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 RuCl2(=CHPh)(PCy3)(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. A number of natural products contain medium-sized saturated as well as unsaturated lactone rings. 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 under high dilution condition or Bayer-Villiger 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 and halicholactone 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. 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,

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\text{Figure 1. Some cyclopropyl-lactone containing oxylipins.}
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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,\(^5a\) which is crucial to the work described herein.
Results and Discussion

Our previous synthesis provided a method for the preparation of compound 7.\textsuperscript{3a} As outlined in the retrosynthetic analysis (Scheme 1), the chiral pool D-glyceraldehyde (8) was obtained from D-mannitol following the literature precedent.\textsuperscript{12} Accordingly, D-mannitol was converted to corresponding 1,2,5,6-diacetonide followed by NaIO\textsubscript{4} assisted cleavage to provide D-glyceraldehyde (8), which was purified by vacuum distillation (b.p. 75-80°C 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 \textsuperscript{1}H NMR spectroscopy.

\begin{equation}
\text{D-Mannitol} \xrightarrow{a} \text{8} \xrightarrow{b} \text{CHO} \xrightarrow{c} 9, 10
\end{equation}

**Scheme 2.** \textit{Reagents and conditions}: (a) DMP, \textit{p}-TSA, DMSO, rt, 68%; (b) NaIO\textsubscript{4} impregnated over silica gel, CH\textsubscript{2}Cl\textsubscript{2}, 0°C, 78%; (c) Ph\textsubscript{3}P=CHCO\textsubscript{2}Et, C\textsubscript{6}H\textsubscript{6}, 90°C, 82%.
The allyl alcohol 11 was secured in excellent yield through the reduction of ester 9 with DIBAL-H at –78°C in CH₂Cl₂. 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 [α]₀ +32.5 (c 3.5, CHCl₃); lit.¹³ [α]₀ +33.9 (c 3.6, CHCl₃). The allylic alcohol was converted to its silyl ether 12 using TBDPSCl and imidazole in dry CH₂Cl₂ 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 protocol¹⁴ using Et₂Zn and CH₂I₂ 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 IBX¹⁵ 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 resolution¹⁶ 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) iBu₂AlH, CH₂Cl₂, -78°C to 0°C, 80%; (b) iBuPh₂SiCl, imidazole, CH₂Cl₂, 0°C to rt, 86%; (c) Et₂Zn, CH₂I₂, CH₂Cl₂, -78°C to -10°C, 95%; (d) Bu₄NF, THF, 0°C to rt, 82%; (e) H₂C=CH-CH₂MgBr, Et₂O, rt, 89%; (f) Candida cylindracea lipase (CCL) (cat.), H₂C=C(CH₃)OAc, hexane, 90% (7a/7b = 1:1); (g) DEAD, PPh₃, AcOH, THF, 0°C.
After enzymatic resolution, the stereochemical assignment of the secondary hydroxyl bearing centre was achieved following modified Mosher’s method. 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.

$\Delta \delta = (\delta_S - \delta_R) \times 10^3$ 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$_3$N in CH$_2$Cl$_2$. The ring-closing metathesis of compound 6 under different reaction condition using Grubbs’ RuCl$_3$(=CHPh)-(PC$_3$)$_2$ catalyst (I) ended up with complete recovery of the starting material. When, we tried the RCM reaction with Grubbs’ RuCl$_2$(=CHPh)(PC$_3$)(IEMS) catalyst (II) in the presence of catalytic amount of Ti(Oi-Pr)$_4$ under high dilution condition (0.001M in CH$_2$Cl$_2$ 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
dilution, the dimer compound was the major product obtained. The exclusive formation of the (Z)-isomer was confirmed by comparing the $^1$H and $^{13}$C NMR, IR, mass, and $[\alpha]_D$ value with the reported data.\textsuperscript{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).\textsuperscript{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

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**Scheme 4.** Reagents and conditions: (a) 4-pentenoyl chloride, Et$_3$N, CH$_2$Cl$_2$, 0°C to rt, 92%; (b) RuCl$_2$(=CHPh)(PCy$_3$)$_2$ (IEMS), Ti(Oi-Pr)$_4$, CH$_2$Cl$_2$, reflux, 71%.

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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 I₂, anisaldehyde reagent in ethanol. Light petroleum refers to mixture of hexanes with bp 60-80 °C.

**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-(4R)-1,3-dioxalan-4-yl]-[(E)-propionate (9).** Colorless liquid; ¹H NMR (CDCl₃) : 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 C₁₀H₁₆O₄ (200.24): C, 60.02; H, 8.46. Found: C, 60.54; H, 8.27.

