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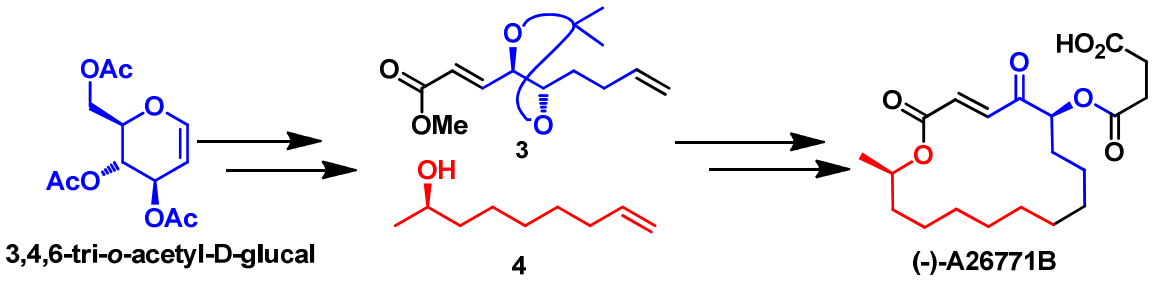
DOI: 10.1039/C4RA17084A

'Glycal Approach to the Syntheis of Macrolide (-)-A26771B'

Puli Saidhareddy and Arun K. Shaw*

A convergent total synthesis of a 16-membered macrolactone natural product (-)-A26771B **1** starting from 3,4,6-tri-*o*-acetyl-D-glucal **7** is reported. The Ferrier rearrangement of acetylated glucal **7**, HWE olefination to get the fragment **3,** cross metathesis between chiral fragments **3** and **4**, Yamaguchi macrolactonization and selective oxidation of the allylic alcohol are the key features of the synthesis.



DOI: 10.1039/C4RA17084A

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Cite this: DOI: 10.1039/c0xx00000x

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ARTICLE TYPE

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Received (in XXX, XXX) Xth XXXXXXXXX 200X, Accepted Xth XXXXXXXXX 200X
DOI: 10.1039/b000000x

Abstract: A convergent total synthesis of a 16-membered macrolactone natural product (-)-A26771B **1** starting from 3,4,6-tri-*o*-acetyl-D-glucal **7** is reported. The Ferrier rearrangement of acetylated glucal **7**, cross metathesis between chiral frgments **3** and **4**, yamaguchi macrolactonization and selective oxidation of the allylic alcohol are the key features of the synthesis.

Introduction

Macrolide antibiotics are safe and effective class of drugs for the treatment of bacterial infections.[1] Most of them target the bacterial ribosome by binding reversibly the 50S subunit in the peptidyl transferase center which ultimately blocks protein synthesis.[2] The macrolide (-)-A26771B was first isolated from the fungus *Pencillium turbatum* by K. H. Michel *et al.* in 1977[3]and later its absolute configuration was established by Kuniaki Tatsuta and his group in 1980.[4] Structurally it possesses γ-oxo-δ-acyloxy-α,β-unsaturated carboxyl functionality and two asymmetric centers 5*S* and 15*R*. It showed moderate activity against Gram-positive bacteria, mycoplasma and fungi.[5] Owing to its interesting structural feature as well as biological activity, its total synthesis became the challenging task to synthetic community. More than ten different synthetic strategies for the title natural product reported so far include stereoselective, asymmetric, chiron approach, etc.[6] Our ongoing interest in chiron based chemistry towards the synthesis of biological active natural products[7] and recently reported macrolide[8] encouraged us to design the synthesis of antibacterial macrolide (-)-A26771B (Figure 1).

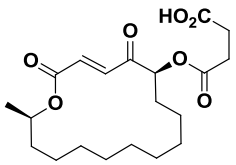

Figure 1: Structure of (-)-A26771B (**1**).

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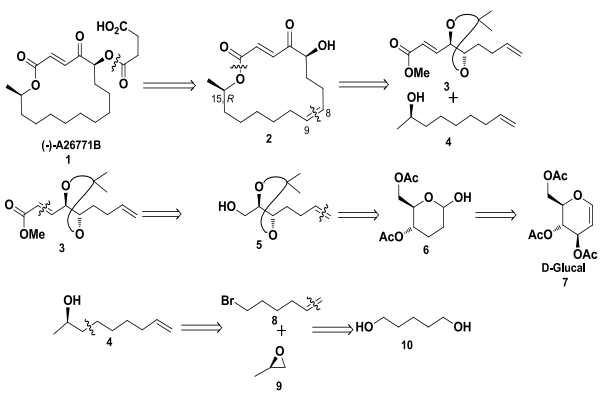
Results and Discussion:

The retrosynthetic analysis of the title macrolide **1** is shown in the Scheme 1. It could be synthesized by esterification of the chiral alcohol **2** with succinic anhydride. This macrolactone could be obtained from fragments **3** and **4,** as the precursors of cross metathesis (CM) followed by Yamaguchi macrolactonization of the resulting CM product. The intermediate **3** could be prepared by Wittig olefination of the aldehyde derived from Swern oxidation of primary alcohol **5** which in turn could be prepared from peracetylated-D-glucal **7** via the 2, 3-dideoxy glucopyranose **6**. The synthesis of the fragment **4** could be possible by treating (*R*)-propylene oxide **9** with the bromide **8.** Its preparation could be anticipated from commercially available 1,5-pentanediol **10**.



Scheme 1: Retrosynthetic analysis of (-)-A26771B

As per the retrosynthesis delineated above, our approach to the total synthesis of **1** was commenced with Ferrier rearrangement of the commercially available peracetylated-D-glucal **7** with benzyl alcohol in the

