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Stereoselective synthesis of the C_1-C_{10} fragment of constanolactones A and B

Sundararaman Varadarajan, Debendra K. Mohapatra and Apurba Datta*

Organic III, Indian Institute of Chemical Technology, Hyderabad - 500 007, India.

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Abstract

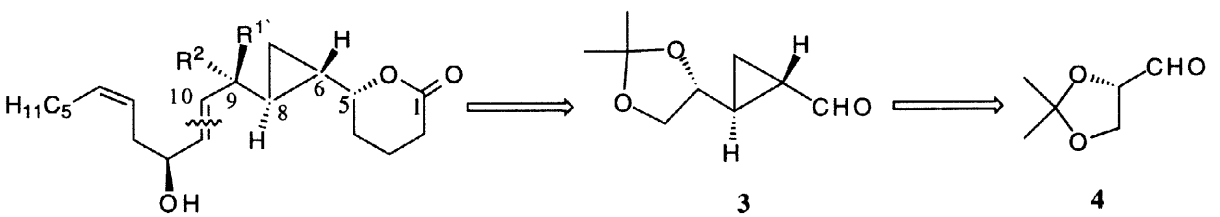
An efficient synthesis of the cyclopropyl-lactone containing right hand fragment (C_1-C_{10}) of the title constanolactones has been developed starting from an easily available (*S*)-glyceraldehyde derivative **4**.

Keywords : constanolactone; oxylipin; cyclopropane; glyceraldehyde.

Constanolactones A (**1**) and B (**2**), isolated from the Oregon coast intertidal red alga *Constantinea simplex* [1,2], belong to a growing class of cyclopropane ring containing fatty acid lactones of marine origin. Structure and absolute configuration of these eicosanoids were determined on the basis of extensive spectroscopic analysis and degradation studies, and were later confirmed by total synthesis [3]. The novel structural features and potential biological activity of these marine oxylipins encouraged us to initiate a programme on their total synthesis. The preliminary results culminating in a stereocontrolled short-step synthesis of the C_1-C_{10} segment of the above compounds are reported herein.

In the only reported synthesis of the title compounds, White *et al* have described an elegant biomimetic route for constructing the cyclopropyl-lactone fragment [3]. The process of introducing the left hand alkenyl side chain however resulted in a mixture of C_9 epimeric products. To develop a more flexible and convergent approach we planned a synthesis involving i) initial formation of a stereodefined bifunctional cyclopropane unit **3** (Scheme 1)

Scheme 1



3 **4**

1, R^1 = H, R^2 = OH; Constanolactone A

2, R^1 = OH, R^2 = H; Constanolactone B

and ii) building up the rest of the target molecule on this preformed cyclopropane skeleton.

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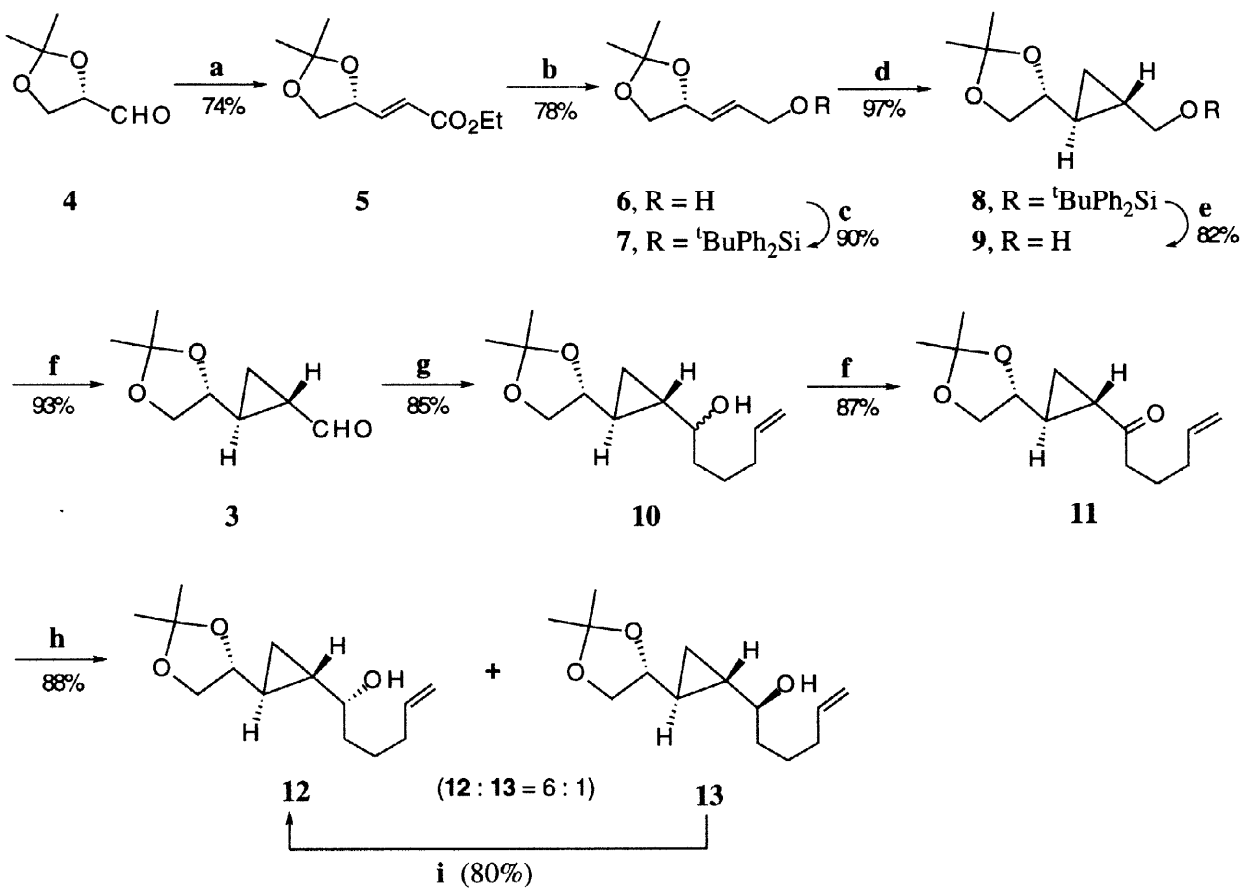
For the proposed synthesis, easily available (*S*)-2,3-isopropylidene glyceraldehyde (**4**) was envisioned to be a suitable precursor, where the aldehyde functionality will allow building up of the cyclopropane unit and the chiral α-hydroxy group can be the gateway to enantiopure C_9 center of the final product.

