Ring-closing metathesis (RCM) reaction: application in the synthesis of cyclopropyl-lactone segment of solandelactones

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Dedicated to Professor (Mrs.) A. Chatterjee on her 85th anniversary

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Abstract

An efficient synthesis of cyclopropyl-lactone containing fragment of solandelactones has been achieved via ring-closing olefinic metathesis reaction. Grubbs' second generation $RuCl_2(=CHPh)(PCy_3)(IEMS)$ catalyst has been successfully and efficiently utilized in the construction of eight-membered lactone ring with *cis*-double bond present in solandelactones.

Keywords: Oxylipins, solandelactones, cyclopropane, ring-closing metathesis, enzymatic resolution

Introduction

The formation of rings represents a central theme in natural product synthesis.[1] A number of natural products contain medium-sized saturated as well as unsaturated lactone rings.[2] This class of compounds continues to generate intense interest from synthetic organic chemists due to their interesting structural features associated with important biological activities. Usually, medium sized lactone rings are achieved by Yamaguchi lactonisation[3] under high dilution condition or Bayer-Villiger[4] ring expansion reaction. In order to facilitate the formation of medium-sized rings, several features should be installed in the substrate so that it can provide some sort of conformational constraint or restraint. For example, under Yamaguchi condition, the eight- and nine-membered lactone rings corresponding to solandelactones[3a] and halicholactone[3b] respectively were facilitated by the presence of *cis*-alkene conformational restraint. Synthesis of medium sized rings by ring closing metathesis (RCM) reaction using Grubbs' catalyst is a formidable challenge despite the use of this methodology for the construction of diverse medium sized cyclic structures.[5-8] Because of the enthalpic as well as entropic influences, eight-membered lactone rings are the most difficult to prepare. Herein, we describe the application of

RCM reaction as flexible approach towards the synthesis of saturated and unsaturated eight-membered lactone rings present in solandelactones.

Solandelactones (**1**) belonging to the growing class of oxylipins containing a *trans*-bifunctional cyclopropane ring and fatty acid lactones of marine origin were isolated from the hydroid *Solanderia secunda* of Korean waters and their structures were elucidated by exhaustive spectroscopic and chemical method.[9] Their structural uniqueness as well as intriguing biological activities led us to synthesize them in a suitable manner. These compounds were found to be structurally similar to some other marine oxylipins *viz* constanolactones (**3**),[10] halicholactone (**2a**) and neohalicholactone (**2b**) (Fig.1).[11] It is interesting to note that all of the above metabolites possess linear C_{20} carbon skeletons derived from eicosanoid origin. In contrast,

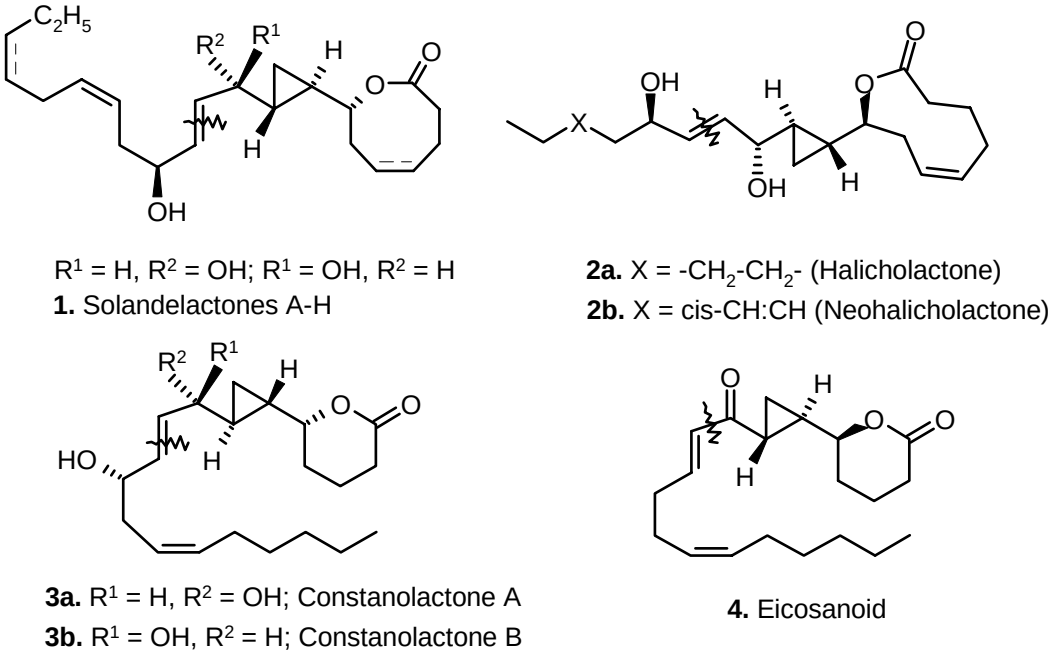
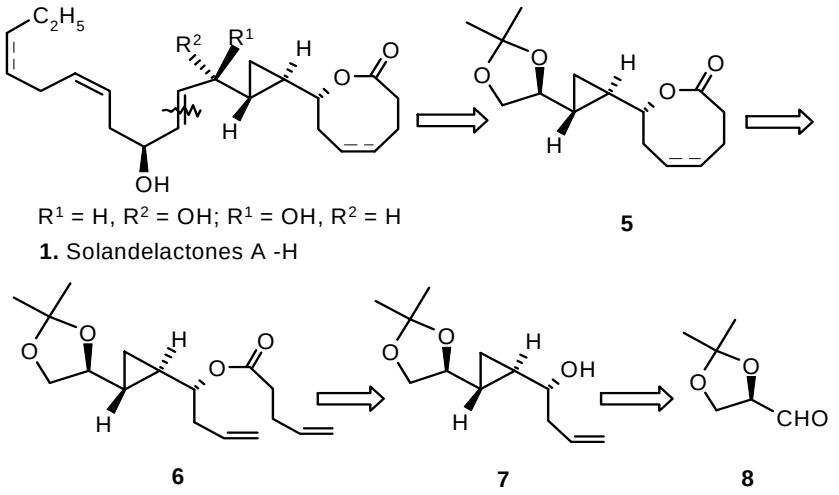