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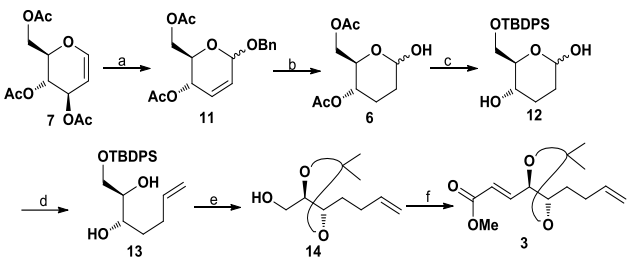
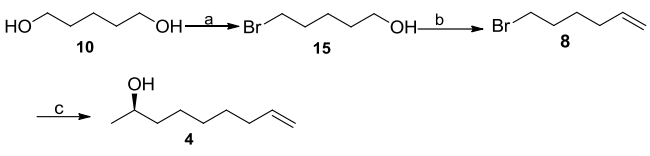
presence of catalytic amount of $InCl_3$[9] to afford 2,3-unsaturated pyranoside **11** in 95% yield. Hydrogenation of the double bond and deprotection of the *O*-benzyl group at anomeric position by H_2 in the presence of Pd/C produced the hemiacetal **6** in 98% yield. Its deacetylation with sodium methoxide in MeOH followed by regioselective protection of the resulting primary OH group with *t*-butylchlorodiphenyl silane (TBDPSCl) and imidazole furnished compound **12** in 92% yield. Its Wittig olefination with methyltriphenylphosphonium bromide in the presence of *t*-BuOK produced the unsaturated alcohol **13** in 60% yield. However, its yield was increased to 81% when *n*-BuLi was used in place of *t*-BuOK. Acetonide protection of the two syn-hydroxyl groups with 2,2-dimethoxy propane (2,2-DMP) in the presence of p-toluenesulfonic acid (PTSA) and deprotection of silyl protecting group with tetrabutylammoniumfluoride (TBAF) in THF afforded primary alcohol **14** in 80% yield over two steps. The fragment **3,** required for ring closing metathesis, was obtained from alcohol **14** by two step reaction sequences (scheme 2). First the alcohol **14** was converted into aldehyde by Swern oxidation. It was used directly without further purification in HWE (Horner-Wadsworth-Emmons) olefination with trimethyl phosphanoacetate in the presence of NaH to obtain (*E*)-α,β-unsaturated methyl ester **3** in 85% yield over two steps.



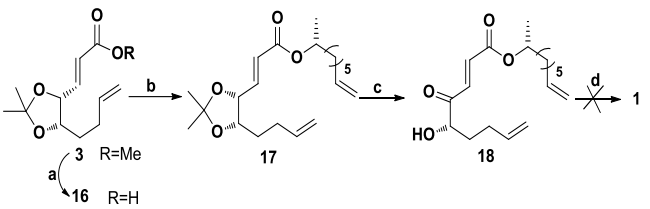
Scheme 2: Synthesis of fragment **3**
Reagents and conditions: (a) BnOH, $InCl_3$, CH_2Cl_2, RT, 10 Min, 95%; (b) H_2, Pd/C, EtOAc, RT, 2-3 hrs, 98%; (c) NaOMe, MeOH, RT, 30 Min, then TBDPSCl, Imidazole, DMF, 0 ºC - RT, 24 hrs, 92%; (d) $(Ph)_3PCH_3Br$, n-BuLi, dry THF, -78 ºC to RT, 2 h, 81%; (e) (i) 2,2-Dimethoxypropane, PTSA, Acetone, 30 min, RT (ii) TBAF, THF, 0 ºC - RT, 3 h, 80%; (f) (i) $(COCl)_2$, DMSO, Et_3N, dry CH_2Cl_2, -78 ºC, 2 h; (ii) $(MeO)_2P(O)CH_2CO_2Me$, NaH, dry Toluene, reflux, 3 h, 85%.

The preparation of C-9 fragment **4**, which contains terminal alkene for the cross metathesis and C2-OH with the required (*R*)-configuration for esterification, was carried out from commercially available 1,5-pentanediol **10** (Scheme 3). The modified literature[10] procedure was followed to obtain the monobromide derivative **15.** According to which, the diol **10** was heated with 47% HBr solution in toluene at 120 ºC to obtain 5-bromopentan-1-ol **15** in 85% yield. The pyridinium chlorochromate (PCC) oxidation of **15** and afterward one carbon Wittig olefination of the resulting aldehyde produced 6-Bromo-1-hexene **8** in 81% yield. Its *in situ* prepared Grignard reagent was treated with (*R*)-propylene oxide **9** in the presence of a catalytic amount of CuCN to deliver the desired *(R)*-non-8-en-2-ol **4** in 89% yield.



Scheme 3: Synthesis of Fragment **4**
Reagents and conditions: (a) 47% HBr, toluene, 120 ºC, 12 hrs, 85%; (b) (i) PCC, molecular sieves 4 Å, CH_2Cl_2, 0 ºC, 4 h; (ii) $(Ph)_3PCH_3Br$, t-BuOK, dry THF, 0 ºC to RT, 2 h, 81%; (c) Mg, dry THF, $C_2H_4Br_2$, 5 h, reflux, then (*R*)-Propyleneoxide, CuCN, dry THF, -15 ºC, 4 h, 89%.

Now we embarked upon synthesis of the title molecule by utilizing the above two fragments (**3** and **4**). Saponification of the unsaturated methyl ester **3** with LiOH in acetonitrile furnished the acid **16.** Its Yamaguchi esterfication with the chiral alcohol **4** afforded the compound **17** in 85% yield.[11] Its acetonide deprotection with PTSA followed by oxidation of the resulting allylic OH to unsaturated diketone **18** with 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) was more successful compared to its oxidation with MnO_2 both in terms of yield and reaction time. Having **18** in our hand, its ring closing metathesis (RCM) either in the presence of Grubb's 1st or 2nd generation catalyst in toluene or DCM was futile (scheme 4).[12]



Scheme 4: Trials to synthesis of (-)-A26771B
(a) LiOH, H_2O, Acetonitrile, 24 h, RT, 90%; (b) 2,4,6-trichlorobenzoyl Chloride, Et_3N, DMAP, THF, **4**, RT, 85%; (c) (i) PTSA, MeOH, RT, 3-4 h; (ii) TEMPO, PTSA, dry DCM, 0 ºC to RT, 6 h, 72%; (d) Grubb's 2nd generation catalyst.

Thus, we changed our strategy as depicted in scheme 5. Accordingly, first the fragments **3** and **4** were tied up by cross metathesis in the presence of Grubb's first generation catalyst in DCM under reflux conditions to obtain the required α,β-unsaturated diene ester **19** in 75 % yield (cis:trans ratio 1:3).[13] The saponification of **19** with LiOH in acetonitrile/H_2O to form the corresponding acid followed by its Yamaguchi's esterification with 2,4,6-

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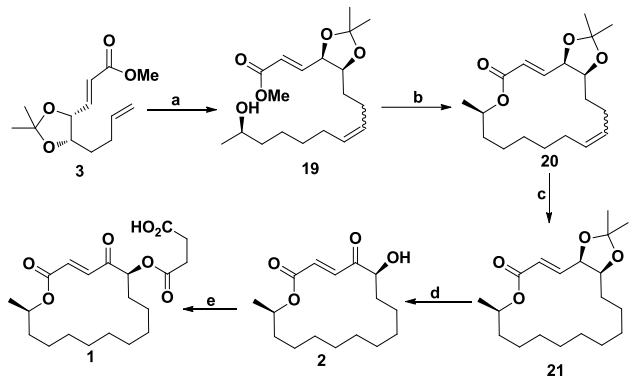
trichlorobenzoylchloride, Et_3N and N, N-Dimethylamino pyridine in toluene successfully furnished the 16 membered cyclized unsaturated ester **20** in 74% yield. Further, the regioselective reduction of the isolated double bond with Rosenmund reducing reagent (H_2/Pd-$BaSO_4$) afforded **21** in 98% yield. Now, its acetonide functional group was subjected to acid hydrolysis with PTSA in MeOH and subsequent selective oxidation of the resulting allylic alcohol functionality by TEMPO in PTSA gave the compound **2** in 86% yield over two steps.



