Cl_2 (2×100 mL). The combined organic part was washed with saturated $NaHCO_3$ solution (15 mL) and brine solution (10 mL) and then dried over anhydrous $MgSO_4$. The solution was then concentrated in *vacuo* and purified by flash chromatography (EtOAc:hexane = 1:20) to yield compound **19** (7.15 g, 95%) as a colorless oil. R_f = 0.30 (EtOAc/hexane, 1:15). $[\alpha]_D^{25}$ = +18.3 (*c* 1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.82 – 7.61 (m, 4H), 7.42 – 7.37 (m, 6H), 5.94 (ddd, *J* = 17.2, 10.3, 7.2 Hz, 1H), 5.41 – 5.31 (m, 1H), 5.22 (d, *J* = 10.2 Hz, 1H), 4.66 (t, *J* = 6.7 Hz, 1H), 4.29 (dd, *J* = 11.9, 6.4 Hz, 1H), 3.70 – 3.64 (m, 2H), 1.45 (s, 3H), 1.38 (s, 3H), 1.05 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 135.6, 133.7, 133.4, 129.7, 127.6, 118.0, 108.6, 78.8, 78.4, 62.8, 27.8, 26.8, 25.4, 19.2. HRMS (ESI) for $C_{24}H_{32}O_3SiNa$ $[M+Na]^+$, calculated: 419.2018, found: 419.2037.

2-((4*S*,5*R*)-5-(((*tert*-butyldiphenylsilyl)oxy)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)ethan-1-ol (20):

To a stirring solution of olefin **19** (7.13 g, 18.05 mmol) in THF (70 mL) at 0 ºC was added BH_3•DMS (9.02 mL, 2 M solution) over 5 minute. After stirring for 2 h at the same temperature, the reaction mixture was diluted with ethyl acetate (90 mL). Then the reaction mixture again cooled to 0 ºC and was quenched by the addition of NaOH (37 mL, 3 N solution) and 30% H_2O_2 (32 mL). After 1 h, the solution was poured into saturated aqueous NaCl (60 mL) and then extracted with ethyl acetate (2×100 mL). The combined organic phases were dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash chromatography (ethyl acetate/hexane = 1:3) afforded alcohol **20** (5.97 g, 80%) as a clear oil. R_f = 0.3 (ethyl acetate/hexane = 1:1). $[\alpha]_D^{25}$ = -5.6 (*c* 1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.64 – 7.68 (m, 4H), 7.49 – 7.30 (m, 6H), 4.38 (dt, *J* = 8.7, 5.5 Hz, 1H), 4.23 (dt, *J* = 7.8, 5.3 Hz, 1H), 3.89 – 3.77 (m, 2H), 3.73 (dd, *J* = 10.5, 7.9 Hz, 1H), 3.66 (dd, *J* = 10.5, 4.8 Hz, 1H), 1.95 – 1.86 (m, 2H), 1.37 (s, 3H), 1.33 (s, 3H), 1.05 (s, 9H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 135.7, 133.3, 133.2,

View Article Online
DOI: 10.1039/D0OB00237B

129.9, 127.9, 108.3, 77.8, 62.7, 61.4, 31.7, 28.2, 27.0, 25.7, 19.3. HRMS (ESI) for $C_{24}H_{34}O_4SiNa$ $[M+Na]^+$, calculated: 437.2124, found: 437.2145.

5-((2-((4*S*,5*R*)-5-(((*tert*-Butyldiphenylsilyl)oxy)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)ethyl)thio)-1-phenyl-1H-tetrazole (21):

To a stirring solution of compound **20** (5.97 g, 14.44 mmol) in anhydrous THF (45 mL) was added triphenylphosphine (5.67 g, 21.6 mmol) and 1-phenyl-5-mercapto-1H-tetrazole (PT-SH; 3.85 g, 21.66 mmol) at -10 ºC. After stirring 15 minute at this temperature DIAD (4.26 mL, 21.66 mmol) in anhydrous THF (10 mL) was added drop wise and the reaction was left to stir for 2 h. Water (20 mL) and EtOAc (60 mL) was added to this mixture and the organic layer was separated. The aqueous part was then washed with EtOAc (2×100 mL). The combined organic part was washed with saturated aq. $NaHCO_3$ solution and brine solution (20 mL). The organic solution was then dried over anhydrous $MgSO_4$ and concentrated under reduced pressure to furnish the crude product, which on purification by flash column chromatography (EtOAc:hexane = 1:10) afforded compound **21** (6.02 g, 90%) as a colorless oil. R_f = 0.4 (EtOAc/hexane, 1:5). $[\alpha]_D^{25}$ = -12.8 (*c* 0.5, $CHCl_3$). IR (neat, ν cm^{-1}): 1357 (s), 1282 (s), 865 (s). ^1H NMR (400 MHz, $CDCl_3$): δ 7.63 (d, *J* = 7.6 Hz, 4H), 7.60 – 7.53 (m, 5H), 7.41 – 7.34 (m, 6H), 4.39 – 4.30 (m, 1H), 4.21 (q, *J* = 6.2 Hz, 1H), 3.69 (d, *J* = 6.3 Hz, 2H), 3.63 – 3.59 (m, 1H), 3.48 (dt, *J* = 13.3, 7.7 Hz, 1H), 2.35 – 2.24 (m, 1H), 2.10 – 2.05 (m, 1H), 1.37 (s, 3H), 1.32 (s, 3H), 0.99 (s, 9H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 154.1, 135.7, 133.9, 133.2, 129.9, 128.0, 124.0, 123.8, 108.4, 78.4, 77.5, 75.9, 62.6, 30.6, 29.8, 28.2, 26.9, 25.7, 19.3. HRMS (ESI) for $C_{31}H_{38}N_4O_3SiSNa$ $[M+Na]^+$, calculated: 597.2332, found: 597.2343.

5-((2-((4*S*,5*R*)-5-(((*tert*-Butyldiphenylsilyl)oxy)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)ethyl)sulfonyl)-1-phenyl-1H-tetrazole (14):

To a stirring solution of sulfide **21** (6.02 g, 13 mmol) in ethanol (80 mL) was added a mixture of $(NH_4)_6Mo_7O_{24}$•$4H_2O$ (2.5 g, 1.95 mmol) and 30% H_2O_2 solution (9.3 mL) at 0 °C. The mixture was then stirred at room temperature for 6 h, and after that the reaction mixture was poured into 10% $Na_2S_2O_3$ solution and extracted with ethyl acetate (2×100 mL). The organic layer was washed with saturated $NaHCO_3$ (10 mL) solution and brine (10 mL), dried over anhydrous $MgSO_4$ and concentrated in *vacuo* to afford the crude sulfone. The crude product was then purified by flash column chromatography (EtOAc/hexane = 1:10) to furnish pure sulfone **14** (5.6 g, 85%) as a colorless gummy oil. R_f = 0.4 (EtOAc/hexane, 1:5). $[\alpha]_D^{25}$ = -14.5 (*c* 0.5, $CHCl_3$). IR (neat, ν cm^{-1}): 1346 (s), 1150 (s), 702 (s). ^1H NMR (400 MHz, $CDCl_3$): δ 7.77 – 7.58 (m, 9H), 7.50 – 7.34 (m, 6H), 4.37 – 4.23 (m, 1H), 4.26 (dt, *J* = 7.7, 5.3 Hz, 1H),

View Article Online
DOI: 10.1039/D0OB00237B

4.08 – 4.0 (m, 1H), 3.90 (ddd, J = 15.1, 10.3, 5.3 Hz, 1H), 3.76 – 3.66 (m, 2H), 2.45 – 2.41 (m, 1H), 2.33 – 2.26 (m, 1H), 1.40 (s, 3H), 1.33 (s, 3H), 1.01 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.4, 135.5, 133.0, 132.9, 132.8, 131.4, 129.9, 129.7, 127.8, 127.8, 125.0, 108.8, 77.1, 75.2, 61.9, 53.7, 27.9, 26.7, 25.5, 23.4, 19.1. HRMS (ESI) for $C_{31}H_{38}N_4O_5SiSNa$ $[M+Na]^+$, calculated: 629.2230, found: 629.2263.

5,7-Dihydroxy-2,2-dimethyl-4*H*-benzo[*d*][1,3]dioxin-4-one (22):

A 100 mL round-bottomed flask equipped with a magnetic stirring bar was charged with 2,4,6-trihydroxy benzoic acid (6.8 g, 40 mmol), acetic anhydride (7 mL), and anhydrous acetone (40 mL). The mixture was cooled to 0 °C and catalytic amount of concentrated H_2SO_4 was added to the stirring mixture. The flask was kept stirring at 0 °C for 12 h. After that time a saturated solution of aqueous $NaHCO_3$ was poured into the reaction mixture, and extracted with ethyl acetate (3 × 80 mL). The combined extracts were washed with water and brine, dried over anhydrous $MgSO_4$, filtered and concentrated to give brown solid. Chromatography of the crude solid over silica gel using EtOAc/petroleum ether (1:10) gave acetonide **22** (5.88 g, 70%) as white solid. R_f = 0.5 (EtOAc/hexane = 1:5). ^{1}H NMR (600 MHz, $CDCl_3$): δ 10.47 (s, 1H), 6.10 (d, J = 2.3 Hz, 1H), 5.98 (d, J = 2.2 Hz, 1H), 1.76 (s, 6H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 165.1, 164.1, 163.2, 157.3, 106.9, 97.6, 95.5, 93.2, 25.6.

