Tetrahedron: *Asymmetry* 25 (2014) 203–211

Contents lists available at ScienceDirect

Tetrahedron: *Asymmetry*

journal homepage: www.elsevier.com/locate/tetasy

A facile chiral pool synthesis of 9-*epi*-decarestrictine-D, decarestrictine-D and O

Kuchena Vamshikrishna, Garlapati Srinu, Pabbaraja Srihari *

Division of Natural Products Chemistry, GCL 1st Floor, CSIR-Indian Institute of Chemical Technology, Hyderabad 500007, India

ARTICLE INFO

Article history:
Received 9 October 2013
Accepted 12 December 2013

ABSTRACT

A facile chiral pool total synthesis of 9-*epi*-decarestrictine-D, decarestrictine-D and O has been achieved from L-(+)-diethyl tartrate. The strategy utilized is conventional and flexible. Wittig homologation and Grubbs ring closing metathesis are the key reactions employed for the synthesis of the title molecules.

1. Introduction

Natural products obtained from fungi have gained significant interest in the synthetic community and the pharmaceutical industry due to their structural diversity and intriguing biological activities.[1] Decarestrictines, the 10-membered lactone secondary metabolites[2] isolated from various *Penicillium* strains, do not display antibacterial or antifungal activities, although a few of them have been found to display significant inhibitory effects on cholesterol biosynthesis and have thus attracted attention toward developing them as a new class of cholesterol-lowering drugs.[3] These metabolite decarestrictines A–O **1**–**9** exhibit similar structural elements that is (i) a 10-membered lactone ring; (ii) an exocyclic methyl group; and (iii) compounds **1**, **2** and **4**–**9** display *E*-configured double bonds (Fig. 1). In addition, variations in the oxygenation pattern ranging from C-3 to C-7 are observed. Decarestrictine D **6** was isolated from the Canadian tuckahoe fungi *Polyporous tuberaster*[4] and named as tuckolide. The structures of these lactones were established by spectroscopic techniques and by X-ray diffraction analysis of **6** and a derivative of **3**. The structural diversity and potent activity as cholesterol lowering drugs is of significant synthetic importance and has resulted in seminal publications in the literature.[5] In a continuation of our research on developing concise approaches for asymmetric total synthesis of biologically active natural products,[6] we became interested in this class of molecules. Herein we report the total synthesis of decarestrictine-D and O, from commercially available L-(+)-diethyl tartrate.

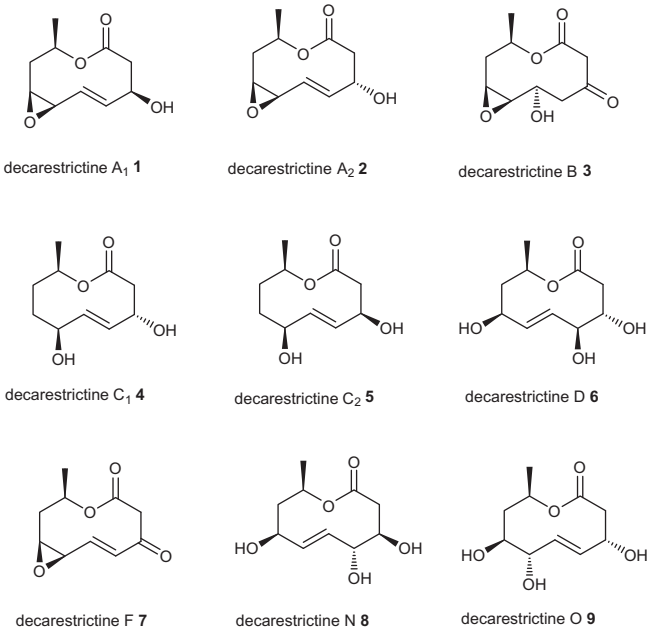

Figure 1. Structures of decarestrictines.

2. Results and discussion

A retrosynthetic analysis of decarestrictine-D and O is depicted in Scheme 1. The target molecule **6** (decarestrictine-D) could be obtained by the coupling of acid **10** with alcohol **11** followed by cyclization through Grubbs' RCM protocol and deprotection of the protecting groups. Acid **10** could be synthesized from **12** in four steps through oxidation, Wittig homologation, deprotection of the silylether, and oxidation of the resulting alcohol to give an acid functionality. The secondary alcohol **11** can be obtained from **12** in five steps involving iodination, reductive elimination, deprotection of the silylether, oxidation, and finally a Grignard reaction. Simultaneously, decarestrictine-O **9** can be synthesized by

* Corresponding author. Tel.: +91 4027191815; fax: +91 4027160512.
E-mail address: srihari@iict.res.in (P. Srihari).

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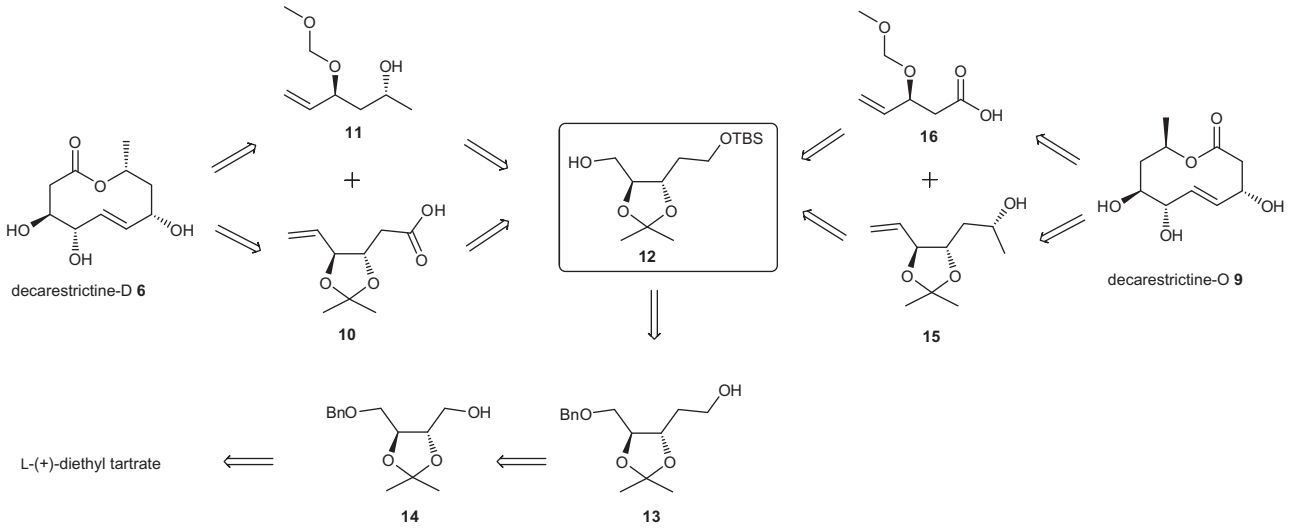
http://dx.doi.org/10.1016/j.tetasy.2013.12.008

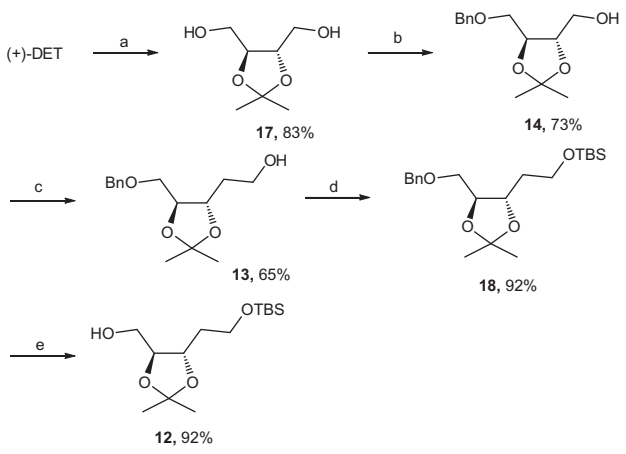


Scheme 1. Retrosynthesis for decarestrictine-D and O.

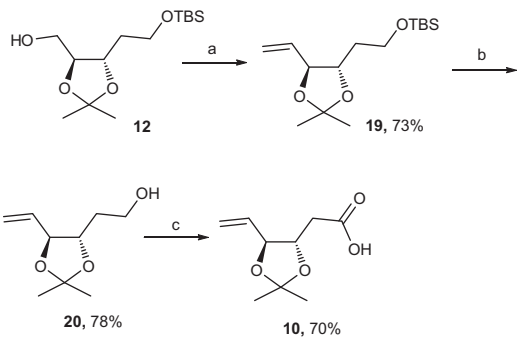
coupling of acid **16** with alcohol **15** followed by ring closing metathesis and global deprotection of the protecting groups. Compound **15** can be synthesized from **12** in five steps (oxidation, 1C-Wittig olefination, silyl deprotection, oxidation, and methyl Grignard reaction), while compound **16** can be obtained from **12** in six steps (vide infra). Intermediate **12** can in turn be synthesized from **13** in two steps that is protection of alcohol **13** as the corresponding silyl ether and deprotection of the benzyl ether. Alcohol **13** can be accessed from compound **14** via a Wittig homologation reaction and reductive opening of the resulting enol ether. Compound **14** in turn can be easily synthesized from commercially available L-(+)-DET in three steps.