Scheme 5: Synthesis of target macrolide (-)-A26771B
(a) Grubb's 1st gen. catalyst, **4**, dry DCM, Reflux, 16 hrs, 75 %; (b) LiOH, H_2O, Acetonitrile, RT, 24 hrs, then 2,4,6-trichlorobenzoyl Chloride, Et_3N, DMAP, THF, 6 hr, RT, 74%; (c) H_2/Pd-$BaSO_4$, EtOAc, RT, 1 h, 98%; (d) (i) PTSA, MeOH, RT, 3-4 h; (ii) TEMPO, PTSA, dry DCM 0 ºC to RT, 6 hrs, 86%; (e) Succinicanhydride, DMAP, CH_2Cl_2, RT, 6 hr, 72%.

Finally esterification of alcohol **2** with succinic anhydride under analogues conditions as reported[6b] produced the target molecule (-)-A26771B (**1**). The boiling point, specific rotation and NMR data of **1** [mp 122-125 ºC, $[\alpha]_D^{20}$ -12.9 (*c* 0.10 in MeOH), lit.[6c,e] m.p:152-155 ºC $[\alpha]_D^{26}$ -13.5 (*c* 0.18.in MeOH)] were in excellent agreement with the reported one.

Conclusion

In summary, we have developed here a concise and chiron approach synthesis to 16-membered macrolide (-)-A26771B in 13 steps with overall yield of 13.7%. The C4 (*S*) stereo center in the starting material **7** was conserved in the final molecule at C5 (*S*), thus showing the right selection of starting material was well conceived. This synthetic approach features a sequence of Ferrier rearrangement, Swern oxidation, HWE olefination, cross metathesis and Yamaguchi esterification.

Experimental section:

General:

The Organic solvents were made anhydrous by standard methods before their use. To monitor the progress of the reaction silica gel (60F-254) 2.5 × 5 cm TLC plates coated with a 0.25 mm thickness were used. Visualization of the spots was done by spraying the plate with $CeSO_4$ (1% in 2N H_2SO_4) and subsequent charring over hot plate. Silica gel (60–120 mesh) and silica gel (230-400 mesh) were used for Column chromatography. All the intermediates were characterized by NMR, IR, ESI-HRMS and optical rotation. NMR experiments were recorded in $CDCl_3$ at 25 ºC. Chemical shift values are given on δ scale with reference to TMS at 0.00 ppm for proton and carbon. The reference $CDCl_3$ appeared at 77.40 ppm for ^{13}C NMR. NMR spectra were recorded on Bruker Avance 300 MHz spectrometer at 300 MHz (^1H) and 75 MHz (^{13}C), 400 MHz spectrometer at 400 MHz (^1H) and 100 MHz (^{13}C). Optical rotations were determined on an HORIBA, high sensitive polarimeter, SEPA-300 using a 1 dm cell at 17 ºC-32 ºC in chloroform and methanol; concentrations mentioned are in g/100 mL. For IR spectra were recorded on Perkin–Elmer 881 and FTIR-8210 PC Shimadzu Spectrophotometers. Mass spectra were recorded on a JEOL JMS-600H high resolution spectrometer using EI mode at 70 eV. ESI-HRMS were recorded on a JEOL-AccuTOF, JMS-T100LC spectrometer.

((2R,3S)-3-acetoxy-6-(benzyloxy)-3,6-dihydro-2H-pyran-2-yl)methyl acetate (11): To a mixture of tri-*O*-acetyl-D-glucal **7** (400 mg, 1.47 mmol) and benzylalcohol (0.2 ml, 1.62 mmol) in dry CH_2Cl_2 (5 ml), anhydrous $InCl_3$ (56 mg, 0.29 mmol) was added at room temperature and the contents were stirred for the 15-20 min. After completion of the reaction (monitored by TLC), the reaction mixture was quenched by the addition of aqueous $NaHCO_3$, extracted with CH_2Cl_2 (3x25 ml), dried over anhydrous sodium sulphate, filtered and concentrated. The residue was subjected to flash column chromatography on silica gel EtOAc/hexane, 10/90 v/v) to obtain pure compound **11** (445 mg, 1.40 mmol) in 95% yield; $[\alpha]_D^{22}$ 125.5 (*c* 0.1, $CHCl_3$); R_f: 0.42 (1:5, EtOAc/Hexane); IR (Neat): ν_{max} 3015, 2930, 2856, 1722, 1656, 1462, 1253, 1122, 1063, 755, 665 cm^{-1}; ^1H (400 MHz, $CDCl_3$): δ 7.23-7.29 (m, 5H), 5.76-5.84 (m, 2H), 5.24-5.28 (m, 2H), 5.06 (bs, 1H), 4.73 (d, *J*=12 Hz, 1H), 4.53 (d, *J*=11.72 Hz, 1H), 4.15-4.20 (m, 1H), 4.04-4.10 (m, 2H), 2.02 (s, 3H), 2.0 (s, 3H); ^{13}C (100 MHz, $CDCl_3$): δ 164.00, 163.50, 130.83, 122.53, 121.10, 120.99, 86.88, 63.52, 60.33, 58.55, 56.17, 46.64, 14.17, 14.01; ESI-HRMS: *m/z* $[M+Na]^+$ calcd for $C_{17}H_{20}O_6Na^+$ 343.1158, measured 343.1147.