Figure 1. Some cyclopropyl-lactone containing oxylipins.

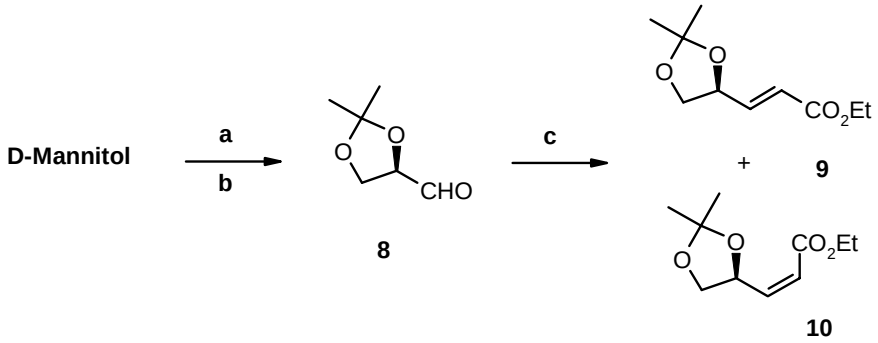
solandelactones with saturated and unsaturated eight-membered lactone rings and C_{22} carbon skeleton are thought to be of docosanoid precursor. We previously developed a highly convergent approach for the formal synthesis of solandelactones,[3a] which is crucial to the work described herein.



Scheme 1

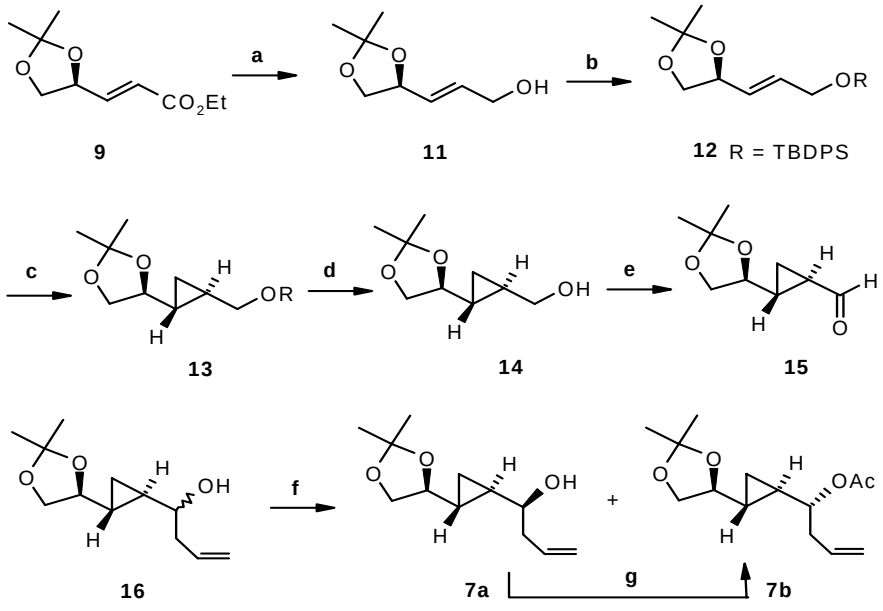
Results and Discussion

Our previous synthesis provided a method for the preparation of compound **7**.[3a] As outlined in the retrosynthetic analysis (Scheme 1), the chiral pool D-glyceraldehyde (**8**) was obtained from D-mannitol following the literature precedent.[12] Accordingly, D-mannitol was converted to corresponding 1,2,5,6-diacetonide followed by $NaIO_4$ assisted cleavage to provide D-glyceraldehyde (**8**), which was purified by vacuum distillation (b.p. 75-80^oC at 30 mm/Hg). D-Glyceraldehyde was then added to the refluxing solution of ethoxycarbonylmethylene triphenylphosphorane in benzene to give a mixture (*E: Z* = 9:1) of geometrical isomers **9** and **10** which were separated by flash chromatography. The predominant (*E*)-olefinic ester obtained after chromatographic separation from minor (*Z*)-isomer, was characterized by ^1H NMR spectroscopy.



