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Solandelactones A-I, Lactonized Cyclopropyl Oxylipins Isolated from the Hydroid *Solanderia secunda*

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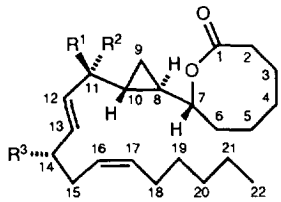
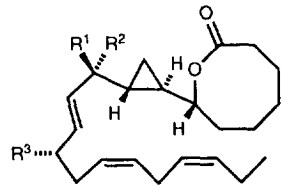
Abstract: Solandelactones A-I(**1**-**9**), cyclopropyl and lactone containing novel docosanoids have been isolated from the hydroid *Solanderia secunda*. The structures of these compounds have been elucidated by combined spectral and chemical studies. Configuration of the cyclopropyl ring has been assigned as the opposite of related oxylipins by NOESY experiments. Absolute stereochemistry has been determined on the basis of chemical transformations and CD measurements of synthetic derivatives. In addition, the biogenetic origin of solandelactones has been discussed. Solandelactones C, D, and G exhibited moderate inhibitory activity against Farnesyl Protein Transferase.

Coelenterates (phylum Cnidaria) are recognized as a very rich source of both biologically active and structurally unique secondary metabolites. However, chemical investigation of these animals has been mainly focused on soft corals (order Alcyonacea, class Anthozoa) and gorgonians (order Gorgonacea, class Anthozoa) while animals of other taxonomic groups have attracted much less attention.[1] Chemistry of the hydroids (class Hydrozoa) has been particularly seldom investigated. As a result, besides a few common steroids and phospholipids, aromatic polyketides and β-carbolines are the only secondary metabolites ever reported.[1-3] In our search for novel bioactive substances from the Korean water organisms, we collected the dark-brown hydroid *Solanderia secunda* off the shore of Jaeju Island.[4] Silica vacuum flash chromatography of the combined dichloromethane and methanol extracts followed by reversed-phase HPLC yielded several cyclopropyl containing fatty acid lactones. Herein we report the isolation, structure determination, and bioactivity of solandelactones A-I, novel lactonized oxylipins derived from docosanoid precursors.

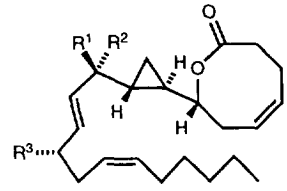
Solandelactone A (**1**) was isolated as an oil which was analyzed for $C_{22}H_{36}O_4$ by high-resolution mass and ^{13}C NMR spectroscopic methods. A carbon signal at δ 176.57 (C) in the ^{13}C NMR spectrum and a strong absorption band at 1730 cm^{-1} in the IR spectrum revealed the presence of a lactone functionality. The absence of signals of both quaternary carbons except the carbonyl one and methine carbons in the region of δ 60 - 30 in the ^{13}C NMR spectrum revealed that **1** was derived from a fatty acid precursor. Three upfield carbon signals



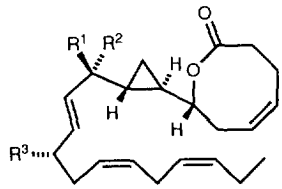
1 $R^1 = R^3 = OH$, $R^2 = H$
2 $R^1 = H$, $R^2 = R^3 = OH$
10 $R^1 = R^3 = OAc$, $R^2 = H$
11 $R^1 = H$, $R^2 = R^3 = OAc$



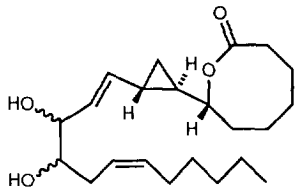
3 $R^1 = R^3 = OH$, $R^2 = H$
4 $R^1 = H$, $R^2 = R^3 = OH$