((2R,3S)-3-acetoxy-6-hydroxytetrahydro-2H-pyran-2-yl)methyl acetate (6): To the stirred solution of compound **11** (200 mg, 0.625 mmol) dissolved in ethyl acetate (5 mL) was added 10% Pd/C (50 mg) and the resulting solution was stirred under hydrogen atmosphere at room temperature for 6 h. The reaction mixture was filtered

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through a short pad of celite bed and it was washed with ethyl acetate (3x4 ml). The combined filtrates were concentrated *in vacuo* to afford a clear oil which was purified by column chromatography (EtOAc/hexane, 22/78 v/v) to afford the pure hemiacetal **6** (142 mg, 0.62 mmol) in 98% yield; R_f: 0.32 (1:2, EtOAc/Hexane); IR (Neat): ν_{max} 3425, 3019, 2931, 1638, 1428, 1217, 1109, 762, 669 cm^{-1}; ^1H (400 MHz, $CDCl_3$): δ 5.31.5.32 (m, 1H), 4.12-4.25 (m, 3H), 3.69-3.74 (m, 1H), 2.1 (s, 3H), 2.06 (s, 3H), 1.99-2.03 (m, 3H), 1.54-1.67 (m, 1H); ^{13}C (100 MHz, $CDCl_3$): 171.23, 170.32, 96.09, 91.16, 75.39, 68.88, 68.17, 67.52, 63.59, 63.54, 31.25, 29.02, 27.13, 23.42, 21.29, 21.25, 21.05; ESI-HRMS: *m/z* $[M+H]^+$ calcd for $C_{10}H_{17}O_6^+$ 233.1025, measured 233.1021.

(5S,6R)-6-((tert-butyldiphenylsilyloxy)methyl)tetrahydro-2H-pyran-2,5-diol (12): Sodium methoxide was added in portion to the stirred solution of compound **6** (500 mg, 2.154 mmol) dissolved in MeOH at room temperature till the P^H of the solution becomes 8-9. The stirring was continued at the same temperature for 1 hour. After completion, the reaction mixture was concentrated to evaporate the solvent. Imidazole (288 mg, 4.24 mmol) and the above crude residue (314 mg, 2.12 mmol) were taken in a two necked 50 ml round bottom flask containing dry DMF (10 ml), equipped with a magnetic stir bar and nitrogen inlet. TBDPSCl (0.7 ml, 2.54 mmol) was added drop wise to it at -18 °C and the resulting reaction mixture was stirred for 24 h at the same temperature. After the completion of the reaction, it was quenched with H_2O and extracted with ether (4x5 ml). The combined organic layers were dried over Na_2SO_4 and the solvent was removed under reduced pressure, followed by silica gel column chromatography of the resulting residue with EtOAc/hexane (15/85 v/v) as an eluent to obtain **12** (753 mg, 1.95 mmol) in 92% yield as a colorless oil; R_f: 0.50 (1:4, EtOAc/Hexane); IR (Neat): ν_{max} 3427, 3015, 2930, 1641, 1427, 1217, 1106, 919, 764 cm^{-1}; ^1H (400 MHz, $CDCl_3$): δ 7.65-7.70 (m, 4H), 7.37-7.46 (m, 6H), 5.17-5.50 (m, 1H), 4.06-4.25 (m, 1H), 3.66-3.96 (m, 3H), 1.78-2.13 (m, 4H), 1.07 (s, 3H); ^{13}C (100 MHz, $CDCl_3$): δ 135.81, 130.07, 129.92, 128.00, 127.92, 103.50, 80.07, 77.14, 64.74, 33.82, 29.93, 27.09; ESI-HRMS: *m/z* $[M+Na]^+$ calcd for $C_{22}H_{30}NaO_4Si^+$ 409.1811, measured 409.1805.

(2R,3S)-1-(tert-butyldiphenylsilyloxy)hept-6-ene-2,3-diol (13): Methyltriphenylphosphonium bromide (1.95 g, 5.46 mmol) was taken in a oven dried double neck round bottom flask added dry THF (10 ml) and the mixture was cooled to -78 °C. *n*-BuLi (0.78 ml, 1.56 mmol, 2 M solution) was added drop wise to the reaction mixture under N_2 atmosphere and the resulting mixture was stirred for 1 h at -30 °C. The compound **12** (300 mg, 0.78 mmol) dissolved in dry THF (8 ml) was added to the above Wittig salt drop wise at -30 °C and the stirring was continued at the same temperature for 30 min. and afterward at room temperature for 3-4 h. After completion of the reaction, quenched with the NH_4Cl and washed with brine solution. The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The silica gel column chromatography of the crude residue using EtOAc/hexane (12.5/87.5 v/v) as an eluent, gave the pure compound **13** in 81% yield; $[\alpha]_D^{26}$ +15.5 (*c* 0.1, $CHCl_3$); R_f: 0.50 (1:4, EtOAc/Hexane); IR (Neat): ν_{max} 3520, 3025, 2920, 1541, 1427, 1217, 1116, 929, 754 cm^{-1}; ^1H (400 MHz, $CDCl_3$): δ 7.58- 7.60 (m, 4H), 7.30-7.37 (m, 6H), 5.69-5.73 (m, 1H), 4.87-4.97 (m, 2H), 3.72-3.74 (m, 2H), 3.62-3.66 (m, 1H), 3.50-3.54 (m, 1H), 2.14-2.18 (m, 1H), 1.95-2.05 (m, 1H), 1.40-1.49 (m, 2H), 0.99 (s, 9H); ^{13}C (100 MHz, $CDCl_3$): δ 138.48, 133.06, 133.00, 130.22, 128.13, 128.11, 115.23, 73.87, 72.49, 64.84, 32.04, 30.28, 27.12, 19.44; ESI-HRMS: *m/z* $[M+H]^+$ calcd for $C_{23}H_{33}O_3Si^+$ 385.2199, measured 385.2175.

((4R,5S)-5-(but-3-enyl)-2,2-dimethyl-1,3-dioxolan-4-yl)methanol (14): To the stirred solution of compound **13** (100 mg, 0.26 mmol) in acetone was added the catalytic amount of PTSA (24.7 mg, 0.13 mmol) and 2,2-DMP (0.05 ml, 0.39 mmol). The stirring was continued till the TLC showed disappearance of the starting material which took 3-4 hrs .The reaction mixture was then neutralized with Et_3N and the solvent was evaporated to obtain the crude light yellow oil which on column chromatography using EtOAc/Hexane (4/96 v/v) gave the pure acetonide protected compound in 95% yield.

