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First Asymmetric Total Synthesis of Aspergillide D

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The first asymmetric total synthesis of 16-membered macrolide aspergillide D is described. The chiral centers of the acid is derived from D-ribose and the alcohol subunit from 1,8-octane diol through Sharpless kinetic resolution, respectively. The other key reactions include Yamaguchi esterification, ring-closing metathesis reaction, and Shiina macrolactonization to construct the fully functionalized macrocycle.

Introduction

In 2013, Qi and co-workers[1] reported the isolation of aspergillide D (**1**), a 16-membered macrolide along with two polyketones, (*R*)-semivioxanthin (**1a**),[2a] (*R*)-semixanthomegnin (**1b**)[2b] and four alkaloids, 5-(1*H*-indol-3-ylmethyl)-imidazolidine-2,4-dione (**1c**), 9α,14-dihydroxy-6β-*p*-nitro-benzoylcinnamolide (**1d**),[2c] 7α,14-dihydroxy-6β-*p*-nitro-benzoylconfertifolin(**1e**),[2c] azonazine(**1f**)[2d] from the extract of the gorgonian-associated fungal stain *Aspergillus* sp. SCSGAF 0076. The assignment of the gross structure of aspergillide D (**1**) was allotted on account of ^{1}H, ^{13}C NMR, and DEPT spectra, which confirmed the presence of one methyl, eight aliphatic methylenes, α,β-unsaturated ester, four oxygenated methines, two double bond equivalents including one unsaturation and molecular formula by HRESIMS (*m/z* 323.1828 [M + Na]$^{+}$). Elucidation of the relative configuration of the natural product **1** was based on NOESY spectrum, large coupling constant (J = 16 Hz) supporting *E*-configured olefinic bond. 14- and 16-membered macrolides isolated from fungi and bacteria generally display antibacterial activity[3,4] but this new macrolide exhibited no antibacterial activity against both *Escherichia coli* and *Staphylococcus aureus*. Compounds **1d** and **1e** showed antiviral activity against H1N1 and H3N2, with IC_{50} values of 7.4 and 4.3 μM for **1d** and IC_{50} values of 36.0 and 12.0 μM for **1e**, respectively. Furthermore, the exploration of structure-activity

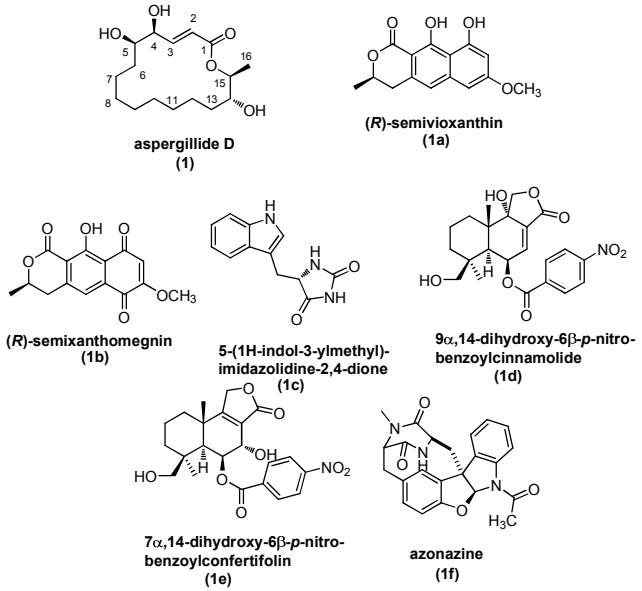

Figure 1. Structure of aspergillide D (**1**), two polyketones (**1a-b**), four alkaloids (**1c-f**).

relationships (SAR) of different macrolides have revealed that the combination of macrolide core and side chain parts were effective for the enhancement of biological activity of the natural product.[5] Generally, the accumulative importance focussed on the aglycons in the structure-activity investigations on such molecules sidelining the contribution of the corresponding carbohydrate components whereas latter part's inclusion can change the solubility, absorption, and interactions with a defined biological

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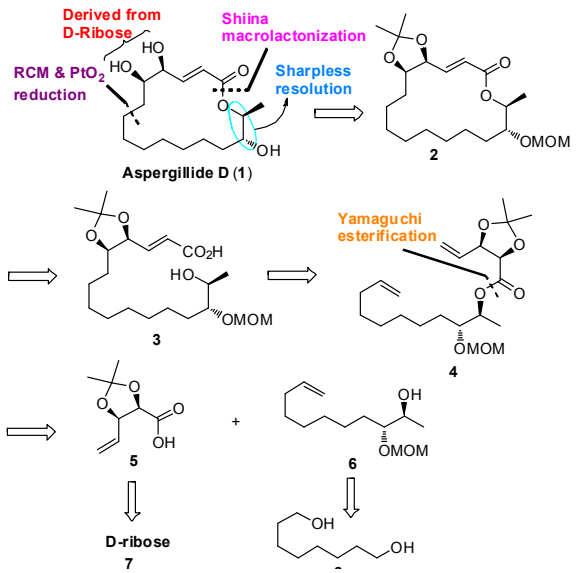
target and can be hampered to a great extent the other way around.[6] The biological activities of aspergillide D has not been extensively explored, presumably due to the scarce natural abundance which can be recouped by total synthesis for further biological evaluation. The quest for improvement of biological significance of aspergillide D with further structure-activity studies, along with its extremely limited supply, prompted us to undertake its chemical synthesis. Herein, we report the first asymmetric total synthesis of **1**, relying on the Shiina macrolactonization[7] as the pivotal step.

According to the retrosynthetic analysis of aspergillide D (**1**) as shown in Scheme 1, macrolactone core **2** of aspergillide D could be synthesized from seco-acid **3** via intramolecular Shiina esterification. Seco-acid **3** which could be obtained from α,β-

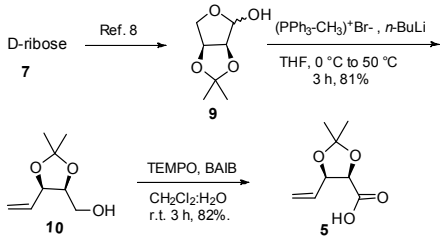


Scheme 1. Retrosynthetic analysis of Aspergillide D (**1**).

unsaturated ester through two carbon homologation on the corresponding lactol of the 14-membered macrolactone with controlled DIBAL-*H* reduction, which in turn could be constructed by ring-closing metathesis reaction of the resulting diene compound **4**, followed by reduction of the unsaturated macrolactone with PtO_2. The diene could be prepared from the coupling of the acid **5** and the alcohol **6** under Yamaguchi coupling conditions. Acid fragment **5** would be obtained from D-ribose following a reported protocol whereas alcohol fragment **6** could be accessed from 1,8-octane diol (**8**) through Sharpless kinetic resolution as the key reaction (Scheme 1).

Results and Discussion

The synthesis of acid fragment **5** was commenced with commercially available D-ribose (**7**) which was converted to lactol **9** following a literature protocol,[8] as shown in Scheme 2. Lactol **9** was synthesized from D-ribose (**7**) by treating with catalytic amount of H_2SO_4 and acetone, which produced 2,3-acetonide, followed by reduction with $NaBH_4$ and subsequent oxidative cleavage of the resulting diol with $NaIO_4$ afforded lactol **9** in quantitative yield. The lactol **9** was then treated with



Scheme 2. Synthesis of the acid fragment **5**.