5 $R^1 = R^3 = OH$, $R^2 = H$
6 $R^1 = H$, $R^2 = R^3 = OH$
12 $R^1 = R^3 = OAc$, $R^2 = H$
13 $R^1 = H$, $R^2 = R^3 = OAc$
14 $R^1 = R^3 = OCOC_6H_4Br$, $R^2 = H$
15 $R^1 = OCOC_6H_4Br$, $R^2 = H$, $R^3 = OH$
16 $R^1 = OH$, $R^2 = H$, $R^3 = OCOC_6H_4Br$
17 $R^1 = H$, $R^2 = R^3 = OCOC_6H_4Br$
18 $R^1 = H$, $R^2 = OCOC_6H_4Br$, $R^3 = OH$
19 $R^1 = H$, $R^2 = OH$, $R^3 = OCOC_6H_4Br$
20 $R^1 = H$, $R^2 = R^3 = OMC$



7 $R^1 = R^3 = OH$, $R^2 = H$
8 $R^1 = H$, $R^2 = R^3 = OH$



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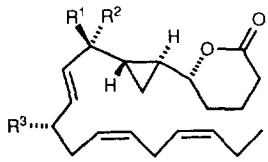
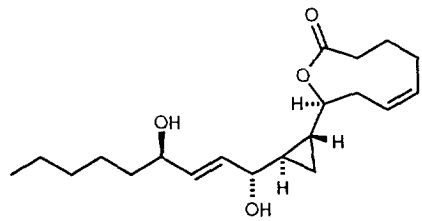


21 constanolactone A
$R^1 = H$, $R^2 = R^3 = OH$
22 constanolactone B
$R^1 = R^3 = OH$, $R^2 = H$



23 halicholactone

at δ 23.04 (CH), 21.43 (CH), and 7.88 (CH_2) in the ^{13}C NMR spectrum and their corresponding proton signals in the region of δ 1.15 - 0.60 in the ^1H NMR spectrum indicated the presence of a cyclopropyl moiety (Table 1).

The gross structure of **1** was determined by a combination of HMQC and ^1H COSY experiments in which it was possible to define the spin system throughout the entire molecule. Compound **1** possessed three oxygen-containing carbons at C-7, C-11, and C-14. Treatment of **1** with acetic anhydride in pyridine yielded the diacetate derivative **10** as a major product. Comparison of the ^1H NMR spectra revealed that signals of the H-11 and H-14 protons of **1** were shifted downfield by 1.19 and 1.09 ppm, respectively, while signal of the H-7 proton was almost unchanged. Therefore, compound **1** must contain an 8-membered lactone ring. This interpretation was confirmed by a HMBC experiment in which the carbonyl carbon exhibited a long-range correlation with the H-7 proton. Thus, the structure of **1** was unambiguously determined as a cyclopropyl containing fatty acid lactone.

Table 1. Carbon NMR Assignments for Solandelactones A-H (**1**-**8**).