5-Hydroxy-7-methoxy-2,2-dimethyl-4*H*-benzo[*d*][1,3]dioxin-4-one (23):

Diethyl azodicarboxylate (6.27 mL, 39.33 mmol) was added to a magnetically stirred solution of phenol **22** (5.88 g, 28.12 mmol) and triphenylphosphine (8.1 g, 30.97 mmol) in THF (45 mL) containing CH_3OH (1.26 mL, 30.97 mmol) and the reaction solution was then maintained at 0 °C under a nitrogen atmosphere. After 4 h the reaction mixture was concentrated under reduced pressure, and the residue thus obtained was subjected to flash chromatography (EtOAc/hexane = 1:10) to afford compound **23** (5.67 g, 90%) as a white crystalline solid. R_f = 0.6 (EtOAc/hexane = 1:5). ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.43 (s, 1H), 6.13 (d, J = 2.3 Hz, 1H), 5.99 (d, J = 2.3 Hz, 1H), 3.80 (s, 3H), 1.72 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.6, 165.1, 163.1, 156.8, 106.9, 95.7, 94.6, 93.0, 55.7, 25.6.

7-Methoxy-2,2-dimethyl-4-oxo-4*H*-benzo[*d*][1,3]dioxin-5-yl trifluoromethanesulfonate (24):

Trifluoromethanesulfonic anhydride (6.0 mL, 35.4 mmol) was added to a magnetically stirred mixture of phenol **23** (5.6 g, 25.3 mmol) and pyridine (46 mL) maintained at 0 °C under a

nitrogen atmosphere. The ensuing mixture was stirred at 0 °C for 1.5 h and then diluted with ethyl acetate (160 mL), and the resulting solution was washed with $CuSO_4$ (3 × 100 mL of a saturated aqueous solution), water (1 × 100 mL), and brine (1 × 70 mL) before being dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting light yellow oil was subjected to flash chromatography (EtOAc/hexane = 1:5) to afford compound **24** (8.55 g, 95%) as a white solid. R_f = 0.3 (EtOAc/hexane = 1:5). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.49 (dd, *J* = 10.0, 2.4 Hz, 2H), 3.86 (s, 3H), 1.71 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.6, 158.8, 157.1, 149.8, 123.5, 120.3, 117.1, 113.9, 106.6, 105.3, 101.1, 100.8, 56.3, 25.4.

7-Methoxy-2,2-dimethyl-5-vinyl-4*H*-benzo[*d*][1,3]dioxin-4-one (25):

To a stirred solution of **24** (8.55 g, 24.03 mmol) in DMF (70 mL) was added triphenylphosphine (450 mg, 1.6 mmol) and LiCl (3.1 g,71.8 mmol) at room temp. Then the reaction mixture was de-gassed for 10 min and to this was added vinyl *n*-tributyltin (7.7 mL, 22 mmol) and $Pd(PPh_3)_4$ (450 mg, 1.6 mmol). The reaction mixture was stirred at room temperature for 4 h and extracted with EtOAc (2 × 120 mL). The combined extracts was washed with water (3 × 100 mL) and brine solution (50 mL), dried over anhydrous $MgSO_4$ and concentrated. The product was purified by silica gel chromatography (EtOAc/hexane = 1:10) to yield **25** as a white solid (4.78 g, 85%). m.p = 144–147°C (uncorrected). R_f = 0.6 (EtOAc/hexane = 1:5). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.70 (ddd, *J* = 17.3, 10.8, 1.6 Hz, 1H), 6.78 (d, *J* = 2.3 Hz, 1H), 6.38 (d, *J* = 2.4 Hz, 1H), 5.68 (dd, *J* = 17.4, 1.4 Hz, 1H), 5.40 (dd, *J* = 11.0, 1.4 Hz, 1H), 3.85 (s, 3H), 1.70 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.9, 160.1, 158.7, 144.1, 135.5, 117.6, 108.5, 105.13, 103.9, 100.7, 55.6, 25.6.

7-Methoxy-2,2-dimethyl-4-oxo-4*H*-benzo[*d*][1,3]dioxine-5-carbaldehyde (15):

To a stirring solution of compound **25** (2.8 g, 12.1 mmol) in DCM (25 mL) at –78 °C was applied a flow of Ozone from an Ozone generator (flow rate 2 L/min) for 15 minute. Then after consumption of all the starting materials as monitored by TLC, TPP (3.8 g, 14.5 mmol) was added to the stirring mixture at –40 °C and allowed to stir at room temperature for 2 h. After completion of the reaction, the solution was concentrated under reduced pressure and the crude product was purified by flash column chromatography (EtOAc /hexane = 1:10) to afford aldehyde **15** (2.54 g, 90%) as a white solid. m.p = 102–104°C (uncorrected). R_f = 0.4 (EtOAc/hexane = 1:5). ^{1}H NMR (200 MHz, $CDCl_3$): δ 10.88 (s, 1H), 7.21 (d, *J* = 2.6 Hz, 1H), 6.67 (d, *J* = 2.6 Hz, 1H), 3.90 (s, 3H), 1.77 (s, 6H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 191.6, 165.5, 159.8, 158.8, 140.3, 109.6, 106.3, 106.1, 56.2, 25.7. HRMS (ESI) for $C_{12}H_{12}O_5Na$ $[M+Na]^+$, calculated: 259.0582, found: 259.0593.

View Article Online
DOI: 10.1039/D0OB00237B

5-((*E*)-3-((4*S*,5*R*)-5-(((*tert*-Butyldiphenylsilyl)oxy)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)prop-1-en-1-yl)-7-methoxy-2,2-dimethyl-4*H*-benzo[*d*][1,3]dioxin-4-one (26):

Sulfone **14** (3.96 g, 6.55 mmol) was dissolved in anhydrous THF (25 mL) and the solution was cooled to -78 ºC. To this solution KHMDS (0.5 M in toluene, 15.7 mL) was added drop wise and stirred for 40 min. Aldehyde **15** (1.85 g , 7.86 mmol) in anhydrous THF (7 mL) was then added to the reaction solution at -78 ºC and the temperature was allowed to attain room temperature slowly. The reaction solution was then quenched with saturated NH_4Cl (5 mL) and extracted with diethyl ether (3×100 mL). The combined organic layer was washed with brine solution and dried with anhydrous $MgSO_4$ and concentrated in *vacuo* to furnish the crude olefin. The crude product was then purified by flash column chromatography (EtOAc/hexane = 1:15) to give *E*-olefin **26** (3.1 g, 78%) as a colorless gummy oil. R_f = 0.60 (EtOAc/hexane, 1:5). $[\alpha]_D^{25}$ = -30.2 (*c* 0.8, $CHCl_3$). IR (neat, ν cm^{-1}): 1732 (s), 1635 (s), 1246 (s). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.69 – 7.65 (m, 4H), 7.55 (d, *J* = 15.8 Hz, 1H), 7.44 – 7.35 (m, 6H), 6.77 (d, *J* = 2.5 Hz, 1H), 6.34 (d, *J* = 2.4 Hz, 1H), 6.28 (dt, *J* = 15.7, 6.9 Hz, 1H), 4.34 (dt, *J* = 9.5, 4.8 Hz, 1H), 4.30 – 4.20 (m, 1H), 3.83 (s, 3H), 3.78 (dd, *J* = 10.7, 7.3 Hz, 1H), 3.71 (dd, *J* = 10.7, 5.0 Hz, 1H), 2.72 – 2.60 (m, 1H), 2.62 – 2.51 (m, 1H), 1.70 (s, 6H), 1.41 (s, 3H), 1.35 (s, 3H), 1.06 (s, 9H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 164.9, 160.3, 158.9, 144.0, 135.8, 133.5, 133.5, 131.4, 130.4, 129.9, 127.9, 108.5, 108.3, 105.1, 104.0, 100.5, 77.9, 77.3, 62.9, 55.8, 33.5, 28.3, 27.1, 25.9, 25.8, 19.4. HRMS (ESI) for $C_{36}H_{44}O_7SiNa$ $[M+Na]^+$, calculated: 639.2754, found: 639.2772.

5-((*E*)-3-((4*S*,5*R*)-5-(Hydroxymethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)prop-1-en-1-yl)-7-methoxy-2,2-dimethyl-4*H*-benzo[*d*][1,3]dioxin-4-one (27):

To a stirred solution of compound **26** (3.1 g, 5.11 mmol) in THF (20 mL) was added tetra butyl ammonium fluoride (1 M in THF, 6.1 mL) at 0 °C and the reaction mixture was allowed to stir at room temperature for 2 h. After completion of the reaction as monitored by TLC, the solvent was evaporated under reduced pressure. Ethyl acetate (80 mL) and water (7 mL) was added to the crude reaction mixture and the aqueous layer was extracted with ethyl acetate (2×80 mL). The combined organic layer was washed with brine and dried over $MgSO_4$. The organic part was evaporated under reduced pressure and the crude material was purified through flash column chromatography (EtOAc/hexane = 1:3) to afford alcohol **27** (1.7 g, 88%) as a clear oil. R_f = 0.25 (EtOAc/hexane = 1:3). $[\alpha]_D^{25}$ = -34.8 (*c* 1, $CHCl_3$) {Lit.[19] $[\alpha]_D^{21}$ = -32.7 (*c* 0.94, $CHCl_3$)}. IR (neat, ν cm^{-1}): 1722 (s), 1694 (s), 1161 (s). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.48 (d, *J* = 15.8 Hz, 1H), 6.74 (d, *J* = 2.5 Hz, 1H), 6.34 (d, *J* = 2.4 Hz, 1H), 6.20 (ddd, *J* = 15.8, 7.7, 6.0 Hz, 1H), 4.36 (dt, *J* = 7.3, 5.9 Hz, 1H), 4.25 (td, *J* = 6.5, 4.6 Hz, 1H), 3.84 (s, 3H), 3.72

(t, *J* = 5.9 Hz, 2H), 2.67 – 2.46 (m, 1H), 1.70 (s, 6H), 1.50 (s, 3H), 1.38 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.8, 160.3, 158.7, 143.6, 130.6, 130.1, 108.5, 108.2, 105.1, 103.7, 100.3, 77.8, 76.3, 61.6, 55.6, 33.0, 28.1, 25.7, 25.6, 25.4. HRMS (ESI) for $C_{20}H_{26}O_7Na$ $[M+Na]^+$, calculated: 401.1576, found: 401.1571.

