



## Studies Towards the Total Syntheses of Solandelactones : Stereoselective Synthesis of the Cyclopropane - Lactone Segment #

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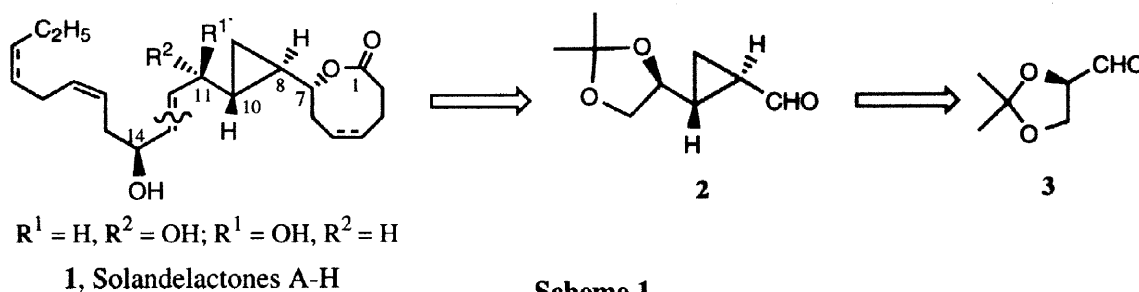
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**Abstract :** A concise stereoselective route to the right hand fragment of solandelactones have been developed, where initial synthesis of the key bifunctional cyclopropane intermediate **2** was followed by construction of the eight-membered lactone ring in good overall yield.

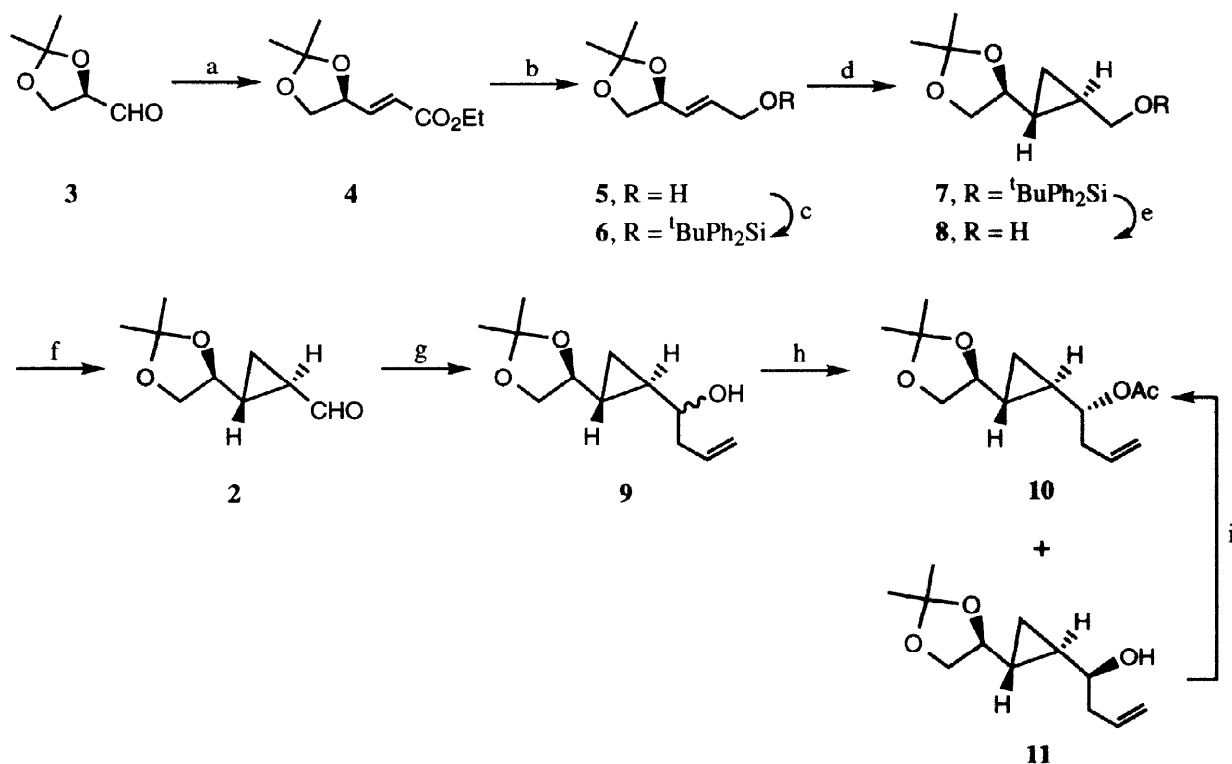
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Solandelactones (**1**), belonging to a growing class of cyclopropane ring containing fatty acid lactones of marine origin, were isolated from the hydroid *Solanderia secunda* off the Korean coast. The structures of these compounds and their absolute stereochemistry have been determined by exhaustive spectral and chemical studies.<sup>1</sup> Thus, solandelactones, having a central *trans*- substituted cyclopropane unit with an eight-membered lactone ring to the right hand side and hydroxy group containing alkenyl chain on the left were found to be structurally similar to some of the other marine derived oxylipins, viz, constanolactones<sup>2</sup>, halicholactone and neohalicholactone.<sup>3</sup> However, while the above compounds are of eicosanoid origin containing a six or nine-membered lactone ring respectively, solandelactones with an eight-membered lactone ring and of C<sub>22</sub> skeletal framework are thought to be derived from docosanoid precursors. Another notable difference is the opposite absolute stereochemistry across the cyclopropane ring in solandelactones compared to the other above mentioned oxylipins. The interesting structural features and potent biological activity of these class of compounds have attracted the attention of a number of organic chemists worldwide.<sup>4</sup> However, till to date there are no reports on the synthesis of solandelactones. This prompted us to initiate studies toward the synthesis of these compounds and in this communication we report the first synthesis of the right hand hemisphere of solandelactones.