Scheme 2. *Reagents and conditions:* (a) DMP, *p*-TSA, DMSO, rt, 68%; (b) $NaIO_4$ impregnated over silica gel, CH_2Cl_2, 0^oC, 78%; (c) $Ph_3P{=}CHCO_2Et$, C_6H_6, 90^oC, 82%.

The allyl alcohol **11** was secured in excellent yield through the reduction of ester **9** with DIBAL-H at –78°C in CH_2Cl_2. In the ^1H NMR of compound **11**, the olefinic proton resonated at 5.90 and 5.65 ppm as multiplets integrating for two protons and disappearance of signal due to methyl and methylene protons of ester functionality confirmed the structure. The optical rotation of compound **11** was found to be in agreement with the reported value $[\alpha]_D$ +32.5 (c 3.5, $CHCl_3$); lit.[13] $[\alpha]_D$ +33.9 (c 3.6, $CHCl_3$). The allylic alcohol was converted to its silyl ether **12** using TBDPSCl and imidazole in dry CH_2Cl_2 at 0°C. The next stage in our synthesis was the stereoselective cyclopropanation of compound **12**. This was accomplished by the standard modified Simmons-Smith cyclopropanation following Taguchi's protocol[14] using Et_2Zn and CH_2I_2 in 95% yield and with >98% de (Scheme 2). Compound **13** obtained showed identical spectral and physical characteristic to that in the literature.[14] The silyl ether was then deprotected by using TBAF in THF at 0°C to obtain the cyclopropyl methanol **14**. Compound **14** was then subjected to mild oxidation condition using IBX[15] to afford the aldehyde **15**. Subsequent addition of aldehyde **15** to allylmagnesium bromide in ether provided the homoallyl alcohol **7** and **7a** as 1:1 diastereomeric mixture in 89% yield, separable with difficulty by repeated column chromatography. This problem is however circumvented by subjecting the homoallyl alcohol mixture to *Candida cylindracea lipase* (CCL) catalyzed enzymatic resolution[16] and the resolution was remarkably high and did not acylate the (*S*)-alcohol **7a** even after prolonged exposure under same reaction condition.



Scheme 3. *Reagents and conditions:* (a) $^iBu_2AlH$, CH_2Cl_2, -78°C to 0°C, 80%; (b) $^tBuPh_2SiCl$, imidazole, CH_2Cl_2, 0°C to rt, 86%; (c) Et_2Zn, CH_2I_2, CH_2Cl_2, -78°C to –10°C, 95%; (d) Bu_4NF, THF, 0°C to rt, 82%; (e) H_2C=CH-CH_2MgBr, Et_2O, rt, 89%; (f) *Candida cylindracea lipase* (CCL) (cat.), H_2C=$C(CH_3)OAc$, hexane, 90% (**7a**/**7b** = 1:1); (g) DEAD, PPh_3, AcOH, THF, 0°C.

After enzymatic resolution, the stereochemical assignment of the secondary hydroxyl bearing centre was achieved following modified Mosher's method.[17] Accordingly, compound **7** was converted to its (*R*)- and (*S*)-(MTPA) ester with α-methoxy-α-(trifluoromethyl)phenyl acetic acid which showed negative chemical shift differences ($\Delta\delta = \delta_S - \delta_R$) for protons on C_1 through C_5 while protons on C_7 through C_9 showed positive differences, which is consistent with C_6 bearing an *R*-configuration (Fig. 2). Although this manipulation gave the desired product **7** along with **7a**, the undesired intermediate was easily converted into **7** in 74% yield via standard Mitsunobu protocol.

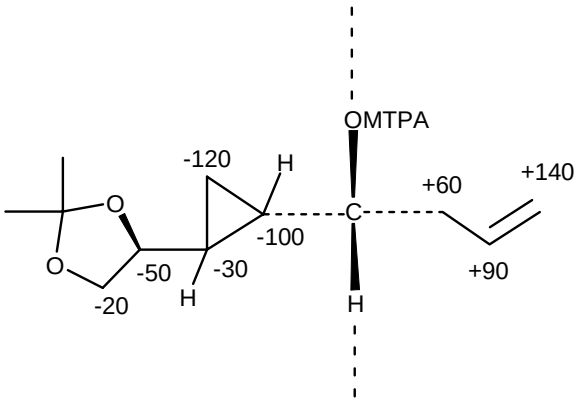
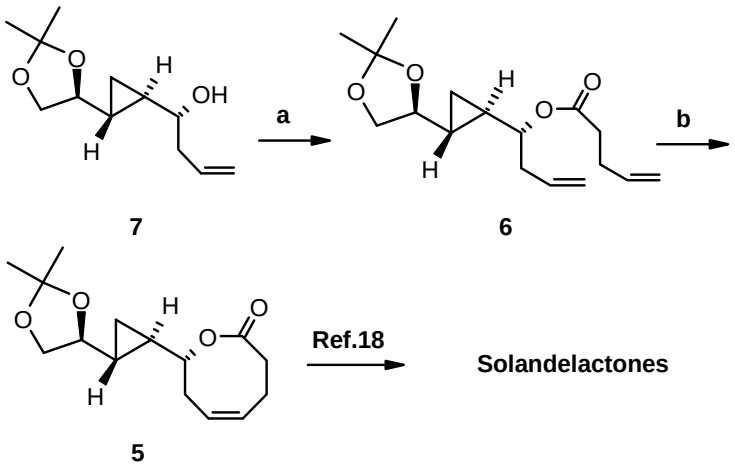