5-(3-((4*S*,5*R*)-5-(Hydroxymethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)propyl)-7-methoxy-2,2-dimethyl-4*H*-benzo[*d*][1,3]dioxin-4-one (12):

Olefin **27** (1.69 g, 4.5 mmol) was taken in a glass vessel with dry EtOAc (15 mL) in argon medium followed by the addition of Pd/C (65 mg, 10%). The vessel was then placed in a Parr hydrogenataion apparatus and the reaction was continued for 3 h at 60 psi at room temperature. After completion of the reaction the solution was filtered through a Celite pad. The Celite pad was washed with EtOAc (150 mL). Combined organic filtrate was then evaporated *in vacuo* and the residue was purified by flash column chromatography (EtOAc/hexane = 1:3) to furnish compound **12** (1.54 g, 92%) as a clear oil. R_f = 0.25 (EtOAc/hexane = 1:3). $[\alpha]_D^{25}$ = -28.7 (*c* 1, $CHCl_3$). IR (neat, ν cm^{-1}): 1725 (s), 1610 (s), 1159 (s). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.46 (d, *J* = 2.4 Hz, 1H), 6.28 (d, *J* = 2.5 Hz, 1H), 4.23 – 4.06 (m, 2H), 3.80 (s, 3H), 3.59 (d, *J* = 5.7 Hz, 2H), 3.11 – 3.08 (m, 1H), 3.04 – 3.00 (m, 1H), 1.85 – 1.74 (m, 1H), 1.67 (s, 6H), 1.62 – 1.55 (m, 3H), 1.44 (s, 3H), 1.33 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 164.8, 160.1, 159.1, 149.3, 112.2, 108.0, 104.8, 104.7, 99.4, 77.9, 76.8, 61.7, 55.5, 34.4, 28.8, 28.2, 27.9, 25.6, 25.5. HRMS (ESI) for $C_{20}H_{28}O_7Na$ $[M+Na]^+$, calculated: 403.1733, found: 403.1747.

(4*S*,5*R*)-5-(3-(7-methoxy-2,2-dimethyl-4-oxo-4*H*-benzo[*d*][1,3]dioxin-5-yl)propyl)-2,2-dimethyl-1,3-dioxolane-4-carbaldehyde (28):

The alcohol **12** (1.5 g, 3.95 mmol) in CH_2Cl_2 (15 mL) was taken in a single neck round bottom flask and cooled to 0 °C. $NaHCO_3$ (1.6 g, 19.5 mmol) was added to the above mixture followed by the addition of Dess-Martin periodinane (2.6 g, 6.24 mmol) at the same temperature. The reaction mixture was then stirred for 2 h. After completion of the reaction it was diluted with CH_2Cl_2 (200 mL). The organic part was then successively washed with saturated $NaHSO_3$ (20 mL), $NaHCO_3$ (20 mL, 5%) and then with brine solution (10 mL). The organic layer was then dried over anhydrous $MgSO_4$ and evaporated in *vacuo*. Purification by flash column chromatography (EtOAc /hexane = 1:5) afforded aldehyde **28** (1.34 g, 90%) as a clear oil. R_f = 0.4 (EtOAc/hexane = 1:3). $[\alpha]_D^{25}$ = -23.8 (*c* 0.5, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.61 (d, *J* = 3.3 Hz, 1H), 6.43 (d, *J* = 2.5 Hz, 1H), 6.28 (d, *J* = 2.5 Hz, 1H), 4.38 (td, *J* = 7.5, 4.3 Hz, 1H), 4.26 (dd, *J* = 7.0, 3.3 Hz, 1H), 3.80 (s, 3H), 3.04 (t, *J* = 7.3 Hz, 2H), 1.87 – 1.75 (m, 2H), 1.67 (s, 6H), 1.66 – 1.59 (m, 2H), 1.55 (s, 3H), 1.38 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 202.2, 165.0, 160.2, 159.3, 149.1, 112.5, 110.6, 105.1, 104.8, 99.6, 82.2, 78.6, 55.7, 34.4, 29.6,

View Article Online
DOI: 10.1039/D0OB00237B

27.9, 27.8, 25.8, 25.5. HRMS (ESI) for $C_{20}H_{26}O_7Na$ $[M+Na]^+$, calculated: 401.1576, found: 401.1582.

Dimethyl 2-((4*S*,5*S*)-5-(3-(7-methoxy-2,2-dimethyl-4-oxo-4*H*-benzo[*d*][1,3]dioxin-5-yl)propyl)-2,2-dimethyl-1,3-dioxolan-4-yl)-2-oxoethylphosphonate (11):

To a solution of dimethyl methylphosphonate (1.54 g, 12.5 mmol) in THF (15 mL) at –78 °C was added *n*-butyllithium (1.6 M in hexanes, 7.8 mL, 12.5 mmol) and the reaction mixture was stirred at –78 °C for 1 h, then aldehyde **28** (935.3 mg, 2.5 mmol) in THF (5 mL) was added dropwise. The resultant mixture was stirred at –78 °C for 2 h, then saturated aq. NH_4Cl solution (8 mL) was added. The mixture was extracted with EtOAc (3×100 mL), then the combined organic extracts were dried over anhydrous $MgSO_4$ and evaporated in *vacuo* to give an oil, which was dissolved in CH_2Cl_2 (20 mL). To this solution at 0 °C was added $NaHCO_3$ (2.1g, 25 mmol) followed by Dess–Martin periodinane (1.9 g, 4.5 mmol) and the reaction mixture was stirred at room temperature for 2 h, then saturated aq. $Na_2S_2O_3$ solution (10 mL) was added and the resultant mixture was stirred at room temperature for 30 min. The mixture was extracted with CH_2Cl_2 (3×80 mL) and the combined organic extracts were dried over anhydrous $MgSO_4$ and concentrated. Purification by flash column chromatography (EtOAc /hexane = 1:2) afforded β-ketophosphonate **11** (720 mg, 58%) as a clear oil. R_f = 0.3 (EtOAc/hexane = 1:1). $[\alpha]_D^{25}$ = -18.9 (*c* 0.5, $CHCl_3$). IR (neat, ν cm^{-1}): 2810 (m), 1665 (s), 1258 (s). ^1H NMR (600 MHz, $CDCl_3$): δ 6.48 (d, *J* = 2.6 Hz, 1H), 6.31 (d, *J* = 2.5 Hz, 1H), 4.49 (d, *J* = 7.7 Hz, 1H), 4.43 (ddd, *J* = 10.7, 7.7, 3.3 Hz, 1H), 3.84 (s, 3H), 3.83 (d, *J* = 6.4 Hz, 3H), 3.81 (d, *J* = 6.3 Hz, 3H), 3.49 (dd, *J* = 21.0, 15.2 Hz, 1H), 3.11 – 3.03 (m, 3H), 1.89 – 1.77 (m, 4H), 1.71 (s, 6H), 1.61 (s, 3H), 1.39 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 202.8, 164.8, 160.0, 159.1, 149.2, 112.2, 110.2, 104.9, 104.7, 99.4, 82.6, 82.6, 78.1, 55.5, 53.2, 53.1, 52.9, 52.9, 38.4, 37.5, 34.2, 30.0, 27.8, 27.0, 25.7, 25.6, 24.8. HRMS (ESI) for $C_{23}H_{33}O_{10}PNa$ $[M+Na]^+$, calculated: 523.1709, found: 523.1699.

5-(3-((4*S*,5*S*)-5-((*S*,*E*)-5-((*tert*-Butyldiphenylsilyl)oxy)hex-2-enoyl)-2,2-dimethyl-1,3-dioxolan-4-yl)propyl)-7-methoxy-2,2-dimethyl-4*H*-benzo[*d*][1,3]dioxin-4-one (10):

To a solution of aldehyde **29** (130.4 mg, 0.40 mmol) and β-ketophosphonate **11** (166 mg, 0.33 mmol) in THF (3.8 mL) and H_2O (0.20 mL) at room temperature was added $Ba(OH)_2$ (52 mg, 0.161 mmol) and the reaction mixture was stirred at room temperature for 2 h, then saturated aq. NH_4Cl solution (2 mL) was added. The mixture was then extracted with EtOAc (3×50 mL) and the combined organic extracts were dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. Purification by flash column chromatography (EtOAc /hexane = 1:10) afforded *E*- olefin **10** (210 mg, 90%) as a colourless gummy oil. R_f = 0.6 (EtOAc/hexane =

1:5). $[\alpha]_D^{25}$ = +16.7 (*c* 1, $CHCl_3$). IR (neat, ν cm^{-1}): 2830 (m), 1680 (s), 870 (s). ^1H NMR (600 MHz, $CDCl_3$): δ 7.68 (d, *J* = 7.4 Hz, 4H), 7.48 – 7.36 (m, 6H), 6.93 (dt, *J* = 15.2, 7.4 Hz, 1H), 6.47 (d, *J* = 15.8 Hz, 1H), 6.44 (d, *J* = 2.6 Hz, 1H), 6.30 (d, *J* = 2.5 Hz, 1H), 4.57 (d, *J* = 7.5 Hz, 1H), 4.42 (td, *J* = 7.2, 3.8 Hz, 1H), 4.01 (q, *J* = 6.0 Hz, 1H), 3.81 (s, 3H), 3.05 (dd, *J* = 9.9, 5.6 Hz, 1H), 3.00 (dd, *J* = 9.8, 5.6 Hz, 1H), 2.38 (t, *J* = 6.8 Hz, 2H), 1.85 – 1.77 (m, 1H), 1.69 (s, 6H), 1.68 – 1.64 (m, 1H), 1.60 (s, 3H), 1.54 – 1.50 (m, 1H), 1.47 – 1.42 (m, 1H), 1.39 (s, 3H), 1.11 (d, *J* = 6.1 Hz, 3H), 1.07 (s, 9H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 197.5, 164.8, 160.0, 159.1, 149.4, 145.2, 135.8, 135.8, 134.3, 133.9, 129.7, 129.6, 128.0, 127.6, 127.5, 112.1, 109.8, 104.8, 104.7, 99.4, 82.0, 78.0, 68.4, 55.5, 42.6, 34.2, 30.3, 27.7, 27.2, 27.0, 25.7, 25.6, 25.1, 23.2, 19.2. HRMS (ESI) for $C_{41}H_{52}O_8SiNa$ $[M+Na]^+$, calculated: 723.3329, found: 723.3357.

