

Studies towards the total synthesis of halicholactone and neohalicholactone: a stereoselective synthesis of C1-C13 fragment

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

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Abstract

A stereoselective synthesis of C1-C13 fragment of halicholactone (**1a**) and neohalicholactone (**1b**) starting from (*R*)-isopropylidene glyceraldehyde is described. Key transformations include Simmons-Smith cyclopropanation, stereoselective reduction, ring-closing metathesis (RCM).

Keywords: Oxylipins, halicholactone, cyclopropane, ring-closing metathesis, homoallyl alcohol

Introduction

Discovery in early 1960 that the marine coral *Plexaura homomalla* produces enormous quantities of prostaglandins¹ initiated a fascinating era in the field of natural products chemistry. After this discovery, a number of secondary and non-primary metabolites produced from marine organisms have been studied extensively which often possess unusual and sometime unexpected biological activities. Interest on the part of chemists have been two fold, natural product chemists have investigated marine organisms as source of the new and unusual molecules, while synthetic organic chemists have followed by targeting these novel structures for development of new analogues and new synthetic methodologies and strategies. In 1989, secondary metabolites halicholactone (**1a**) and neohalicholactone (**1b**) showing lipoxygenase inhibitor activity were isolated from the marine sponge *Halichondria okadai* by the Yamada group.² The structure of halicholactone (**1a**) and neohalicholactone (**1b**) were originally formulated on the basis of spectroscopic data and partial degradation and the relative stereochemistry by X-ray diffraction analysis of neohalicholactone (**1b**).³ It is likely that the halicholactone originates from transformation analogous to those represented for the constanolactones except initiated through a 15-lipoxygenase introduced hydroperoxide.

The elegant structural and stereochemical features of halicholactone (**1a**) and neohalicholactone (**1b**) (Figure 1) decorated with dense functionalities that include an unsaturated nine-membered lactone, a *trans*-disubstituted cyclopropane ring and five stereocenters present a considerable challenge as synthetic targets, particularly with respect to stereochemistry and functional group sensitivity, attracted our attention to undertake its synthesis. Although, a few number of partial and total synthesis have been reported,⁴ the stereoselective construction of the stereogenic centers of C-9 to C-12 is still remained to be solved.