C#	1	2	3	4	5	6	7	8
1	176.57 s	176.55 s	176.55 s	176.56 s	176.99 s	176.88 s	176.90 s	176.84 s
2	32.66 t	32.74 t	32.70 t	32.75 t	37.69 t	37.69 t	37.71 t	37.70 t
3	29.02 t	29.07 t	29.05 t	29.07 t	24.38 t	24.41 t	24.42 t	24.42 t
4	24.14 t	24.16 t	24.17 t	24.16 t	131.73 d	131.70 d	131.82 d	131.76 d
5	26.44 t	26.49 t	26.47 t	26.49 t	128.11 d	127.99 d	128.10 d	127.99 d
6	37.05 t	37.11 t	37.07 t	37.10 t	34.21 t	34.30 t	34.23 t	34.31 t
7	81.47 d	81.58 d	81.46 d	81.54 d	80.87 d	80.76 d	80.79 d	80.70 d
8	21.43 d	20.46 d	21.44 d	20.47 d	20.56 d	19.73 d	20.60 d	19.76 d
9	7.88 t	8.96 t	7.87 t	8.94 t	7.96 t	9.02 t	7.97 t	8.99 t
10	23.04 d	23.22 d	23.04 d	23.21 d	23.31 d	23.49 d	23.32 d	23.49 d
11	74.60 d	74.74 d	74.57 d	74.71 d	74.36 d	74.74 d	74.37 d	74.69 d
12	133.16 d	133.58 d	133.07 d	133.47 d	133.09 d	133.91 d	133.03 d	133.50 d
13	131.67 d	131.64 d	131.80 d	131.73 d	132.72 d	132.80 d	132.71 d	132.83 d
14	71.42 d	71.56 d	71.37 d	71.50 d	71.42 d	71.57 d	71.40 d	71.48 d
15	35.30 t	35.32 t	35.30 t	35.30 t	35.26 t	35.29 t	35.30 t	35.29 t
16	124.03 d	124.04 d	124.44 d	124.41 d	124.08 d	124.02 d	124.47 d	124.39 d
17	134.01 d	133.92 d	126.66 d	126.60 d	133.85 d	133.62 d	126.66 d	126.60 d
18	27.43 t	27.43 t	25.73 t	25.73 t	27.40 t	27.82 t	25.74 t	25.73 t
19	29.27 t	29.26 t	131.92 d	131.90 d	29.24 t	29.26 t	131.82 d	131.93 d
20	31.49 t	31.49 t	132.29 d	132.32 d	31.47 t	31.50 t	132.24 d	132.30 d
21	22.54 t	22.54 t	20.60 t	20.60 t	22.51 t	22.53 t	20.60 t	20.59 t
22	14.05 q	14.04 q	14.23 q	14.24 q	14.02 q	14.04 q	14.23 q	14.24 q

Measured in $CDCl_3$ solutions at 125 MHz. Assignments were aided by DEPT and HMQC experiments.

Solandelactone A possessed two double bonds at C-12 and C-16. The geometry of these functionalities was assigned as 12*E* and 16*Z*, respectively by decoupling of allylic protons and subsequent measurements of coupling constants between the olefinic protons ($J_{12,13}$ = 15.6 Hz; $J_{16,17}$ = 10.8 Hz). In the same manner, the geometry of the cyclopropyl ring was assigned as *trans* ($J_{8,9} = J_{9,10}$ = 8.8 and 5.4 Hz). The relative and absolute configurations of the asymmetric carbon centers (C-7, C-8, C-10, C-11, and C-14) are discussed later.

A closely related compound, solandelactone B (**2**) was isolated as an oil and the molecular formula of $C_{22}H_{36}O_4$ was deduced by a combination of high-resolution mass and ^{13}C NMR spectrometry. The spectral data for this compound were almost identical to those derived from **1**. Careful examination of the ^{13}C NMR data revealed that the amounts of differences of the chemical shifts between **1** and **2** were larger for the C-9 ~ C-12 carbons ($\Delta\delta$ 0.14 ~ 1.08) than others ($\Delta\delta$ 0 ~ 0.14). This observation was interpreted that **1** and **2** were epimeric to each other at C-10 and/or C-11 asymmetric carbon centers.

Due to the overlapping of the H-9 proton signals, **2** was converted to the diacetate derivative **11** by treatment with acetic anhydride in pyridine. Proton decoupling experiments showed that the cyclopropyl ring of **11** had the same *trans* geometry as **10**. However, significant differences of the coupling constants between

the H-11 and adjacent protons were revealed. The coupling constants between the H-11 proton and H-10, H-12, and H-13 protons were 3.2, 8.3, and 1.5 Hz, respectively in **10** while the corresponding constants were 7.3, 5.4, and 0 Hz, respectively in **11**. Therefore, solandelactone B was defined as the 11-epimer of solandelactone A. This interpretation is further discussed later.