5-(3-((4*S*,5*S*)-2,2-dimethyl-5-((9*S*,*E*)-9,12,12-trimethyl-11,11-diphenyl-2,4,10-trioxa-11-silatridec-6-en-5-yl)-1,3-dioxolan-4-yl)propyl)-7-methoxy-2,2-dimethyl-4*H*-benzo[*d*][1,3]dioxin-4-one (31):

To a stirring solution of enone **10** (82.8 mg, 0.12 mmol) in methanol (2 mL) at 0 ºC was added $CeCl_3$ (47.2 mg, 0.125 mmol) and then $NaBH_4$ (4.8 mg, 0.125 mmol). The reaction mixture was stirred at room temperature for 2 h, then saturated aq. NH_4Cl solution (2 mL) was added. The mixture was extracted with EtOAc (3×30 mL) and the combined organic extracts were dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. Purification by flash column chromatography (EtOAc /hexane = 1:5) afforded alcohol (74.8 mg, 90%) as a colorless oil. R_f = 0.3 (EtOAc/hexane = 1:5).

To a stirring solution of the above alcohol (74.8 mg, 0.11 mmol) in dry CH_2Cl_2 (1.5 mL) was added diisopropylethylamine (0.18 mL, 1.08 mmol) at 0 °C. After 15 min of stirring MOM-Cl (methoxymethyl chloride; 0.05 mL, 0.64 mmol) was added and the reaction solution was stirred for further 12 h at room temperature. The reaction was diluted with CH_2Cl_2 (50 mL) and washed with saturated $NaHCO_3$ (5 mL), H_2O (5 mL) and brine (5 mL). The combined organic part was dried over anhydrous $MgSO_4$ and then concentrated *in vacuo*. The crude material was then purified by flash column chromatography (EtOAc/hexane = 1: 20) to afford compound **31** (70 mg, 90%) as a colourless liquid. R_f = 0.6 (EtOAc/hexane = 1:5). IR (neat, ν cm^{-1}): 1665 (s), 1170 (s). ^1H NMR (400 MHz, $CDCl_3$) δ 7.73 – 7.59 (m, 4H), 7.46 – 7.33 (m, 6H), 6.46 (d, *J* = 2.5 Hz, 1H), 6.29 (d, *J* = 2.5 Hz, 1H), 5.75 (dt, *J* = 14.9, 7.2 Hz, 1H), 5.27 (dd, *J* = 15.5, 7.0 Hz, 1H), 4.71 (d, *J* = 6.7 Hz, 1H), 4.57 (d, *J* = 6.7 Hz, 1H), 4.07 – 3.99 (m, 3H), 3.89 (q, *J* = 5.9 Hz, 1H), 3.80 (s, 3H), 3.37 (s, 3H), 3.03 (dt, *J* = 8.5, 5.5 Hz, 2H), 2.21 (t, *J* = 6.6 Hz, 2H), 1.86 – 1.79 (m, 1H), 1.68 (s, 6H), 1.59 – 1.53 (m, 3H), 1.44 (s, 3H), 1.35 (s, 3H), 1.07 (d, *J* = 6.5 Hz, 3H), 1.05 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.9, 160.1, 159.2, 149.8, 135.9,

134.6, 134.4, 133.3, 129.7, 129.6, 128.3, 127.7, 127.6, 112.2, 108.4, 104.9, 104.9, 99.3, 93.3, 80.0, 74.8, 69.1, 55.6, 55.6, 42.5, 34.6, 29.9, 28.2, 27.7, 27.1, 26.2, 25.7, 22.9, 19.3. HRMS (ESI) for $C_{43}H_{58}O_9SiNa$ $[M+Na]^+$, calculated: 769.3748, found: 769.3773.

(3a*S*,8*S*,17a*S*,*E*)-11-hydroxy-13-methoxy-4-(methoxymethoxy)-2,2,8-trimethyl-3a,4,7,8,15,16,17,17a-octahydro-10*H*-benzo[*c*][1,3]dioxolo[4,5-*h*][1]oxacyclotetradecin-10-one (33):

Compound **31** (45 mg, 0.06 mmol) was dissolved in anhydrous THF (2 mL) in a polyethylene vessel and HF-pyridine (400 µL) was added to it at 0 ºC. The mixture was then stirred for 2 h at room temperature followed by addition of EtOAc (40 mL) and brine solution (5 mL). The organic layer was separated and the aqueous layer was twice washed with EtOAc (50 mL). The combined organic part was washed with brine (5 mL) and the solution was dried over anhydrous $MgSO_4$ and concentrated in *vacuo*. The crude material was then purified by flash column chromatography (EtOAc /hexane = 1:1) to afford **32** (28 mg, 90%) as a colourless oil. R_f = 0.25 (EtOAc/hexane = 1:1).

To a stirring solution of NaH (60%, 14 mg, 0.33 mmol) in dry THF (4 mL) at 0 °C, compound **32** (28 mg, 0.055 mmol) in dry THF (2 mL) was slowly added. Then the reaction mixture was stirred at room temperature for 2 h. After completion of the reaction as monitored by TLC, saturated aq. NH_4Cl solution (5 mL) was added. The mixture was extracted with EtOAc (3×40 mL). The combined organic part was washed with brine (5 mL) and the solution was dried over anhydrous $MgSO_4$ and concentrated in *vacuo*. The crude material was then purified by flash column chromatography (EtOAc /hexane = 1:5) to afford **33** (20 mg, 80%) as a colourless oil. R_f = 0.5 (EtOAc/hexane = 1:3). IR (neat, ν cm^{-1}): 1655 (s), 1270 (s), 1148 (s). ^1H NMR (400 MHz, $CDCl_3$): δ 11.49 (s, 1H), 6.33 (d, *J* = 2.7 Hz, 1H), 6.29 (d, *J* = 2.7 Hz, 1H), 5.83 (ddd, *J* = 15.7, 8.6, 5.4 Hz, 1H), 5.47 (dt, *J* = 15.0, 4.5 Hz, 1H), 5.41 – 5.33 (m, 1H), 4.75 (d, *J* = 6.9 Hz, 1H), 4.58 (d, *J* = 6.9 Hz, 1H), 4.09 – 4.05 (m, 2H), 4.03 – 3.96 (m, 1H), 3.79 (s, 3H), 3.39 (s, 3H), 3.23 – 3.12 (m, 1H), 2.86 (dt, *J* = 12.6, 6.3 Hz, 1H), 2.68 – 2.61 (m, 1H), 2.46 (dt, *J* = 15.8, 8.3 Hz, 1H), 1.71 – 1.65 (m, 3H), 1.54 – 1.46 (m, 1H), 1.45 (s, 3H), 1.44 (d, *J* = 8 Hz, 3H), 1.33 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.4, 164.8, 163.9, 147.3, 132.7, 128.9, 110.6, 107.4, 105.8, 99.2, 92.9, 79.2, 77.2, 74.9, 71.7, 55.6, 55.2, 38.5, 33.7, 28.5, 28.2, 28.1, 25.7, 19.9. HRMS (ESI) for $C_{24}H_{34}O_8Na$ $[M+Na]^+$, calculated: 473.2151, found: 473.2165.

(3*S*,8*S*,9*S*,*E*)-7,8,9,16-tetrahydroxy-14-methoxy-3-methyl-3,4,7,8,9,10,11,12-octahydro-1*H*-benzo[*c*][1]oxacyclotetradecin-1-one (34):

To a solution of **33** (14 mg, 0.03 mmol) in THF (1 mL) was added HCl (2 N, 40 µL) and stirred for 4 h at room temperature. The reaction solution was then quenched with saturated aqueous $NaHCO_3$ solution (1 mL) and extracted with EtOAc (3×30 mL). The organic layers were combined and dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure to afford the crude product. The crude product was then purified on flash column chromatography (EtOAc /hexane = 1:1) to provide **34** (10 mg, 90%) as a white powder. m.p = 114–117°C (uncorrected). IR (KBr, ν cm^{-1}): 3335 (br), 2905 (m), 1645 (s), 1253 (s). ^1H NMR (600 MHz, $CDCl_3$): δ 11.52 (s, 1H), 6.35 (d, *J* = 2.5 Hz, 1H), 6.32 (d, *J* = 2.5 Hz, 1H), 5.96 – 5.88 (m, 1H), 5.69 (dd, *J* = 15.5, 8.6 Hz, 1H), 5.31 (ddd, *J* = 9.1, 6.2, 3.1 Hz, 1H), 4.17 (t, *J* = 8.8 Hz, 1H), 3.82 (s, 4H), 3.69 (dd, *J* = 9.1, 2.2 Hz, 1H), 3.09 – 3.02 (m, 1H), 2.95 – 2.90 (m, 1H), 2.61 (d, *J* = 15.4 Hz, 1H), 2.57 – 2.49 (m, 1H), 1.90 – 1.86 (m, 1H), 1.72 (ddd, *J* = 11.8, 6.9, 3.3 Hz, 2H), 1.52 – 1.48 (m, 1H), 1.46 (d, *J* = 6.2 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 171.2, 164.8, 163.9, 146.8, 132.2, 131.9, 109.6, 106.1, 98.9, 76.1, 72.4, 71.8, 71.4, 55.3, 38.6, 33.7, 30.9, 25.8, 20.1. HRMS (ESI) for $C_{19}H_{26}O_7Na$ $[M+Na]^+$, calculated: 389.1576, found: 389.1589.