$PPh_3{=}CH_2$ in THF at 50 °C to afford alcohol **10** in 81% yield. The primary alcohol group was then transformed to its corresponding carboxylic acid functionality by treating with BAIB in presence of TEMPO in a mixture of CH_2Cl_2 and water as solvent at room temperature to furnish **5** in 82% yield.[9]

The synthesis of alcohol fragment **6** was initiated with commercially available 1,8-octane diol (**8**) and mono-PMB protection with 4-methoxybenzyl alcohol in presence of Amberlyst-15 in CH_2Cl_2 furnished PMB ether **11** in 89% yield.[10] The primary alcohol **11** was oxidized under Swern conditions[11] to obtain the corresponding aldehyde, which was treated with vinylmagnesium bromide in presence of CuI (catalytic), immediately after purification through flash chromatography, to afford racemic allylic alcohol **12** in 74% yield over two steps. The allylic alcohol **12** was transformed to the enantiomerically rich epoxy alcohol **13** in 43% yield under Sharpless kinetic resolution conditions by employing requisite equivalents of (−)-DIPT and $Ti(O\mathit{i}Pr)_4$ in presence of 0.5 equivalent of *t*-BuOOH in CH_2Cl_2 at −20 °C.[12] The optical rotation of the compound **13** was found to be $[\alpha]_D^{20}$ −4.90 (*c* 2.1, $CHCl_3$) and the enantiomeric purity was determined by HPLC analysis. The free secondary hydroxy functionality of **13** was masked as its MOM ether to afford **14** in 93% yield by treating with MOMCl and *N*,*N*-diisopropylethylamine (DIPEA) in CH_2Cl_2. The PMB protecting group was oxidatively removed upon treatment with DDQ in CH_2Cl_2:H_2O (9:1) under phosphate buffer solution (pH = 7) to

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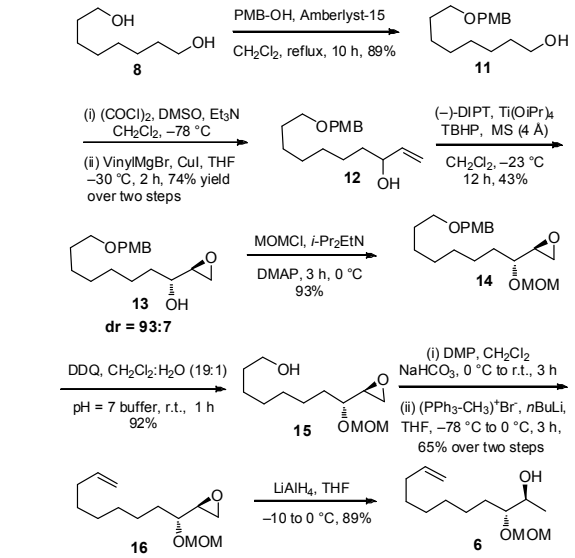
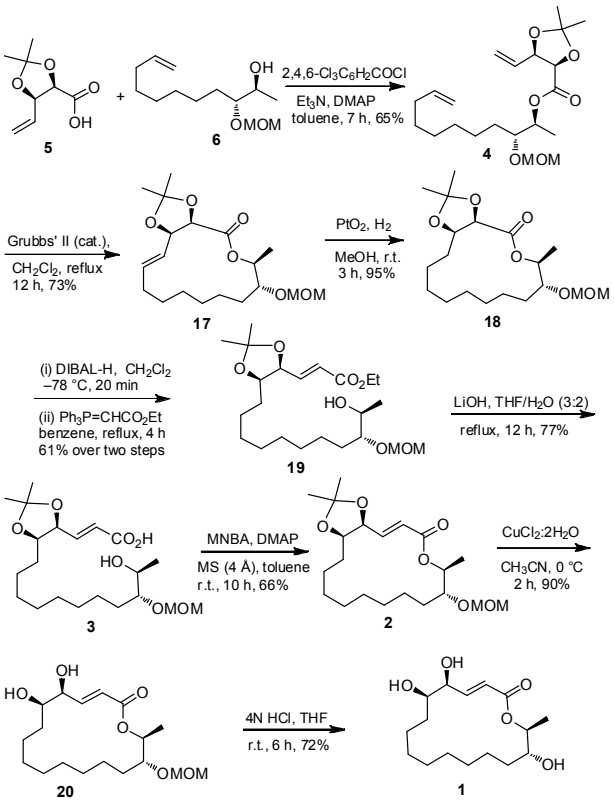
provide **15** in 92% yield.[13] The primary group **15** was then converted to the corresponding terminal alkene by a two step sequence involving oxidation to corresponding aldehyde with



Scheme 3. Synthesis of the alcohol fragment **7**.

Dess-Martin periodinane in CH_2Cl_2,[14] followed by treatment with $PPh_3{=}CH_2$ to produce alkene **16** in 65% yield over two steps (Scheme 3). The terminal epoxide **16** was reductively cleaved with $LiAlH_4$ in THF at −10 °C to obtain **6** in 89% yield.

Having synthesized both the desired fragments in a simple and efficient manner, we turned our attention to couple the acid **5** and the alcohol **6** followed by crucial ring-closing metathesis reaction of the resulting diene **4**. When the coupling was initially attempted in the presence of DCC (dicyclohexyl carbodiimide)[15] and EDCI (*N*-ethyl-*N'*-(dimethylaminopropyl)carbodiimide),[16] DMAP in CH_2Cl_2, both the reaction conditions afforded product with low yield and non-reproducible, anticipating the vulnerability of acid moiety **5**. Pleasingly, under Yamaguchi esterification[17] conditions, the diene ester **4** was obtained in 65% yield, which set the stage for RCM reaction to prepare 14-membered unsaturated lactone **17**. The diene ester was dissolved in degassed CH_2Cl_2 and refluxed with Grubbs' 2nd generation catalyst under high dilution conditions to furnish the desired macrolactone **17** as major isomer in 73% yield.[18] Hydrogenation of unsaturated lactone compound **17** was effected in presence of catalytic amount of PtO_2 under H_2 atmosphere in MeOH to afford 14-membered saturated lactone **18** in 95% yield. The reduction of macrolactone **18** in CH_2Cl_2 was efficiently carried out with DIBAL-*H* at −78 °C into the corresponding lactol, which was immediately subjected to $Ph_3P{=}CHCO_2Et$ in refluxing benzene after purification through a flash silica gel chromatography to produce α,β-unsaturated ester **19** in 61% yield over two steps (Scheme 7).[19] The ester functionality of **19**, was hydrolyzed under



Scheme 4. Total synthesis of aspergillide D (**1**).

basic conditions with LiOH in THF/H_2O (3:2) to afford the requisite seco-acid **3** of aspergillide D, which set the stage for crucial Shiina macrolactonization. The azeotropic seco-acid moiety with anhydrous benzene, was macrocyclized under Shiina's protocol utilizing 2-methyl-6-nitrobenzoic anhydride as acid activating agent, to furnish the key fully functionalized macrolactone **2** in 51% yield over two steps.[7] Global deprotection of **2** having acetonide group and MOM-ether to the corresponding hydroxy groups was attempted under different acidic conditions, which led to the formation of inseparable mixture of products along with decomposition of the starting material. Then, it was planned to deprotect the acetonide group of **2** selectively in the presence of MOM ether by treating with 3 equivalents $CuCl_2{\cdot}2H_2O$ in CH_3CN at 0 °C which produced the diol **20** in 90% yield.[20] Deprotection of MOM-protecting group was the remaining task to complete the synthesis of proposed structure of aspergillide D. After achieving the acetonide deprotection, the deprotection of MOM ether with $CuCl_2{\cdot}2H_2O$ in

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Table 1: ^{1}H and ^{13}C NMR data of natural and synthetic aspergillide D