Figure 2. $\Delta\delta = (\delta_S - \delta_R) \times 10^3$ for (*R*)- and (*S*)-MTPA esters of compound **7**.

The next phase of our endeavor was the formation of eight-membered lactone ring with *Z*-double bond. Esterification of homoallyl alcohol **7** was achieved by the treatment with 4-pentenoyl chloride and Et_3N in CH_2Cl_2. The ring-closing metathesis of compound **6** under different reaction condition using Grubbs' $RuCl_2(=CHPh)\text{-}(PCy_3)_2$ catalyst (**I**) ended up with complete recovery of the starting material. When, we tried the RCM reaction with Grubbs' $RuCl_2(=CHPh)(PCy_3)(IEMS)$ catalyst (**II**) in the presence of catalytic amount of $Ti(O\textit{i}\text{-}Pr)_4$ under high dilution condition (0.001M in CH_2Cl_2 at reflux), the desired *Z*-isomer **5** was obtained in 71% yield along with the corresponding dimer (10%). It is worth mentioning that under low



Scheme 4. *Reagents and conditions:* (a) 4-pentenoyl chloride, Et_3N, CH_2Cl_2, 0°C to rt, 92%; (b) $RuCl_2(=CHPh)(PCy_3)$ (IEMS), $Ti(O\textit{i}\text{-}Pr)_4$, CH_2Cl_2, reflux, 71%.

dilution, the dimer compound was the major product obtained. The exclusive formation of the (*Z*)-isomer was confirmed by comparing the ^1H and ^{13}C NMR, IR, mass, and $[\alpha]_D$ value with the reported data.[3a] Had it been a mixture of (*Z*)- and (*E*)- isomer, we would have a complicated ^{13}C NMR spectrum. The chemical shifts of olefinic carbons appeared at 127.6 and 129.0 ppm indicating the presence of *cis*-double bond. The total synthesis of solandelactones (**1**) can be achieved by introducing the side chains using the synthetic protocol published for the synthesis of constanolactones (**3**).[18]

Conclusions

In summary, we have demonstrated the feasibility of achieving saturated and unsaturated lactone rings present in solandelactones employing ring-closing metathesis. The synthesis of right hand hemisphere of solandelactones disclosed herein is noteworthy for the simplicity of the C-C bond formation, which we believe will prove advantageous in the synthesis of related cyclopropyl and lactone containing oxylipins. Synthesis of other related biologically active compounds via RCM is the subject of current interest and will be reported in due course.

Experimental Section

General Procedures. Solvents were purified and dried by standard procedures before use. Column chromatography was carried out with silica gel (60-120 mesh). Infrared spectra were recorded with Shimadzu IR 470 and Perkin-Elmer 683 spectrometers. Proton NMR spectra were recorded on Bruker AC-200 machine in $CDCl_3$ with TMS as internal standard. Mass spectra

were obtained with Finningen MAT 1210 mass spectrometer. Optical rotations were measured with digital polarimeter. Elemental analysis was done on elemental analyzer model 1108 EA. All reactions were monitored on 0.25 mm E-Merck pre-coated silica gel (TLC) plates (60F-254) with UV or I_2, anisaldehyde reagent in ethanol. Light petroleum refers to mixture of hexanes with bp 60-80 ^oC.

Wittig Reaction

To a refluxing solution of carboethoxymethylene triphenylphosphorane (31.32g, 90.0 mmol) in benzene (200mL) was added slowly a solution of (*R*)-isopropylidene glyceraldehyde **8** (8.0g, 60 mmol) in benzene (50mL) via cannula. The reaction mixture was refluxed for 6h and cooled to room temperature. Benzene was evaporated under reduced pressure. The residue was triturated with diisopropyl ether (3x100mL) to discard the insoluble triphenylphosphine oxide. All diisopropyl ether portions were combined and concentrated. The crude compound was then purified by silica gel column chromatography using ethyl acetate/light petroleum ether (1:9) to afford 8.88g (74%) of (*E*)-isomer **9** and 0.96g (8%) of (*Z*)-isomer **10** (overall yield 82%).