(3*S*,8*S*,9*S*,*E*)-8,9,16-trihydroxy-14-methoxy-3-methyl-3,4,9,10,11,12-hexahydro-1*H*-benzo[*c*][1]oxacyclotetradecine-1,7(8*H*)-dione (L-783290):

To the solution of compound **34** (8 mg, 0.02 mmol) in DCM (1 mL) at 0 °C was added Dess–Martin periodinane (9.8 mg, 0.02 mmol) and the reaction mixture was stirred at room temperature for 10 min, then saturated aq. $Na_2S_2O_3$ solution (0.5 mL) was added and the resultant mixture was stirred at room temperature for 5 min. The mixture was extracted with CH_2Cl_2 (3×15 mL) and the combined organic extracts were dried over anhydrous $MgSO_4$ and concentrated. Purification by flash column chromatography (EtOAc /hexane = 1:1) afforded **L-783290** (5.5 mg, 0.015 mmol, 73%) as a white powder, m.p = 134–138 °C (uncorrected). R_f = 0.25 (EtOAc/hexane = 1:1). $[\alpha]_D^{25}$ = +8.9 (*c* 0.25, $CHCl_3$). IR (KBr, ν cm^{-1}): 2822 (m), 1680 (s), 1245 (s). ^1H NMR (500 MHz, CD_2Cl_2): δ 11.83 (s, 1H), 7.03 (dt, *J* = 15.3, 7.4 Hz, 1H), 6.45 – 6.29 (m, 3H), 5.69 –5.62 (m, 1H), 4.69 (s, 1H), 3.96 (s, 1H), 3.83 (s, 3H), 3.13 (ddd, *J* = 15.1, 11.8, 3.5 Hz, 1H), 2.93 – 2.83 (m, 1H), 2.62 – 2.57 (m, 2H), 1.77 – 1.69 (m, 2H), 1.65 (s, 1H), 1.49 (d, *J* = 6.5 Hz, 3H), 1.39 – 1.30 (m, 1H). ^{13}C NMR (125 MHz, CD_2Cl_2): δ 199.3, 171.3, 166.2, 164.7, 147.7, 143.7, 131.5, 109.5, 104.9, 99.3, 77.3, 73.3, 71.3, 55.7, 38.0, 36.2, 32.8, 26.9, 19.2.

HRMS (ESI) for $C_{19}H_{24}O_7Na$ $[M+Na]^+$, calculated: 387.1420, found: 387.1434.

(*S*)-5-(trimethylsilyl)pent-4-yn-2-ol (SI-1):

View Article Online
DOI: 10.1039/D0OB00237B

To a solution of trimethylsilylacetylene (2.2 mL, 15.5 mmol) in dry THF (20 mL), *n*-BuLi (11.2 mL, 1.6 M in hexane, 18.06 mmol) was added at -78 °C. The reaction mixture was then stirred at the same temperature for 1 h and then '*S*'- propylene oxide (1.2 mL, 17.2 mmol) in THF and BF_3•Et_2O (2.4 mL, 18.9 mmol) were added simultaneously. The reaction mixture was stirred at 0 °C for 4 h and then allowed to warm at room temperature. After 4 h the reaction solution was quenched with saturated NH_4Cl (5 mL) and extracted with Et_2O (3×100 mL). The organic layers were combined and dried over anhydrous $MgSO_4$ and concentrated under reduced pressure to yield the crude product. The crude product was then purified through flash column chromatography (EtOAc /hexane = 1:10) to provide **SI-1** (2.1 g, 80%) as a gummy oil. R_f = 0.3 (EtOAc/hexane; 1:10). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.91 (d, *J* = 5.3 Hz, 1H), 2.37 (qd, *J* = 16.7, 5.9 Hz, 2H), 1.23 (d, *J* = 6.1 Hz, 3H), 0.13 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 103.2, 87.4, 66.2, 30.4, 22.2, 0.04. HRMS (ESI) for $C_8H_{16}OSiNa$ $[M+Na]^+$, calculated: 179.0868, found: 179.0875.

(*S*)-1-methoxy-4-((pent-4-yn-2-yloxy)methyl)benzene (35):

To a suspension of NaH (60%, 338.4 mg, 8.46 mmol) in dry THF (20 mL), compound **SI-1** (1.2 g, 7.69 mmol) in dry THF (7 mL) was added drop wise at 0 °C. After that the reaction mixture was stirred for 25 minute at room temperature, it was then cooled to 0 °C and freshly prepared PMB-Br (1.7 g, 8.46 mmol) in dry THF (5 mL) was added to the reaction mixture. The reaction mixture was stirred at room temperature for 2 h and the reaction solution was quenched with saturated NH_4Cl solution (10 mL). The organic layer was separated and the aqueous part was washed with ethyl acetate (2×150 mL). Combined organic layer was washed with brine (20 mL) and dried over anhydrous $MgSO_4$. The solvent was then evaporated under reduced pressure and the crude residue was purified by flash column chromatography (EtOAc/hexane = 1:30) to furnish compound **35** (1.33 g, 85%) as a colorless oil. R_f = 0.4 (EtOAc/hexane; 1:20). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.30 (d, *J* = 8.5 Hz, 2H), 6.90 (d, *J* = 8.6 Hz, 2H), 4.53 (s, 2H), 3.82 (s, 3H), 3.70 (td, *J* = 6.4, 5.7 Hz, 1H), 2.51 (ddd, *J* = 16.6, 4.9, 2.7 Hz, 1H), 2.37 (ddd, *J* = 16.7, 7.1, 2.7 Hz, 1H), 2.02 (t, *J* = 2.7 Hz, 1H), 1.32 (d, *J* = 6.2 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 159.2, 130.6, 129.2, 113.8, 81.3, 72.9, 70.3, 69.8, 55.3, 26.0, 19.5. HRMS (ESI) for $C_{13}H_{16}O_2Na$ $[M+Na]^+$, calculated: 227.1048, found: 227.1056.

5-(3-((4*S*,5*S*)-5-((5*S*)-1-Hydroxy-5-((4-methoxybenzyl)oxy)hex-2-yn-1-yl)-2,2-dimethyl-1,3-dioxolan-4-yl)propyl)-7-methoxy-2,2-dimethyl-4*H*-benzo[*d*][1,3]dioxin-4-one (13):

To a solution of **35** (61.2 mg, 0.3 mmol) in THF (2 mL) at –78 °C was added *n*-butyllithium (1.6 M in hexanes, 0.21 mL, 0.325 mmol) and the reaction mixture was stirred at –78 °C for 1

h, then aldehyde **28** (95 mg, 0.25 mmol) in THF (0.5 mL) was added dropwise. Then the reaction was allowed to come to room temperature and saturated aq. NH_4Cl solution (2 mL) was added. The mixture was extracted with EtOAc (3×60 mL), then the combined organic extracts were dried over anhydrous $MgSO_4$ and evaporated in *vacuo* to afford the crude product. The crude residue was purified by flash column chromatography (EtOAc/hexane = 1:3) to furnish the inseparable diastereomeric mixture of compound **13** (120 mg, 82%) as a colorless oil. R_f = 0.25 (EtOAc/hexane; 1:3). IR (neat, ν cm^{-1}): 1725 (s), 1610 (s), 1576 (s), 1157 (s). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.28 (d, *J* = 6.1 Hz, 2H), 6.88 (d, *J* = 8.1 Hz, 2H), 6.49 (s, 1H), 6.31 (s, 1H), 4.49 (s, 2H), 4.32 (d, *J* = 7.6 Hz, 1H), 4.27 – 4.19 (m, 1H), 4.08 (dt, *J* = 13.4, 6.2 Hz, 1H), 3.83 (s, 3H), 3.80 (s, 3H), 3.68 (q, *J* = 6.3 Hz, 1H), 3.18 – 3.10 (m, 1H), 3.09 – 2.99 (m, 1H), 2.56 (dd, *J* = 16.6, 4.9 Hz, 1H), 2.38 (dd, *J* = 16.6, 7.5 Hz, 1H), 1.89 – 1.81 (m, 4H), 1.70 (s, 6H), 1.49 (s, 3H), 1.37 (s, 3H), 1.29 (d, *J* = 6.3 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 164.8, 160.0, 159.1, 159.1, 149.4, 130.6, 129.2, 129.2, 113.7, 112.2, 108.4, 104.8, 99.3, 84.0, 80.4, 79.6, 77.1, 73.0, 70.3, 61.3, 55.5, 55.2, 34.4, 29.1, 28.1, 28.0, 26.3, 25.6, 25.6, 25.4, 19.7. HRMS (ESI) for $C_{33}H_{42}O_9Na$ $[M+Na]^+$, calculated: 605.2727, found: 605.2756.