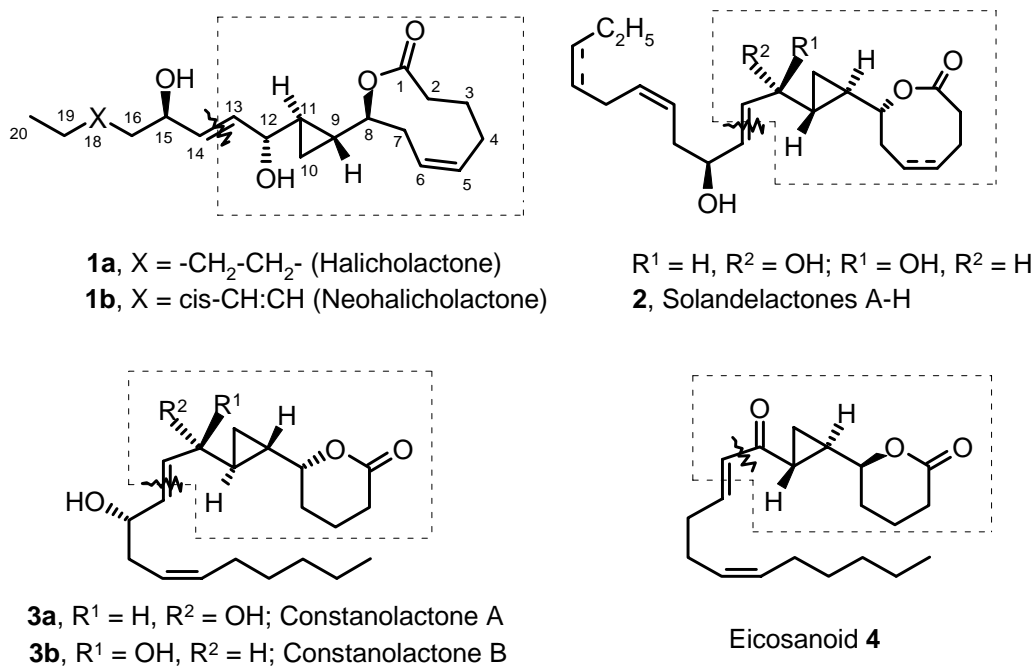
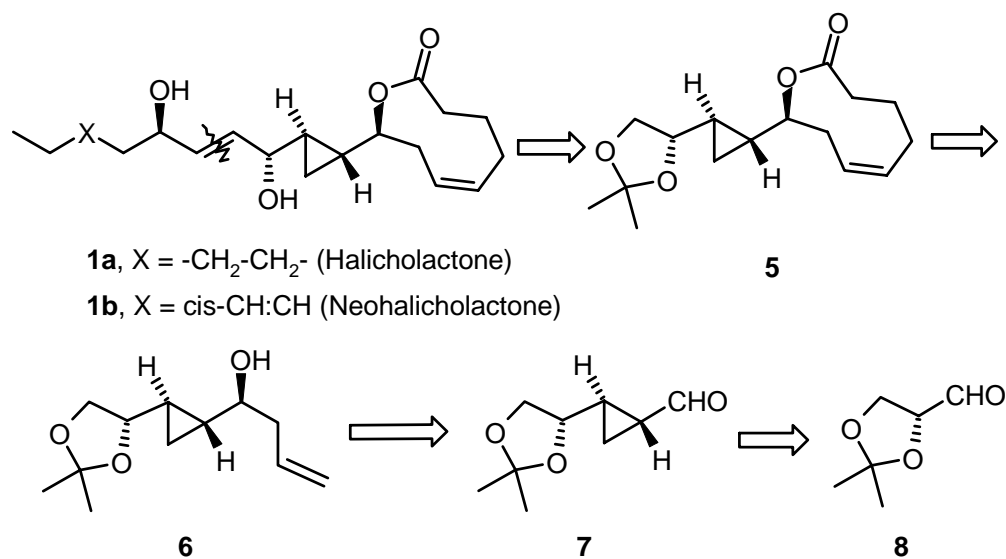


Figure 1. Some cyclopropyl-lactone containing oxylipins.

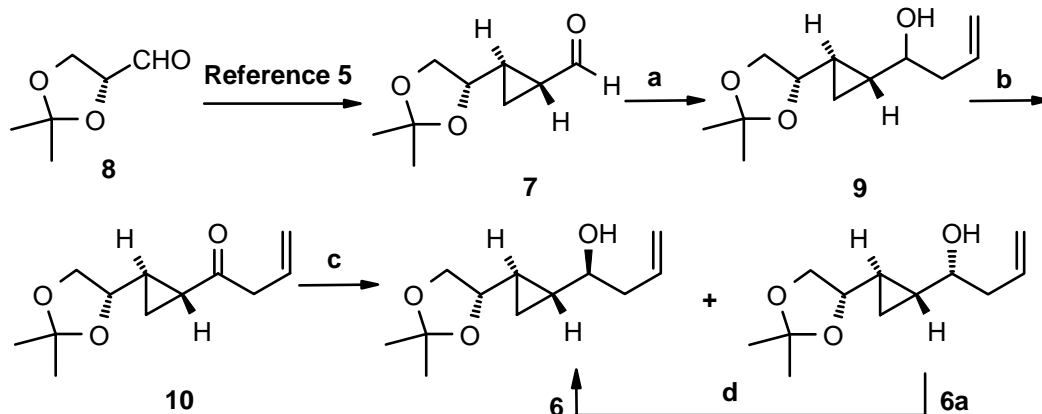
Our interest for the synthesis of natural products in a concise manner and to fix the stereogenic centers from C-9 to C-12 of halicholactone (**1a**) and neohalicholactone (**1b**), described herein is an efficient chiral pool approach taking (*R*)-2,3-*O*-isopropylidene glyceraldehyde (**8**) as the starting material as depicted in the retrosynthetic analysis (Scheme 1).