TBAF (0.88 ml, 1.0 M solution in THF, 0.88 mmol) was added drop wise to a stirred solution of above pure compound (250 mg, 0.59 mmol) in THF (10 mL) at 0 °C and the stirring was continued for 3 h. After disappearance of the starting material, the reaction mixture was quenched with water and the organic layer was separated. The aqueous layer was extracted with EtOAc (3x5 ml) and the combined organic layers were dried over Na_2SO_4. The solvent was removed *in vacuo* and the crude reaction mixture was purified by silica gel column chromatography by using EtOAc/hexane (20/80, v/v) as an eluent, to furnish the compound **14** in 80% yield; $[\alpha]_D^{26}$ +47.1 (*c* 0.4, $CHCl_3$); R_f: 0.50 (1:4, EtOAc/Hexane); IR (Neat): ν_{max} 3682, 3449, 3018, 2937, 1520, 1216, 760, 671 cm^{-1}; ^1H (400 MHz, $CDCl_3$): δ 5.71-5.79 (m, 1H), 4.91-5.01 (m, 2H), 4.07-4.13 (m, 2H), 3.53-3.56 (m, 2H), 2.18-2.22 (m, 1H), 2.03-2.11 (m, 2H), 1.46-1.64 (m, 2H), 1.40 (s, 3H), 1.29 (s, 3H); ^{13}C (100 MHz, $CDCl_3$): δ 137.86, 115.41, 108.28, 78.09, 76.45, 61.92, 30.82, 28.43, 25.71; ESI-

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DOI: 10.1039/C4RA17084A

HRMS: *m/z* $[M+H]^+$ calcd for $C_{10}H_{21}O_3^+$ 187.1334, measured 187.1327.

(E)-methyl 3-((4R)-5-(but-3-enyl)-2,2-dimethyl-1,3-dioxolan-4-yl)acrylate (3): A solution of oxalylchloride (0.41 ml, 4.83 mmol) dissolved in dry DCM (5 ml) in a 50 ml double necked round bottom flask equipped with a magnetic stir bar and nitrogen inlet was cooled at -78 °C. To this solution, DMSO (0.68 ml, 9.66 mmol) was added drop wise and the stirring was continued for 5 min. The alcohol **14** (600 mg, 3.22 mmol) dissolved in DCM was added drop wise to the above reaction mixture and the stirring was further continued for 30 min at the same temperature. Afterward, Et_3N (2.25 ml, 16.1 mmol) was now added drop wise to it and the stirring was continued till the completion of the reaction. The reaction mixture was quenched with saturated NH_4Cl and extracted with DCM (3x5 ml). The combined organic layers were dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude aldehyde was used for the next step without further purification.

To a solution of NaH (60% dispersion in mineral oil, 191 mg, 4.77 mmol) in dry THF (5 mL) was added the methyl 2-(dimethoxyphosphoryl)acetate (1.07 g, 4.77 mmol) at 0 °C. After stirring at room temperature for 30 min, a solution of the crude aldehyde in THF (5 mL) obtained above was added to it and the mixture was further stirred for another 10 min. It was diluted with saturated solution of $NaHCO_3$, and extracted with EtOAc. The combined organic layers were dried (Na_2SO_4), filtered, and concentrated to give a residue, which was purified by column chromatography using EtOAc/hexane (3/97, v/v) as an eluent to afford the unsaturated ester **3** in 85% yield (over two steps); $[\alpha]_D^{26}$ -42.0 (*c* 0.3, $CHCl_3$); R_f: 0.71 (1:10, EtOAc/Hexane); IR (Neat): ν_{max}= 3019, 2928, 2854, 1721, 1643, 1215, 758, 669 cm^{-1};^1H (400 MHz, $CDCl_3$): δ 6.78 (dd, J_1=6.15, J_2=15.67 Hz, 1H), 6.01 (dd, J_1=1.46, J_2=15.60 Hz, 1H), 5.69-5.76 (m, 1H), 4.90-5.00 (m, 2H), 4.56-4.60 (m, 1H), 4.15-4.20 (m, 1H), 3.68 (s, 3H), 2.02-2.19 (m, 2H), 1.50-1.54 (m, 2H), 1.44 (s, 3H), 1.31 (s, 3H); ^{13}C (100 MHz, $CDCl_3$): δ 166.62, 144.15, 137.80, 122.88, 115.55, 109.15, 77.78, 77.49, 51.91, 30.59, 30.09, 28.26, 25.77; ESI-HRMS: *m/z* $[M+H]^+$ calcd for $C_{13}H_{21}O_4^+$ 241.1440, measured 241.1421.

5-bromo-1-pentanol (15): To the stirred solution of 1,5-pentanediol **10** (17 g, 0.16 mmol) dissolved in toluene was added 47% aqueous HBr (0.19 mmol, 10.7 ml) at room temperature and the mixture was refluxed using Dean stark apparatus for 4-5 hrs. It was brought to room temperature and quenched with 1M NaOH at 0 °C. The two layers were separated and the organic layer was diluted with EtOAc and washed thoroughly with water and brine. The combined organic layers were dried over Na_2SO_4 and the solvent was removed under reduced pressure. The yellow crude was subjected to silica gel column chromatography in EtOAc/hexane (20/80 v/v) to obtain pure compound **15** (yellow oil) in 85% yield.

6-bromo-1-hexene (8): A solution of 5-Bromopentanol **15** (2 g, 0.012 mmol) in CH_2Cl_2 (10 ml) was added drop wise to a suspension of PCC (3.8 g, 0.018 mmol) and 4 Å molecular sieves (800 mg) in CH_2Cl_2 (10 ml) at 0ºC. The reaction was stirred vigorously at 0ºC for 3 h, diethyl ether (6 ml) was then added and the mixture was stirred for an additional 1 hour. The suspension was filtered over a silica gel pad (petroleum ether:ethyl acetate, 80:20, 300 mL). The solvent was evaporated under reduced pressure to give the corresponding aldehyde that was used immediately in the next step.

Methyltriphenylphosphonium bromide (29 g, 0.083 mmol) and potassium *tert*-butoxide (6.2 g, 0.055 mmol) was taken in an oven dried two neck RB flask. The mixture was cooled to 0 °C and charged the flask with THF (20 ml) under N_2 atmosphere. The reaction mixture was stirred at the same temperature for 1 hr till the yellow color was appeared. The crude aldehyde (4.5 g , 0.027 mmol) dissolved in dry THF (8 ml) was added to the above Wittig salt drop wise at 0 °C . Afterward, the temperature of the reaction bath was raised to room temperature (25^0C). When the reaction was completed (2 h), the reaction mixture was quenched with the NH_4Cl and washed with brine solution. The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The silica gel column chromatography of the crude residue mixture using EtOAc/hexane (0.5/99.5 v/v) as an eluent, yielded the pure compound **8** in 81% yield; R_f: 0.80 (Pure hexane); IR (Neat): ν_{max} 3020, 2975, 2927, 2855, 1634, 849, 757 cm^{-1}; ^1H NMR (400MHz, $CDCl_3$): δ 5.67-5.77 (m, 1H), 4.89-4.98 (m, 2H), 3.34 (t, *J*=6.82 Hz, 2H), 1.99-2.04 (m, 2H), 1.77-1.84 (m, 2H), 1.44-1.51 (m, 2H); ^{13}C (100 MHz, $CDCl_3$): δ 138.34, 115.22, 33.91, 33.03, 32.39, 27.58; ESI-HRMS: *m/z* $[M]^+$ calcd for $C_6H_{11}Br^+$ 162.0044, measured 162.0033.