As per the retrosynthesis (Scheme 1), our strategy involved i) initial stereodefined synthesis of a

pivotal bifunctional cyclopropane moiety, and ii) construction of the required lactone ring on the preformed cyclopropane unit. The synthesis began from (*R*)-2,3-*O*-isopropylidene glyceraldehyde (**3**)<sup>5</sup> which was converted to the corresponding *E*-allyl alcohol **5** (Scheme 2) under standard reaction conditions.<sup>6</sup>



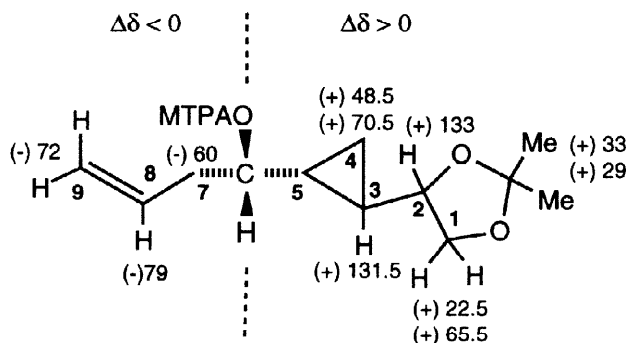
**a.**  $\text{Ph}_3\text{P}=\text{CHCO}_2\text{Et}$ ,  $\text{C}_6\text{H}_6$ ,  $\Delta$ , 90%. **b.**  $^i\text{Bu}_2\text{AlH}$ ,  $\text{CH}_2\text{Cl}_2$ ,  $-78^\circ\text{C}$ , 82%. **c.**  $^t\text{BuPh}_2\text{SiCl}$ , imidazole,  $\text{CH}_2\text{Cl}_2$ , 82%. **d.**  $\text{Et}_2\text{Zn}$ ,  $\text{CH}_2\text{I}_2$ ,  $\text{CH}_2\text{Cl}_2$ ,  $-78^\circ\text{C}$  to  $0^\circ\text{C}$ , 94%. **e.**  $\text{Bu}_4\text{NF}$ , THF, 83%. **f.** 2-Iodoxybenzoic acid, DMSO, THF, 97%. **g.**  $\text{H}_2\text{C}=\text{CH}-\text{CH}_2\text{MgBr}$ ,  $\text{Et}_2\text{O}$ , 89%. **h.** *Candida cylindracea* lipase (CCL) (cat.),  $\text{H}_2\text{C}=\text{C}(\text{CH}_3)\text{OAc}$ , hexane, 91% (10/11 = 1/1.2). **i.**  $\text{Ph}_3\text{P}$ ,  $\text{EtO}_2\text{CN}=\text{NCO}_2\text{Et}$ , gl. AcOH, THF, 85%.