**Ethyl-3-[2,2,dimethyl-(4R)-1,3-dioxalan-4-yl]-[(Z)-propionate (10).** Colorless liquid; ¹H NMR (CDCl₃) : 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 C₁₀H₁₆O₄ (200.24): C, 60.02; H, 8.46. Found: C, 60.82; H, 8.46.

**3-[2,2,Dimethyl-(4S)-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 CH₂Cl₂ was added DIBAL-H solution (40.84 mL, 1M solution in toluene) at –78 °C. The reaction mixture was then stirred for 1h at the same temperature and allowed to warm to 0 °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 CH₂Cl₂ (2x70 mL). Combined organic extracts were dried over Na₂SO₄ (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; [α]D = +32.5 (c 3.5, CHCl₃), lit. ¹H NMR (CDCl₃) : 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 C₈H₁₄O₃ (158.20): C, 60.73; H, 8.91. Found: C, 60.24; H, 8.96.

**(1E)-(4S)-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 CH₂Cl₂ (40 mL) was added imidazole (6.45g, 94.92 mmol) at 0 °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$_2$O (20 mL) was added to it. Organic layer was separated and aqueous layer was extracted with CH$_2$Cl$_2$ (2x50 mL). Combined organic extracts were washed successively with water, brine, dried over Na$_2$SO$_4$ (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; [α]$_D$ = +22.4 (c 1.2, CHCl$_3$), lit. $^{14}$ [α]$_D$ = +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$_2$Zn (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$_2$Cl$_2$ (200 mL) at -78°C. After 10 min, CH$_2$I$_2$ (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$_4$Cl. Organic layer was separated and aqueous layer was extracted with CH$_2$Cl$_2$ (2x100 mL). Combined organic extracts were washed successively with water, brine, dried over Na$_2$SO$_4$ (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; [α]$_D$ = -7.6 (c 1.2, CHCl$_3$), lit. $^{14}$ [α]$_D$ = -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 washed with ethyl acetate/light petroleum ether (1:19) to give 9.34g (95%) of pure cyclopropyl methanol 14. Colorless liquid; [α]$_D$ = +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$_9$H$_{16}$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-(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$_2$O (10 mL) was added to the reaction mixture, precipitated solid was filtered off and the filtrate was diluted with H$_2$O (50 mL) and extracted with ether (4x50 mL). The combined organic layers were washed successively with aqueous NaHCO$_3$, H$_2$O, brine and dried over Na$_2$SO$_4$ (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\(_3\)) : \(\delta\) 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\(_9\)H\(_{14}\)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\(_2\)O, brine and dried over Na\(_2\)SO\(_4\) (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)-Dimethyl-(4S)-1,3-dioxalan-4-yl]-1(R,2R)-cyclopropyl]-1S)-3-buten-1-ol (7). Colorless liquid; \(^1\)H NMR (CDCl\(_3\)) : \(\delta\) 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)-Dimethyl-(4S)-1,3-dioxalan-4-yl]-1(R,2R)-cyclopropyl]-1R)-3-buten-1-ol (7a). Colorless liquid; \(\delta\) 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)-Dimethyl-(4S)-1,3-dioxalan-4-yl]-1(R,2R)-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; \(\delta\) 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 PPh3 (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 CH2Cl2 and was washed successively with aqueous NaHCO3, H2O, brine and dried over Na2SO4 (anhydrous). The solvent was removed under reduced pressure and the crude product was dissolved in MeOH and treated with K2CO3 (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 CH2Cl2 (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. 1H NMR (CDCl3) 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 CH2Cl2 (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. 1H NMR (CDCl3) 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 CH2Cl2 (10 mL) was added Et3N (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; [α]D −12.86 (c 1.05, CHCl3); IR(neat) 1738 cm−1; 1H NMR (CDCl3) 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); 13C NMR (125 MHz, CDCl3) 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$^+\cdot$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(Oi-Pr)$_4$ (0.01 mL, 0.03mmol) in anhydrous CH$_2$Cl$_2$ (200 mL) was refluxed for 2h under an argon atmosphere. Grubbs’ “second generation” catalyst (20 mg) in dry CH$_2$Cl$_2$ (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; [α]$_D$ – 4.58 (c 0.4, CHCl$_3$), lit.$^{3a}$ [α]$_D$ = - 4.66 (c 0.9, CHCl$_3$); IR(neat) 1746 cm$^{-1}$; $^1$H 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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References