(R)-non-8-en-2-ol (4): A portion of 6-bromo-1-hexene **8** (approx. 50 mg) dissolved in dry THF (10 ml) and magnesium turnings (178 mg, 7.33 mmol) were taken in a 50 ml two necked round bottom flask, equipped with a magnetic stir bar, a N_2 inlet and a rubber septum. Two drops of dibromoethane was added to it and the reaction mixture was refluxed under vigorous stirring followed by the drop wise addition of the remaining solution of 6-bromo-1-hexene **8** (700 mg, 3.66 mmol) in THF (5 ml) to it., The resulting reaction reaction mixture was continued

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to reflux for another 4 h and afterward the solution was cooled to room temperature.

To another 50 ml two necked round bottom flask equipped with a magnetic stir bar, a N_2 inlet and a rubber septum, were added (*R*)-propyleneoxide **9** (0.26 ml, 3.66 mmol) and CuCN (16.4 mg, 0.183 mmol) in dry THF (15 ml) and the reaction mixture was cooled to -15 °C. To this stirred solution, the above freshly prepared Grignard reagent was added drop wise by using a long needle. After completion of the addition, the stirring was continued at -15 °C for 4 h and an additional 2 h at room temperature. After completion of the reaction, a saturated solution of NH_4Cl was added and stirring was continued until a blue aqueous layer was obtained. The two layers were separated and the aqueous layer was extracted with ether (3x10 ml). The organic layers were combined, dried over Na_2SO_4 and evaporated *in vacuo*. The crude residue was purified by silica gel column chromatography using EtOAc/hexane (12/88 v/v) as an eluent to furnish the pure compound **4** in 89% yield (555 mg, 3.26 mmol); $[\alpha]_D^{21}$ -12.1 (*c* 0.1 in $CHCl_3$); R_f: 0.55 (1:5 EtOAc/Hexane); IR (Neat): ν_{max} 3433, 3019, 2974, 2928, 2856, 1639, 757 cm^{-1}; ^1H NMR (400MHz, $CDCl_3$); δ 5.76-5.86 (m, 1H), 4.91-5.01 (m, 2H), 3.78-3.79 (m, 1H), 2.01-2.05 (m, 2H), 1.62 (br s, 1H), 1.26-1.41 (m, 8H), 1.18 (d, *J*=6.0 Hz, 3H);^{13}C NMR (100 MHz, $CDCl_3$) δ 139.49, 114.47, 68.44, 39.70, 29.94, 29.79, 29.41, 29.25, 26.09; ESI-HRMS: *m/z* $[M+H]^+$ calcd for $C_9H_{19}O^+$ 143.1436, measured 143.1431.

(E)-3-((4R,5S)-5-(but-3-enyl)-2,2-dimethyl-1,3-dioxolan-4-yl)acrylic acid (16): To a stirred solution of compound **3** (400 mg, 1.65 mmol) dissolved in acetonitrile (10 ml) was added LiOH (159 mg, 6.65 mmol) and small amount of water (3 ml) at room temperature and stirring was continued at the same temperature for overnight. After completion of the reaction, the reaction mixture was acidified with NH_4Cl and extracted with ether. The organic layers were dried over Na_2SO_4, filtered and concentrated under reduced vacuum. The crude residue was purified by column chromatography in EtOAc-Hexane (38/62 v/v) as an eluent furnishing acid **16** (339 mg, 1.48 mmol) in 90% yield; $[\alpha]_D^{23}$ +3.5 (*c* 0.1 in $CHCl_3$); R_f: 0.43 (1:1, EtOAc/Hexane); IR (Neat): ν_{max} 3440, 3010, 2925, 2845, 1705, 1645, 1205, 758, 669 cm^{-1}; ^1H (400 MHz, $CDCl_3$): δ 6.95 (dd, J_1=5.88, J_2=15.56 Hz, 1H), 6.07-6.11 (m, 1H), 5.75-5.83 (m, 1H), 4.97-5.07 (m, 2H), 4.67-4.70 (m, 1H), 4.24-4.29 (m, 1H), 2.21-2.25 (m, 1H), 2.04-2.13 (m, 1H), 1.55-1.61 (m, 1H), 1.52 (s, 3H), 1.46-1.50 (m, 1H), 1.38 (s, 3H). ^{13}C (100 MHz, $CDCl_3$): δ 170.97, 146.54, 137.72, 122.48, 115.64, 109.30, 77.78, 77.35, 30.57, 30.13, 29.93, 28.22, 25.74. ESI-HRMS: *m/z* $[M+H]^+$ calcd for $C_{12}H_{19}O_4^+$ 227.1283, measured 227.1292.

(E)-((R)-non-8-en-2-yl) 3-((4S,5S)-5-(but-3-enyl)-2,2-dimethyl-1,3-dioxolan-4-yl)acrylate (17): To a stirred solution of **16** (350 mg, 1.67 mmol) in THF (7 ml) were added Et_3N (0.27 ml, 2 mmol) and 2,4,6-trichlorobenzoyl chloride (0.31 ml, 2 mmol) and the stirring was continued for 1 h at room temperature. The reaction mixture was now added to another RB containing a solution of alcohol **4** (300 mg, 2 mmol) and DMAP (1 g, 8.36 mmol) in toluene (5 ml) and the resulting mixture was heated at reflux for 3 h. The reaction mixture was then cooled to room temperature and quenched with saturated $NaHCO_3$ solution. The two layers were separated and the aqueous layer was extracted with EtOAc (3x5 ml). The combined organic layers were dried over Na_2SO_4, concentrated under reduced pressure and purified by silica gel column chromatography using EtOAc/hexane (8/92 v/v) as an eluent to afford the compound **17** in 85% yield (498 mg, 1.42 mmol); R_f: 0.6 (1:9 EtOAc/Hexane); IR (Neat): ν_{max} 3410, 3019, 2933, 2928, 2860, 1709, 1121, 759 cm^{-1}; ^1H (400 MHz, $CDCl_3$): δ 6.75 (dd, *J*1=6.38, *J*2=15.61 Hz, 1H), 5.98 (dd, J_1=1.51, J_2=15.61 Hz, 1H), 5.67-5.78 (m, 2H), 4.84-4.99 (m, 5H), 4.57 (td, *J*1=1.34, *J*2=6.36, *J*3=12.77 Hz, 1H), 4.15-4.20 (m, 1H), 2.12-2.19 (m, 1H), 1.94-2.07 (m, 3H), 1.39-1.55 (m, 9H), 1.24-1.30 (m, 9H), 1.16 (d, *J*=6.20 Hz, 3H). ^{13}C (100 MHz, $CDCl_3$): δ 165.77, 143.30, 139.15, 137.79, 123.90, 115.48, 114.50, 109.06, 77.74, 77.58, 71.43, 36.11, 33.86, 30.53, 30.05, 29.10, 28.97, 28.25, 25.74, 25.43, 20.18; ESI-HRMS: *m/z* $[M+H]^+$ calcd for $C_{21}H_{35}O_4^+$ 351.2535, measured 351.2530.