**Scheme 2**

Protection of the hydroxy group as its TBDPS ether **6** and subsequent chelation controlled modified Simmons-Smith cyclopropanation following a reported procedure<sup>6</sup> yielded the known cyclopropane derivative **7** with high diastereoselectivity  $\{[\alpha]_{\text{D}} = -7.5$  ( $c = 1.2$ ,  $\text{CHCl}_3$ ); lit.<sup>6</sup>  $[\alpha]_{\text{D}} = -7.9$  ( $c = 1.5$ ,  $\text{CHCl}_3$ )}. Deprotection of the silyl ether and IBX oxidation<sup>7</sup> of the resulting primary alcohol formed the key bifunctional cyclopropane **2** in high overall yield. The cyclopropane derivative **2** with the required (*R,R*)-configuration and appropriate functionalities represents a convenient launching pad for synthesizing the title compounds. Reaction of the aldehyde **2** with allylmagnesium bromide afforded the alcohol **9** as a diastereomeric mixture, separable with difficulty by repeated column chromatography. This problem was however circumvented by subjecting the alcohol mixture **9** to *Candida cylindracea* lipase (CCL) catalyzed enzymatic resolution<sup>8</sup>, yielding the corresponding acetate **10** (45%) and alcohol **11** (55%) with high optical purity (>95%). It is worth mentioning that the selectivity of CCL towards the above resolution is remarkably high and does not acylate the  $\beta$ -alcohol **11** even after prolonged exposure under the described reaction condition.

Stereochemical assignment at the hydroxy bearing center was achieved by the modified Mosher's

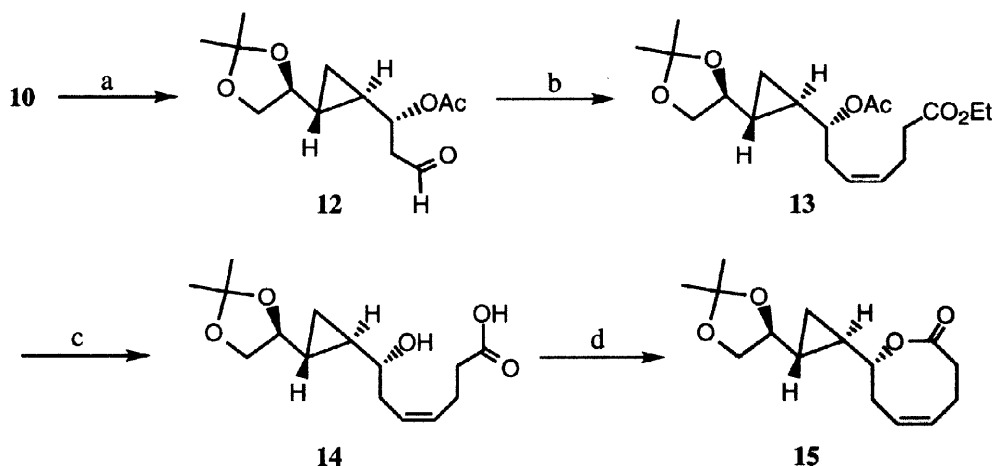
method.<sup>9</sup> Thus, esterification of the alcohol **11** with both (*R*)- and (*S*)- $\alpha$ -methoxy- $\alpha$ -(trifluoromethyl)phenylacetic acid (MTPA) demonstrated positive chemical shift differences ( $\Delta\delta = \delta_S - \delta_R$ ) for protons on C-1 through C-4 (Figure 1), while protons on C-7 through C-9 showed negative differences, which is consistent with C-6 bearing an *S*-configuration. By corollary, the acetate derivative **10** thus has the correct stereochemistry as in



**Figure 1.**  $\Delta\delta = (\delta_S - \delta_R) \times 10^3$  for (*R*)- and MTPA esters of compound **11**

the target compounds. Having confirmed the stereochemistry, the undesired isomer **11** was also converted to the required acetate **10** *via* a standard Mitsunobu protocol (Scheme 2).