Accordingly, the (*S*)-glyceraldehyde acetonide **4** [4] was converted to the *E*-allyl alcohol **6** (Scheme 2) under standard reaction conditions [5]. Protection of the primary hydroxy group as its TBDPS ether **7** and subsequent chelation controlled Simmons-Smith cyclopropanation, following a reported procedure [5], cleanly afforded the corresponding cyclopropane derivative **8** in good yield and high optical purity {$[\alpha]_D = 7.55$ (c=1.2, $CHCl_3$) ; *ent* **8** : $[\alpha]_D$= -7.9 (c=1.15, $CHCl_3$) [5]}. Removal of the silyl protecting group and oxidation

Scheme 2



a. Ph_3P:$CHCO_2Et$, C_6H_6, Δ. **b.** DIBAL-H, CH_2Cl_2, -78°C. **c.** *t*-$BuPh_2SiCl$, imidazole, CH_2Cl_2. **d.** Et_2Zn, CH_2I_2, CH_2Cl_2, -78°C. **e.** Bu_4NF, THF. **f.** 2-Iodoxybenzoic acid, DMSO, THF. **g.** H_2C:$CH(CH_2)_2CH_2MgBr$, Et_2O. **h.** K-selectride (1M soln. in THF), -78°C. **i.** Ph_3P, EtO_2CN:NCO_2Et, 4-$NO_2C_6H_4CO_2H$, THF, then K_2CO_3, MeOH.

of the resulting hydroxy compound **9** provided the key cyclopropyl aldehyde **3**. This pivotal intermediate with the required stereochemistry and proper funcional groups represents an ideal building block for the intended synthesis. Having synthesized the cyclopropyl core, stereoselective formation of the 2-pyrone ring was next undertaken. Thus reaction of

aldehyde **3** with the Grignard reagent derived from 5-bromopentene afforded a mixture (7:3) of the diastereomeric products **10**. Better selectivity could however be achieved *via* oxidation of **10** to the corresponding ketone **11** and its stereoselective reduction with K-selectride® (potassium tri-*sec*-butylborohydride) resulting in a 6:1 mixture of diastereomeric alcohols **12** and **13** which could be separated by flash chromatography.

Stereochemical assignment at the newly created center was performed by the modified Mosher's method [6]. Thus, esterification of the minor isomer **13** with both (*S*)- and (*R*)-α-methoxy-α-(trifluoromethyl)phenylacetic acid (MTPA) showed positive chemical shift differences ($\Delta\delta = \delta_S - \delta_R$) for protons on C-1 through C-5 (Figure 1), while protons on C-7 through C-11 showed negative chemical shift differences, which is indicative of C-6 bearing an *S*- configuration. By corollary, the corresponding stereogenic center in the major isomer