Scheme 1

Results and Discussion

From the retrosynthetic analysis of halicholactone (**1a**) and neohalicholactone (**1b**) (Scheme 1), the (*R*)-2, 3-*O*-isopropylidene glyceraldehyde (**8**) was chosen as suitable starting material which was converted to cyclopropyl carboxaldehyde **7** following the method reported by us.⁵ Subsequent addition of aldehyde **7** to allylmagnesium bromide in ether provided the homoallyl alcohol **6** and **6a** 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 oxidation under IBX⁶ condition and selective reduction of the keto-compound **10** with K-selectride⁶ provided the diastereomers **6** and **6a** in the ratio of 9:1. The diastereomers were separated by column chromatography (Scheme 2). The selectivity in reduction was rationalized on the basis of chelation controlled Cram's model. Interaction between cyclopropyl C-C bonds and carbonyl π orbitals is maximized when the cyclopropyl and carbonyl groups are oriented orthogonally. Both the bisect *S*-(*cis*) conformation and *S*-(*trans*) conformation are able to provide maximum stabilization. Mark Lautens *et al.* reported that treatment of tributylsilyl cyclopropyl ketone with LiBH₄ resulted in a diastereomeric mixture of 2.5:1 and explained the stereoselectivity by proposing the following *S*-(*cis*) model.⁷ But S. Shuto and co-workers reported the reverse stereoselectivity with DIBAL-H (Figure 2) and it was explained by *S*-(*trans*) model.⁸



Scheme 2. Reagents and conditions: (a) H₂C=CH-CH₂MgBr, Et₂O, rt, (**6/6a** = 1:1), 87%; (b) IBX, DMSO, THF, 3h, 90%; (c) K-selectride, THF, -78°C, 4h, (**6/6a** = 9:1), 87%; (d) (1) DEAD, PPh₃, AcOH, THF, 0°C; (2) K₂CO₃, MeOH, rt, 2h, 76% over two steps.

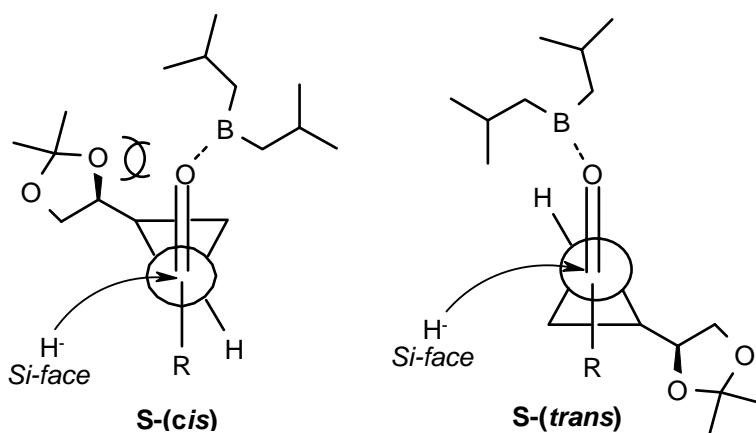


Figure 2. Conceivable transition states of the hydride reduction of cyclopropyl ketones.

When DIBAL-H is coordinated to the carbonyl group, due to steric repulsion between the two bulky isobutyl group and the substituent in the cyclopropyl group, *S*-(*trans*) conformation is preferred. The same argument holds true in the case of K-selectride, which demands a lot of steric repulsion due to its three *sec*-butyl groups. The newly created secondary hydroxyl group bearing center was assigned following modified Mosher's method.⁹ Accordingly, minor isomer **6a** 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 C₁ through C₅ while protons on C₇ through C₉ showed positive differences, which is consistent with C₆ bearing an *R*-configuration (Figure 3). The major *S*-isomer was the result of the hydride attack from the less hindered *Re*-face in the *S*-(*trans*) conformation. Although this manipulation gave

the desired product **6** along with **6a**, the undesired intermediate was easily converted into **6** in 71% yield over two steps *via* standard Mitsunobu protocol.¹⁰