Ethyl-3-[2,2,dimethyl-(4*R*)-1,3-dioxalan-4-yl]-(*E*)-propionate (9). Colorless liquid; ^1H NMR ($CDCl_3$) : δ 1.25 (t, *J* = 8.0 Hz, 3H), 1.32 (s, 3H), 1.40 (s, 3H), 3.62 (t, *J* = 8.8 Hz, 1H), 4.15 (m, 3H), 4.64 (m, 1H), 6.08 (d, *J* = 16.0 Hz, 1H), 6.85 (dd, *J* = 6.5 and 16.0 Hz, 1H); Anal. Calcd for $C_{10}H_{16}O_4$ (200.24): C, 60.02; H, 8.46. Found: C, 60.54; H, 8.27.

Ethyl-3-[2,2,dimethyl-(4*R*)-1,3-dioxalan-4-yl]-(*Z*)-propionate (10). Colorless liquid; ^1H NMR ($CDCl_3$) : δ 1.25 (t, *J* = 8.0 Hz, 3H), 1.38 (s, 3H), 1.45 (s, 3H), 3.65 (t, *J* = 8.2 Hz, 1H), 4.17 (q, *J* = 8.0 Hz, 2H), 4.36 (t, *J* = 8.0 Hz, 1H), 5.45 (m, 1H), 5.85 (d, *J* = 12.0 Hz, 1H), 6.35 (dd, *J* = 6.2 and 12.0 Hz, 1H); Anal. Calcd for $C_{10}H_{16}O_4$ (200.24): C, 60.02; H, 8.46. Found: C, 60.82; H, 8.46.

3-[2,2,Dimethyl-(4*S*)-1,3-dioxalan-4-yl]-(*E*)-2-propene-1-ol (11). To a solution of compound (*E*)-ester **9** (8.0g, 40 mmol) in anhydrous CH_2Cl_2 was added DIBAL-H solution (40.84 mL, 1M solution in toluene) at –78^{o}C. The solution was stirred for 1h at same temperature and allowed to warm to 0^{o}C slowly. After completion of the reaction (monitored by TLC), MeOH (20 mL) was added slowly followed by the addition of cold aqueous saturated sodium potassium tartrate (50 mL). The biphasic mixture was stirred for further 2h and then partitioned. Aqueous layer was extracted with CH_2Cl_2 (2x70 mL). Combined organic extracts were dried over Na_2SO_4 (anhydrous) and purified by silica gel column chromatography using ethyl acetate/light petroleum ether (1:4) to obtain 5.43g (86%) of pure allyl alcohol **11**. Colorless viscous liquid; $[\alpha]_D$ = +32.5 (c 3.5, $CHCl_3$), lit.[13] $[\alpha]_D$ = +33.9 (c 3.6, $CHCl_3$); ^1H NMR ($CDCl_3$) : δ 1.35 (s, 3H), 1.40 (s, 3H), 1.45 (s, 3H), 3.56 (t, *J* = 6.2 Hz, 1H), 4.12 (m, 3H), 4.52 (m, 1H), 5.65 (m, 1H), 5.88 (m, 1H); Anal. Calcd for $C_8H_{14}O_3$ (158.20): C, 60.73; H, 8.91. Found: C, 60.24; H, 8.96.

(1*E*)-(4*S*)-3-[(*tert*-Butyldiphenylsilyl)oxy]-1-(2,2,dimethyl-1,3-dioxalan-4-yl)-1-propene (12). To a solution of allyl alcohol **11** (5.0g, 31.64 mmol) in anhydrous CH_2Cl_2 (40 mL) was added imidazole (6.45g, 94.92 mmol) at 0^{o}C. The reaction mixture was then stirred for 15 min. at the same temperature and TBDPS-Cl (9.65 mL, 37.96 mmol) was added. The reaction mixture was

allowed to warm to room temperature and stirred overnight. After completion of the reaction (monitored by TLC), H_2O (20 mL) was added to it. Organic layer was separated and aqueous layer was extracted with CH_2Cl_2 (2x50 mL). Combined organic extracts were washed successively with water, brine, dried over Na_2SO_4 (anhydrous) and purified by silica gel column chromatography using 5% ethyl acetate/light petroleum ether to afford 10.0g (80%) of pure silyl ether **12**. Colorless liquid; $[\alpha]_D$ = +22.4 (c 1.2, $CHCl_3$), lit.[14] $[\alpha]_D$ = +23.0 (c 1.11, $CHCl_3$); ^{1}H NMR ($CDCl_3$) : δ 0.98 (s, 9H), 1.25 (s, 3H), 1.34 (s, 3H), 3.46 (t, *J* = 6.7 Hz, 1H), 3.98 (m, 1H), 4.12 (d, *J* = 5.7 Hz, 2H), 4.30 (q, *J* = 6.6 Hz, 1H), 5.67 (m, 2H), 7.30 (m, 6H), 7.54 (m, 4H); Anal. Calcd for $C_{24}H_{32}SiO_3$ (396.61): C, 72.68; H, 8.13. Found: C, 72.94; H, 8.42.