Position	Natural	Synthetic	Position	Natural	Synthetic
	δ_H (*J* in Hz)	δ_H (*J* in Hz)		δ_C	δ_C
H-2	6.08, (dd, 1.5, 15.5)	6.11, (dd, 1.7, 15.9)	C-1	166.0	165.6
H-3	6.93, (dd, 5.0, 16.0)	6.92, (dd, 5.2, 15.7)	C-2	122.0	122.5
H-15	4.81, m	4.87, m	C-3	146.6	145.8
H-4	4.44, (ddd, 1.3, 2.6, 4.7)	4.50, m	C-4	74.0	74.02
H-5	3.69, m	3.74, m	C-5	74.1	74.5
H-6a, H-13a	1.58, m	1.66-1.52, m	C-6	31.8	32.1
H-7~ H-12	1.45-1.13, m	1.44-1.14, m	C-7	27.8	27.9
H-14	3.47, m	3.54, m	C-8	27.5	27.6
H-6b	1.32, m	1.48, m	C-9	23.2	23.4
H-16	1.38, (d, 6.0)	1.36, (d, 6.3)	C-10	22.9	23.0
H-13b	1.26, m	–	C-11	26.1	26.3
			C-12	26.0	26.3
			C-13	29.7	30.0
			C-14	73.8	73.97
			C-15	73.7	73.7
			C-16	17.6	17.6

CH_3CN at room temperature was investigated which led to furnish the requisite product along with the decomposition product. Finally, treatment of the MOM-ether **20** with 4N HCl in THF, successfully afforded aspergillide D in 72% yield. The specific rotation $\{[\alpha]_D^{20} = -9.42$ (*c* 0.1, MeOH)$\}$ of synthetic compound **1** was in good agreement with the data reported[1] for the natural product $\{[\alpha]_D^{20} = -11.1$ (*c* 0.1, MeOH)$\}$ and the spectral data (^{1}H NMR and ^{13}C NMR taken at 40 ^{o}C as the compound was partially soluble in $CDCl_3$) were also in good agreement with the natural product data except few chemical shifts differs to a little extent (Table 1), thus, represents the first asymmetric total synthesis of 16-membered macrolactone aspergillide D.

Conclusions

In conclusion, the first asymmetric total synthesis of aspergillide D was achieved in 18 longest linear step sequences. The intramolecular Shiina coupling was successfully applied to the synthesis of 16-membered macrolactone ring of aspergillide D. Other key features of the synthesis include the preparation of both desired fragments from commercial available cheaper starting materials in a concise and convergent manner and the successful use of Sharpless resolution, Yamaguchi esterification, and RCM reaction. Hopefully, the current synthesis will provide considerable flexibility to a variety of structural analogues of aspergillide D for further biological studies.

Experimental Section

General Remarks: Air and/or moisture sensitive reactions were carried out in anhydrous solvents under an atmosphere of argon in an oven or flame-dried glassware. All anhydrous solvents were distilled prior to use: THF, benzene, toluene, diethyl ether from Na and benzophenone; CH_2Cl_2, DMSO, DMF, hexane from CaH_2; MeOH, EtOH from Mg cake. Commercial reagents were used without purification. Column chromatography was carried out by using silica gel (60–120 mesh). Specific optical rotations $[\alpha]_D$ are given in 10^{-1} $degcm^2g^{-1}$. Infrared spectra were recorded in $CHCl_3$/neat (as mentioned) and reported in wave number (cm^{-1}). TOF analyzer type was used for the HRMS measurement. ^{1}H and ^{13}C NMR chemical shifts are reported in ppm downfield from tetramethylsilane and coupling constants (*J*) are reported in hertz (Hz). The following abbreviations are used to designate signal multiplicity: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad.

8-((4-Methoxybenzyl)oxy)octan-1-ol (11): To a stirred solution of 1,8-octanediol (**8**) (18.0 g, 123.29 mmol) and catalytic amount of Amberlyst-15 resin (1.8 g, 10% w/w) in CH_2Cl_2 (100 mL) was added 4-methoxybenzyl alcohol (15.28 mL, 123.29 mmol) at room temperature and heated to reflux at 50 °C for 10 h. After completion of the reaction (monitored by TLC), it was filtered through a pad of Celite. The residue was washed with CH_2Cl_2 (2 × 40 mL). The combined organic layer was dried over anhydrous Na_2SO_4, concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography (EtOAc/hexane = 1:3) to obtain the desired alcohol **11** (29.19 g,

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89%) as a colorless liquid. IR (neat): 3409, 2930, 2855, 1612, 1513, 1247, 1095, 1036, 821 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.26 (d, J = 8.7 Hz, 2H), 6.87 (d, J = 8.7 Hz, 2H), 4.43 (s, 2H), 3.80 (s, 3H), 3.62 (t, J = 6.6 Hz, 2H), 3.43 (t, J = 6.7 Hz, 2H), 1.65-1.50 (m, 5H), 1.40-1.27 (m, 7H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.0, 130.7, 129.2, 113.7, 72.5, 70.1, 62.9, 55.2, 32.7, 29.7, 29.4, 29.3, 26.1, 25.6 ppm; HRMS (ESI): m/z calcd for $C_{16}H_{26}O_3Na$ $[M + Na]^+$ 289.1774; Found: 289.1766.

10-((4-Methoxybenzyl)oxy)dec-1-en-3-ol (12): To a stirred solution of anhydrous dimethyl sulfoxide (19.67 mL, 277.44 mmol) in CH_2Cl_2 (120 mL), was added oxalyl chloride (16.8 mL, 184.96 mmol) drop-wise at −78 °C under N_2 atmosphere. The reaction mixture was stirred for 30 min before alcohol **11** (24.6 g, 92.84 mmol) in CH_2Cl_2 (80 mL) was added slowly. The reaction mixture was stirred for 45 min at same temperature. Then triethylamine (51.50 mL, 369.92 mmol) was added drop-wise and allowed to stir for 1 h at −78 °C. The reaction was allowed to stir at room temperature for additional 1 h. After completion of the reaction (monitored by TLC), the reaction mixture was quenched with water. The aqueous phase was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layer was washed with brine (100 mL), dried over Na_2SO_4 and evaporated to dryness under reduced pressure. The crude aldehyde was purified by flash chromatography and immediately used in the next reaction without further characterization.

Vinyl magnesium bromide (122.16 mL, 122.16 mmol) (1 M solution in THF) was added dropwise to a solution of CuI (1.55 g, 8.14 mmol) in THF (130 mL) at −20 °C. The mixture was stirred for 30 min. and aldehyde (21.5 g, 81.44 mmol) in THF (60 mL) was added dropwise to the above mixture at the same temperature. After 2 h, the reaction (monitored by TLC) was quenched with a saturated NH_4Cl solution (75 mL) and diluted with ethyl acetate (100 mL). The organic layer was separated and the aqueous layer extracted with ethyl acetate (3 × 50 mL). The combined organic layer was washed with brine (70 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give the crude mass. Purification by silica gel column chromatography (EtOAc/hexane = 3:7) afforded the desired allyl alcohol **12** (19.98 g, 74% yield over two steps) as a colorless liquid. IR (neat): 3438, 2931, 2855, 1611, 1513, 1463, 1247, 1096, 821 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): 7.26 (d, J = 8.7 Hz, 2H), 6.87 (d, J = 8.7 Hz, 2H), 5.85 (m, 1H), 5.21 (m, 1H), 5.09 (td, J = 1.4, 10.4 Hz, 1H), 4.42 (s, 2H), 4.07 (m, 1H), 3.80 (s, 3H), 3.42 (t, J = 6.7 Hz, 2H), 1.62-1.56 (m, 2H), 1.54-1.46 (m, 2H), 1.39-1.27 (m, 8H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 159.0, 141.3, 130.7, 129.2, 114.4, 113.7, 73.1, 72.4, 70.1, 55.2, 36.9, 29.7, 29.4, 29.3, 26.1, 25.2; HRMS (ESI) calcd for $C_{18}H_{28}O_3Na$ $[M + Na]^+$ 315.1931; Found: 315.1939.