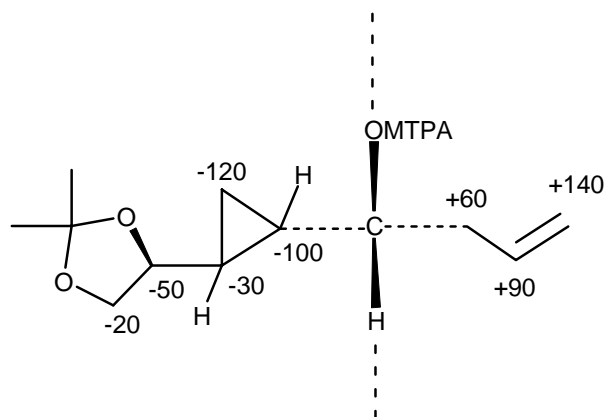
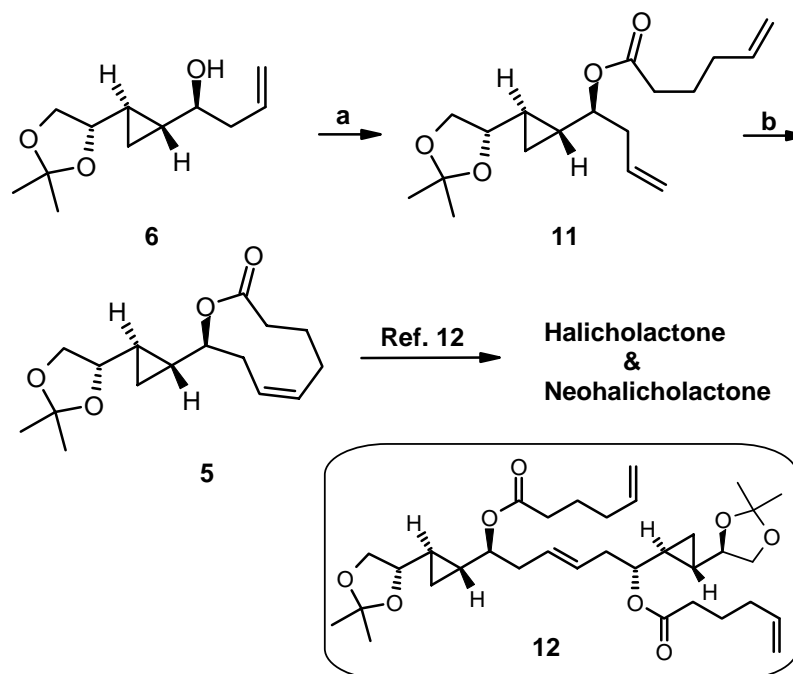


Figure 3. $\Delta\delta = (\delta_S - \delta_R) \times 10^3$ for (*R*)- and (*S*)-MTPA esters of compound **6a**.

Having obtained the required homoallyl alcohols starting from (*R*)-2, 3-*O*-isopropylidene glyceraldehyde (**8**) in high yield and good selectivity, the next job was to construct the nine-membered lactone ring with *Z*-double bond. The required isomer **6** was then treated with 5-hexenoic acid and EDCI in CH_2Cl_2 to afford the ester **11** in 92% yield. The spectral information from ^1H and ^{13}C NMR, IR, mass spectra and elemental analysis proved the structure **11** beyond doubt. In the IR spectrum, an intense peak at 1725 cm^{-1} indicated the presence of ester functionality. In ^1H NMR, two terminal olefinic protons were resonated at 5.68 and 4.98 ppm respectively. The rest of the protons resonated at their expected chemical shift regions. The carbonyl peak of the ester functionality appeared at 172.6 ppm and two terminal olefins at 137.7, 133.5, 117.7 and 115.3 ppm respectively in ^{13}C NMR, confirmed the assigned structure **11**.