The synthesis of decarestrictine-D **6** started from commercially available (+)-diethyl L-tartrate. L-(+)-DET upon reaction with 2,2-dimethoxy propane in dry benzene in the presence of a catalytic amount of anhydrous *p*-toluenesulfonic acid under reflux conditions furnished the acetonide protected diester, which upon reduction with lithium aluminum hydride in dry THF furnished 1,4-diol **17** (Scheme 2).[7] Selective mono benzylation of diol **17** was achieved with BnBr in the presence of NaH to yield the corresponding benzyl ether **14** in 73% yield. Alcohol **14** was subjected to a Swern oxidation[8,6b] followed by Wittig homologation using methoxymethyl triphenylphosphonium chloride and lithium hexamethyldisilazide in dry THF to give the enol ether, which upon hydrolysis using $Hg(OAc)_2$ followed by an in situ reduction with $NaBH_4$ in THF/water (1:1.2) afforded homologated alcohol **13**.[9,6h] Protection of the resulting primary alcohol **13** as the corresponding *tert*-butyldimethylsilyl ether **18** was achieved with *tert*-butyldimethylsilyl chloride (TBDMSCl) and imidazole in 92% yield. Debenzylation of **18** with Pd/C in dry THF gave the key intermediate **12** in 92% yield.

Compound **12** was used to access other fragments **10**, **11**, **15,** and **16** (vide infra). While compounds **10** and **11** can be utilized for the construction of decarestrictine-D, compounds **15** and **16** were utilized for the preparation of decarestrictine-O. The synthesis of fragment **10** began with the oxidation reaction of **12** under Swern[8] conditions to provide the aldehyde, which was subjected to a one carbon Wittig homologation reaction with methyltriphenylphosphonium iodide and potassium *tert*-butoxide to provide olefin **19** (Scheme 3). Compound **19** upon desilylation with TBAF afforded alcohol **20** which was oxidized to the aldehyde with IBX and further oxidized to acid **10** under Pinnick–Lindgren conditions[10] in 70% yield.

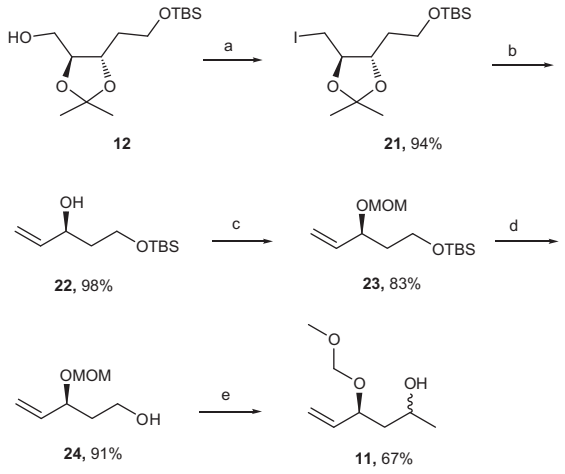


Scheme 2. Synthesis of fragment **12**. Reagents and conditions: (a) (i) 2,2-DMP, benzene, cat. *p*TSA, 80 °C, 12 h, 92%, (ii) $LiAlH_4$, THF, 45 °C, 5 h; (b) BnBr, NaH, THF, 0 °C to rt, 12 h; (c) (i) $(COCl)_2$, DMSO, CH_2Cl_2, Et_3N, −78 °C, 2.5 h, 85%, (ii) $PPh_3CH_2OCH_3Cl$, LiHMDS, THF, −10 °C to rt, 12 h, (iii) $Hg(OAc)_2$, THF, then H_2O (1.2 ratio w.r.t THF), $NaBH_4$, 0 °C to rt, 1 h; (d) imidazole, TBDMSCl, CH_2Cl_2, 0 °C to rt, 2 h; (e) H_2, Pd/C, THF, rt, 12 h.



Scheme 3. Synthesis of fragment **10**. Reagents and conditions: (a) (i) $(COCl)_2$, DMSO, CH_2Cl_2, Et_3N, −78 °C, 2.5 h, (ii) PPh_3CH_3I, ^tBuOK, THF, 0 °C to rt, 12 h; (b) 1.0 M TBAF, THF, 0 °C to rt, 2 h; (c) (i) IBX, CH_2Cl_2, DMSO, 0 °C to rt, 6 h, 87%; (ii) 2-methyl-2-butene, NaH_2PO_4, $NaClO_2$, ^tBuOH:H_2O (1:1), acetone, 0 °C to rt, 12 h.

Alcohol **12** was converted into the corresponding iodide **21**[11] upon treatment with I_2, TPP, and imidazole in dry THF at room temperature and subjected to a ring opening reaction with ^{n}BuLi to afford chiral allyl alcohol **22** in 98% yield (Scheme 4). Protection of the secondary alcohol **22** as the corresponding methoxymethyl ether was achieved with chloromethylmethyl ether and *N*,*N*-diisopropylethylamine in CH_2Cl_2 to afford **23**. Desilylation of **23** with 1 M *tetra*-*n*-butylammonium flouride (TBAF) afforded the primary alcohol **24**, which was oxidized to the aldehyde and then subjected to a Grignard reaction with methyl magnesium bromide to provide **11** as an inseparable mixture of diastereomers in a 6:4 ratio.[12]



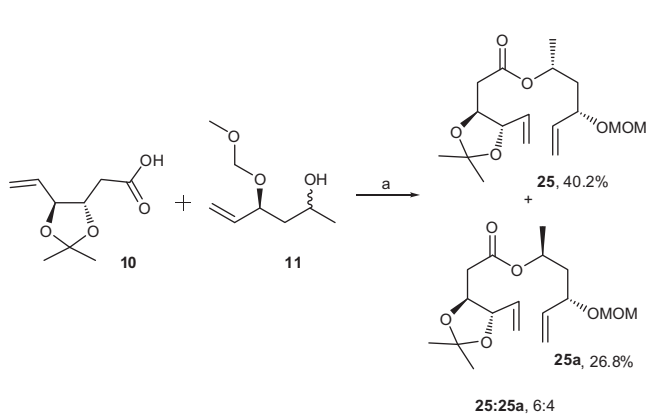
Scheme 4. Synthesis of fragment **11**. Reagents and conditions: (a) I_2, TPP, imidazole, THF, 0 °C to rt, 2 h; (b) ^{n}BuLi, THF, −78 °C, 2 h; (c) MOMCl, DIPEA, CH_2Cl_2, 0 °C to rt, 12 h; (d) 1.0 M TBAF, THF, 0 °C to rt, 2 h; (e) (i) IBX, CH_2Cl_2, DMSO, 0 °C to rt, 6 h, (ii) MeMgI, diethylether, −40 °C, 3 h, (diastereomers in a 6:4 ratio).

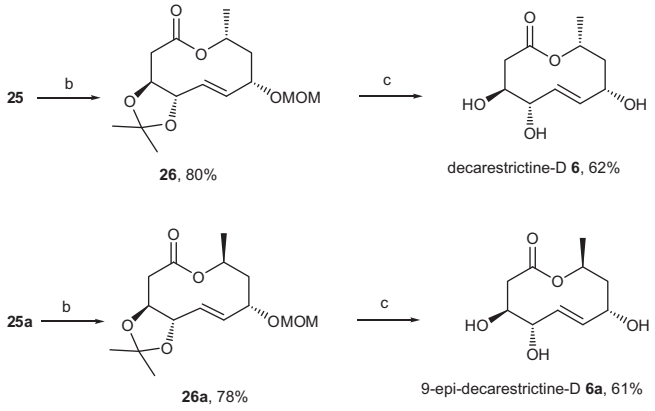
With the key intermediates **10** and **11** in hand, the stage was set for the construction of the target molecule **6** (Scheme 5). Coupling of acid **10** with alcohol **11** using DCC, DMAP in CH_2Cl_2 yielded esters **25** (40.2%) and **25a** (26.8%) respectively in 6:4 ratio which were easily separable through column chromatography at this stage. Independent ring closing metathesis reaction of **25** and **25a** with Grubbs' 2nd generation[13,14] catalyst in CH_2Cl_2 provided the corresponding lactones **26** and **26a** respectively. Finally global deprotection of compound **26** and also its C9-epimer **26a** was achieved using $BF_3{\cdot}OEt_2$, in DMS[15] to get the decarestrictine-D **6** and 9-*epi*-decarestrictine respectively.