(*R*)-8-((4-Methoxybenzyl)oxy)-1-((*S*)-oxiran-2-yl)octan-1-ol (13): At first, 4 Å molecular sieves (12.7 g) and CH_2Cl_2 (90 mL) were placed in a two-necked 250 mL round bottomed flask, followed by the addition of $Ti(O^iPr)_4$ (2.45 mL, 8.24 mmol) and (−)-diisopropyltartrate (2.0 mL, 9.50 mmol) at –25 °C under nitrogen and the resulting mixture was stirred for 30 min. The allylic alcohol **12** (18.5 g, 63.36 mmol) was then added and stirred for 30 min, after which *t*-BuOOH (4.9 mL, 31.68 mmol) (6.5 M in toluene) was added over 20 min at the same temperature. Then the reaction mixture was stirred for 12 h at the same temperature. After monitoring resolution of the racemic alcohol (monitored by TLC), the reaction mixture was warmed to 0 °C and whole reaction mixture was filtered through sintered funnel. Then quenched by water (40 mL) and stirred vigorously for 30 min and the filtrate were again stirred along with 20% aqueous NaOH solution (15 mL). The biphasic solution was separated and aqueous layer was extracted with CH_2Cl_2 (3 × 60 mL). The combined organic extracts were dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The crude residue was purified by silica gel column chromatography (EtOAc/hexane = 2:3) to afford pure epoxy alcohol **13** (8.39 g, 43%) as a colorless liquid. $[\alpha]_D^{20}$ −4.90 (*c* 2.1, $CHCl_3$); IR (neat): 3426, 2925, 2854, 1610, 1512, 1461, 1247, 1093, 1034, 823 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): 7.26 (d, J = 8.7 Hz, 2H), 6.87 (d, J = 8.7 Hz, 2H), 4.42 (s, 2H), 3.86-3.77 (m, 4H), 3.43 (t, J = 6.6 Hz, 2H), 3.00 (m, 1H), 2.79 (m, 1H), 2.72 (dd, J = 4.0, 5.0 Hz, 1H), 1.65-1.44 (m, 4H), 1.43-1.23 (m, 8H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 159.0, 130.7, 129.2, 113.7, 72.5, 70.1, 68.4, 55.2, 54.5, 43.4, 33.4, 29.7, 29.5, 29.3, 26.1, 25.2; HRMS (ESI) calcd for $C_{18}H_{28}O_4Na$ $[M + Na]^+$ 331.1880; Found: 331.1891.

(*S*)-2-((*R*)-8-((4-Methoxybenzyl)oxy)-1-(methoxymethoxy)oct-yl)oxirane (14): To a stirred solution of compound **13** (8.1 g, 26.30 mmol) in CH_2Cl_2 (60 mL), was added diisopropyl ethylamine (13.74 mL, 78.9 mmol) and stirred for 30 min at 0 °C under N_2 atmosphere. Methoxymethyl chloride (3.0 mL, 39.45 mmol) was added to the reaction mixture at same temperature.

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The reaction was continued to stir for 3 h at room temperature. After completion of the reaction (monitored by TLC), it was quenched with water (30 mL). The organic layer was separated and the aqueous layer extracted with CH_2Cl_2 (2 × 50 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and removed under reduced pressure. The crude mass was purified by silica gel chromatography (EtOAc/hexane = 1:3) to afford **14** (8.61 g, 93%) as a colorless liquid. $[\alpha]_D^{20}$ +6.81 (*c* 1.60, $CHCl_3$); IR (neat): 2931, 2855, 1612, 1513, 1461, 1247, 1099, 1035, 802 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): 7.26 (d, *J* = 8.6 Hz, 2H), 6.87 (d, *J* = 8.7 Hz, 2H), 4.65 (ABq, *J* = 6.9, 66.8 Hz, 2H), 4.43 (s, 2H), 3.80 (s, 3H), 3.43 (t, *J* = 6.7 Hz, 2H), 3.39 (m, 1H), 3.36 (s, 3H), 2.90 (m, 1H), 2.78 (dd, *J* = 4.0, 5.2 Hz, 1H), 2.72 (dd, *J* = 2.6, 5.3 Hz, 1H), 1.68-1.55 (m, 4H), 1.49 (m, 1H), 1.40-1.28 (m, 7H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.0, 130.7, 129.1, 113.7, 95.9, 76.2, 72.4, 70.1, 55.4, 55.2, 53.2, 45.5, 32.8, 29.7, 29.5, 29.3, 26.1, 25.0; ESI-HRMS Calcd for $C_{20}H_{32}O_5Na$ $[M + Na]^+$ 375.2142; found: 375.2150.

(*R*)-8-(Methoxymethoxy)-8-((*S*)-oxiran-2-yl)octan-1-ol (15): To a stirred solution of PMB ether **14** (7.4 g, 21.02 mmol) in CH_2Cl_2 (50 mL), was added phosphate buffer (pH^7) solution (3 mL) at 0 °C followed by DDQ (7.16 g, 31.53 mmol). The reaction mixture was continued to stir for 1 h at room temperature. After completion of the reaction (monitored by TLC), it was quenched with saturated $NaHCO_3$ solution (40 mL). The organic layer was separated and the aqueous layer extracted with CH_2Cl_2 (2 × 50 mL). The combined organic layer was washed with brine (50 mL), dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure to obtain the crude product which on purification by silica gel column chromatography (EtOAc/hexane = 2:3) furnished the corresponding diol **15** (4.49 g, 92%) as colorless liquid. $[\alpha]_D^{20}$ +8.73 (*c* 1.5, $CHCl_3$); IR (neat): 3444, 2930, 2856, 1465, 1366, 1149, 1103, 1034, 919, 755 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): 4.65 (ABq, *J* = 6.9, 65.3 Hz, 2H), 3.63 (t, *J* = 6.7 Hz, 2H), 3.41-3.36 (m, 4H), 2.90 (m, 1H), 2.78 (m, 1H), 2.72 (m, 1H), 1.69-1.46 (m, 5H), 1.42-1.30 (m, 7H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 95.9, 76.3, 62.8, 55.4, 53.3, 45.6, 32.9, 32.7, 29.5, 29.2, 25.6, 25.0 ppm; ESI-HRMS Calcd for $C_{12}H_{25}O_4$ $[M + H]^+$ 233.1747; found: 233.1755.

(*S*)-2-((*R*)-1-(Methoxymethoxy)non-8-en-1-yl)oxirane (16): To a stirred solution of primary alcohol **15** (4.0 g, 17.24 mmol) in CH_2Cl_2 (45 mL) at 0 °C, was added Dess-Martin periodinane (10.97 g, 25.86 mmol). The reaction mixture was stirred at 0 °C for 3 h. After completion of the reaction (monitored by TLC), it was quenched with saturated aqueous $NaHCO_3$ solution (30 mL) and stirred for another 30 min. The organic layer was separated and the aqueous layer extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layer was evaporated under reduced pressure to afford a crude residue which was immediately used for the next reaction.