Our final task ring-closing metathesis (RCM)¹¹ was then attempted on **11**. So, treatment of **11** with Grubbs' first generation catalyst in refluxing CH_2Cl_2 provided after 24h the desired nine-membered lactone **5** in 64% yield along with the corresponding dimer **12** (10%) (Scheme 3). In ^1H NMR, the frequencies corresponding to olefinic protons appeared at 5.46 ppm as a multiplet, four allylic and two methylene protons adjacent to the carbonyl group resonated between 2.46 ppm to 2.07 ppm and other protons at their respective regions. ^{13}C NMR was in consistent with the assigned structure. *Cis*-geometry was ascertained by comparing the ^{13}C NMR value of olefin carbons with our earlier report.^{4a} IR absorption at 1739 cm^{-1} confirmed the lactone ring and in EIMS a signal at $[\text{M}-\text{CH}_3]^+$ substantiated the proposed structure. It is noteworthy to mention here that the Grubbs' second generation catalyst provided the same product with high yield (76%) and dimer **12** (11%) under high dilution condition in 16h. The total synthesis of halicholactone (**1a**) and neohalicholactone (**1b**) can be achieved by introducing the side chains using the synthetic protocol published for the synthesis of constanolactones (**3**).¹²



Scheme 3. Reagents and conditions: (a) 5-hexenoic acid, EDCI, CH₂Cl₂, 6h, 92%; (b) RuCl₂=CHPh(Cy₃P)(IEMS), Ti(Oi-Pr)₄, CH₂Cl₂ (0.1mM), reflux, 16h, 76%.

Conclusions

In conclusion, the present synthesis compares well with the earlier reported synthesis of the halicholactone **1a** and neohalicholactone **1b** and offers an efficient alternative route to this important class of compounds and their analogs. The strategy and the approach described is of general applicability for the formation of a library of other related compounds of structural and biological importance by simply changing the side chain as well as lactone ring size. In addition, presence of a stereodefined hydroxyl group at C-12 and a primary hydroxyl group at C-13 of compound **5** enable us to fix the stereogenic centers from C-9 to C-12 and provides the necessary functionalities required for the total synthesis of target molecules.

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 CDCl₃ with TMS as internal standard. Mass spectra were obtained with Finningan 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.

Grignard Reaction

To an ice cooled solution of aldehyde **7** (2.9g, 17.0 mmol) in anhydrous ether (20 mL) was added dropwise 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 NaHCO₃, H₂O, brine and dried over Na₂SO₄ (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 **9**.

1-[2-[2, 2-Dimethyl-(4S)-1, 3-dioxolan-4-yl]-(1R, 2R)-cyclopropyl]-but-3-en-1-one (10). To a stirred solution of 2-iodoxybenzoic acid (IBX) (4.95g, 17.68 mmol) in DMSO (30 ml), was added a solution of homoallyl alcohol **9** (2.50g, 11.79 mmol) in anhydrous THF (20 ml) at room temperature and stirring was continued for further 6h. After completion of the reaction (monitored by TLC), H₂O (10 ml) was added to the reaction mixture, precipitated solid was filtered off and the filtrate was diluted with H₂O (50 ml) and extracted with ether (4x50 ml). The combined organic layers were washed successively with aqueous NaHCO₃, H₂O, brine, and dried over Na₂SO₄ (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 (1:9) to afford 2.23g (90%) of pure cyclopropyl ketone **10**. Colorless liquid; [α]_D = - 59.7 (c 1.30, CHCl₃); ¹H NMR (200 MHz, CDCl₃): δ 1.08 (m, 1H), 1.26 (m, 1H), 1.34 (s, 3H), 1.40 (s, 3H), 1.63 (m, 1H), 1.98 (m, 1H), 3.32 (dd, *J* = 1.5, 6.2 Hz, 1H), 3.66 (t, *J* = 7.39 Hz, 1H), 3.87 (dd, *J* = 6.6, 8.1 Hz, 1H), 5.19 (m, 2H), 5.93 (m, 1H); ¹³C NMR (50 MHz, CDCl₃): 206.7, 130.5, 118.9, 109.3, 76.2, 69.1, 48.5, 26.6, 26.5, 25.6, 24.2, 14.2: Anal. Calcd for C₁₂H₁₈O₃ (210.27): C, 68.54; H, 8.63. Found: C, 69.22; H, 8.45.