(S,E)-((R)-non-8-en-2-yl) 5-hydroxy-4-oxonona-2,8-dienoate (18): To the stirred solution of compound **17** (65 mg, 0.185 mmol) in MeOH was added PTSA (18 mg, 0.09 mmol) and stirring was continued for 3-4 hrs. After completion of the reaction, the reaction mixture was neutralized with NEt_3 and concentrated under vacuum. The crude product was diluted with EtOAc, wash with the water and the aqueous layer was extracted with EtOAc (3x5 ml). The combined organic layers were concentrated in rotavapour.

PTSA (61 mg, 0.32 mmol) was added to the above crude diol (50 mg, 0.16 mmol) dissolved in dry DCM followed by addition of TEMPO (50 mg, 0.32 mmol) at 0 °C. After being stirred for 6 hrs at room temperature, the solvent was evaporated and the resulting residue was purified by column chromatography to obtain the pure compound **18** in 72% over two steps. R_f: 0.65 (1:8 EtOAc/Hexane); IR (Neat): ν_{max} 3390, 3138, 2928, 2856, 1720, 1706, 1639, 757 cm^{-1}; ^1H (400 MHz, $CDCl_3$): δ 7.13(d, *J*=15.79 Hz, 1H), 6.76 (d, *J*=15.79 Hz, 1H), 5.67-5.80 (m, 2H), 4.85-4.99 (m, 5H), 4.36-4.40 (m, 1H), 3.28 (d, *J*=5.06 Hz, 1H),

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2.07-2.24 (m, 2H), 1.84-2.0 (m, 2H), 1.49-1.59 (m, 6H), 1.25-1.33 (m, 4H), 1.21 (d, *J*=6.32 Hz, 3H). ^{13}C (100 MHz, $CDCl_3$): δ 200.99, 165.01, 139.26, 137.45, 134.57, 133.80, 116.43, 114.75, 75.98, 73.20, 36.13, 34.01, 33.25, 30.08, 29.42, 29.22, 29.10, 25.56, 20.24; ESI-HRMS: *m/z* $[M+H]^+$ calcd for $C_{18}H_{29}O_4^+$ 309.2066, measured 309.2055.

(2E)-methyl 3-((4R,5S)-5-((R)-9-hydroxydec-3-enyl)-2,2-dimethyl-1,3-dioxolan-4-yl)acrylate (19): A solution of α,β-unsaturated ester **3** and alcohol **4** in dry DCM was added to a oven dried two neck RB flask, fitted one side with condenser and other side stopper, containing Grubb's 1st generation catalyst and the reaction mixture was heated to reflux in an inert atmosphere for 6 to 8 hrs. After completion of the reaction, the solvent was evaporated and the crude was subjected to column chromatography to obtain the pure compound **19** (both cis-trans isomer 1:3 from HPLC and NMR) in 75% yields; ESI-HRMS: *m/z* $[M+H]^+$ calcd for $C_{19}H_{33}O_5^+$ 341.2328, measured 341.2351.

(3aR,4E,8R,17aS)-2,2,8-trimethyl-8,9,10,11,12,13,17,17a-octahydro-3aH-[1,3]dioxolo[4,5-e][1]oxacyclohexadecin-6(16H)-one (20): To a stirred solution of compound **19** (70 mg, 0.21 mmol) dissolved in acetonitrile (5 ml) was added LiOH (25 mg, 1.03 mmol) and a small amount of water (2 ml) at room temperature and stirring was continued at the same temperature for overnight. After completion of the reaction, the reaction mixture was quenched with saturated NH_4Cl and extracted with ether (5x5 ml). The combined organic layers were dried over Na_2SO_4, filtered and concentrated.

To a stirred solution of above crude compound (50 mg, 0.153 mmol) in THF (7 ml) were added Et_3N (0.02 ml, 0.183 mmol) and 2,4,6-trichlorobenzoyl chloride (0.02 ml, 0.183 mmol). Its stirring was continued for 1 h at room temperature. The reaction mixture was now added to a solution of DMAP (95 mg, 0.765 mmol) in toluene (5 ml) and the resulting mixture was reflux for 3 h. After completion of the reaction, it was then cooled to room temperature and quenched with saturated $NaHCO_3$ solution. The two layers were separated and the aqueous layer was extracted with EtOAc (3x5 ml). The combined organic layers were dried over Na_2SO_4, concentrated under reduced pressure and purified by silica gel column chromatography using EtOAc/hexane (8/92 v/v) as an eluent to afford the compound **20** in 74% yield (284 mg, 0.58 mmol); $[\alpha]_D^{26}$ -11.8 (*c* 0.1, $CHCl_3$); R_f: 0.50 (1:4, EtOAc/Hexane); IR (Neat): ν_{max} 3682, 3449, 3018, 2937, 1520, 1205, 758, 669 cm^{-1}; ^{1}H (400 MHz, $CDCl_3$): δ 6.78 (dd, J_1=6.17, J_2=15.62 Hz, 1H), 6.01 (d, *J*=15.62 Hz, 1H), 5.25-5.99 (m, 2H), 4.56-4.58 (m, 1H), 4.15-4.19 (m, 1H), 3.66-3.73 (m, 4H), 1.90-2.10 (m, 1H), 1.44 (s, 3H), 1.30 (s, 3H), 1.19-1.22 (m, 10H), 1.12 (d, *J*=6.05 Hz, 3H); ^{13}C (100 MHz, $CDCl_3$): δ 165.90, 143.67, 132.67, 125.64, 124.04, 108.67, 81.48, 78.25, 35.75, 32.32, 31.60, 30.09, 29.87, 29.75, 28.60, 28.51, 27.84, 27.41, 27.09, 26.71, 25.84, 23.96, 23.08, 20.84; ESI-HRMS: *m/z* $[M+H]^+$ calcd for $C_{19}H_{31}O_4^+$ 323.2222, measured 323.2214.