Methyltriphenylphosphonium bromide (15.04 g, 42.13 mmol) was dissolved in THF (50 mL) and cooled to –78 ºC. *n*-Butyllithium (14.04 mL, 2.5 M in hexane, 35.11 mmol) was added drop wise to the above stirred solution which turned into light orange solution. It was then warmed to 0 ºC for 45 min and again cooled to –78 ºC. The crude aldehyde (3.23 g, 14.04 mmol) in THF (20 mL) was added to the reaction mixture drop wise. The reaction mixture was stirred at the same temperature for 1 h then warmed to 0 °C for 2 h. After complete consumption of the starting material (monitored by TLC), the reaction was quenched with saturated NH_4Cl solution (30 mL) and warmed to room temperature. The organic phase was separated and the aqueous phase extracted with ethyl acetate (2 × 30 mL). The combined organic layers were washed with brine (25 mL), dried over Na_2SO_4 and concentrated under reduced pressure. Purification by silica gel column chromatography (EtOAc/hexane = 1:4) afforded the desired compound **16** (2.56 g, 65% over two steps) as a colorless liquid. $[\alpha]_D^{20}$ +9.48 (*c* 0.5, $CHCl_3$); IR (neat): 2927, 2855, 1741, 1641, 1150, 1104, 1038, 916, 557 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): 5.80 (m, 1H), 4.99 (dd, *J* = 1.5, 17.1 Hz, 1H), 4.92 (dd, *J* = 1.2, 10.2 Hz, 1H), 4.64 (ABq, *J* = 6.9, 66.2 Hz, 2H), 3.39 (m, 1H), 3.36 (s, 3H), 2.89 (m, 1H), 2.77 (dd, *J* = 4.0, 5.2 Hz, 1H), 2.71 (dd, *J* = 2.6, 5.2 Hz, 1H), 2.07-2.00 (m, 2H), 1.69-1.56 (m, 2H), 1.50 (m, 1H), 1.44-1.28 (m, 7H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 139.1, 114.2, 96.0, 76.3, 55.4, 53.3, 45.6, 33.7, 32.9, 29.5, 29.0, 28.8, 25.1 ppm; ESI-HRMS Calcd for $C_{13}H_{24}O_3Na$ $[M + Na]^+$ 251.1618; found: 251.1627.

(2*S*,3*R*)-3-(Methoxymethoxy)undec-10-en-2-ol (6): To a stirring suspension of $LiAlH_4$ (0.38 g, 10.83 mmol) in dry THF (10 mL) was dropwise added a solution of epoxide **16** (1.9 g, 8.33 mmol) in dry THF (30 mL) at 0 ºC. The reaction mixture was allowed to warm to room temperature, and stirred for 3 h. The reaction was quenched by the addition of water (20 mL). The mixture was filtered with a pad of Celite and washed with ethyl acetate (3 × 40 mL), washed with brine (15 mL), and dried over

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Na_2SO_4. The combined organic layers were concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (EtOAc/hexane = 3:7) to afford **6** (1.71 g, 89%) as a colorless liquid. $[\alpha]_D^{20}$ −10.29 (*c* 0.6, $CHCl_3$); IR (neat): 3430, 2926, 2854, 1640, 1460, 1147, 1100, 1034, 910 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): 5.81 (m, 1H), 5.03-4.92 (m, 2H), 4.70 (ABq, *J* = 6.9, 47.3 Hz, 2H), 3.75 (m, 1H), 3.50 (m, 1H), 3.44 (s, 3H), 3.13 (bs, 1H), 2.04 (q, *J* = 6.7 Hz, 2H), 1.55-1.43 (m, 2H), 1.42-1.35 (m, 3H), 1.34-1.26 (m, 5H), 1.14 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 139.0, 114.1, 97.5, 85.1, 68.9, 55.7, 33.7, 30.9, 29.4, 28.9, 28.7, 25.9, 17.0; HRMS (ESI) calcd for $C_{13}H_{30}O_3N$ $[M + NH_4]^+$ 248.2220; Found: 248.2233.

(3a*S*,6a*S*)-2,2-Dimethyltetrahydrofuro[3,4-d][1,3]dioxol-4-ol (9): To a stirred solution of D-ribose monoacetonide (3.5 g, 18.42 mmol) in dry methanol (30 mL), $NaBH_4$ (1.05 g, 27.63 mmol) was added in small portions at 0 ºC, then the resulting reaction mixture was stirred at room temperature for 1 h. After complete consumption of the starting material (monitored by TLC), the solvent was evaporated under reduced pressure. The crude residue was dissolved in *t*-BuOH:H_2O (30:20 mL), $NaIO_4$ (15.76 g, 73.68 mmol) was added in small portions at 0 ºC. Then the resulting reaction mixture was stirred at room temperature for 10 h until complete consumption of stirring material (monitored by TLC). The reaction mixture was filtered to remove solid residue, washed with ethyl acetate (2 × 30 mL) and quenched by the addition of saturated $NaHCO_3$ solution (30 mL). The filtrate was extracted with ethyl acetate (2 × 40 mL), dried over Na_2SO_4, and concentrated under reduced pressure. Purification of the crude product by silica gel column chromatography (EtOAc/hexane = 1:3) afforded **9** (2.27 g, 77%) as a colorless liquid. $[\alpha]_D^{20}$ −73.8 (*c* 1.9, $CHCl_3$); IR (neat): 3448, 2923, 2854, 1631, 1465, 1219, 770 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 5.43 (s, 1H), 4.84 (m, 1H), 4.58 (d, *J* = 6.0 Hz, 1H), 4.08-3.99 (m, 2H), 1.48 (s, 3H), 1.33 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 112.2, 101.5, 85.0, 79.8, 71.6, 26.0, 24.6 ppm; ESI-HRMS Calcd for $C_7H_{12}O_4Na$ $[M + Na]^+$ 183.0628; found: 183.0649.

((4*S*,5*R*)-2,2-Dimethyl-5-vinyl-1,3-dioxolan-4-yl)methanol (10): Methyltriphenylphosphonium bromide (13.40 g, 37.5 mmol) was dissolved in THF (30 mL) and cooled to −78 ºC. *n*-Butyllithium (12.5 mL, 2.5 M in hexane, 31.25 mmol) was added drop wise to the above stirred solution which turned into light orange solution. It was then warmed to 0 ºC for 45 min and again cooled to −78 ºC. The crude aldehyde **9** (2.0 g, 12.5 mmol) in THF (15 mL) was added to the reaction mixture drop wise. The reaction mixture was stirred at 0 ºC for 1 h and then warmed to 50 °C. After complete consumption of the starting material (monitored by TLC), the reaction was quenched with saturated NH_4Cl solution (20 mL) and warmed to room temperature. The organic phase was separated and the aqueous phase extracted with ethyl acetate (2 × 50 mL). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4 and concentrated under reduced pressure. Purification by silica gel column chromatography (EtOAc/hexane = 1:6) afforded the desired compound **10** (1.6 g, 81%) as a colorless liquid. $[\alpha]_D^{20}$ −26.09 (*c* 0.5, $CHCl_3$); IR (neat): 3384, 2924, 2854, 1717, 1461, 1376, 1215, 1075, 1045, 930 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): 5.87 (m, 1H), 5.40 (dt, *J* = 1.4, 17.2 Hz, 1H), 5.28 (dt, *J* = 1.4, 10.4 Hz, 1H), 4.65 (m, 1H), 4.27 (m, 1H), 3.60-3.57 (m, 2H), 1.51 (s, 3H), 1.40 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 132.9, 119.0, 108.9, 78.3, 78.2, 62.0, 27.8, 25.2; HRMS (ESI) calcd for $C_8H_{14}O_3Na$ $[M + Na]^+$ 181.0835; Found: 181.0841.