Two closely related metabolites, solandelactones C (**3**) and D (**4**) were isolated under the same HPLC condition (50% CH_3CN in water). Spectral data of these compounds were highly compatible with those obtained for **1** and **2**. The only significant differences in the ^1H and ^{13}C NMR spectra were those corresponding to an additional double bond. The position of this double bond was assigned to C-19 by a combination of ^1H COSY and HMQC experiments. Based on the coupling constants between the olefinic protons ($J_{19,20}$ = 11.2 and 12.2 Hz for **3** and **4**, respectively), geometry of the C-19 double bond was assigned as *Z* for both compounds.

Solandelactones E (**5**) and F (**6**) were isolated as oils. Both compounds were analyzed for $C_{22}H_{34}O_4$ by high-resolution mass and ^{13}C NMR spectrometry. The structures of these compounds were determined as 4,5-didehydro derivatives of solandelactones A and B by combined spectral analyses. The geometry of the new double bonds was assigned as *Z* for both compounds from the measurement of coupling constants of the H-5 olefinic proton ($J_{4,5}$ = 11.3 Hz for **5** and 11.7 Hz for **6**).

Two more fatty acid lactones, solandelactones G (**7**) and H (**8**) were isolated as oils. Molecular formula of $C_{22}H_{30}O_4$ was deduced for each compound by a combination of high-resolution mass and ^{13}C NMR spectrometry. The structures of these compounds were determined as 4,5,19,20-tetradehydro derivatives of **1** and **2** by a combination of ^1H COSY and HMQC experiments. The geometry of double bonds was assigned as 4*Z*, 12*E*, 16*Z*, and 19*Z* by decoupling of allylic protons and subsequent measurements of coupling constants between the olefinic protons.

Solandelactones A-H possessed asymmetric carbon centers at the same positions (C-7, C-8, C-10, C-11, and C-14). The relative and absolute configurations of these centers were determined by following the methods developed by Nagle and Gerwick for the structure determination of constanolactones A (**21**) and B (**22**), related oxylipins isolated from the red alga *Constantinea simplex*.[5,6] Considering the additional rigidity of lactone ring by the presence of a double bond at C-4 and the yields of isolation, solandelactones E (**5**) and F (**6**) were selected for stereochemical studies. Solandelactones E and F were converted to the diacetate derivatives **12** and **13**, respectively by treatment with acetic anhydride in pyridine. An NOESY spectrum of **12** showed several interactions among the protons of the cyclopropyl ring and the vicinity (Figure 1). The H-7 proton was correlated with the H-9β (δ 0.78) and H-10 protons while the H-11 proton was correlated with the H-8 and H-9α (δ 0.60) protons. Also observed were nOe between the H-8 and the H-6α (δ 2.56) and H-6β (δ 2.16) protons and between the H-10 and H-6β proton. In addition, the interactions between the H-12 proton and the H-9α and H-10 were observed. Therefore, the relative configurations of C-7 ~ C-11 of **12** were defined as 7*R**,8*R**,10*R**,11*S**. NOESY data of **13** were similar to those obtained for **12**. The similar nOe between the cyclopropyl protons and the lactone ring protons of **13** were also observed in **12**. However, significant differences were observed on the nOe with the H-12 proton. In **12**, the H-12 olefinic proton was interacted with the H-9α and H-10 protons. In contrast, the H-12 proton in **13** was interacted with the H-8 and H-10 ones (Figure 1). These differences were thought to be due to the opposite configuration at C-11. Thus, the relative configurations of **13** were defined as 7*R**,8*R**,10*R**,11*R**.