1-[2-[(2, 2)-Dimethyl-(4S)-1,3-dioxolan-4-yl]-(1R, 2R)-cyclopropyl]-(1S)-3-buten-1-ol (6 and 6a). To a stirred solution of cyclopropyl ketone **17** (1.0g, 4.76 mmol) in anhydrous THF (30 ml), was added K-selectride (7.42 ml, 7.43 mmol, 1.0M solution in THF) at -78°C, and stirred for 2h at the same temperature. Methanol was added and the reaction mixture was brought to room temperature. After removal of the solvent at reduced pressure, the residue was treated with 2.0 M NaOH (15 ml) solution, extracted with ethyl acetate (2x50 ml). Combined organic layers was dried over Na₂SO₄ and concentrated to afford the crude product, which on flash chromatographic separation using ethyl acetate/petroleum ether (1:4) to afford 792mg of major isomer **6** and 88mg of minor isomer **6a**.

1-[2-[(2,2)-Dimethyl-(4S)-1,3-dioxalan-4-yl]-(1R,2R)-cyclopropyl]-(1S)-3-buten-1-ol (6). Colorless liquid; ¹H NMR (CDCl₃) : 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 $\text{C}_{12}\text{H}_{20}\text{O}_3$ (212.29): C, 67.89; H, 9.49. Found: C, 68.24; H, 9.57.

1-[2-[(2, 2)-Dimethyl-(4S)-1,3-dioxolan-4-yl]-(1R, 2R)-cyclopropyl]-(1R)-3-buten-1-ol (6a). 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 $\text{C}_{12}\text{H}_{20}\text{O}_3$ (212.29): C, 67.89; H, 9.49. Found: C, 67.55; H, 9.26.

Mitsunobu Reaction. To a solution of **6a** (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 **6**.

(S)-Mosher's ester. To a solution of **6a** (20mg, 0.1 mmol) in anhydrous CH_2Cl_2 (1 ml) was added *S*-(-)- α -methoxy- α -(trifluoromethyl)phenylacetic 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 34mg (78%) of pure (*S*)-MTPA ester. ^1H 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 **6a** (20mg, 0.1 mmol) in anhydrous CH_2Cl_2 (1 ml) was added *R*-(-)- α -methoxy- α -(trifluoromethyl)phenylacetic 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 (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).

Hex-5-enoic acid-1-[2-(2, 2-dimethyl-[1,3]dioxolan-4-yl)-(1R, 2R)-cyclopropyl]-but-3-enyl ester (11). To a solution of 5-hexenoic acid (129mg, 1.13 mmol) in anhydrous CH_2Cl_2 (10 ml) was added EDCI (269 mg, 1.41 mmol) at 0°C and stirred for 30 min at the same temperature. To