(4*R*,5*R*)-2,2-Dimethyl-5-vinyl-1,3-dioxolane-4-carboxylic acid (5): To a stirred solution of **10** (1.7 g, 10.76 mmol) in MeCN:H_2O (2:1, 24 mL) were added $PhI(OAc)_2$ (8.66 g, 26.90 mmol) and TEMPO (0.336 g, 2.15 mmol). The reaction mixture was stirred at room temperature for 3 h. After completion of the reaction (monitored by TLC), it was extracted with ethyl acetate (3 × 20 mL). The combined organic layers were washed with brine (40 mL), dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The crude product was purified by silica gel column chromatography (EtOAc/hexane = 1:1) to afford desired acid **5** (1.52 g, 82%) as a colorless liquid. $[\alpha]_D^{20}$ −2.78 (*c* 2.8, $CHCl_3$); IR (neat): 2927, 2855, 1733, 1420, 1377, 1215, 1165, 1091, 875 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): 5.79 (ddd, *J* = 7.0, 10.4, 17.2 Hz, 1H), 5.46 (d, *J* = 17.1 Hz, 1H), 5.31 (d, *J* = 10.4 Hz, 1H), 4.85 (t, *J* = 7.2 Hz, 1H), 4.69 (d, *J* = 7.5 Hz, 1H), 1.62 (s, 3H), 1.41 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 174.0, 131.6, 119.8, 111.3, 78.5, 77.2, 26.8, 25.3; HRMS (ESI) calcd for $C_8H_{12}O_4Na$ $[M + Na]^+$ 195.0628; Found: 195.0621.

(4*R*,5*R*)-(2*S*,3*R*)-3-(Methoxymethoxy)undec-10-en-2-yl-2,2-dimethyl-5-vinyl-1,3-dioxolane-4-carbo xylate (4): To a stirred solution of the acid **5** (1.15 g, 6.70 mmol) in dry toluene (15 mL), Et_3N (1.0 mL, 7.17 mmol) followed by 2,4,6-trichlorobenzoyl

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chloride (1.12 mL, 7.17 mmol) was added at 0 °C under N_2 atmosphere and continued to stir for 45 min at room temperature. DMAP (0.58 g, 4.78 mmol) and alcohol **6** (1.1 g, 4.78 mmol) dissolved in dry toluene (20 mL) was added to reaction mixture dropwise at 0 °C and allowed to stir for 7 h at room temperature. After completion of the reaction (monitored by TLC), it was quenched with water (20 mL). The reaction mixture was extracted with ethyl acetate (3 × 40 mL). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na_2SO_4 and solvent evaporated under reduced pressure. The crude mass was purified by silica gel column chromatography (EtOAc/hexane = 1:9) to furnish **4** (1.19 g, 65%, based on the starting alcohol) as a colorless liquid. $[\alpha]_D^{20}$ +2.34 (*c* 0.45, $CHCl_3$); IR (neat): 2925, 2853, 2311, 1756, 1377, 1194, 1096, 1038, 918 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 5.77 (m, 2H), 5.41 (d, *J* = 17.0 Hz, 1H), 5.25 (d, *J* = 10.3 Hz, 1H), 5.07-4.89 (m, 3H), 4.78 (t, *J* = 7.2 Hz, 1H), 4.70 (d, *J* = 6.7 Hz, 1H), 4.65 (d, *J* = 7.2 Hz, 1H), 4.60 (d, *J* = 6.7 Hz, 1H), 3.60 (m, 1H), 3.36 (s, 3H), 2.07-1.99 (m, 2H), 1.62 (s, 3H), 1.53-1.25 (m, 13H), 1.17 (d, *J* = 6.5 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 168.8, 139.0, 132.4, 119.4, 114.2, 111.0, 96.1, 78.9, 78.5, 77.3, 73.0, 55.7, 33.7, 30.8, 29.4, 28.9, 28.8, 27.0, 25.6, 25.5, 14.5 ppm; ESI-HRMS Calcd for $C_{21}H_{40}O_6N$ $[M + NH_4]^+$ 402.2850; found: 402.2871.

(3a*R*,6*S*,7*R*,15a*R*,*E*)-7-(Methoxymethoxy)-2,2,6-trimethyl-6,7,8,9,10,11,12,13-octahydro-3a*H*-[1,3]dioxolo[4,5-c][1]oxa cyclotetradecin-4(15a*H*)-one (17): A flame-dried round-bottomed flask was charged with a solution of ester **4** (0.6 g, 1.6 mmol) in CH_2Cl_2 (500 mL). The solution was degassed for 20 min under argon atmosphere. Grubbs' 2nd generation catalyst (132 mg, 0.16 mmol) was subsequently added to the solution, which was again degassed for 15 min. The reaction mixture was stirred for 12 h under refluxing conditions. After completion of the reaction (monitored by TLC), solvent was evaporated under reduced pressure. Purification of the crude residue by silica gel column chromatography (EtOAc/hexane = 1:9) afforded **17** (404 mg, 73%) as a colorless liquid. $[\alpha]_D^{20}$ +29.53 (*c* 0.35, $CHCl_3$); IR (neat): 2926, 2856, 1728, 1457, 1246, 1193, 1091, 1035, 976, 722 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ = 5.86 (m, 1H), 5.48 (dd, *J* = 6.9, 15.5 Hz, 1H), 5.10 (m, 1H), 4.82 (t, *J* = 7.0 Hz, 1H), 4.77 (d, *J* = 6.7 Hz, 1H), 4.72-4.68 (m, 2H), 3.72 (q, *J* = 5.3 Hz, 1H), 3.41 (s, 3H), 2.17-2.04 (m, 2H), 1.65-1.55 (m, 5H), 1.49-1.22 (m, 14H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 169.3, 136.0, 124.2, 110.7, 95.6, 78.6, 78.3, 77.5, 72.5, 55.7, 30.3, 29.2, 27.1, 26.4, 26.2, 25.6, 25.3, 20.9, 15.7 ppm; ESI-HRMS Calcd for $C_{19}H_{36}O_6N$ $[M + NH_4]^+$ 374.2537; found: 374.2564.

(3a*R*,6*S*,7*R*,15a*R*)-7-(Methoxymethoxy)-2,2,6-trimethyldeca-hydro-3a*H*-[1,3]dioxolo[4,5-c][1]oxa-cyclotetradecin-4(6*H*)-one (18): A catalytic amount of PtO_2 was added in one portion to a solution of **17** (270 mg, 0.76 mmol) in ethyl acetate (5 mL). The reaction vessel was evacuated under vacuum and placed under H_2 balloon pressure. The reaction mixture was allowed to stir at room temperature for 3 h until complete consumption of the starting material (monitored by TLC). The reaction was filtered through a small pad of Celite and washed with ethyl acetate (2 × 15 mL). The combined organic layer was concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (EtOAc/hexane = 1:9) to provide the desired product **18** (255 mg, 95%) as a colorless oil. $[\alpha]_D^{20}$ −6.12 (*c* 0.65, $CHCl_3$); IR (neat): 2927, 2853, 2310, 1732, 1457, 1375, 1219, 1044, 772 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ = 4.90 (m, 1H), 4.72 (d, *J* = 6.9, Hz, 1H), 4.65 (d, *J* = 6.9, Hz, 1H), 4.51 (d, *J* = 6.6 Hz, 1H), 4.27 (m, 1H), 3.67 (m, 1H), 3.37 (s, 3H), 1.53 (s, 3H), 1.49-1.37 (m, 7H), 1.36-1.20 (m, 15H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 170.4, 110.6, 95.3, 79.0, 77.9, 77.4, 70.8, 55.8, 27.72, 27.67, 27.1, 26.6, 25.7, 25.5, 23.5, 22.4, 21.9, 18.0, 17.6 ppm; HRMS (ESI) calcd for $C_{19}H_{34}O_6Na$ $[M + Na]^+$ 381.2248; Found: 381.2259.