Comparison of these results with stereochemistry of related compounds revealed a significant difference

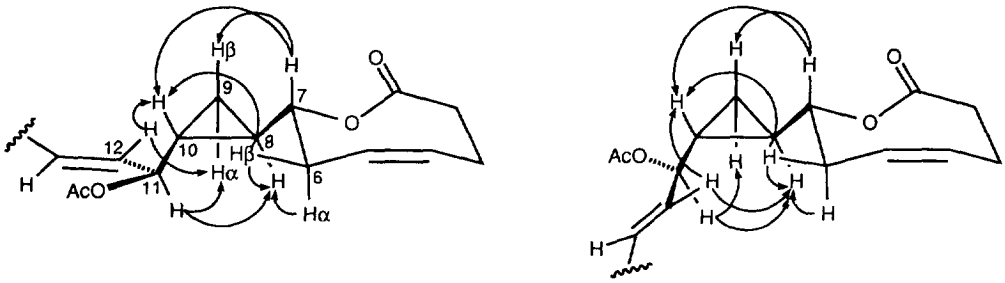


Figure 1. Selected nOe correlations based on NOESY experiments of **12** (left) and **13** (right).

of the relative configurations between the cyclopropyl and lactone ring. Constanolactones A (**21**) and B (**22**), metabolites of the red alga *C. simplex*, have been reported to have the relative configurations of 5*R**,6*S**,8*S**, 9*S** and 5*R**,6*S**,8*S**,9*R**, respectively.[5,6] Halicholactone (**23**) isolated from the sponge *Halichondria okadai* and the brown alga *Laminaria sinclairii* had the relative configuration of 8*R**,9*S**,11*S**,12*R**.[7-9] Careful examination of the three-dimensional model showed that the C-9 methylene group was facing the oxygen of lactone ring in **12** and **13** while the same methylene was facing the C-6 methylene group in constanolactones and halicholactone.[10,11]

The absolute configurations of these centers were determined by chemical transformation and CD measurements. Treatments of **5** and **6** with *p*-bromobenzoyl chloride in pyridine/dichloromethane yielded the bis(*p*-bromobenzoyl), 11-(*p*-bromobenzoyl), and 14-(*p*-bromobenzoyl) derivatives (**14**, **15**, and **16** from **5**; **17**, **18**, and **19** from **6**). The relative configurations of asymmetric centers were confirmed by NOESY experiments of **14** and **17** in which nOe interactions very similar to those of the diacetates **12** and **13** were observed. The only difference was the disappearance of nOe interactions between the H-6β proton and the H-8 and H-10 protons in both of the bis(*p*-bromobenzoyl) derivatives. This may be due to the conformational change of the C-11 asymmetric center by the replacement of the acetoxyl group with the bulky *p*-bromobenzoyl group. The CD spectrum of **18** gave maximum at 242.5 nm (Δε +7.13, Figure 2). Therefore, the absolute configurations of the C-11 asymmetric center was assigned as *R*. Although CD spectrum of the less stable **15** was not obtained, differences of the NOESY data defined *S* configuration for this compound.

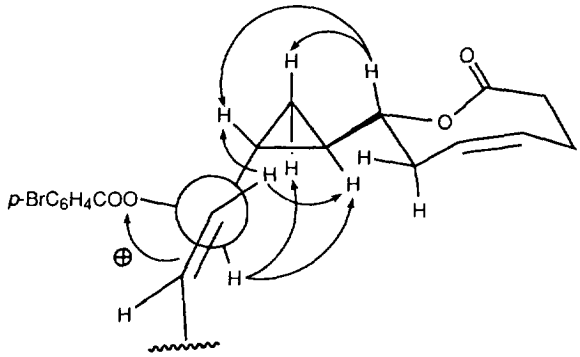
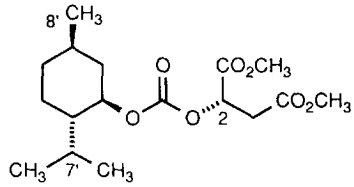


Figure 2. Newman projection of favored conformation of **18** based upon NOESY experiments and CD analysis.