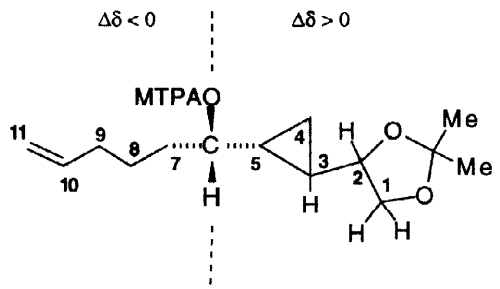
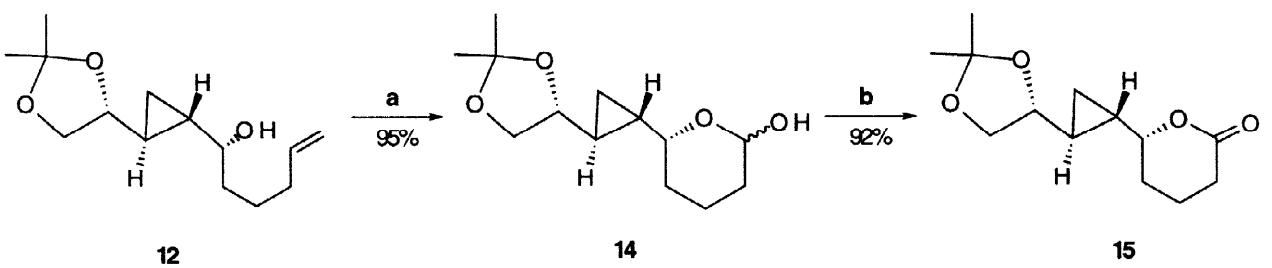


Figure 1. $\Delta\delta = (\delta_S - \delta_R) \times 10^3$ for (*R*)- and (*S*)-MTPA esters of compound **13**

12 is in *R*-configuration, which incidently is of appropriate stereochemistry for the proposed synthesis. Complete material recovery could be achieved by converting **13** to the major isomer **12** *via* a standard Mitsunobu protocol (Scheme 2). Finally, dihydroxylation of the alkene **12** (Scheme 3) and oxidative cleavage of the resulting diol moiety directly afforded the lactol **14**. Subsequent oxidation uneventfully led to the intended cyclopropyl lactone **15** in good overall yield.[1]

Scheme 3



12 **14** **15**

a. i) OsO_4 (cat), NMO, acetone. ii. $NaIO_4$ (impregnated over silica gel), CH_2Cl_2, 0°C. **c.** PDC, CH_2Cl_2.

In conclusion, an efficient stereoselective synthesis of the right hand segment of the title constanolactones could be achieved in a relatively short reaction sequence starting from a commonly available chiral building block. Other useful features of the above synthesis are the presence of a stereodefined hydroxy functionality at C_9 which can lead to either

constanolactone A or constanolactone B (*via* C_9 inversion) in enantiopure form, whereas the primary hydroxy group at C_{10} provides an useful handle, required for introducing the left hand alkenyl side chain towards total synthesis of the above compounds.

Acknowledgments

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[1] All the compounds synthesized were fully characterized by their spectral and analytical data. Characteristic data for some of the key compounds are given below :

9: $[\alpha]_D$ = 16.5 (c=2.2, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$) δ 0.55 (m, 1H), 0.64 (m, 1H), 0.85 (m, 1H), 1.03 (m, 1H), 1.30 (s, 3H), 1.41 (s, 3H), 1.48 (br s, 1H), 3.38 (dd, *J* = 6.52 and 11 Hz, 1H), 3.5 (dd, *J* = 6.5 and 11 Hz, 1H), 3.61 (m, 2H), 4.04 (m, 1H), EIMS 157 ($M^+ - CH_3$).

3: $[\alpha]_D$ = 18.2 (c=1.3, $CHCl_3$); IR (neat) 1709 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.21 (m, 2H), 1.32 (s, 3H), 1.4 (s, 3H), 1.68 (m, 1H), 1.86 (m, 1H), 3.74 (m, 2H), 4.07 (m, 1H), 9.12 (d, *J* = 5.6 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 199.9, 109.5, 76.4, 69.0, 26.6, 25.5, 23.8, 11.8; FABMS 171 (MH^+).

12: $[\alpha]_D$ = 15.5 (c=1.5, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$) δ 0.58 (m, 2H), 0.87 (m, 2H), 1.32 (s, 3H), 1.40 (s, 3H), 1.54 (m, 4H), 2.07 (m, 2H), 3.04 (m, 1H), 3.59 (m, 2H), 4.04 (m, 1H), 4.96 (m, 2H), 5.78 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 138.5, 114.5, 108.9, 79.0, 74.4, 69.0, 36.6, 33.6, 26.7, 25.6, 24.8, 22.0, 18.4, 7.7; EIMS 225 ($M^+ - CH_3$).

13: $[\alpha]_D$ = 10.8 (c=1.4, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$) δ 0.6 (m, 2H), 0.85 (m, 2H), 1.3 (s, 3H), 1.38 (s, 3H), 1.5 (m,4H), 2.07 (m, 2H), 2.99 (m, 1H), 3.58 (m, 2H), 4.03 (m, 1H), 4.96 (m, 2H), 5.76 (m, 1H).

15: $[\alpha]_D$ = -12.2 (c=1, $CHCl_3$); IR (neat) 1724 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.55 (m, 1H), 0.69(m, 1H), 1.05 (m, 2H), 1.3 (s, 3H), 1.37 (s, 3H), 1.55 - 2.01 (m, 4H), 2.46 (m, 2H), 3.52 - 3.78 (m, 3H), 4.05 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 171.2, 108.8, 83.3, 78.1, 69.1, 29.3, 27.7, 26.5, 25.5, 19.8, 19.3, 18.2, 6.8; EIMS 225 ($M^+ - CH_3$).