(*E*)-Ethyl-3-((4*S*,5*R*)-5-((9*R*,10*S*)-10-hydroxy-9-(methoxymeth oxy)undecyl)-2,2-dimethyl-1,3-diox- olan-4-yl)acrylate (3): To a stirred solution of lactone **18** (140 mg, 0.39 mmol) in CH_2Cl_2 (15 mL), DIBAL-*H* (0.36 mL, 1.4 M solution in toluene, 0.51 mmol) was added slowly at −78 °C under nitrogen atmosphere. The solution was stirred for 20 min at same temperature and allowed to warm to 0 °C slowly. After completion of the reaction (monitored by TLC), MeOH (0.2 mL) was added slowly followed by the addition of cold aqueous saturated sodium potassium tartrate (15 mL). The biphasic mixture was stirred for further 2 h and separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic phase was dried over Na_2SO_4 and concentrated under reduced pressure. The crude residue (111 mg, 79%) was used for the next step without further purification.

The lactol compound (111 mg, 0.31 mmol) in benzene (10 mL), was added $Ph_3P{=}CHCO_2Et$ (0.161 mg, 0.46 mmol) at room temperature. The reaction mixture was heated to 90 °C for 4 h.

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After completion of the reaction (monitored by TLC), the reaction mixture was concentrated under reduced pressure. Purification by silica gel column chromatography (EtOAc/hexane = 3:7) afforded α,β-unsaturated ester **3** (102 mg, 77%; 61% over two steps) as a colorless liquid. $[\alpha]_D^{20}$ +7.18 (*c* 0.3, $CHCl_3$); IR (neat): 2925, 2854, 1731, 1608, 1459, 1382, 1272, 1038, 721 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 6.82 (dd, *J* = 6.2, 15.7 Hz, 1H), 6.04 (dd, *J* = 1.5, 15.7 Hz, 1H), 4.73 (d, *J* = 7.0 Hz, 1H), 4.65-4.60 (m, 2H), 4.24-4.16 (m, 3H), 3.74 (m, 1H), 3.48 (m, 1H), 3.42 (s, 3H), 1.74 (br s, 1H), 1.52-1.40 (m, 7H), 1.39-1.33 (m, 5H), 1.32-1.20 (m, 13H), 1.12 (d, *J* = 6.6 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 166.0, 143.8, 122.9, 108.7, 97.6, 85.1, 78.3, 77.3, 69.0, 60.5, 55.8, 31.0, 30.4, 29.6, 29.41, 29.39, 28.0, 26.3, 26.0, 25.5, 17.1, 14.2 ppm; ESI-HRMS Calcd for $C_{23}H_{42}O_7Na$ $[M + Na]^+$ 453.2823; found: 453.2824.

(3a*S*,8*S*,9*R*,17a*R*,*E*)-9-(Methoxymethoxy)-2,2,8-trimethyl-9,10,11,12,13,14,15,16,17,17a-decahydro-3a*H*-[1,3]dioxolo-[4,5-e][1]oxacyclohexadecin-6(8*H*)-one (2): To a stirred solution of the ester **3** (64 mg, 0.15 mmol) in THF (8 mL), was added aqueous solution of LiOH (37 mg, 0.9 mL, 0.89 mmol) at room temperature. The reaction mixture was allowed to stir at 70 °C for 12 h. After completion of the reaction (monitored by TLC), it was cooled to 0 °C. The reaction mixture was acidified with 1 M HCl until pH = 5.0 and diluted with ethyl acetate (15 mL). The aqueous layer extracted with ethyl acetate (3 × 15 mL). The combined organic layer were washed with brine (30 mL), dried over anhydrous Na_2SO_4 and evaporated to dryness under reduced pressure. The crude mass was dried through azeotropic mixture with dry benzene to afford **19** (46 mg, 77%) as a colorless liquid.

4 Å molecular sieves (114 mg) and toluene (50 mL) were placed in a two-necked 250 mL round bottomed flask, followed by the addition of DMAP (70 mg, 0.57 mmol) and MNBA (59 mg, 0.17 mmol) at 0 °C under nitrogen atmosphere. The crude seco-acid **19** (azeotroped with benzene two times) (46 mg, 0.114 mmol) was dissolved in toluene (20 mL) and added to the above mixture for 10 h with the help of syringe pump at room temperature. After completion of the reaction (monitored by TLC), MS 4 Å was removed by filtration and the filtrate was evaporated under reduced pressure. The resulting residue was purified by flash chromatography (EtOAc/hexane = 1:9) to provide macrolactone **2** (29 mg, 66%) as a colorless liquid. $[\alpha]_D^{20}$ −3.28 (*c* 0.5, $CHCl_3$); IR (neat): 2917, 1636, 1430, 1373, 1337, 1163, 1115, 1061, 898 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): 6.82 (dd, *J* = 7.2, 15.7 Hz, 1H), 6.03 (dd, *J* = 1.1, 15.7 Hz, 1H), 5.02 (m, 1H), 4.66 (dd, *J* = 6.9, 11.1 Hz, 2H), 4.61 (m, 1H), 4.21 (dd, *J* = 6.3, 13.6 Hz, 1H), 3.56 (m, 1H), 3.38 (s, 3H), 1.63-1.48 (m, 7H), 1.47-1.35 (m, 7H), 1.33-1.14 (m, 11H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 164.7, 142.7, 124.1, 108.6, 95.9, 79.1, 78.4, 77.3, 71.0, 55.8, 29.7, 29.6, 29.5, 28.0, 27.8, 26.9, 26.6, 25.4, 23.2, 22.5, 17.7 ppm; HRMS (ESI) calcd for $C_{21}H_{36}O_6Na$ $[M + Na]^+$ 407.2404; Found: 407.2410.

(5*S*,6*R*,15*R*,16*S*,*E*)-5,6-Dihydroxy-15-(methoxymethoxy)-16-methyloxacyclohexadec-3-en-2-one (20): To a stirred solution of **2** (13 mg, 0.034 mmol) in CH_3CN (8 mL), was added $CuCl_2 \cdot 2H_2O$ (9 mg, 0.050 mmol) at 0 °C. The reaction mixture was allowed to stir for 2 h at the same temperature. After complete conversion (monitored by TLC), the reaction was quenched by a saturated $NaHCO_3$ solution (5 mL). The aqueous layer extracted with ethyl acetate (3 × 10 mL), the combined organic layer were washed with brine (10 mL) and dried over anhydrous Na_2SO_4. The combined organic solvent was removed under reduced pressure. The residue was purified by column chromatography with silica gel (EtOAc/hexane = 2:3) to give **20** (10 mg, 90%) as a clear liquid. $[\alpha]_D^{20}$ −4.08 (*c* 0.3, $CHCl_3$); IR (neat): 3414, 2923, 2855, 1716, 1628, 1457, 1393, 1096, 1028, 767 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): 6.93 (dd, *J* = 4.8, 15.8 Hz, 1H), 6.11 (dd, *J* = 1.7, 15.8 Hz, 1H), 5.00 (m, 1H), 4.66 (d, *J* = 2.5 Hz, 2H), 4.50 (m, 1H), 3.77 (m, 1H), 3.55 (m, 1H), 3.38 (s, 3H), 2.56 (br s, 1H), 2.13 (br s, 1H), 1.68-1.52 (m, 3H), 1.50-1.16 (m, 16H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.3, 145.6, 122.3, 95.9, 79.4, 73.8, 73.5, 71.3, 55.8, 29.9, 29.6, 28.3, 27.3, 26.5, 26.1, 23.1, 22.6, 17.7 ppm; HRMS (ESI) calcd for $C_{18}H_{32}O_6Na$ $[M + Na]^+$ 367.2091; Found: 367.2097.