it, homoallyl alcohol **6** (0.2g, 0.94 mmol) was added. The reaction mixture was then brought to room temperature. After completion of the reaction (monitored by TLC), the reaction mixture was diluted with CH₂Cl₂ (15 ml) and washed with water (2x20 ml). The organic layer was dried over anhydrous Na₂SO₄, concentrated and the residue was purified by silica gel column chromatography using ethyl acetate/light petroleum ether (1:19) to afford 0.267g (92%) of pure compound **11**. Colorless viscous liquid; $[\alpha]_D = -15.82$ ($c = 1.19$, CHCl₃); ¹H NMR (200 MHz, CDCl₃) δ : 5.68 (m, 2H, 2xCH-olefin), 4.98 (m, 4H, 2xCH₂-olefin), 4.30 (dd, 1H, $J = 6.6, 14.6$ Hz, -(C=O)-O-CH-), 3.95 (dd, 1H, $J = 5.9, 7.3$ Hz, O-CH-), 3.52 (m, 2H, -O-CH₂-), 2.32 (m, 2H, -(C=O)-CH₂-), 2.22 (t, 2H, $J = 7.7$ Hz, -CH₂-), 2.05 (dd, 2H, $J = 5.8, 10.2$ Hz, -CH₂-), 1.65 (m, 2H, -CH₂-), 1.33 (s, 3H, -CH₃), 1.25 (s, 3H, -CH₃), 0.97 (m, 1H, -CH-cyclopropyl), 0.84 (m, 1H, -CH-cyclopropyl), 0.65 (m, 1H, -CH-cyclopropyl), 0.51 (m, 1H, -CH-cyclopropyl); IR (chloroform) 1725 cm⁻¹; ¹³C NMR (50 MHz, CDCl₃) δ : 172.9 (C=O), 137.7 (-CH=CH₂), 133.5 (-CH=CH₂), 117.7 (-CH=CH₂), 115.3 (-CH=CH₂), 108.9 (-O-C-O-), 78.5 (-(C=O)-O-CH-), 75.5 (-O-CH-), 69.1 (-O-CH₂-), 39.0 [-(C=O)-CH₂-], 33.8 (-CH₂-), 33.0 (-CH₂-), 26.6 (-CH₃), 25.6 (-CH₃), 24.2 (-CH₂-), 19.1(2x-CH-cyclopropyl), 8.2 (-CH₂-cyclopropyl); EIMS: (308) m/s [M⁺]; Anal. Calcd. For C₁₈H₂₈O₄ (308.42): C, 70.10; H, 9.15. Found: C, 69.55; H,

9-[2-(2, 2-Dimethyl-[1, 3]-dioxolan-4-yl)-(1R, 2R)-cyclopropyl]-4, 5, 8, 9-tetrahydro-3H-oxonin-2-one (5). A solution of **11** (0.1g, 0.34 mmol) and freshly distilled Ti(Oi-Pr)₄ (0.01 ml, 0.03mmol) in anhydrous CH₂Cl₂ (200 ml) was refluxed for 2h under an argon atmosphere. Grubbs' "second generation" catalyst (10 mg) in dry CH₂Cl₂ (5 ml) was added to it. The reaction mixture was then refluxed for 14h. 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 69mg (76%) of pure compound **5**. Colorless liquid; $[\alpha]_D = -56.14$ ($c = 1.54$, CHCl₃); ¹H NMR (200 MHz, CDCl₃) δ : 5.46 (m, 2H, 2xCH-olefin), 4.20 (m, 1H, -(C=O)-O-CH-), 4.06 (m, 1H, -O-CH-), 3.62 (m, 2H, -O-CH₂-), 2.46 (m, 2H, -(C=O)-CH₂-), 2.26 (m, 2H, -CH₂-), 2.07 (m, 2H, -CH₂-), 1.85 (m, 2H, -CH₂-), 1.41 (s, 3H, -CH₃), 1.31 (s, 3H, -CH₃), 1.00 (m, 1H, -CH-cyclopropyl), 0.87 (m, 1H, -CH-cyclopropyl), 0.75 (m, 1H, -CH-cyclopropyl), 0.62 (m, 1H, -CH-cyclopropyl); IR (chloroform): 1739 cm⁻¹; ¹³C NMR (125 MHz, CDCl₃) δ : 173.7 (C=O), 134.6 (-CH=CH-), 124.7 (-CH=CH-), 109.1 (-O-C-O-), 78.4 [-(C=O)-O-CH-], 76.2 (-O-CH-), 69.3 (-O-CH₂-), 33.9 [-(C=O)-CH₂-], 33.6 (-CH₂-), 26.8 (-CH₃), 26.5 (-CH₂-), 25.8 (-CH₃), 25.4 (-CH₂-), 19.6 (-CH-cyclopropyl), 19.1 (-CH-cyclopropyl), 8.0 (-CH₂-cyclopropyl); EIMS: (265) m/s [M-CH₃]⁺; Anal. Calcd. For C₁₆H₂₄O₄ (280.37): C, 68.55; H, 8.63. Found: C, 69.12; H, 9.04.