(1*R*, 2*R*, 4*S*)-2-[(*tert*-Butyldiphenylsilyl)oxy]methyl-1-(2,2,dimethyl-1,3-dioxalan-4-yl)-1-cyclopropane (13). Et_2Zn (142.5 mL, 115.9 mmol, 1M solution in hexane) was added dropwise to a clear solution of TBDPS-ether **12** (9.5g, 23.2 mmol) in anhydrous CH_2Cl_2 (200 mL) at -78°C. After 10 min, CH_2I_2 (9.3 mL, 115.9 mmol) was added through syringe. The reaction mixture was stirred at the same temperature for 4h and then at 0°C for 20h. The reaction mixture was poured into a saturated solution of NH_4Cl. Organic layer was separated and aqueous layer was extracted with CH_2Cl_2 (2x100 mL). Combined organic extracts were washed successively with water, brine, dried over Na_2SO_4 (anhydrous) and purified by silica gel column chromatography using ethyl acetate/light petroleum ether (1:19-1:9) to give 9.34g (95%) of pure cyclopropyl derivative **13**. Colorless liquid; $[\alpha]_D$ = -7.6 (c 1.2, $CHCl_3$), lit.[14] $[\alpha]_D$ = -7.9 (c 1.1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) : δ 0.54 (m, 2H), 0.72 (m, 1H), 0.96 (m, 1H), 1.05 (s, 9H), 1.35 (s, 3H), 1.40 (s, 3H), 3.46 (m, 2H), 3.68 (m, 2H), 4.05 (m, 1H), 7.36 (m, 6H), 7.64 (m, 4H); Anal. Calcd for $C_{25}H_{34}SiO_3$ (410.64): C, 73.12; H, 8.34. Found: C, 72.94; H, 8.76.

2-[2,2-Dimethyl-(4*S*)-1,3-dioxalan-4-yl]-(1*R*, 2*R*)-cyclopropyl methanol (14). To a stirred solution of cyclopropyl compound **13** (9.0g, 22.0 mmol) in anhydrous THF (50 mL) at 0°C, was added tetrabutyl ammonium fluoride (32.9 mL, 32.9 mmol, 1M solution in THF) dropwise and stirring was continued for 1h at 0°C. The reaction mixture was then brought to room temperature and stirred overnight. The solvent was removed under reduced pressure and the crude product was purified by silica gel column chromatography using ethyl acetate/light petroleum ether (1:4) to afford 3.25g (86%) of pure cyclopropyl methanol **14**. Colorless liquid; $[\alpha]_D$ = +16.5 (c 1.25, $CHCl_3$); ^{1}H NMR ($CDCl_3$) : δ 0.52 (m, 2H), 0.82 (m, 1H), 0.95 (m, 1H), 1.25 (s, 3H), 1.37 (s, 3H), 3.34 (m, 1H), 3.55 (m, 3H), 4.05 (m, 1H); Anal. Calcd for $C_9H_{16}O_3$ (172.23): C, 62.76; H, 9.36. Found: C, 62.84; H, 9.72.

2-[2,2,Dimethyl-(4*S*)-1,3-dioxalan-4-yl]-(1*R*, 2*R*)-cyclopropane-1-carboxaldehyde (15). To a stirred solution of 2-iodoxybenzoic acid (IBX) (7.81g, 27.9 mmol) in DMSO (20 mL), was added a solution of cyclopropyl methanol **14** (3.2g, 18.6 mmol) in anhydrous THF (10 mL) at room temperature and stirring was continued for further 6h. After completion of the reaction (monitored by TLC), H_2O (10 mL) was added to the reaction mixture, precipitated solid was filtered off and the filtrate was diluted with H_2O (50 mL) and extracted with ether (4x50 mL). The combined organic layers were washed successively with aqueous $NaHCO_3$, H_2O, brine and dried over Na_2SO_4 (anhydrous). The solvent was removed under reduced pressure and the crude

product was purified by silica gel column chromatography using ethyl acetate/light petroleum ether (1:6) to afford 2.97g (94%) of pure cyclopropyl aldehyde **15**. Colorless liquid; ^{1}H NMR ($CDCl_3$) : δ 1.25 (m, 2H), 1.35 (s, 3H), 1.40 (s, 3H), 1.65 (m, 1H), 1.87 (m, 1H), 3.68 (t, *J* = 6.2 Hz, 1H), 3.84 (m, 1H), 4.10 (m, 1H), 9.18 (d, *J* = 6.2 Hz, 1H); Anal. Calcd for $C_9H_{14}O_3$ (170.21): C, 63.50; H, 8.28. Found: C, 62.94; H, 8.36.

Grignard reaction

To an ice cooled solution of aldehyde **15** (2.9g, 17.0 mmol) in anhydrous ether (20 mL) was added dropwise to an ether solution of allyl magnesium bromide [prepared from allyl bromide (2.94 mL, 34.0 mmol) and Mg (1.22g, 51.0 mmol) in ether (50 mL)] and stirring was continued for 3h at room temperature. The reaction mixture was then quenched with 5% HCl (20 mL) and extracted with ethyl acetate (3x50 mL). The combined organic layers were washed successively with aqueous $NaHCO_3$, H_2O, brine and dried over Na_2SO_4 (anhydrous). The solvent was removed under reduced pressure and the crude product was purified by silica gel column chromatography using ethyl acetate/light petroleum ether (1:4) to afford 3.14g (87%) of pure homoallyl alcohol diastereomers **16**.