5-(3-((4*S*,5*S*)-5-((5*S*,*Z*)-1-Hydroxy-5-((4-methoxybenzyl)oxy)hex-2-en-1-yl)-2,2-dimethyl-1,3-dioxolan-4-yl)propyl)-7-methoxy-2,2-dimethyl-4*H*-benzo[*d*][1,3]dioxin-4-one (36):

Lindlar catalyst (4 mg) was added to the compound **13** (105.2 mg, 0.18 mmol) dissolved in ethyl acetate (6 mL). The mixture was then stirred under H_2 atmosphere (through H_2 balloon) for 3 h. After completion of the reaction (TLC analysis) it was filtered through a Celite pad. The Celite pad was then washed with EtOAc (100 mL). The combined organic filtrate was evaporated in *vacuo* and the residue was purified by flash column chromatography (EtOAc/hexane = 1: 3) to afford compound **36** (95 mg, 90%) as a clear oil. $\mathbf{R_f}$ = 0.30 (EtOAc/hexane, 1: 3). IR (neat, ν cm^{-1}): 1727 (s), 1619 (s), 1204 (s). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.27 (d, *J* = 8.5 Hz, 2H), 6.87 (d, *J* = 8.4 Hz, 2H), 6.47 (d, *J* = 2.8 Hz, 1H), 6.30 (d, *J* = 2.5 Hz, 1H), 5.74 – 5.62 (m, 1H), 5.55 (dt, *J* = 10.2, 8.8 Hz, 1H), 4.52 (d, *J* = 11.4 Hz, 1H), 4.44 – 4.37 (m, 2H), 4.13 – 4.08 (m, 1H), 3.97 (t, *J* = 6.1 Hz, 1H), 3.82 (s, 3H), 3.80 (s, 3H), 3.61 (q, *J* = 6.0 Hz, 1H), 3.15 – 3.08 (m, 1H), 3.03 – 2.97 (m, 1H), 2.45 – 2.38 (m, 1H), 2.39 – 2.32 (m, 1H), 1.85 – 1.78 (m, 2H), 1.69 (s, 6H), 1.63 – 1.56 (m, 2H), 1.50 (s, 3H), 1.36 (s, 3H), 1.22 (d, *J* = 6.2 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$): δ 164.8, 160.0, 159.1, 159.1, 149.5, 130.8, 130.7, 130.4, 130.3, 130.3, 129.3, 129.3, 113.7, 112.2, 112.2, 108.1, 107.9, 104.8, 104.7,

View Article Online
DOI: 10.1039/D0OB00237B

99.3, 99.3, 80.6, 77.1, 77.1, 73.7, 73.4, 70.1, 70.1, 65.6, 65.3, 55.5, 55.2, 35.3, 34.9, 34.4, 34.4, 29.5, 29.4, 28.0, 28.0, 27.9, 27.8, 25.7, 25.6, 25.6, 25.6, 25.4, 19.6, 19.3. HRMS (ESI) for $C_{33}H_{44}O_9Na$ $[M+Na]^+$, calculated: 607.2883, found: 607.2892.

5-(3-((4*S*,5*S*)-5-((5*S*,*Z*)-1-((*tert*-butyldimethylsilyl)oxy)-5-((4-methoxybenzyl)oxy)hex-2-en-1-yl)-2,2-dimethyl-1,3-dioxolan-4-yl)propyl)-7-methoxy-2,2-dimethyl-4*H*-benzo[*d*][1,3]dioxin-4-one (37):

Imidazole (18.4 mg, 0.27 mmol) was added to a solution of **36** (95 mg, 0.16 mmol) in anhydrous CH_2Cl_2 (1.5 mL) at room temperature. After stirring for 15 min TBS-Cl (51.7 mg, 0.34 mmol) was added to the reaction vessel and stirred for 3 h. After completion of the reaction, water (3 mL) and CH_2Cl_2 (40 mL) was added to the reaction mixture and the organic layer was washed with excess water and brine. The organic layer was dried over $MgSO_4$ and evaporated to dryness to afford the crude silylated compound, which was purified by silica gel chromatography (EtOAc/hexane = 1:10) to get the compound **37** (99.8 mg, 88%). R_f = 0.6 (EtOAc/hexane; 1:3). IR (neat, ν cm^{-1}): 1722 (s), 1632 (s), 1170 (s). ^1H NMR (600 MHz, $CDCl_3$): δ 7.27 (d, *J* = 11.2 Hz, 2H), 6.88 (d, *J* = 8.4 Hz, 2H), 6.49 (d, *J* = 2.5 Hz, 1H), 6.31 (d, *J* = 2.6 Hz, 1H), 5.61 – 5.50 (m, 2H), 4.54 – 4.46 (m, 2H), 4.42 (t, *J* = 9.8 Hz, 1H), 4.05 – 4.01 (m, 1H), 3.94 (dq, *J* = 12.0, 6.4, 5.9 Hz, 1H), 3.83 (s, 3H), 3.81 (s, 3H), 3.60 – 3.55 (m, 1H), 3.16 – 3.12 (m, 1H), 3.06 – 2.98 (m, 1H), 2.40 – 2.31 (m, 1H), 2.28 (dt, *J* = 14.2, 6.7 Hz, 1H), 1.80 (ddd, *J* = 15.5, 8.1, 4.3 Hz, 2H), 1.70 (s, 6H), 1.68 – 1.63 (m, 2H), 1.47 (s, 3H), 1.32 (s, 3H), 1.23 (d, *J* = 6.1 Hz, 3H), 0.90 (s, 9H), 0.09 (s, 3H), 0.09 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 164.7, 159.9, 159.1, 159.0, 149.7, 131.6, 130.9, 129.2, 129.1, 127.6, 113.7, 112.1, 107.8, 104.7, 99.3, 81.6, 77.4, 74.2, 70.1, 68.0, 55.5, 55.2, 35.3, 34.5, 29.4, 28.0, 27.5, 25.9, 25.7, 25.6, 19.8, 18.2, -3.9, -4.4. HRMS (ESI) for $C_{39}H_{58}O_9SiNa$ $[M+Na]^+$, calculated: 721.3748, found: 721.3762.

5-(3-((4*S*,5*S*)-5-((5*S*,*Z*)-1-((*tert*-butyldimethylsilyl)oxy)-5-hydroxyhex-2-en-1-yl)-2,2-dimethyl-1,3-dioxolan-4-yl)propyl)-7-methoxy-2,2-dimethyl-4*H*-benzo[*d*][1,3]dioxin-4-one (38):

Compound **37** (63.9 mg, 0.09 mmol) was dissolved in CH_2Cl_2/phosphate buffer (pH = 7.0; 19:1, 2 mL) and the solution was cooled to 0 ºC. DDQ (24.5 mg, 0.108 mmol) was added portion wise to the solution and the mixture was stirred at this temperature for 2 h. After completion, the reaction mixture was passed through a pad of Celite and the residue was then washed with CH_2Cl_2 (100 mL). The combined organic fraction was washed with water and brine solution. The organic layer was then dried over anhydrous $MgSO_4$ and evaporated in

vacuo. Purification by flash column chromatography (EtOAc/hexane = 1:3) afforded compound **38** (45 mg, 85%) as a colorless oil. R_f = 0.25 (EtOAc/hexane = 1:3). IR (neat, ν cm^{-1}): 1675 (s), 1224 (s). ^{1}H NMR (600 MHz, $CDCl_3$): δ 6.51 (d, *J* = 2.7 Hz, 1H), 6.32 (s, 1H), 5.65 (dt, *J* = 10.5, 7.6 Hz, 1H), 5.56 (dt, *J* = 11.1, 7.6 Hz, 1H), 4.59 (dd, *J* = 9.5, 5.1 Hz, 1H), 4.12 (q, *J* = 3.8 Hz, 1H), 4.04 (t, *J* = 5.6 Hz, 1H), 3.86 (d, *J* = 6.9 Hz, 1H), 3.84 (s, 3H), 3.17 – 3.13 (m, 1H), 3.08 – 2.99 (m, 1H), 2.40 – 2.30 (m, 1H), 2.28 – 2.18 (m, 1H), 1.87 – 1.76 (m, 4H), 1.71 (s, 6H), 1.47 (s, 3H), 1.34 (s, 3H), 1.26 (d, *J* = 6.5 Hz, 3H), 0.89 (s, 9H), 0.09 (s, 3H), 0.07 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 164.8, 160.1, 159.1, 149.7, 132.2, 128.2, 112.2, 107.9, 104.8, 104.7, 99.4, 80.9, 77.6, 67.8, 67.3, 55.5, 38.1, 34.5, 29.6, 28.1, 27.4, 25.9, 25.9, 25.7, 25.6, 23.1, 18.1, -4.0, -4.5. HRMS (ESI) for $C_{31}H_{50}O_8SiNa$ $[M+Na]^+$, calculated: 601.3173, found: 601.3195.

(3a*S*,8*S*,17a*S*,*Z*)-4-((*tert*-Butyldimethylsilyl)oxy)-11-hydroxy-13-methoxy-2,2,8-trimethyl-3a,4,7,8,15,16,17,17a-octahydro-10*H*-benzo[*c*][1,3]dioxolo[4,5-*h*][1]oxacyclotetradecin-10-one (39):

To a stirring solution of NaH (60%, 18 mg, 0.45 mmol) in dry THF (5 mL) at 0 °C, compound **38** (43.4 mg, 0.075 mmol) in dry THF (2 mL) was slowly added. Then the reaction mixture was stirred at room temperature for 2 h. After completion of the reaction as monitored by TLC, saturated aq. NH_4Cl solution (3 mL) was added. The mixture was extracted with EtOAc (3×40 mL). The combined organic part was washed with brine (5 mL) and the solution was dried over anhydrous $MgSO_4$ and concentrated in *vacuo*. The crude material was then purified by flash column chromatography (EtOAc /hexane = 1:10) to afford **39** (32 mg, 82%) as a colourless oil. High polar R_f = 0.45 (EtOAc/hexane = 1:5). Less polar (major isomer) R_f = 0.5 (EtOAc/hexane = 1:5). $[\alpha]_D^{25}$ = +19.8 (*c* 1, $CHCl_3$). IR (neat, ν cm^{-1}): 1645 (s), 1253 (s), 1160 (s). ^{1}H NMR (600 MHz, $CDCl_3$) δ 12.08 (s, 1H), 6.35 (d, *J* = 2.8 Hz, 1H), 6.28 (d, *J* = 2.8 Hz, 1H), 5.55 (ddd, *J* = 12.0, 6.3, 2.7 Hz, 1H), 5.48 (td, *J* = 11.0, 2.3 Hz, 1H), 5.37 (td, *J* = 10.6, 2.7 Hz, 1H), 4.44 (t, *J* = 9.4 Hz, 1H), 3.91 (dd, *J* = 8.7, 5.6 Hz, 1H), 3.84 (d, *J* = 5.4 Hz, 1H), 3.81 (s, 3H), 3.27 (dt, *J* = 12.3, 7.5 Hz, 1H), 2.91 – 2.81 (m, 1H), 2.48 (ddd, *J* = 12.9, 8.1, 5.2 Hz, 1H), 2.36 (dq, *J* = 16.0, 2.7 Hz, 1H), 1.82 – 1.74 (m, 1H), 1.68 (dt, *J* = 13.1, 4.1 Hz, 1H), 1.63-1.58 (m, 2H), 1.49 (s, 3H), 1.47 (d, *J* = 6.2 Hz, 3H), 1.33 (s, 3H), 0.89 (s, 9H), 0.13 (s, 3H), 0.11 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 171.4, 165.8, 164.0, 147.9, 131.5, 128.9, 110.6, 107.5, 105.0, 99.1, 81.8, 77.4, 72.0, 67.9, 55.3, 35.9, 35.5, 31.5, 31.3, 28.2, 25.8, 25.5, 21.1, 18.3, -4.2, -4.3. HRMS (ESI) for $C_{28}H_{44}O_7SiNa$ $[M+Na]^+$, calculated: 543.2754, found: 543.2763.