2.1. Synthesis of decarestrictine-O

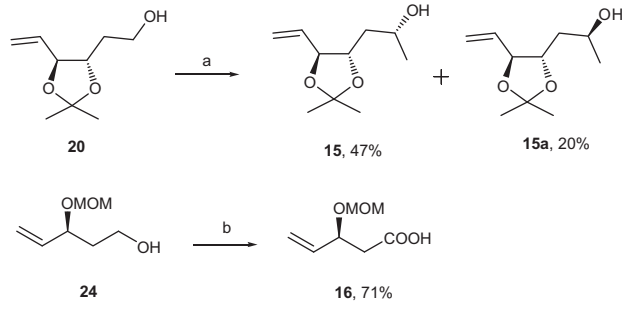
The synthesis of fragment **15** and **16** is shown in Scheme 6. Accordingly, alcohol **20** was oxidized to aldehyde using IBX and then subjected to a Grignard reaction with 3 M methylmagnesium iodide in diethyl ether to furnish the easily separable secondary alcohols **15**[5k,5l] (47% yield) and its diastereomer **15a** (20% yield) in 7:3 ratio respectively. The other fragment **16** was prepared from alcohol **24** in two steps that is IBX mediated oxidation followed by Pinnick oxidation[10] to provide the acid fragment **16**.

The coupling of key fragments **15** and **16** was achieved under standard conditions with DCC and DMAP in CH_2Cl_2 to provide ester

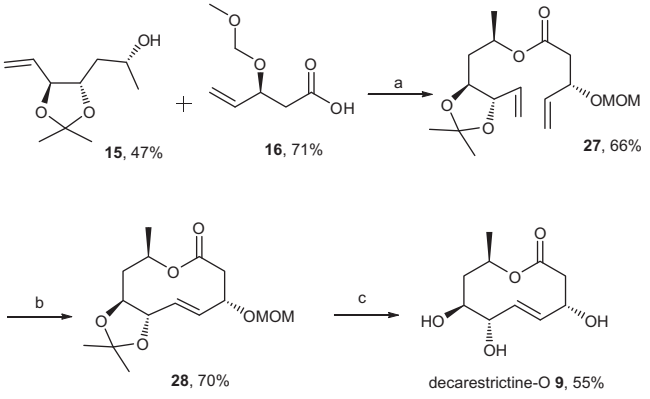




Scheme 5. Synthesis of decarestrictine-D, 9-*epi*-decarestrictine-D. Reagents and conditions: (a) DCC, DMAP, CH_2Cl_2, 0 °C to rt, 12 h, (**25**:**25a**, 6:4); (b) Grubb's 2nd generation catalyst, CH_2Cl_2, reflux, 24 h, for **26**, **26a**; (c) $BF_3{\cdot}OEt_2$, DMS, 0 °C, 20 min, **6**, and **6a**.



Scheme 6. Synthesis of fragments **15** and **16**. Reagents and conditions: (a) (i) IBX, CH_2Cl_2, DMSO, 0 °C to rt, 6 h, (ii) MeMgI, diethylether, −40 °C, 5 h, (**15**:**15a**, 7:3); (b) (i) IBX, CH_2Cl_2, DMSO, 0 °C to rt, 6 h, 81%, (ii) 2-methyl-2-butene, NaH_2PO_4, $NaClO_2$, ^{t}BuOH/H_2O (1:1), acetone, 0–5 °C, 12 h.



Scheme 7. Synthesis of decarestrictine-O. Reagents and conditions: (a) DCC, DMAP, CH_2Cl_2, 0 °C to rt, 12 h; (b) Grubb's 2nd generation catalyst, CH_2Cl_2, reflux, 12 h; (c) (i) $BF_3{\cdot}OEt_2$, DMS, 0 °C, 20 min, (ii) 1 M HCl, THF, 2 h.

27 (Scheme 7) in 65% yield. The di-olefin **27** was subjected to a ring closing metathesis reaction with Grubbs' 2nd generation catalyst to provide the precursor **28** exclusively in the *E*-form (the geometry was confirmed by the coupling constant value J = 15.8 Hz for one of the olefinic proton). Compound **28** upon exposure to 1 M HCl at room temperature underwent a one-pot isopropylidene and MOM deprotection to yield the target molecule decarestrictine-O in 55% yield.

3. Conclusion

In conclusion, we have accomplished the total synthesis of decarestrictine-D and O from a common intermediate involving conventional reactions. Both the coupling partners were prepared from a single raw material; the commercially available (+)-diethyl L-tartrate. The strategy utilized is flexible and can be further exploited toward the synthesis of other decanolide natural products and their analogues in order to screen their biological activities.

4. Experimental

4.1. General

^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ or acetone-d_6, CD_3OD as solvent on 300 MHz, 500 MHz, and 600 MHz spectrometer at ambient temperature. Coupling constants J are given in Hz. Chemical shifts are reported in ppm on a scale downfield from TMS as the internal standard and signal patterns are indicated as follows: s = singlet, d = doublet, t = triplet, q = quartet, sext = sextet, m = multiplet, br = broad. FTIR spectra were recorded on KBr pellets (Neat) or in $CHCl_3$ and reported in wave numbers (cm^{-1}). Optical rotations were measured on a digital polarimeter using a 1 mL cell with a 1 dm path length. For low (MS) and high (HRMS) resolution, m/z ratios are reported as values in atomic mass units. Mass analysis was carried out in the ESI mode. All reagents were of reagent grade and used without further purification unless specified otherwise. Solvents for reactions were distilled prior to use: THF, and diethyl ether were distilled from Na and benzophenone ketyl; MeOH from Mg and I_2; CH_2Cl_2 from CaH_2. All air or moisturesensitive reactions were conducted under a nitrogen or argon atmosphere in flame-dried or oven-dried glassware with magnetic stirring. Column chromatography was carried out using silica gel (100–200 mesh) packed in glass columns. Technical grade ethyl acetate and petroleum ether used for column chromatography were distilled prior to use.

4.1.1. 2-((4*S*,5*S*)-2,2-Dimethyl-5-vinyl-1,3-dioxolan-4-yl)acetic acid 10

To a clear solution of IBX (3.25 g, 11.6 mmol, 2.0 equiv), in a 1:1 ratio of dry DMSO and CH_2Cl_2 (20 mL), was added compound **20** (1.0 g, 5.8 mmol, 1.0 equiv) in dry CH_2Cl_2 (10 mL) at 0 °C over 5 min. The reaction mixture was allowed to warm to room temperature, and stirred at the same temperature for 6 h. After complete consumption of the starting material, the reaction mixture was quenched with the addition of water (15 mL), and the white solid formed was filtered over a small pad of Celite, and the filtrate then extracted with diethyl ether (2 × 10 mL). The combined organic layer was washed with brine (10 mL), and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure to give a crude product, which was purified by flash column chromatography to give the aldehyde (0.86 g, 87%) as a yellow liquid. R_f = 0.80 (hexane/EtOAc, 80:20). The aldehyde (0.86 g, 5.1 mmol, 1.0 equiv) obtained above was dissolved in ^{t}BuOH (22.5 mL), H_2O (22.5 mL) and acetone (12.6 mL) in a 100-mL round-bottom flask. Next, 2 M 2-methyl-2-butene (9.34 mL, 3.7 equiv) was added via syringe, followed by NaH_2PO_4 (3.54 g, 22.7 mmol, 4.5 equiv) and $NaClO_2$ (80% technical grade, 2.06 g, 22.7 mmol, 4.5 equiv) as solids. The biphasic reaction was stirred vigorously for 12 h, after which saturated aqueous NH_4Cl (10 mL) was added. The reaction mixture was extracted with CH_2Cl_2 (3 × 15 mL) and the combined organic layer was dried over Na_2SO_4, filtered, and concentrated in vacuo to give a crude liquid, which was purified by column chromatography to give acid **10** (0.66 g, 70%) as a light yellow liquid; R_f = 0.20 (hexane/EtOAc, 80:20); $[\alpha]_D^{25} = -29.2$ (c 1.8, $CHCl_3$); IR ν_{max} (Neat): 3424, 2989, 1767, 1164, 931 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.88–5.76 (m, 1H), 5.39 (d, J = 17.0 Hz, 1H), 5.29 (d, J = 10.4 Hz, 1H), 4.13–4.06 (m, 2H), 2.66–2.58 (m, 2H), 1.44 (s, 3H), 1.43 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$); δ 176.0, 134.3, 119.8, 109.5, 82.1, 76.4, 36.7, 27.0, 26.9; ESIMS: m/z 209 $[M+Na]^+$; HRESIMS for $C_9H_{14}O_4Na$ $[M+Na]^+$ found 209.07854 calcd 209.07843.

4.1.2. ((4*S*,5*S*)-5-(2-(*tert*-Butyldimethylsilyloxy)ethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)methanol 12

To a solution of compound **18** (8.0 g, 21.1 mmol, 1.0 equiv) in anhydrous THF (20 mL) was treated with 10% Pd/C (300 mg). The flask was filled with H_2 and stirred for 12 h after the reaction mixture was filtered on a pad of Celite using EtOAc (100 mL). The filtrate was concentrated under reduced pressure to give a crude material, which was purified by column chromatography R_f = 0.10 (hexane/EtOAc, 90:10) to give **12** (5.62 g, 92% yield) as a yellow oil; $[\alpha]_D^{25} = -19.5$ (c 2.3, $CHCl_3$); IR ν_{max} (Neat): 3458, 2931, 1375, 1253, 1094, 838 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.03–3.99 (m, 1H), 3.84–3.71 (m, 4H), 3.66–3.64 (m, 1H), 2.05 (br s, 1H), 1.87–1.76 (m, 2H), 1.41 (s, 3H), 1.39 (s, 3H), 0.89 (s, 9H), 0.06 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 108.5, 81.3, 74.5, 62.1, 59.9, 36.1, 27.3, 26.9, 25.8, 18.2, −5.4; ESIMS: m/z 291 $[M+H]^+$; HRESIMS for $C_{14}H_{31}O_4Si$ $[M+H]^+$ found 291.19882 calcd 291.19861.