Stereochemistry of the remaining C-14 asymmetric carbon center was assigned by CD measurements of the 14-(*p*-bromobenzoyl) derivatives **16** and **19**. CD spectra of **16** and **19** gave maxima at almost identical wave lengths and with similar intensities (242.3 nm, $\Delta\varepsilon$ +10.67 for **16**; 241.8 nm, $\Delta\varepsilon$ +13.67 for **19**). Therefore, the absolute configuration was assigned as *S* for both compounds. This interpretation was confirmed by formation of bis(menthoxycarbonyl)solandelactone F (**20**) followed by ozonolysis and comparison of spectral data with synthetic compounds.[6] Compound **6** was converted to bis(menthoxycarbonyl) derivative **20** by treatment with (-)-menthoxycarbonyl(MC) chloride in toluene/pyridine. Ozonolysis of **20** followed by an oxidative workup and methylation yielded dimethyl-MC-malate (**24**). Comparison of the ^{1}H NMR data with synthetic 2*S* and 2*R* dimethyl-MC malates showed that **24** had 2*S* configuration.[12] The absolute configuration of this asymmetric center was further confirmed by GC analysis in that **24** showed very similar retention time with the authentic 2*S* dimethyl-MC-malate. Combining these results with those for other asymmetric centers, the absolute configuration of solandelactone E (**5**) was determined as 7*R*,8*R*,10*R*,11*S*,14*S*. The absolute configuration of the 11-epimeric solandelactone F (**6**) was assigned as 7*R*,8*R*,10*R*,11*R*,14*S*.



24

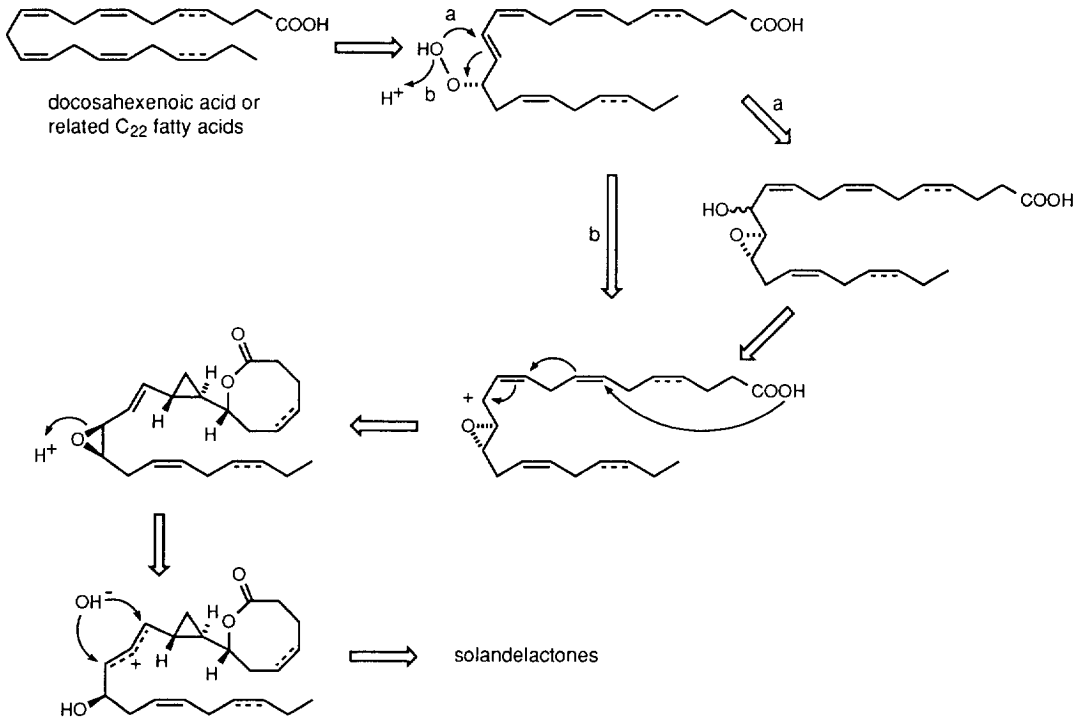
Comparison of the ^{13}C NMR data revealed that chemical shifts of the carbons at C-8 ~ C-12 were influenced by stereochemistry of the hydroxyl-bearing carbon at C-11 (Table 1). The C-9, C-10, C-11, and C-12 carbons of **5** were more shielded than the same carbons of **6** while the effect for the C-8 carbon was opposite. Based upon these interpretations, comparison of the ^{13}C NMR data for these carbons between the 11-epimeric solandelactones revealed that **1**, **3**, and **7** had the same stereochemistry at C-11 as **5** while **2**, **4**, and **8** had the same stereochemistry as **6**. Since chemical shifts of the carbons at C-12 ~ C-15 were almost identical for **1-8**, stereochemistry of the C-14 asymmetric center may be the same for all of the solandelactones. Therefore, the absolute configurations of **1**, **3**, and **7** may be assigned as 7*R*,8*R*,10*R*,11*S*,14*S*. The absolute configurations of **2**, **4**, and **8** may be assigned as 7*R*,8*R*,10*R*,11*R*,14*S*.