(3a*S*,8*S*,17a*S*,*Z*)-4,11-dihydroxy-13-methoxy-2,2,8-trimethyl-3a,4,7,8,15,16,17,17a-octahydro-10*H*-benzo[*c*][1,3]dioxolo[4,5-*h*][1]oxacyclotetradecin-10-one (40):

View Article Online
DOI: 10.1039/D0OB00237B

Compound **39** (23.1 mg, 0.044 mmol) was dissolved in anhydrous THF (2 mL) in a polyethylene vessel and HF-pyridine (300 µL) was added to it at 0 ºC. The mixture was then stirred for 3 h at room temperature followed by addition of EtOAc (25 mL) and brine solution (5 mL). The organic layer was separated and the aqueous layer was washed with (2×30 mL) EtOAc. The combined organic part was washed with brine (5 mL) and the solution was dried over anhydrous $MgSO_4$ and concentrated in *vacuo*. The crude material was then purified by flash column chromatography (EtOAc /hexane = 1:3) to afford **40** (17.23 mg, 90%) as a colourless oil. High polar R_f = 0.3 (EtOAc/hexane = 1:1). Less polar (major isomer) R_f = 0.35 (EtOAc/hexane = 1:1). $[\alpha]_D^{25}$ = +26.6 (*c* 1, $CHCl_3$). IR (neat, ν cm^{-1}): 1642 (s), 1252 (s), 1040 (s).^{1}H NMR (600 MHz, $CDCl_3$) δ 11.99 (s, 1H), 6.36 (d, *J* = 2.7 Hz, 1H), 6.29 (d, *J* = 2.7 Hz, 1H), 5.67 – 5.58 (m, 2H), 5.33 – 5.23 (m, 1H), 4.37 (t, *J* = 9.6 Hz, 1H), 4.07 (q, *J* = 6.3 Hz, 1H), 3.81 (s, 3H), 3.76 (dd, *J* = 9.3, 5.3 Hz, 1H), 3.31 (dt, *J* = 12.6, 7.4 Hz, 1H), 2.96 – 2.86 (m, 1H), 2.56 – 2.49 (m, 1H), 2.49 – 2.44 (m, 1H), 1.81 – 1.76 (m, 1H), 1.71 (ddd, *J* = 15.3, 7.5, 4.3 Hz, 1H), 1.68 – 1.59 (m, 2H), 1.53 (s, 3H), 1.47 (d, *J* = 6.4 Hz, 3H), 1.39 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 171.3, 165.6, 163.9, 147.3, 131.8, 130.7, 110.7, 107.8, 105.3, 99.1, 79.9, 77.8, 71.6, 64.6, 55.3, 35.7, 35.4, 29.9, 29.0, 28.2, 25.6, 21.0. HRMS (ESI) for $C_{22}H_{30}O_7Na$ $[M+Na]^+$, calculated: 429.1889, found: 429.1896.

(3a*S*,8*S*,17a*S*,*Z*)-11-Hydroxy-13-methoxy-2,2,8-trimethyl-7,8,15,16,17,17a-hexahydro-4H-benzo[*c*][1,3]dioxolo[4,5-*h*][1]oxacyclotetradecine-4,10(3a*H*)-dione (41):

To the solution of compound **40** (17.23 mg, 0.04 mmol) in DCM (1.5 mL) at 0 °C was added Dess–Martin periodinane (18.6 mg, 0.05 mmol) and the reaction mixture was stirred at room temperature for 2 h, then saturated aq. $Na_2S_2O_3$ solution (0.5 mL) was added and the resultant mixture was stirred at room temperature for 30 min. The mixture was extracted with CH_2Cl_2 (3×30 mL) and the combined organic extracts were dried over anhydrous $MgSO_4$ and concentrated. Purification by flash column chromatography (EtOAc /hexane = 1:10) afforded enone **41** (12 mg, 0.03 mmol, 70%) as a white powder. m.p = 120–122 °C (uncorrected). R_f = 0.4 (EtOAc/hexane = 1:5). $[\alpha]_D^{25}$ = +5.7 (*c* 0.5, $CHCl_3$). IR (KBr, ν cm^{-1}): 1645 (s), 1614 (s), 1255 (s), 1168 (s).^{1}H NMR (600 MHz, $CDCl_3$) δ 11.99 (s, 1H), 6.43 – 6.40 (m, 1H), 6.36 (d, *J* = 2.7 Hz, 1H), 6.27 (d, *J* = 2.7 Hz, 1H), 6.15 (d, *J* = 11.8 Hz, 1H), 5.56 (ddd, *J* = 10.9, 6.1, 2.6 Hz, 1H), 4.72 (d, *J* = 6.8 Hz, 1H), 4.35 (ddd, *J* = 10.1, 6.7, 3.7 Hz, 1H), 3.82 (s, 3H), 3.24 (td, *J* = 11.7, 4.7 Hz, 1H), 2.40 – 2.32 (m, 3H), 2.10 – 2.01 (m, 1H), 1.90 – 1.86 (m, 1H), 1.79 (dt, *J* = 14.0, 3.8 Hz, 2H), 1.65 (s, 3H), 1.44 (d, *J* = 6.2 Hz, 3H), 1.39 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 201.1, 171.3, 165.8, 164.1, 147.8, 145.3, 126.5, 110.9, 109.4, 104.7, 99.2, 81.9, 77.3,

72.4, 55.2, 36.8, 36.4, 30.4, 27.0, 26.1, 24.1, 20.9. HRMS (ESI) for $C_{22}H_{28}O_7Na$ $[M+Na]^+$ calculated: 427.1733, found: 427.1748.

(3*S*,8*S*,9*S*,*Z*)-8,9,16-Trihydroxy-14-methoxy-3-methyl-3,4,9,10,11,12-hexahydro-1*H*-benzo[*c*][1]oxacyclotetradecine-1,7(8*H*)-dione (L-783277):

Compound **41** (0.01 mmol, 4.3 mg) was dissolved in DCM:MeOH (1:1) in an one neck round bottled flask and *p*-toluenesulfonic acid (1 mg, 0.005 mmol) was added to it at 0 °C. Then the reaction mixture was stirred for 3 h at room temperature and then saturated $NaHCO_3$ (50 µL) solution was added. The resultant reaction mixture was stirred at room temperature for additional 15 minute. The mixture was extracted with EtOAc (3×15 mL) and the combined organic extracts were dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. Purification by flash column chromatography (EtOAc /hexane = 1:3) afforded **L-783277** (3 mg, 0.008 mmol, 75%) as a white powder. m.p = 144-147 °C (uncorrected). R_f = 0.35 (EtOAc/hexane = 1:1). $[\alpha]_D^{25}$ = +10.2 (*c* 0.5, $CHCl_3$). IR (KBr, ν cm^{-1}): 2932 (m), 1662 (s), 1248 (s). ^{1}H NMR (600 MHz, CD_2Cl_2) δ 12.22 (s, 1H), 6.37 (dd, *J* = 11.5, 3.1 Hz, 1H), 6.31 (d, *J* = 2.5 Hz, 1H), 6.28 (d, *J* = 2.5 Hz, 1H), 6.24 (td, *J* = 11.2, 2.5 Hz, 1H), 5.42 – 5.38 (m, 1H), 4.58 (d, *J* = 3.1 Hz, 1H), 3.82 – 3.77 (m, 1H), 3.79 (s, 3H), 3.32 (dt, *J* = 17.3, 11.3 Hz, 1H), 2.95 (ddd, *J* = 15.3, 11.8, 3.7 Hz, 1H), 2.55 – 2.50 (m, 1H), 2.42 – 2.36 (m, 1H), 1.75 – 1.68 (m, 1H), 1.50 – 1.47 (m, 1H), 1.46 – 1.39 (m, 1H), 1.41 (d, *J* = 5.9 Hz, 3H), 1.13 – 1.02 (m, 1H). ^{13}C NMR (150 MHz, CD_2Cl_2): δ 200.3, 172.2, 166.7, 164.8, 148.0, 146.6, 126.6, 109.7, 105.0, 99.4, 81.5, 74.0, 73.5, 55.8, 37.5, 37.0, 33.4, 29.4, 21.1.

^{1}H NMR (600 MHz, $CDCl_3$): δ 12.18 (s, 1H), 6.39 (dd, *J* = 11.6, 3.2 Hz, 1H), 6.35 (d, *J* = 2.4 Hz, 1H), 6.29 (m, 2H), 5.44 (m, 1H), 4.55 (d, *J* = 2.1 Hz, 1H), 3.83 (bs, 1H), 3.82 (s, 3H), 3.67 (d, *J* = 4.3 Hz, 1H), 3.37 (dt, *J* = 17.5, 11.3 Hz, 1H), 2.95 (t, *J* = 13.0 Hz, 1H), 2.57 (d, *J* = 17.2 Hz, 1H), 2.51 – 2.45 (m, 1H), 2.07 – 2.02 (m, 2H), 1.75 (d, *J* = 8.7 Hz, 1H), 1.44 (d, *J* = 6.0 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 199.6, 171.6, 166.5, 164.3, 147.0, 146.4, 126.1, 109.5, 104.9, 99.0, 80.8, 73.2, 73.2, 55.3, 37.1, 36.5, 33.0, 28.8, 20.9.