(5*S*,6*R*,15*R*,16*S*,*E*)-5,6,15-Trihydroxy-16-methyloxacyclohexadec-3-en-2-one (1): Compound **20** (6.5 mg, 0.019 mmol) was dissolved in THF (2 mL) and aqueous 4 N HCl (9 µL, 0.038 mmol) was added at 0 °C. The reaction mixture was stirred at room temperature for 6 h and then quenched with saturated aqueous $NaHCO_3$ solution. The aqueous layer was extracted with ethyl acetate (3 × 5 mL) and the combined organic layer was washed with brine (10 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Purification of the crude residue by silica gel column chromatography (EtOAc/hexane =

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1:1) afforded **1** (4.1 mg, 72%) as a amorphous solid. $[\alpha]_D^{20}$ −9.42 (*c* 0.1, $CHCl_3$); IR (neat): 3447, 2923, 2853, 1716, 1461, 1376, 1251, 1170, 1099, 771 cm^{-1}; ^1H NMR (at 40 ^oC as the compound was not completely soluble in $CDCl_3$) (500 MHz, $CDCl_3$): 6.92 (dd, *J* = 5.2, 15.7 Hz, 1H), 6.11 (dd, *J* = 1.7, 15.9 Hz, 1H), 4.87 (m, 1H), 4.50 (m, 1H), 3.74 (m, 1H), 3.54 (m, 1H), 2.38 (br s, 1H), 2.00 (br s, 1H), 1.66-1.52 (m, 2H), 1.48 (m, 1H), 1.40 (m, 1H), 1.36 (d, *J* = 6.3 Hz, 3H), 1.38-1.14 (m, 12H) ppm; ^{13}C NMR (at 40 ^oC as the compound was not completely soluble in $CDCl_3$) (125 MHz, $CDCl_3$): δ 165.6, 145.8, 122.5, 74.5, 74.02, 73.97, 73.7, 32.1, 30.0, 27.9, 27.6, 26.3, 23.4, 23.0, 17.6 ppm; HRMS (ESI) calcd for $C_{16}H_{28}O_5Na$ $[M + Na]^+$ 323.1829; Found: 323.1847.

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References

1 J. Bao, X. Y. Xu, X. Y. Zhang and S. H. Qi, *Nat. Prod. Commun.* 2013, **8**, 1127-1128.

2 a) H. Yada, H. Sato, H. Toshima, M. Deura and A.Ichihara, *Biosci. Biotechnol. Biochem.* 2001, **65**, 484-486; b) J. J. Fang, G. Ye, W. L. Chen and W. M. Zhao, *Phytochemistry* 2003, **69**, 1279-1286; c) G. N. Belofsky, P. R. Jensen, M. K. Renner and W. Fenical, *Tetrahedron* 1998, **54**, 1715-1724; d) Q. X. Wu, M. S. Crews, M. Draskovic, J. Sohn, T. A. Johnson, K. Tenny, F. A. Valeriote, X. J. Yao, L. F. Bjeldanes and P. Crews, *Org. Lett.* 2010, **12**, 4458-4461.

3 a) S. W. Yang, T. M. Chan, J. Terracciano, D. Loebenberg, M. Patel and M. Chu, *J. Antibiot.* 2005, **58**, 535-538; b) K. Kito, R. Ookura, S. Yoshida, M. Namikoshi, T. Ooi and T. Kusumi, *Org. Lett.* 2008, **10**, 225-228.

4 a) C. M. M. Franco, J. N. Gandhi, S. Chatterjee and B. N. Ganguli, *J. Antibiot.* 1987, **40**, 1361-1367; b) J. S. Park, H. O. Yang and H. C. Kwon, *J. Antibiot.* 2009, **62**, 171-175; c) K. Ditrich, T. Bube, R. Sturmer and R. W. Hoffmann, *Angew. Chem. Int. Ed*. 1986, **25**, 1028-1030; d) R. N. Asolkar, R. P. Maskey, E. Helmke and H. Laatsch, *J. Antibiot.* 2002, **55**, 893-898.

5 M. Ueda, M. Yamaura, Y. Ikeda, Y. Suzuki, K. Yoshizato, I. Hayakawa and H. Kigoshi, *J. Org. Chem.* 2009, **74**, 3370–3377.

6 X. M. Yu, H. Han and B. S. J. Blagg, *J. Org. Chem*. 2005, **70**, 5599-5605.

7 a) I. Shiina, M. Kubota and R. Ibuka, *Tetrahedron Lett.* 2002, ***43***, 7535-7539; b) I. Shiina, M. Kubota, H. Oshiumi and M. Hashizume, *J. Org. Chem*. 2004, **69**, 1822−1830; c) A. Parenty, X. Moreau and J. M. Champagne, *Chem. Rev*. 2006, **106**, 911–939.

8 L. Nagarapu, S. Karnakanti and R. Bannu, *Tetrahedron* 2012, **68**, 5829-5832.

9 J. B. Epp and T. S. Widlanski, *J. Org. Chem*. 1999, **64**, 293-295.

10 S. P. Chavan and K. R. Harele, *Tetrahedron Lett*., 2012, **53**, 4683.

11 A. J. Mancuso, S.-L. Huang and D. Swern, *J. Org. Chem.* 1978, **43**, 2480.

12 V. S. Martin, S. S. Woodward, T. Katsuki, Y. Yamada, M. Ikeda and K. B. Sharpless, *J. Am. Chem. Soc.* 1981, **103**, 6237.

13 K. Horita, T. Yoshioka, T. Tanaka, Y. Oikawa and O. Yonemitsu, *Tetrahedron* 1986, **42**, 3021.

14 a) D. B. Dess and J. C. Martin, *J. Org. Chem*. 1983, **48**, 4155; b) D. B. Dess and J. C. Martin, *J. Am. Chem. Soc*. 1991, **113**, 7277.

15 a) A. Williams and I. T. Ibrahim, *Chem. Rev.* 1981, **81**, 589–636; b) M. Mikolajczyk and P. Kielbasin´ ski, *Tetrahedron* 1981, **37**, 233–284; c) B. Neises and W. Steglich, *Angew. Chem. Int. Ed. Engl.* 1978, **17**, 522–524.

16 a) S. Nozaki and I. Muramatsu, *Bull. Chem. Soc. Jpn.* 1982, **55**, 2165-2168; b) J. C.Sheehan, J. Preston and P. A. Cruickshank, *J. Am. Chem. Soc.* 1965, **87**, 2492-2493.

17 J. Inanaga, K. Hirata, H. Saeki, T. Katsuki and M. Yamaguchi, *Bull. Chem. Soc. Jpn.* 1979, **52**, 1989.

18 a) T. E. Wilhelm, T. R. Belderrain, S. N. Brown, R. H. Grubbs, *Organometallics* 1997, **16**, 386; b) A. K. Chatterjee, T.-L. Choi, D. P. Sanders and R. H. Grubbs, *J. Am. Chem. Soc*. 2003, **125**, 11360.

19 a) B. K. Jena and D. K. Mohapatra, *Tetrahedron Lett*. 2013**, 54**, 3415-3418; b) B. K. Jena and D. K. Mohapatra, *Tetrahedron* 2015**, 71**, 5678-5692.

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DOI: 10.1039/C6OB02435A

20 P. Saravanan, M. Chandrashekar, R. Vijaya and V. K. Singh, *Tetrahedron Lett*. 1998, **39**, 3091.