4.1.3. 2-((4*S*,5*S*)-5-(Benzyloxymethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)ethanol 13

To the solution of dry DMSO (11.3 mL, 158.7 mmol, 4.0 equiv) in dry CH_2Cl_2 (50 mL) was added dropwise oxalyl chloride (6.9 mL, 79.4 mmol, 2.0 equiv) at −78 °C over 15 min and stirred for 20 min at the same temperature. To this reaction mixture, compound **14** (10.0 g, 39.7 mmol, 1.0 equiv) in dry CH_2Cl_2 (60 mL) was added drop wise over 15 min at −78 °C and the reaction mixture was stirred at the same temperature for 2 h. The reaction was quenched with Et_3N (33.0 mL, 238.1 mmol, 6.0 equiv) at −78 °C, and then allowed to warm to room temperature, after which water (100 mL) was added, the organic layer was separated, the aqueous layer was extracted with CH_2Cl_2 (2 × 100 mL), the combined organic layer washed with brine (80 mL), dried over anhydrous Na_2SO_4, and the solvent was removed under reduced pressure to give a crude aldehyde, which was utilized for the next reaction without further purification (8.5 g, 85%). To a cooled (−10 °C), stirred suspension of (methoxymethyl)triphenylphosphonium chloride (29.1 g, 85.0 mmol, 2.5 equiv) in 200 mL of dry THF under an N_2 atmosphere was added (79.9 mL, 2.35 equiv) 1.0 M lithium *bis*(trimethylsilyl) amide in THF. The reaction mixture was stirred at the same temperature for 30 min. This solution was transferred via cannula to a solution of the above aldehyde in THF (100 mL). The resulting solution was then stirred at −10 °C for 2 h and then allowed to warm to room temperature, and stirred for 10 h. The reaction mixture was diluted with saturated aq $NaHCO_3$ (200 mL) and extracted with Et_2O (3 × 100). The combined organic layer was washed with brine (100 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give a crude enol ether, which was purified by flash column chromatography to give a yellowish liquid (6.2 g, 65%). This enol ether was dissolved in 70 mL of THF, to which was added $Hg(OAc)_2$ (10.7 g, 33.5 mmol,

1.5 equiv) at 0 °C and then allowed to warm to room temperature. The reaction mixture was stirred at same temperature for 30 min. To this mixture was added H_2O (84 mL) (1.2 times w.r.t to THF), and the reaction mixture was cooled to 0 °C, after which $NaBH_4$ (5.08 g, 133.1 mmol, 6.0 equiv) was added to the reaction mixture portionwise over 30 min. Next the reaction mixture was allowed to warm to room temperature over 30 min. and then stirred for another 30 min. The organic layer was separated and the aqueous layer was extracted with EtOAc (2 × 80 mL). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, concentrated under reduced pressure, and purified with column chromatography to give **13** (5.4 g, 91%) as a colorless liquid. R_f = 0.5 (hexane/EtOAc, 50:50). $[\alpha]_D^{25} = -7.9$ (*c* 1.7, $CHCl_3$); IR ν_{max} (Neat): 3442, 2872, 1453, 1374, 1216, 1083 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.38–7.28 (m, 5H), 4.62–4.54 (m, 2H), 4.02–3.89 (m, 2H), 3.78 (t, *J* = 6.0 Hz, 2H), 3.65–3.53 (m, 2H), 2.48 (br s, 1H), 1.94–1.75 (m, 2H), 1.42 (s, 3H), 1.40 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$); δ 137.6, 128.3, 127.6, 127.5, 108.9, 79.6, 77.4, 73.5, 70.2, 60.2, 35.2, 27.1, 26.8; ESIMS: *m*/*z* 289 $[M+Na]^+$; HRESIMS for $C_{15}H_{22}O_4Na$ $[M+Na]^+$ found 289.14163 calcd 289.14103.

4.1.4. ((4*S*,5*S*)-5-(Benzyloxymethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)methanol 14

A solution of diol **17** (30.0 g, 185.2 mmol, 1.0 equiv) in dry THF (200 mL) was slowly added to a suspension of 60% NaH (7.8 g, 194.5 mmol, 1.05 equiv) in dry THF (100 mL) at 0 °C over a period of 30 min and the resulting mixture was stirred at ambient temperature for 1 h until the evolution of gas had ceased. To this mixture was added dropwise a solution of benzyl bromide (21.9 mL, 185.2 mmol, 1.0 equiv) over 30 min and the resulting mixture was stirred for 12 h. The reaction mixture was then quenched with ice flakes at 0 °C and extracted with EtOAc (2 × 200 mL). The organic layer was washed with brine (200 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure, purified with silica gel column chromatography to give **14** (34.0 g, 73%) as a yellowish liquid; R_f = 0.6 (hexane/EtOAc, 80:20); $[\alpha]_D^{25} = +8.3$ (*c* 1.0, $CHCl_3$); IR ν_{max} (Neat): 3466, 2988, 2932, 2872, 1453, 1375, 1250, 1216, 1167, 1085, 847, 741, 699 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.38–7.28 (m, 5H), 4.56 (m, 2H), 4.02–3.96 (m, 1H), 3.92–3.86 (m, 1H), 3.74–3.63 (m, 3H), 3.54–3.48 (m, 1 H), 2.18 (br s, 1H), 1.39 (s, 3 H), 1.38 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 137.4, 128.3, 127.6, 127.5, 109.2, 79.4, 76.3, 73.4, 70.2, 62.2, 26.8, 26.7; ESIMS: *m*/*z* 275 $[M+Na]^+$.

4.1.5. (*R*)-1-((4*S*,5*S*)-2,2-Dimethyl-5-vinyl-1,3-dioxolan-4-yl)-propan-2-ol 15

To a clear solution of IBX (0.65 g, 2.3 mmol, 2.0 equiv), in anhydrous DMSO and anhydrous CH_2Cl_2 (1:1 ratio, 10 mL), was added compound **20** (0.20 g, 1.2 mmol, 1.0 equiv) dissolved in dry CH_2Cl_2 (5 mL) at 0 °C over 5 min. The reaction mixture was allowed to warm to room temperature, and stirred at the same temperature for 6 h. After complete consumption of the starting material, the reaction mixture was quenched with water (5 mL), and the white solid formed was filtered off over a small pad of Celite. The filtrate was then extracted with diethyl ether (2 × 10 mL), washed with brine (5 mL), and dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure to give a crude aldehyde, which was utilized for the next step without further purification. To a solution of the above prepared aldehyde in diethyl ether (8 mL), was added dropwise a 3 M solution of methyl magnesium iodide in diethyl ether (1.57 mL, 4.0 equiv), at −40 °C over 15 min. The reaction mixture was stirred at same temperature for 3 h and after complete consumption of the starting material, the reaction mixture was quenched with saturated aq NH_4Cl (5 mL), at −40 °C and then allowed to warm to room temperature. The organic layer was separated and the aqueous layer was extracted with diethyl ether (2 × 8 mL). The combined organic layer was washed with brine (5 mL) and dried over anhydrous Na_2SO_4. Evaporation of the solvent under reduced pressure afforded a crude product, which was purified by column chromatography R_f = 0.40 (hexane/EtOAc, 80:20) to give **15** (0.101 g, 47%) and **15a**, (0.04 g, 20%) as a light yellowish oil; $[\alpha]_D^{25} = -5.9$ (*c* 1.7, $CHCl_3$); IR ν_{max} (Neat): 3432, 2985, 1375, 1239, 1047, 989 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 5.85–5.73 (m, 1H), 5.39–5.24 (m, 2H), 4.12–3.99 (m, 2H), 3.98–3.89 (m, 1H), 2.43 (br s, 1H), 1.79–1.58 (m, 2H), 1.42 (s, 3H), 1.41 (s, 3H), 1.22 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$); δ 134.7, 119.3, 108.9, 82.3, 77.9, 65.1, 39.2, 27.2, 26.9, 23.6; ESIMS: *m*/*z* 209 $[M+Na]^+$; HRESIMS for $C_{10}H_{18}O_3Na$ $[M+Na]^+$ found 209.11549 calcd: 209.11482.