HRMS (ESI) for $C_{19}H_{24}O_7Na$ $[M+Na]^+$, calculated: 387.1420, found: 387.1442.

Conflicts of Interest

The authors declare no competing financial interest.

Acknowledgments

Financial support from CSIR (Grant No: 02(0244)/15/EMR-II), India, is gratefully acknowledged. One of the authors, JC is thankful to DST-India for a research fellowship. DST-

View Article Online
DOI: 10.1039/D0OB00237B

India is thanked for the 500 MHz NMR machine (Grant No: SR/FST/ CSII-026/2013) at the Department of Chemistry, IIT-KGP.

References:

1. (a) N. Jana and S. Nanda, *New*. *J*. *Chem*., 2018, **42**, 17803-17873. (b) C. Napolitano and P. V. Murphy, *Wiley-VCH*., 2014, 273-319. (c) N. Winssinger and S. Barluenga, *Chem*. *Comm*., 2007, 22-36. (d) T. Hofmann and K. –H. Altmann, *C*. *R*. *Chim.*, 2008, **11**, 1318-1335. (e) S. Barluenga, P.-Y Dakas, M. Boulifa, E. Moulin and N. Winssinger, *C. R. Chim.*, 2008, **11**, 1306–1317. (f) Brase, S.; Encinas, A.; Keck, J.; Nising, C. F. *Chem. Rev.* **2009,** *109* (9), 3903-3990.

2. (a) A. Dombrowski, R. Jenkins, S. Raghoobar, G. Bills, J. Polishook, F. Peláez, B. Burgess, A. Zhao, L. Huang, Y. Zhang and M. Goetz, *J. Antibiot.,* 1999, **52**, 1077-1085. (b) T. W. Schulte, S. Akinaga, S. Soga, W. Sullivan, B. Stensgard, D. Toft and L. M. Neckers, *Cell Stress Chaperones*, 1998, **3**, 100-108. (c) S. V. Sharma, T. Agatsuma and H. Nakano, *Oncogene*, 1998, **16**, 2639-2645.

3. (a) P. –Y. Dakas, S. Barluenga, F. Totzke, U. Zirrgiebel and N. Winssinger, *Angew*. *Chem*. *Int*. *Ed*., 2007, **46**, 6899-6902. (b) A. Schirmer, J. Kennedy, S. Murli, R. Reid, D. V. Santi and *Proc*. *Natl*. *Acad*. *Sci*. *U.S.A*., 2006, **103**, 4234-4239. (c) M. Isaka and C. Suyarnsestakorn, *J. Org. Chem***.,** 2002, **67**, 1561-1566. (d) E. Moulin, V. Zoete, S. Barluenga, M. Karplus and N. Winssinger, *J. Am. Chem. Soc*., 2005, **127**, 6999–7004. (e) J. Ninomiya-Tsuji, T. Kajino, K. Ono, T. Ohtomo and M. Matsumoto, *J. Biol. Chem.,* 2003, **278**, 18485-18490.
4. G. A. Ellestad, F. M. Lovell, N. A. Perkinson, R. T. Hargreaves and W. J. McGahren, *J. Org. Chem.,* 1978, **43**, 2339-2343.

5. (a) A. Dombrowski, R. Jenkins, S. Raghoobar, G. Bills, J. Polishook, F. Peláez, B. Burgess, A. Zhao, L. Huang, Y. Zhang and M. Goetz, *J. Antibiot.,* 1999, **52**, 1077-1085. (b) A. Zhao, S. H. Lee, M. Mojena, R. G. Jenkins, D. R. Patrick, H. E. Huber, M. A Goetz, O. D. Hensens, D. L. Zink, D. Vilella, A. W. Dombrowski, R. B. Lingham, L. Huang, *J. Antibiot*., 1999, **52,** 1086-1094.

6. (a) M. S. R. Nair and S. T. Carey, *Tetrahedron Lett*., 1980, **21**, 2011-2012. (b) M. S. R. Nair, S. T. Carey and J. C. James, *Tetrahedron,* 1981, **37**, 2445; (c) T. Agatsuma, A. Takahashi, C. Kabuto and S. Nozoe, *Chem*. *Pharm*. *Bull*., 1993, **41**, 373.

7. V. Hellwig, A. Mayer-Bartschmid, H. Muller, G. Greif and G. Kleymann, *J. Nat*. *Prod*., 2003, **66**, 829-837.

8. (a) P. Delmotte and J. Delmotte-Plaquee, *Nature*, 1953, **171**, 344-345. (b) R. N. Mirrington, E. Ritchie, C. W. Shoppee, W. C. Taylor and S. Sternhell, *Tetrahedron Lett*., 1964, **5**, 365-370. (c) T. J. Turbyville, E. M. K. Wijeratne, M. X. Liu, A. M. Burns and C. J. Seliga, *J. Nat. Prod*., 2006, **69**, 178-184**.**

9. F. M. Talontsi, P. Facey, M. D. K. Tatong, M. Tofazzal Islam, H. Frauendorf, S. Draeger, A. vonTiedemann and H. Laatsch, *Phytochemistry*, 2012, **83,** 87-94.

View Article Online
DOI: 10.1039/D0OB00237B

10. T. Hofmann and K. –H. Altmann, *Synlett*, 2008, 1500-1504.

11. A. Lin, A. C. Willis and M. G. Banwell, *Tetrahedron Lett.,* 2010, **51**, 1044-1047.

12. (a) H. G. Choi, J. B. Son, D. -S. Park, Y. J. Ham, J. -M. Hah and T. Sim, *Tetrahedron Lett.,* 2010, **51**, 4942-4944. (b) A. Srinivas Reddy, C. Kishore and B. V. A. Subba Reddy, *Tetrahedron Lett.*, 2014, **55,** 5420-5422. (c) P. –Y. Dakas, R. Jogireddy, G. Vallot, S. Barluenga and N. Winssinger, *Chem*. *Eur*. *J*., 2009, **15**, 11490-11497. (d) A. Lin, A. C. Willis and M. G. Banwell, *Heterocycles*, 2010, **82**, 313-318.

13. (a) N. Jana and S. Nanda, *Eur*. *J*. *Org*. *Chem*., 2012, 4313-4320. (b) N. Jana, D. Das and S. Nanda, *Tetrahedron*, 2013, **69**, 2900-2908. (c) P.Pal, N. Jana and S. Nanda, *Org*. *Biomol*. *Chem*., 2014, **12**, 8257-8274. (d) P. Pal, J. Chakraborty, A. Mali and S. Nanda, *Tetrahedron*, 2016, **72**, 2336-2348. (e) J. Chakraborty and S. Nanda, *Org*. *Biomol*. *Chem*., 2019, **17**, 7369-7379.

14. (a) G.W. Heberlig, M. Wirz, M. Wang and C. N. Boddy, *Org. Lett.,* 2014, **16**, 5858−5861. (b) S. Wang, Y. Xu, E. A. Maine, E. M. Wijeratne, P. Espinosa-Artiles, A. A. Gunatilaka, I. Molnar, *Chem*. *Biol*., 2008, **15**, 1328-1338. (c) C. D. Reeves, Z. Hu, R. Reid and J. T. Kealey, *Appl*. *Environ*. *Microbiol*., 2008, **74**, 5121-5129. (d) M. Wang, H. Zhou, M. Wirz and Y. C. N. Tang, Boddy, *Biochemistry*, 2009, **48**, 6288-6290. (e) H. Zhou, K. Qiao, Z. Gao, M. J. Meehan, J. W. Li, X. Zhao, P. C. Dorrestein, J. C. Vederas and Y. Tang, *J*. *Am*. *Chem*. *Soc*., 2010, **132**, 4530-4531.

15. A. Bhattacharjee and J. K. De Brabander, *Tetrahedron Lett.,* 2000, **41**, 8069–8073.

16. A. Gille and M. Hiersemann, *Org. Lett.,* 2010, **12**, 5258–5261.

17. P. Srihari, B. Mahankali and K. Rajendraprasad, *Tetrahedron Lett.,* 2012, **53***,* 56-59.

18. J. K. Stille, *Angew. Chem. Int. Ed.,* 1986, **25**, 508-524**.**

19. (a) C. Aïssa, *Eur. J. Org. Chem.,* 2009**, 12**, 1831-1844. (b) P. R. Blakemore, W. J. Cole, P. J. Kocieński and A. Morley, *Synlett*., 1998, 26-28.

20. K. C. Nicolaou, X. Jiang, P. J. Lindsay-Scott, A. Corbu, S. Yamashiro, A. Bacconi, V. M. Fowler, *Angew. Chem. Int. Ed.,* 2011, **50**, 1139 –1144.

21. N. Jana, T. Mahapatra and S. Nanda. *Tetrahedron: Asymmetry,* 2009, **20**, 2622–2628.

22. W. S. Wadsworth, *Org.React*., 1977, **25**, 73.

23. J. L. Luche, *J. Am. Chem. Soc.,* 1978*,* **100***,* 2226–2227.

24. (a) D. B. Dess and J. C. Martin, *J*. *Org*. *Chem*., 1983, **48**, 4155-4156. (b) H. Miyatake-Ondozabal and A. G. Barrett, *Org Lett*., 2010, **12**, 5573-5575.

25. (a) J. D. White, T. C. Somers and G. *J.* Nagabushana Reddy, *Org. Chem.,* 1992, **57**, 4991–4998. (b) Y. Kobayashi, S. Yoshida, M. Asano, A. Takeuchi and H. P. Acharya, *J. Org. Chem.,* 2007, **72**, 1707–1716. (c) L. A. Paquette and J. E. Hofferberth, *J. Org. Chem.,* 2003, **68**, 2266–2275.