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References

1. (a) Bergstrom, S.; Danielsson, H.; Samuelsson, B. *Biochim. Biophys. Acta* **1961**, *90*, 207. (b) Bergstrom, S. *Science* **1967**, *157*, 382. and references therein. (c) Corey, E. J.; Noyori, R.; Schaaf, T. K. *J. Am. Chem. Soc.* **1970**, *92*, 2586. and references therein.
2. Niwa, H.; Wakmatsu, K.; Yamada, K. *Tetrahedron Lett.* **1989**, *30*, 4543.
3. Kigoshi, H.; Niwa, H.; Yamada, K.; Stout, T. J.; Clardy, J. *Tetrahedron Lett.* **1991**, *32*, 2427.
4. (a) Mohapatra, D. K.; Datta, A. *J. Org. Chem.* **1998**, *63*, 642. (b) Baba, Y.; Saha, G.; Nakao, S.; Iwata, C.; Tanaka, T.; Ibuka, T.; Ohishi, H.; Takemoto, Y. *J. Org. Chem.* **2001**, *66*, 81. (c) Takemoto, Y.; Baba, Y.; Saha, G.; Nakao, S.; Iwata, C.; Tanaka, T.; Ibuka, T. *Tetrahedron Lett.* **2000**, *41*, 3653. (d) Critcher, D. J.; Connolly, S.; Wills, M. *J. Org. Chem.* **1997**, *62*, 6638. (e) Critcher, D. J.; Connolly, S.; Mahon, M. F.; Wills, M. *J. Chem. Soc., Chem. Commun.* **1995**, *2*, 139. (f) Critcher, D. J.; Connolly, S.; Wills, M. *Tetrahedron Lett.* **1995**, *36*, 3763.
5. (a) Morikawa, T.; Sasaki, H.; Hanai, R.; Shibuya, A.; Taguchi, T. *J. Org. Chem.* **1994**, *59*, 97. (b) Vardarajan, S.; Mohapatra, D. K.; Datta, A. *Tetrahedron Lett.* **1998**, *39*, 1075.
6. Frigeno, M.; Santagostino, M. *Tetrahedron Lett.* **1994**, *35*, 8019.
7. Lautens, M.; Delanghe, P. H. M. *J. Org. Chem.* **1995**, *60*, 2474.
8. Kazuta, Y.; Abe, H.; Yamamoto, T.; Matsuda, A.; Shuto, S. *J. Org. Chem.* **2003**, *68*, 3511. and references therein.
9. (a) Ohtani, I.; Kusumi, J.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092. (b) Yoshida, W. Y.; Bryan, P. J.; Baker, B. J.; McClintock, J. B. *J. Org. Chem.* **1995**, *60*, 780.
10. Mitsunobu, O. *Synthesis* **1981**, 1.
11. For recent reviews of olefinic metathesis, see: (a) Schuster, M.; Blechert, S. *Angew Chem. Int. Ed. Engl.* **1997**, *36*, 2037. (b) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413. (c) Armstrong, S. K. *J. Chem. Soc., Perkin. Trans. 1* **1998**, 371. (d) Schrock, R. R. *Tetrahedron* **1999**, *55*, 8141. (e) Wright, D. L. *Curr. Org. Chem.* **1999**, *3*, 211. (f) Furstner, A. *Angew Chem. Int. Ed.* **2000**, *39*, 3012. (g) Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res.* **2001**, *34*, 18.
12. Yu, J.; Lai, J.-Y.; Ye, J.; Balu, N.; Reddy, L. M.; Duan, W.; Fogel, E. R.; Capdevila, J. H.; Falck, J. R. *Tetrahedron Lett.* **2002**, *43*, 3939.