Degradative oxidation of the olefin **10** to aldehyde **12** (Scheme 3) followed by a *cis*-selective Wittig reaction with the reagent derived from 4-carboethoxybutyl triphenylphosphonium bromide in presence of NaHMDS at  $-78^\circ\text{C}$ <sup>10</sup> yielded the corresponding ester **13** in good yield. Only the *Z*-isomer was detected by



a. i.  $\text{OsO}_4(\text{cat})$ , NMO, acetone. ii.  $\text{NaIO}_4$  (silica gel impregnated),  $\text{CH}_2\text{Cl}_2$ , 82% (two steps)  
b.  $\text{BrPh}_3\text{PCH}_2\text{CH}_2\text{CH}_2\text{CO}_2\text{Et}$ , NaHMDS, THF,  $-78^\circ\text{C} \rightarrow \text{rt.}$ , 77%. c. LiOH, THF, MeOH  
 $\text{H}_2\text{O}$ , rt., 94%. d. 2,4,6- $\text{Cl}_3\text{C}_6\text{H}_2\text{COCl}$ ,  $\text{Et}_3\text{N}$ , DMAP, toluene,  $\Delta$ , 63%.

**Scheme 3**

NMR ( $^1\text{H}$  and  $^{13}\text{C}$ ) studies. Simultaneous deprotection of the ester functionalities gave the lactone precursor hydroxy acid **14** in almost quantitative yield. Finally, lactonisation of the acid **14** under Yamaguchi condition<sup>11</sup> cleanly afforded the expected eight-membered lactone **15**<sup>12</sup> in 63% yield, thereby culminating in an efficient synthesis of the targeted right hand fragment of solandelactones. The smooth formation of the eight-membered lactone ring further proves the *cis*-geometry across the double bond, which probably provides both an enthalpic and entropic assistance to the above cyclisation.

In conclusion, an efficient stereoselective synthesis of the required cyclopropane and lactone containing right hand segment of solandelactones was achieved in a relatively short reaction sequence and in good overall yield, starting from an easily available (*R*)-glyceraldehyde derivative. Moreover, the presence of a stereodefined hydroxy group at C-11 and a primary hydroxyl at C-12 of compound **15** provides the necessary functionalities required for the total syntheses of the title compounds.

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## References and Notes

- # IICT communication No. 3909
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12. All the compounds synthesized were fully characterized by IR, <sup>1</sup>H and <sup>13</sup>C NMR and mass spectral data. Characteristic data for compounds **10** and **15** are as follows :  
**10** : viscous liquid; [ $\alpha$ ]<sub>D</sub> = -10.4 (c = 1.25, CHCl<sub>3</sub>); IR (neat) 1736 cm<sup>-1</sup>; <sup>1</sup>HNMR (200 MHz, CDCl<sub>3</sub>)  $\delta$  0.65 (m, 2H), 0.91 (m, 2H), 1.31 (s, 3H), 1.40 (s, 3H), 2.04 (s, 3H), 2.37 (t, *J* = 6.5 Hz, 2H), 3.58(m,2H), 4.02 (m, 1H), 4.37 (m, 1H), 5.08 (m, 2H), 5.74 (m, 1H); <sup>13</sup>CNMR (50 MHz, CDCl<sub>3</sub>)  $\delta$  170.5, 133.4, 117.7, 108.9, 78.7, 75.7, 69.0, 39.0, 26.7, 25.6, 21.0, 19.6, 19.1, 8.3; EIMS : 239 (M<sup>+</sup> -CH<sub>3</sub>).  
**15** : viscous liquid; [ $\alpha$ ]<sub>D</sub> = -4.66 (c = 0.9, CHCl<sub>3</sub>); IR (neat) 1748 cm<sup>-1</sup>; <sup>1</sup>HNMR (200 MHz, CDCl<sub>3</sub>)  $\delta$  0.72 (m, 2H), 0.98 (m, 2H), 1.32 (s, 3H), 1.40 (s, 3H), 2.05 - 2.38 (m, 3H), 2.47-2.91(m, 3H), 3.64 (m, 2H), 4.05 (m, 2H), 5.73 (m, 2H); <sup>13</sup>CNMR (50 MHz, CDCl<sub>3</sub>)  $\delta$  176.7, 132.9, 127.9, 109.0, 80.3, 78.3, 69.0, 37.7, 34.2, 26.7, 25.6, 24.4, 19.2, 19.1, 8.3; EIMS : 252 (MH<sup>+</sup> -CH<sub>3</sub>).