4.1.6. (*S*)-3-(Methoxymethoxy)pent-4-enoic acid 16

To a clear solution of IBX (5.75 g, 20.5 mmol, 2.0 equiv), in a 1:1 ratio of dry DMSO and CH_2Cl_2 (60 mL), was added compound **24** (1.50 g, 10.3 mmol, 1.0 equiv) in dry CH_2Cl_2 (15 mL) at 0 °C over 5 min. The reaction mixture was allowed to warm to room temperature, and stirred at same temperature for 6 h. After the complete consumption of the starting material, the reaction mixture was quenched with water (30 mL), and the white solid formed was filtered off over a pad of Celite. The filtrate was then extracted with diethyl ether (3 × 20 mL), and washed with brine (20 mL), and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure to give a crude aldehyde (1.2 g, 81%). To a solution of the aldehyde (1.2 g, 8.3 mmol, 1.0 equiv) in ^tBuOH (30 mL), H_2O (30 mL) and acetone (17.5 mL) in a 250-mL round-bottom flask, 2 M 2-methyl-2-butene (15.4 mL, 30.8 mmol, 3.7 equiv) was added via syringe, followed by NaH_2PO_4 (5.85 g, 37.5 mmol, 4.5 equiv) and $NaClO_2$ (80% technical grade, 3.39 g, 37.5 mmol, 4.5 equiv) as solids. The biphasic reaction was stirred vigorously 12 h, after which saturated aqueous NH_4Cl (30 mL) was added. The reaction mixture was extracted with CH_2Cl_2 (3 × 30 mL) and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo to give a crude liquid, which was purified by column chromatography R_f = 0.20 (hexane/EtOAc, 80:20) to afford **10** (0.95 g, 71%) as a light transparent liquid; $[\alpha]_D^{25} = -77.3$ (*c* 0.75, $CHCl_3$); IR ν_{max} (Neat): 3400, 2949, 1716, 1151, 1032, 924 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 5.79–5.67 (m, 1H), 5.32 (d, *J* = 17.4 Hz, 1H), 5.25 (d, *J* = 10.6 Hz, 1H), 4.70 (d, *J* = 6.8 Hz, 1H), 4.56 (d, *J* = 6.8 Hz, 1H), 4.53–4.46 (m, 1H), 3.35 (s, 3H), 2.74–2.52 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$); δ 175.6, 136.2, 118.3, 93.7, 73.5, 55.3, 40.5.

4.1.7. ((4*S*,5*S*)-2,2-Dimethyl-1,3-dioxolane-4,5-diyl)dimethanol 17

A solution of (+)-diethyl L-tartrate (50.0 g, 242.7 mmol, 1.0 equiv) and *p*-toluenesulfonic acid (375 mg, 2.2 mmol, 0.01 equiv) in benzene (500 mL) and 2,2-dimethoxypropane (44.5 mL, 364.1 mmol, 2.5 equiv) was heated at reflux for 12 h. The mixture was allowed to cool to ambient temperature, washed with an aq saturated sodium bicarbonate solution (150 mL) and then dried over anhydrous Na_2SO_4. The solvent was evaporated and the residue was purified by column chromatography (hexane/EtOAc 8:2) to give the acetonide protected DET (55.0 g, 92%), as a colorless liquid. The above prepared solution of acetonide protected compound (55.0 g, 223.6 mmol, 1 equiv) in dry THF (300 mL) was slowly added to a suspension of $LiAlH_4$ (12.1 g, 317.7 mmol, 1.8 equiv) in dry THF (200 mL) at 0 °C over a period of 30 min. The resulting mixture was heated at 45 °C for 5 h to complete the reaction. The reaction was quenched carefully with a saturated aq Na_2SO_4 solution (300 mL) at 0 °C and the resulting suspension was stirred for 3 h before it was filtered through a pad of silica gel. The filtrate was dried over anhydrous Na_2SO_4, the solvent was evaporated and the residue was purified by column chromatography to give diol **17** (27.8 g, 83%), as a colorless

liquid; R_f = 0.30 (hexane/EtOAc, 60:40); $[\alpha]_D^{25} = +10.8$ (*c* 0.5, MeOH); IR (Neat): 3401, 2988, 2935, 2881, 1376, 1251, 1218, 1165, 1108, 1053, 844 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 3.97–3.89 (m, 2H), 3.76–3.65 (m, 4H), 1.39 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 109.2, 78.3, 62.0, 26.8; ESIMS: *m*/*z* 185 $[M+Na]^+$.

4.1.8. (2-((4*S*,5*S*)-5-((Benzyloxymethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)ethoxy)(*tert*-butyl)dimethylsilane 18

To compound **13** (0.9 g, 3.4 mmol, 1.0 equiv) in anhydrous CH_2Cl_2 (15.0 mL) was added imidazole (0.3 g, 4.4 mmol, 1.3 equiv) at room temperature. The mixture was then stirred at room temperature for 20 min after which the reaction mixture was cooled to 0 °C, and to this was added *tert*-butyldimethylsilylchloride (TBDMSCl) (0.6 g, 4.1 mmol, 1.2 equiv) portionwise. The reaction mixture was allowed to warm to room temperature and stirred for 2 h. Water (15 mL) was then added to the reaction mixture and the organic layer was separated and the aqueous layer extracted with CH_2Cl_2 (2 × 15 mL). The combined organic layer was washed with brine (15 mL), dried over anhydrous Na_2SO_4 and then the solvent was removed under reduced pressure to give the crude material, which was purified by column chromatography to give **18** (1.184 g, 92%) as a yellow oil; R_f = 0.90 (hexane/EtOAc, 90:10); $[\alpha]_D^{25} = -16.50$ (*c* 1.0, $CHCl_3$); IR ν_{max} (Neat): 2931, 1252, 1094, 838 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.35–7.27 (m, 5H), 4.63–4.54 (m, 2H), 3.98–3.86 (m, 2H), 3.80–3.67 (m, 2H), 3.58 (d, *J* = 4.5 Hz, 2H), 1.88–1.69 (m, 2H), 1.41 (s, 3H), 1.39 (s, 3H), 0.88 (s, 9H), 0.04 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 137.9, 128.3, 127.5, 108.7, 79.9, 74.9, 73.9, 70.3, 59.7, 36.2, 27.2, 26.9, 25.9, 18.2, −5.5; ESIMS: *m*/*z* 381 $[M+H]^+$; HRESIMS for $C_{21}H_{37}O_4Si[M+H]^+$ found 381.24625 calcd 381.24556.

4.1.9. *tert*-Butyl-(2-((4*S*,5*S*)-2,2-dimethyl-5-vinyl-1,3-dioxolan-4-yl)ethoxy)dimethylsilane 19

To a solution of dry DMSO (2.50 mL, 34.5 mmol, 4.0 equiv) in dry CH_2Cl_2 (10 mL) was added dropwise oxalyl chloride (1.51 mL, 17.3 mmol, 2.0 equiv) at −78 °C over 15 min and stirred for 20 min at the same temperature. To this mixture, compound **12** (2.50 g, 8.6 mmol, 1.0 equiv) in dry CH_2Cl_2 (25 mL) was added dropwise over 15 min at −78 °C and the reaction mixture was stirred at the same temperature for 2 h. The reaction was quenched with Et_3N (7.18 mL, 51.7 mmol, 6.0 equiv) at −78 °C, and the reaction mixture was then allowed to warm to room temperature, after which water (30 mL) was added, the organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 20 mL). The combined organic layers were washed with brine (20 mL), and dried over anhydrous Na_2SO_4, the solvent was evaporated under reduced pressure to give a crude aldehyde, which was utilized for the next reaction without further purification. The aldehyde obtained was taken in dry THF (20 mL) and added to a mixture of methyltriphenylphosphoniumiodide (10.50 g, 25.7 mmol, 3.0 equiv) and potassium *tert*-butoxide (2.70 g, 24.1 mmol, 2.8 equiv) in dry THF (50 mL), at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred for 12 h. The reaction mixture was quenched with water (20 mL) and diluted with diethyl ether and hexane (1:1) (60 mL). The white precipitate formed was filtered off through a small pad of Celite and the filtrate was dried over anhydrous Na_2SO_4. Evaporation of the solvent under reduced pressure gave a crude material, which was purified by column chromatography to give **19** (1.80 g, 73%) as a light yellowish oil; R_f = 0.90 (hexane/EtOAc, 90:10); $[\alpha]_D^{25} = -10.0$ (*c* 1.05, $CHCl_3$); IR ν_{max} (Neat): 2932, 2859, 1374, 1253, 1090, 837 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 5.83–5.77 (m, 1H), 5.36 (td, *J* = 1.1, 17.3 Hz, 1H), 5.24 (d, *J* = 10.2 Hz, 1H), 4.03 (t, *J* = 8.3 Hz, 1H), 3.82–3.69 (m, 3H), 1.83–1.77 (m, 1H), 1.75–1.69 (m, 1H), 1.41 (s, 3H), 1.40 (s, 3H), 0.88 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$); δ 135.2, 118.4, 108.4, 82.5, 77.3, 59.7, 34.9, 27.2, 26.8, 25.8, 18.2, −5.4, −5.5; ESIMS: *m*/*z* 309 $[M+Na]^+$; HRESIMS for $C_{15}H_{30}O_3NaSi$ $[M+Na]^+$ found 309.18628 calcd 309.18564.