1-[2-[(2,2)-Dimethyl-(4*S*)-1,3-dioxalan-4-yl]-(1*R*,2*R*)-cyclopropyl]-(1*S*)-3-buten-1-ol (7). Colorless liquid; ^{1}H NMR ($CDCl_3$) : δ 0.40-0.70 (m, 2H), 0.77-1.06 (m, 2H), 1.28 (s, 3H), 1.44 (s, 3H), 2.30 (m, 2H), 3.05 (m, 1H), 3.65 (m, 3H), 4.06 (m, 2H), 5.10 (m, 2H), 5.84 (m, 1H); ^{13}C NMR ($CDCl_3$): 7.9, 18.7, 21.6, 25.6, 26.7, 69.2, 73.9, 79.1, 108.8, 118.0, 134.3; Anal. Calcd for $C_{12}H_{20}O_3$ (212.29): C, 67.89; H, 9.49. Found: C, 68.24; H, 9.57.

1-[2-[(2, 2)-Dimethyl-(4*S*)-1,3-dioxalan-4-yl]-(1*R*,2*R*)-cyclopropyl]-(1*R*)-3-buten-1-ol (7a). Colorless liquid; δ 0.60 (m, 2H), 0.86 (m, 2H), 1.28 (s, 3H), 1.42 (s, 3H), 1.68 (br s, 1H), 2.30 (m, 2H), 3.07 (m, 1H), 3.60 (m, 2H), 4.16 (m, 1H), 5.15 (m, 2H), 5.84 (m, 1H); ^{13}C NMR ($CDCl_3$): 7.9, 18.7, 21.6, 25.6, 26.7, 69.2, 73.9, 79.1, 108.8, 118.0, 134.3; Anal. Calcd for $C_{12}H_{20}O_3$ (212.29): C, 67.89; H, 9.49. Found: C, 67.55; H, 9.26.

4-[2-[(2,2)-Dimethyl-(4*S*)-1,3-dioxalan-4-yl]-(1*R*,2*R*)-cyclopropyl]-4-methyl carbonyloxy buten-1-ol (7b). To a stirred solution of homoallyl alcohol **16** (diastereomeric mixture) (3.0g, 14.2 mmol) in anhydrous hexane (20 mL) was added isopropenyl acetate (9.46 mL, 85.2 mmol) followed by Candida cylindracea lipase (CCL) (0.5g). The reaction mixture was stirred for 24h. The solid was then filtered off and solvent was removed under reduced pressure. The crude residue was purified by silica gel column chromatography using ethyl acetate/light petroleum ether (1:19-1:5) to afford 1.65g (46%) of pure homoallyl acetate **7b** and 1.2g (43%) of homoallyl alcohol **7a** (total 89% yield). Colorless liquid; δ 0.62 (m, 2H), 0.88 (m, 2H), 1.28 (s, 3H), 1.42 (s, 3H), 2.04 (s, 3H), 2.36 (m, 2H), 3.57 (m, 2H), 4.04 (m, 1H), 4.38 (m, 1H), 5.15 (m, 2H), 5.78 (m, 1H); ^{13}C NMR ($CDCl_3$): 8.3, 19.1, 19.4, 21.0, 26.6, 26.7, 39.0, 69.1, 75.7, 78.6, 108.9, 117.8, 133.4, 170.3.

Mitsunobu reaction

To a solution of **7a** (1.2g, 5.66 mmol) in anhydrous THF (30 mL) was added PPh_3 (4.45g, 16.98 mmol) and glacial acetic acid (1 mL) and the resultant mixture was cooled to 0°C. To it, diethyl azodicarboxylate (DEAD) (3.13 mL, 19.81 mmol) diluted with anhydrous THF (5 mL) was added dropwise. The reaction mixture was then brought to room temperature and stirred overnight. After removal of the solvent, the residue was taken in CH_2Cl_2 and was washed successively with aqueous $NaHCO_3$, H_2O, brine and dried over Na_2SO_4 (anhydrous). The solvent was removed under reduced pressure and the crude product was dissolved in MeOH and treated with K_2CO_3 (0.3g). The solid was then filtered off, filtrate concentrated and the residue was purified by silica gel column chromatography using ethyl acetate/light petroleum ether (1:5) to afford 0.91g (76% after two steps) of pure homoallyl alcohol **7**.

(*S*)-Mosher's ester. To a solution of **7** (20mg, 0.1 mmol) in anhydrous CH_2Cl_2 (1 mL) was added *S*-(-)- α -methoxy- α -(trifluoromethyl)phenyl acetic acid (*S*-MTPA) (35mg, 0.156 mmol) N,N-dicyclohexyl carbodiimide (DCC) (30 mg, 0.17 mmol) and catalytic amount of DMAP. The reaction mixture was stirred overnight at room temperature. The solid was filtered off, filtrate concentrated and the residue was purified by silica gel column chromatography using ethyl acetate/light petroleum ether (1:19) to afford 35mg (80%) of pure (*S*)-MTPA ester. ^{1}H NMR ($CDCl_3$) δ 0.64 (m, 1H), 0.77 (m, 1H), 0.94 (m, 2H), 1.31 (s, 3H), 1.39 (s, 3H), 2.50 (m, 2H), 3.59 (m, 6H), 3.98 (m, 1H), 4.67 (m, 1H), 5.15 (m, 2H), 5.75 (m, 1H), 7.40 (m, 3H), 7.53 (m, 2H).