(3aR,8R,17aS,E)-2,2,8-trimethyl-9,10,11,12,13,14,15,16,17,17a-decahydro-3aH-[1,3]dioxolo[4,5-e][1]oxacyclohexadecin-6(8H)-one (21): To the stirred solution of compound **20** (50 mg, 0.109 mmol) dissolved in ethyl acetate (5 mL) was added 5% Pd on $BaSO_4$ (15 mg) and the resulting solution was stirred under hydrogen atmosphere at room temperature for 1 h. The reaction mixture was filtered through a short pad of celite bed and it was washed after filtration with ethyl acetate (4 ml) for 2-3 times. The combined filtrates were concentrated *in vacuo* to afford a clear oil which was subjected to column chromatography (EtOAc/hexane, 6/94 v/v) to give the pure compound **21** in 98% yield (49.2 mg, 0.11 mmol); $[\alpha]_D^{22}$ +8.2 (*c* 0.1 in $CHCl_3$); R_f: 0.43 (1:9, EtOAc/Hexane); IR (Neat): ν_{max} 3015, 2930, 2856, 1722, 1656, 1462, 1253, 1122, 1063, 755, 665 cm^{-1}; ^{1}H NMR (400MHz, $CDCl_3$) δ 6.83 (dd, J_1=8.32, J_2=15.8 Hz, 1H), 6.06 (dd, J_1=1.4, J_2=15.6 Hz, 1H), 4.64-4.68 (m, 1H), 4.23-4.28 (m, 1H), 4.05-4.11 (m, 1H), 2.02-2.30 (m, 4H), 1.54-1.53-1.64 (m, 8H), 1.29-1.47 (m, 10H), 1.25 (d, *J*=6.28 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.97, 145.06, 123.44, 109.44, 75.14, 73.73, 71.57, 36.08, 32.44, 30.08, 28.70, 28.16, 27.95, 27.62, 27.50, 26.78, 24.67, 23.97, 20.84; ESI-HRMS: *m/z* $[M+Na]^+$ calcd for $C_{26}H_{46}NaO_8^+$ 325.2379, measured 325.2360.

(6S,16R,E)-6-hydroxy-16-methyloxacyclohexadec-3-ene-2,5-dione (2): To the stirred solution of compound **21** (30 mg, 0.092 mmol) in THF was added PTSA (9 mg, 0.046 mmol) at room temperature and continued the stirring for 3 hrs. After completion of the reaction (monitored by TLC), it was neutralized with triethylamine and the entire solution was concentrated under *vacuum*.

To the above crude product (15 mg, 0.053 mmol) in dry DCM (5 ml) was added PTSA (17 mg, 0.11 mmol) and TEMPO (17 mg, 0.11mmol) at 0 °C. After stirring for 6 hrs at room temperature, the solvent was evaporated and the resulting residue was purified by column chromatography to obtain a pure white solid **2** in 86% yield over two steps. $[\alpha]_D^{26}$ +21.8 (*c* 0.1, $CHCl_3$); R_f: 0.50 (1:4, EtOAc/Hexane); IR (Neat): ν_{max} 3449, 3018, 2937, 1702, 1690, 1520, 1205, 758, 669 cm^{-1}; ^{1}H (400 MHz, $CDCl_3$): δ 7.23 (d, *J*=15.76 Hz, 1H), 6.87 (d, *J*=15.8 Hz, 1H), 4.98-5.14 (m, 1H), 4.47-4.51 (m, 1H), 3.38 (d, *J*=5.32 Hz, 1H), 2.31-2.31 (m, 2H), 1.95-2.03 (m, 1H), 1.62-1.71

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DOI: 10.1039/C4RA17084A

(m, 6H), 1.29-1.44 (m, 13 H); ^{13}C (100 MHz, $CDCl_3$): δ 200.95, 164.97, 137.41, 134.53, 75.94, 73.16, 36.10, 33.95, 33.73, 29.68, 29.39, 29.36, 29.02, 28.88, 25.36, 20.84; ESI-HRMS: *m/z* $[M+H]^+$ calcd for $C_{16}H_{27}O_4^+$ 283.1909, measured 283.1920.

(-)-A26771B (1): A solution of above macrolide **2** (15 mg, 0.053 mmol), succinic anhydride (10.6 mg, 0.106 mmol), and DMAP (12.7 mg, 0.106 mmol) in CH_2Cl_2 (3 mL) was stirred for 24 h at room temperature. Evaporation of the solvent followed by the purification of the crude product by flash chromatography (SiO_2; 5% MeOH/CH_2Cl_2) afforded 10 mg (72%) of the title macrolide **1** as a white solid: $[\alpha]_D^{26}$ -12.4 (*c* 0.05, MeOH); R_f. 0.21 (5% MeOH/CH_2Cl_2); IR (Neat): ν_{max} 3150, 3019, 2938, 2855, 1742, 1703, 1381, 1300, 1196, 1158, 669 cm^{-1}; ^1H (400 MHz, $CDCl_3$) δ 7.23 (d, *J*=15.8, 1H), 6.87 (d, *J*=15.8, 1H), 5.14 (d, *J*=1.6 Hz 1H), 4.98-5.01 (m, 1H), 2.72-2.79 (m, 4H), 2.22-2.31 (m, 2H), 1.95-2.03 (m, 1H), 1.54-1.71 (m, 6H), 1.42-1.44 (m, 13H); ^{13}C (100 MHz, $CDCl_3$) δ 200.99, 178.02, 171.02, 165.01, 139.26, 133.80, 75.98, 73.20, 49.13, 36.13, 34.01, 33.25, 30.08, 29.42, 29.22, 29.10, 25.56, 20.24. ESI-HRMS: *m/z* $[M+Na]^+$ calcd for $C_{20}H_{31}O_7^+$ 383.2070, measured 383.2075.

Acknowledgement

We are thankful to SAIF, CDRI, for providing spectral data. P.S. thanks the CSIR, New Delhi for awarding Senior Research Fellowship and Mr. A. K. Pandey for technical assistance. CDRI Manuscript No. 329/2014/AKS

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[13] In order to improve its yield, the cross metathesis between **3** and **4** was carried out in the presence of Grubb's 2nd generation catalyst to afford **19**. Unfortunately it was isolated with low yield (49 %) along with considering amount of dimer of the side chain.