4.1.10. 2-((4*S*,5*S*)-2,2-Dimethyl-5-vinyl-1,3-dioxolan-4-yl)-ethanol 20

To a solution of compound **19** (1.80 g, 6.3 mmol, 1.0 equiv) in dry THF (20 mL) was added dropwise a 1.0 M TBAF solution in THF (9.44 mL, 1.5 equiv) over 10 min at 0 °C. The reaction mixture was then allowed to warm to room temperature while stirring for 2 h. After complete consumption of the starting material (monitored by TLC), the reaction mixture was quenched with saturated aq NH_4Cl (15 mL), and diluted with EtOAc (10 mL) and water (10 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (2 × 15 mL). The combined organic layer was washed with brine (15 mL), and dried over anhydrous Na_2SO_4. Evaporation of the solvent under reduced pressure followed by silica gel column chromatography afforded alcohol **20** (0.85 g, 78%) as a light yellowish oil; R_f = 0.20 (hexane/EtOAc, 80:20); $[\alpha]_D^{25} = -7.2$ (*c* 0.8, $CHCl_3$); IR ν_{max} (Neat): 3425, 2986, 2880, 1375, 1241, 1058, 873 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 5.84–5.73 (m, 1H), 5.35 (d, *J* = 16.8 Hz, 1H), 5.25 (d, *J* = 10.2 Hz, 1H), 4.04 (t, *J* = 7.7 Hz, 1H), 3.85–3.76 (m, 3H), 2.45 (br s, 1H), 1.89-1.69 (m, 2H), 1.40 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$); δ 134.7, 119.0, 108.9, 82.5, 79.0, 60.1, 33.8, 27.1, 26.8; ESIMS: *m*/*z* 195 $[M+Na]^+$; HRESIMS for $C_9H_{16}O_3Na$ $[M+Na]^+$ found 195.09971 calcd 195.09917.

4.1.11. *tert*-Butyl-2-((4*S*,5*R*)-5-(iodomethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)ethoxy)dimethylsilane 21

To a solution of compound **12** (3.7 g, 12.6 mmol, 1.0 equiv) in dry THF (40 mL) were added imidazole (2.6 g, 38.3 mmol, 3.0 equiv), and TPP (6.68 g, 25.5 mmol, 2.0 equiv) at room temperature. The reaction mixture was cooled to 0 °C and to this, molecular I_2 (7.13 g, 28.1 mmol, 2.2 equiv) in dry THF (70 mL) was added dropwise over 15 min. The reaction mixture was then allowed to warm to room temperature and stirred at the same temperature for 2 h. After complete consumption of the starting material, the reaction mixture was quenched with a saturated aq $Na_2S_2O_3{\cdot}5H_2O$ (100 mL) solution and then diluted with EtOAc (50 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (2 × 50 mL). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, and evaporated under reduced pressure to give a crude material, which was purified by flash column chromatography to give **21** (4.8 g, 94%) as a light yellowish liquid. R_f = 0.90 (hexane/EtOAc, 90:10); $[\alpha]_D^{25} = -28.3$ (*c* 0.6, $CHCl_3$); IR ν_{max} (Neat): 2931, 1375, 1252, 1093, 836 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 3.92–3.88 (m, 1H), 3.82–3.68 (m, 3H), 3.36–3.25 (m, 2H), 1.91–1.84 (m, 1H), 1.82–1.76 (m, 1H), 1.44 (s, 3H), 1.41 (s, 3H), 0.90 (s, 9H), 0.07 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 108.8, 79.6, 78.5, 59.5, 36.4, 27.5, 27.3, 25.9, 18.2, 5.8, −5.3, −5.4; ESIMS: *m*/*z* 401 $[M+H]^+$; HRESIMS for $C_{14}H_{30}O_3ISi$ $[M+H]^+$ found 401.10071 calcd 401.10034.

4.1.12. (*S*)-5-(*tert*-Butyldimethylsilyloxy)pent-1-en-3-ol 22

To a solution of compound **21** (4.8 g, 12.0 mmol, 1.0 equiv) in dry THF (50 mL) was added dropwise 1.6 M ^{n}BuLi (15.0 mL, 2.0 equiv) at −78 °C over 15 min. The reaction mixture was then stirred at the same temperature for 2 h. After complete consumption of the starting material, the reaction mixture was quenched with water (50 mL), at −78 °C and allowed to warm to room temperature. The reaction mixture was diluted with EtOAc (50 mL), the organic layer was separated, the aqueous layer was extracted with EtOAc (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 give a crude material, which was purified by column chromatography to give **22** (2.54 g, 98%) as light yellowish liquid. R_f = 0.50 (hexane/EtOAc, 90:10); $[\alpha]_D^{25} = +11.76$ (*c* 0.34, $CHCl_3$); IR ν_{max} (Neat): 3424, 2954, 1468, 1254, 1099, 836 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 5.93–5.82 (m, 1H), 5.27 (d, *J* = 17.2 Hz, 1H), 5.10 (d, *J* = 10.4 Hz, 1H), 4.42–4.32 (m, 1H), 3.94–3.75 (m, 2H), 1.83–1.65 (m, 2H), 0.89 (s, 9H), 0.07 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 140.5, 114.0, 73.3, 61.8, 38.1, 25.8, 18.0, −5.6; ESIMS: *m*/*z* 217 $[M+H]^+$; HRESIMS for $C_{11}H_{25}O_2Si$ $[M+H]^+$ found 217.16208, calcd 217.16183.

4.1.13. (*S*)-9,9,10,10-Tetramethyl-5-vinyl-2,4,8-trioxa-9-silaundecane 23

To a solution of compound **22** (1.0 g, 4.6 mmol, 1.0 equiv) in dry CH_2Cl_2 (10 mL) was added DIPEA (3.23 mL, 18.5 mmol, 4.0 equiv) at room temperature, and stirred for 15 min. The reaction mixture was cooled to 0 °C and to this was added dropwise methoxymethyl chloride (0.75 mL, 9.3 mmol, 2.0 equiv), over 5 min. Next, the reaction mixture was allowed to warm to room temperature and stirred at the same temperature for 12 h. After complete consumption of the starting material, the reaction mixture was washed with aqueous saturated $CuSO_4$ (3 × 10 mL). The organic layer was washed with brine (10 mL), dried over anhydrous Na_2SO_4, and evaporated under reduced pressure to give a crude material, which was purified by column chromatography to give **23** (1.0 g, 83%) as a light yellowish liquid. R_f = 0.70 (hexane/EtOAc, 90:10); $[\alpha]_D^{25} = -51.6$ (*c* 0.53, $CHCl_3$); IR ν_{max} (Neat): 2927, 1254, 1096, 1035, 836 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 5.75–5.64 (m, 1H), 5.24–5.16 (m, 2H), 4.69 (d, *J* = 6.6 Hz, 1H), 4.54 (d, *J* = 6.8 Hz, 1H), 4.17 (q, *J* = 7.2, 13.4 Hz, 1H), 3.77–3.63 (m, 2H), 3.36 (s, 3H), 1.89–1.78 (m, 1H), 1.75–1.66 (m, 1H), 0.89 (s, 9H), 0.04 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 138.3, 117.0, 93.9, 74.3, 59.3, 55.3, 38.6, 25.9, 25.8, 18.2, −5.4; ESIMS: *m*/*z* 261 $[M+H]^+$.

4.1.14. (*S*)-3-(Methoxymethoxy)pent-4-en-1-ol 24

To a solution of compound **23** (1.0 g, 3.9 mmol, 1.0 equiv) in dry THF (10 mL), was added dropwise a 1.0 M TBAF solution in THF (5.8 mL, 5.8 mmol, 1.5 equiv) over 10 min at 0 °C. The reaction mixture was then allowed to warm to room temperature while stirring for 2 h. After complete consumption of the starting material, the reaction mixture was quenched with a saturated aq NH_4Cl (5 mL) solution, diluted with EtOAc (5 mL), and water (5 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (2 × 10 mL). The combined organic layer was washed with brine (10 mL), dried over anhydrous Na_2SO_4, and evaporated under reduced pressure to give a crude material, which was purified by column chromatography to give alcohol **24** (0.51 g, 91%) as a colorless oil. R_f = 0.50 (hexane/EtOAc, 60:40); $[\alpha]_D^{25} = -92.0$ (*c* 0.40, $CHCl_3$); IR ν_{max} (Neat): 3421, 2947, 1152, 1097, 1031, 923 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 5.77–5.65 (m, 1H), 5.26–5.18 (m, 2H), 4.69 (d, *J* = 6.8 Hz, 1H), 4.54 (d, *J* = 6.8 Hz, 1H), 4.24 (d, *J* = 7.6, 13.6 Hz, 1H), 3.83–3.69 (m, 2H), 3.38 (s, 3H), 2.40 (br s, 1H), 1.85–1.79 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 137.5, 117.2, 93.7, 75.6, 59.3, 55.3, 37.6.