(*R*)-Mosher's ester. To a solution of **7** (20mg, 0.1 mmol) in anhydrous CH_2Cl_2 (1 mL) was added *R*-(-)- α -methoxy- α -(trifluoromethyl)phenyl acetic acid (*R*-MTPA) (35mg, 0.156 mmol) N,N-dicyclohexyl carbodiimide (DCC) (30 mg, 0.17 mmol) and catalytic amount of DMAP. The reaction mixture was stirred overnight at room temperature. The solid was filtered off, filtrate concentrated and the residue was purified by silica gel column chromatography using ethyl acetate/light petroleum ether (1:19) to afford 35mg (80%) of pure (*R*)-MTPA ester. ^{1}H NMR ($CDCl_3$) δ 0.74 (m, 1H), 0.80 (m, 1H), 1.06 (m, 2H), 1.32 (s, 3H), 1.41 (s, 3H), 2.44 (m, 2H), 3.61 (m, 6H), 4.03 (m, 1H), 4.60 (m, 1H), 5.06 (m, 2H), 5.61 (m, 1H), 7.40 (m, 3H), 7.54 (m, 2H).

Pent-4-enoic acid-1-[2-(2,2-dimethyl-[1,3]dioxalan-4-yl)-cyclopropyl]-but-3-enyl ester (6). To a solution of **7** (0.2g, 0.94 mmol) in anhydrous CH_2Cl_2 (10 mL) was added Et_3N (0.19 mL, 1.41 mmol) at 0°C and stirred for 10 min at the same temperature. To it, 4-pentenoylchloride (0.1 mL, 1.12 mmol) was added. The reaction mixture was then brought to room temperature. After completion of the reaction (monitored by TLC), the solid was filtered off, filtrate concentrated and the residue was purified by silica gel column chromatography using ethyl acetate/light petroleum ether (1:19) to afford 0.255g (92%) of pure compound **6**.

Colorless viscous liquid; $[\alpha]_D$ –12.86 (c 1.05, $CHCl_3$); IR(neat) 1738 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.63 (m, 1H), 0.72 (m, 1H), 0.89 (m, 1H), 0.95 (m, 1H), 1.32 (s, 3H), 1.40 (s, 3H), 2.37 (m, 6H), 3.61 (m, 2H), 4.03 (m, 1H), 4.43 (m, 1H), 5.07 (m, 4H), 5.77 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 8.06, 19.09, 25.58, 26.62, 28.84, 33.61, 39.03, 68.93, 75.46, 78.21, 108.73, 115.37,

117.62, 133.35, 136.48, 171 .97; EIMS: m/z [280, (MH^+-CH_3)]; Anal. Calcd. For $C_{17}H_{26}O_4$ (294.39): C, 69.36; H, 8.90; Found: C, 69.51; H, 9.49.

8-[2(2,2-Dimethyl-[1,3]dioxalan-4-yl)-cyclopropyl]-3,4,7,8-tetrahydro-oxacin-2-one (5). A solution of **6** (0.1g, 0.34 mmol) and freshly distilled Ti(O*i*-Pr)$_4$ (0.01 mL, 0.03mmol) in anhydrous CH_2Cl_2 (200 mL) was refluxed for 2h under an argon atmosphere. Grubbs' "second generation" catalyst (20 mg) in dry CH_2Cl_2 (5 mL) was added to it. The reaction mixture was then refluxed for 48h. After completion of the reaction (monitored by TLC), the reaction mixture was filtered through a pad of silica gel. The organic solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography using ethyl acetate/light petroleum ether (1:9) to afford 64mg (71%) of pure compound **5**. Colorless liquid; $[\alpha]_D$ – 4.58 (c 0.4, $CHCl_3$), lit.[3a] $[\alpha]_D$ = - 4.66 (c 0.9, $CHCl_3$); IR(neat) 1746 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.63 (m, 1H), 0.71 (m, 1H), 0.96 (m, 2H), 1.31 (s, 3H), 1.40 (s, 3H), 2.25-2.44 (m, 6H), 3.61 (m, 2H), 4.02 (m, 1H), 4.40 (m, 1H), 5.10 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 9.45, 18.94, 19.03, 25.62, 26.72, 27.26, 33.91, 36.93, 69.05, 76.28, 78.88, 109.11, 127.64, 129.02, 172.67; EIMS : m/z [252, (MH^+ - CH_3)]; Anal. Calcd. For $C_{15}H_{22}O_4$ (266.34) : C, 67.65; H, 8.33; Found: C, 68.28; H, 7.83.

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