4.1.15. (2*R*,4*S*)-4-(Methoxymethoxy)hex-5-en-2-yl 2-((4*S*,5*S*)-2,2-dimethyl-5-vinyl-1,3-dioxolan-4-yl)acetate 25 and (2*S*,4*S*)-4-(methoxymethoxy)hex-5-en-2-yl 2-((4*S*,5*S*)-2,2-dimethyl-5-vinyl-1,3-dioxolan-4-yl)acetate 25a

To a clear solution of IBX (5.75 g, 20.5 mmol, 2.0 equiv), in a 1:1 ratio of dry DMSO and CH_2Cl_2 (60 mL), was added compound **24** (1.50 g, 10.3 mmol, 1.0 equiv) in dry CH_2Cl_2 (15 mL) at 0 °C over 5 min. The reaction mixture was then allowed to warm to room temperature, and stirred at same temperature for 6 h. After complete consumption of the starting material, the reaction mixture was quenched with water (30 mL) and the resulting white solid formed was filtered over a pad of Celite. The filtrate was then extracted with diethyl ether (3 × 20 mL), washed with brine (20 mL), and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure to give the crude product, which was utilized for the next reaction without further purification. To a solution of the above prepared aldehyde in diethyl ether (20 mL), was added dropwise a 3 M solution of methyl magnesium iodide (13.7 mL, 4.0 equiv), at −40 °C over 15 min. The reaction mixture was then stirred at the same temperature for 3 h. After complete consumption of the starting material, the reaction mixture was quenched with saturated aq NH_4Cl (15 mL), at −40 °C and then allowed to warm to room temperature. The organic layer was separated and the aqueous layer was extracted with diethyl ether (2 × 10 mL). The combined organic layer was washed with brine (10 mL), and dried over anhydrous Na_2SO_4. Evaporation of the solvent followed by purification with column chromatography gave an inseparable mixture of diastereomers **11** (1.10 g, 67.0%) as a light yellowish oil R_f = 0.40 (hexane/EtOAc, 80:20).

To a solution of acid **10** (0.4 g, 2.2 mmol, 1.0 equiv), in dry CH_2Cl_2 was added mixture of diastereomers **11** (0.28 g, 1.7 mmol, 0.8 equiv), DCC (0.89 g, 4.3 mmol, 2.0 equiv), DMAP (0.53 g, 4.3 mmol, 2.0 equiv) at room temperature. The reaction mixture was stirred at the same temperature for 12 h, then concentrated under reduced pressure and purified by column chromatography to give **25** (0.23 g, 40.2%) and it's diastereomer **25a** (0.15 g, 26.8%) (6:4 ratio) as colorless oils; R_f = 0.30 (hexane/EtOAc, 90:10); **25**: $[\alpha]_D^{25} = -55.9$ (*c* 1.1, $CHCl_3$); IR ν_{max} (Neat): 2985, 1736, 1178, 1033, 924 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 5.86–5.79 (m, 1H), 5.71–5.64 (m, 1H), 5.38 (dd, *J* = 0.9, 17.2 Hz, 1H), 5.27 (dd, *J* = 1.2, 10.2 Hz, 1H), 5.24–5.20 (m, 1H), 5.19–5.17 (m, 1H), 5.14–5.10 (m, 1H), 4.67 (d, *J* = 6.7 Hz, 1H), 4.49 (d, *J* = 6.7 Hz, 1H), 4.14–4.04 (m, 3H), 3.32 (s, 3H), 2.59–2.50 (m, 2H), 1.83–1.71 (m, 2H), 1.41 (s, 6H), 1.25 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$); δ 170.0, 138.0, 134.6, 119.5, 117.3, 109.2, 93.9, 82.2, 76.8, 73.8, 68.4, 55.7, 42.0, 37.2, 27.1, 26.9, 20.5; ESIMS: *m*/*z* 351 $[M+Na]^+$; HRESIMS for $C_{17}H_{28}O_6Na$ $[M+Na]^+$ found 351.17734, calcd 351.17781.

25a: $[\alpha]_D^{25} = -28.1$ (*c* 1.6, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 5.88–5.76 (m, 1H), 5.70–5.58 (m, 1H), 5.38 (d, *J* = 16.8 Hz, 1H), 5.32–5.17 (m, 3H), 5.07–4.97 (m, 1H), 4.67 (d, *J* = 6.8 Hz, 1H), 4.51 (d, *J* = 6.6 Hz, 1H), 4.14–4.04 (m, 3H), 3.36 (s, 3H), 2.54 (d, *J* = 5.7 Hz, 2H), 2.10–1.97 (m, 1H), 1.68–1.59 (m, 1H), 1.42 (s, 3H), 1.41 (s, 3H), 1.27 (d, *J* = 6.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$); δ 169.6, 137.4, 134.6, 119.5, 118.2, 109.2, 93.6, 82.2, 76.7, 74.4, 68.7, 55.5, 41.4, 37.3, 27.1, 26.9, 20.1.

4.1.16. (3a*S*,7*R*,9*S*,11a*S*,*E*)-9-(Methoxymethoxy)-2,2,7-trimethyl-3a,4,8,9-tetrahydro-7*H*-[1,3]dioxolo[4,5-*d*]oxecin-5(11a*H*)-one 26

To a degassed solution of compound **25** (0.03 g, 0.1 mmol, 1.0 equiv), in dry CH_2Cl_2 (100 mL) was added Grubbs' II generation catalyst (0.008 g, 0.01 mmol, 0.1 equiv) and the reaction mixture was refluxed for 24 h. The reaction mixture was concentrated under reduced pressure and purified by column chromatography to give **26** (0.022 g, 80%) as a colorless oil; R_f = 0.50 (hexane/EtOAc, 80:20); $[\alpha]_D^{25} = -8.3$ (*c* 0.6, $CHCl_3$); IR ν_{max} (Neat): 2932, 1727, 1236, 1074 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 5.92–5.78 (m, 2H), 5.07–5.03 (m, 1H), 4.68 (d, *J* = 6.7 Hz, 1H), 4.50 (d, *J* = 6.7 Hz, 1H), 4.27–4.23 (m, 1H), 4.20 (t, *J* = 8.5 Hz, 1H), 3.97–3.92 (m, 1H), 3.35 (s, 3H), 2.42 (dd, *J* = 10.8, 14.8 Hz, 1H), 2.10–2.06 (m,1H), 1.91–1.82 (m, 1H), 1.79–1.72 (m, 1H), 1.44 (s, 3H), 1.41 (s, 3H), 1.25 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$); δ 168.9, 132.2, 131.6, 109.3, 93.9, 82.2, 75.2, 69.9, 68.4, 55.5, 42.8, 38.3, 26.9, 21.8; ESIMS: *m*/*z* 323 $[M+Na]^+$.

4.1.17. (3a*S*,7*S*,9*S*,11a*S*,*E*)-9-(Methoxymethoxy)-2,2,7-trimethyl-3a,4,8,9-tetrahydro-7*H*-[1,3]dioxolo[4,5-*d*]oxecin-5(11a*H*)-one 26a

Similar procedure was followed as used earlier for the synthesis of **26** to give **26a** in 78% yield as a colorless liquid; $[\alpha]_D^{25} = +24.4$ (*c* 0.9, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): δ 5.91 (dd, *J* = 1.8, 15.6 Hz, 1H), 5.56 (ddd, *J* = 1.8, 9.5, 15.6 Hz, 1H), 5.24–5.18 (m, 1H), 4.65 (s, 2H), 4.45 (br s, 1H), 4.06 (t, *J* = 9.0 Hz, 1H), 3.77–3.72 (m, 1H), 3.36 (s, 3H), 2.78 (dd, *J* = 2.4, 11.3 Hz, 1H), 2.36 (t, *J* = 11.3 Hz, 1H), 1.85–1.83 (m, 2H), 1.43 (s, 3H), 1.42 (s, 3H), 1.21 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$); δ 170.3, 138.8, 119.9, 108.8, 95.0, 84.6, 77.5, 71.7, 67.8, 55.5, 39.5, 37.3, 26.9, 26.8, 21.3.

4.1.18. (4*S*,5*S*,8*S*,10*R*,*E*)-4,5,8-Trihydroxy-10-methyl-4,5,9,10-tetrahydro-3*H*-oxecin-2(8*H*)-one 6 (decarestrictine-D)

To a solution of compound **26** (0.022 g, 0.073 mmol, 1.0 equiv) in DMS (3 mL), were added 3 drops of $BF_3{\cdot}OEt_2$ at 0 °C, and the reaction mixture was stirred at same temperature for 30 min. The reaction mixture was quenched with solid $NaHCO_3$ (0.5 g) and filtered through small pad of Celite. The filtrate was concentrated under reduced pressure to give the crude product, which was purified by flash column chromatography to give **6** (0.010 g, 62%) as a white solid $R_f = 0.10$ (hexane/EtOAc, 40:60); $[\alpha]_D^{25} = -47.85$ (*c* 0.7, $CHCl_3$); IR ν_{max} (KBr): 3408, 2924, 1710, 1272, 1043 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 5.95–5.80 (m, 2H), 5.30–5.18 (m, 1H), 4.41 (br s, 1H), 4.22–4.15 (m, 1H), 4.06–4.03 (m, 1H), 2.61 (dd, *J* = 1.7, 14.5 Hz, 1H), 2.39 (dd, *J* = 6.4, 14.4 Hz, 1H), 1.96–1.76 (m, 2H), 1.25 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$); δ 174.6, 133.7, 129.8, 74.0, 72.5, 72.2, 68.2, 43.0, 33.2, 21.2; ESIMS: *m*/*z* 217 $[M+H]^+$; HRESIMS for $C_{10}H_{17}O_5$ $[M+H]^+$ found 217.10701 calcd 217.10705.

4.1.19. (4*S*,5*S*,8*S*,10*S*,*E*)-4,5,8-Trihydroxy-10-methyl-4,5,9,10-tetrahydro-3*H*-oxecin-2(8*H*)-one 6a (*9-epi*-decarestrictine-D)

A similar procedure was followed as used earlier for the synthesis of **6** to give **6a** in 61% yield as a colorless liquid from **26a**; $[\alpha]_D^{25} = -4.2$ (*c* 0.7, MeOH); ^1H NMR (300 MHz, $CDCl_3$ + acetone-d_6): δ 5.82 (dd, *J* = 1.9, 15.7 Hz, 1H), 5.51–5.42 (m, 1H), 5.38–5.27 (m, 1H), 4.48 (br s, 1H), 3.88–3.77 (m, 2H), 2.47 (dd, *J* = 2.8, 13.2 Hz, 1H), 2.21 (dd, *J* = 10.9, 13.0 Hz, 1H), 1.80–1.76 (m, 2H), 1.16 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$ + acetone-d_6); δ 172.5, 137.9, 124.9, 80.9, 74.9, 68.2, 66.3, 42.4, 41.8, 22.2.

4.1.20. (*S*)-((*R*)-1-((4*S*,5*S*)-2,2-Dimethyl-5-vinyl-1,3-dioxolan-4-yl)propan-2-yl) 3-(methoxymethoxy)pent-4-enoate 27

To a solution of compound **15** (0.065 g, 0.35 mmol, 1.0 equiv), and compound **16** (0.061 g, 0.38 mmol, 1.1 equiv), in dry CH_2Cl_2 (5 mL) was added DCC (0.144 g, 0.69 mmol, 2.0 equiv), and DMAP (0.085 g, 0.69 mmol, 2.0 equiv), at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred at same temperature for 12 h. After the reaction mixture was concentrated, the crude product was purified by column chromatography to give **27** (0.075 g, 66%) as a transparent liquid. $R_f = 0.60$ (hexane/EtOAc, 80:20); $[\alpha]_D^{25} = -45.8$ (*c* 0.90, $CHCl_3$); IR ν_{max} (Neat): 2985, 1736, 1375, 1178, 1034, 927 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 5.81–5.70 (m, 2H), 5.37–5.21 (m, 4H), 5.07 (qt, *J* = 5.9, 12.5, 19.1 Hz, 1H), 4.68 (d, *J* = 6.6 Hz, 1H), 4.54 (d, *J* = 6.6 Hz, 1H), 4.47 (q, *J* = 7.3, 13.2 Hz, 1H), 3.95 (t, *J* = 8.1 Hz, 1H), 3.71 (dt, *J* = 2.9, 8.8 Hz, 1H), 3.34 (s, 3H), 2.62–2.59 (m, 1H), 2.49–2.45 (m, 1H), 1.85–1.82 (m, 1H), 1.69–1.65 (m, 1H), 1.38 (s, 3H), 1.36 (s, 3H), 1.26 (d, *J* = 5.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$); δ 170.0, 136.6, 134.8, 119.2, 118.1, 108.8, 93.9, 82.7, 76.9, 73.7, 68.9, 55.5, 41.1, 38.2, 27.2, 26.8, 20.6; ESIMS: *m*/*z* 351 $[M+Na]^+$; HRESIMS for $C_{17}H_{28}O_6Na$ $[M+Na]^+$ found 351.17868 calcd 351.17781.

4.1.21. (3a*S*,5*R*,9*S*,11a*S*,*E*)-9-(Methoxymethoxy)-2,2,5-trimethyl-4,5,8,9-tetrahydro-3a*H*-[1,3]dioxolo[4,5-*d*]oxecin-7(11a*H*)-one 28

To a degassed solution of compound **27** (0.075 g, 0.23 mmol, 1.0 equiv), in dry CH_2Cl_2 (200 mL) was added Grubbs' II generation catalyst (0.019 g, 0.023 mmol, 0.1 equiv) and the reaction mixture was refluxed for 24 h. The reaction mixture was concentrated under reduced pressure and then purified by column chromatography to give **28** (0.048 g, 70%) as a colorless oil. $R_f = 0.30$ (hexane/EtOAc, 80:20); $[\alpha]_D^{25} = -58.5$ (*c* 0.85, $CHCl_3$); IR ν_{max} (Neat): 2983, 1733, 1374, 1236, 1158, 1040, 998 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 5.86 (dd, *J* = 2.3, 15.8 Hz, 1H), 5.67 (dd, *J* = 9.4, 15.8 Hz, 1H), 5.10–5.06 (m, 1H), 4.70 (s, 2H), 4.63 (br s, 1H), 4.07 (t, *J* = 9.0 Hz, 1H), 3.64 (t, *J* = 8.7 Hz, 1H), 3.40 (s, 3H), 2.67 (dd, *J* = 3.0, 12.4 Hz, 1H), 2.48 (dd, *J* = 4.1, 12.4 Hz, 1H), 2.04–1.92 (m, 2H), 1.40 (s, 3H), 1.39 (s, 3H), 1.22 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$); δ 168.8, 134.9, 123.9, 108.1, 94.7, 84.0, 81.5, 70.6, 69.2, 55.6, 42.6, 38.5, 27.0, 26.9, 21.9; ESIMS: *m*/*z* 323 $[M+Na]^+$; HRESIMS for $C_{15}H_{24}O_6Na$ $[M+Na]^+$ found 323.14630 calcd. 323.14651.

4.1.22. (4*S*,7*S*,8*S*,10*R*,*E*)-4,7,8-Trihydroxy-10-methyl-3,4,7,8,9,10-hexahydrooxecin-2-one 9 (decarestrictine-O)

To a solution of compound **28** (20 mg, 0.0067 mmol, 1.0 equiv) in DMS (3 mL), were added 3 drops of $BF_3{\cdot}OEt_2$ at 0 °C, and the reaction mixture was stirred at the same temperature for 20 min. The reaction mixture was quenched with solid $NaHCO_3$ (0.5 g) and filtered through a pad of Celite. The filtrate was concentrated under reduced pressure to give a crude product, which was purified by flash column chromatography to give a MOM deprotected alcohol as a transparent liquid. To the above-synthesized alcohol in THF (3 mL) was added 1 M HCl (3 mL), at room temperature and the reaction mixture was stirred at same temperature for 2 h. After complete consumption of the starting material, the reaction mixture was quenched by the addition of solid $NaHCO_3$ (1.0 g), and then diluted with EtOAc (2 mL) and water (2 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (2 × 5 mL). The combined organic layer was washed with brine (5 mL), and dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure to give a crude product, which was purified by column chromatography to give **9** (8 mg, 55%) as a white gummy solid. $R_f = 0.10$ (hexane/EtOAc, 40:60); $[\alpha]_D^{25} = -22.5$ (*c* 0.2, MeOH); lit.[5l] $[\alpha]_D^{25} = -18.0$ (*c* 0.2, MeOH); IR ν_{max} (KBr): 3415, 2904, 1702, 1276, 1088 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$ + CD_3OD): δ 5.94 (dd, *J* = 3.2, 15.7 Hz, 1H), 5.59 (dd, *J* = 10.8, 15.7 Hz, 1H), 4.80 (qt, *J* = 6.7, 13.6 Hz, 1H), 4.68 (q, *J* = 4.6, 7.2 Hz, 1H), 3.80 (t, *J* = 9.0 Hz, 1H), 3.43 (t, *J* = 9.0 Hz, 1H), 2.58 (dd, *J* = 3.7, 11.9 Hz, 1H), 2.49 (dd, *J* = 3.5, 11.9 Hz, 1H), 2.00–1.94 (m, 1H), 1.80 (d, *J* = 15.9 Hz, 1H), 1.25 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$ + CD_3OD); δ 171.8, 137.5, 126.9, 79.9, 77.1, 70.8, 67.9, 44.4, 44.1, 23.2; ESIMS: *m*/*z* 239 $[M+Na]^+$; HRESIMS for $C_{10}H_{16}O_5Na$ $[M+Na]^+$ found 239.08890 calcd for 239.08899.

Acknowledgments

V.K. thanks CSIR, New Delhi, G.S. thanks UGC, New Delhi for financial assistance. The authors thank CSIR, New Delhi for a research grant under XII Five year plan programme ORIGIN (budget head CSC-0108) and partial funding from CSIR Young Scientist Award Scheme (P-81-113).

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