An additional oxylipin, solandelactone I (**9**) was isolated as an oil of composition $C_{22}H_{36}O_4$ as determined by high-resolution mass and ^{13}C NMR spectrometry. NMR data showed that compound **9** possessed the same 8-membered lactone and cyclopropyl rings as other solandelactones. However, ^{1}H COSY data showed that the H-10 proton at δ 1.41 (1H, m) was directly coupled to an olefinic proton at δ 5.37 (1H, dd, 15.1, 8.3) instead of a hydroxyl-bearing methine proton as observed in **1-8**. A combination of the ^{1}H COSY and HMQC experiments determined the structure of **9** as a cyclopropyl containing C_{22} fatty acid lactone possessing double bonds at C-11 and C-16 and hydroxyl groups at C-13 and C-14, respectively. The geometry of double bonds was determined as 11*E* and 16*Z*, respectively by analysis of coupling constants ($J_{11,12}$ = 15.1 Hz, $J_{16,17}$ = 9.8 Hz). Similarly the geometry of the cyclopropyl ring was determined as *trans* ($J_{8,9}$ = 8.3 and 5.4 Hz; $J_{9,10}$ = 8.3 and 5.4 Hz). NOe irradiation of the H-7 proton significantly enhanced signal of the H-10

proton. Therefore, the relative configurations of lactone-cyclopropyl part must be 7*R**,8*R**,10*R**. Comparison of the NMR data with analogous oxylipins revealed that chemical shifts of the protons and carbons at C-13 and C-14 were almost identical to those of *erythro* diols (11*S**,12*S**).[6,13] Since the epimeric *threo* diol has not been isolated from this work, however, the configuration of these asymmetric centers has been remained as tentative.[14]

Cyclopropyl and lactone containing oxylipins have been isolated from various marine invertebrates and algae.[5-8, 15-18] All of these metabolites possess linear C_{20} carbon skeletons derived from eicosanoid precursors. In contrast, solandelactones possess C_{22} carbon skeletons undoubtedly derived from docosahexenoic acid (DHA) and/or related docosanoid(s). To the best of our knowledge, these are the first example of marine oxylipins derived from docosanoid precursor(s).

Scheme 1. Proposed biosynthetic pathway of solandelactones.



Biosynthetic pathway of solandelactones is thought to be analogous to those proposed for constanolactones.[6,18] Lipoxygenase-induced oxidation of a polyunsaturated docosanoid fatty acid would form a hydroperoxy acid which would be in turn converted to an epoxy-cation either directly or via an epoxy-alcohol (Scheme 1). Formation of the lactone and cyclopropyl ring would be induced in the process of stabilizing this epoxy-cation. Ring-opening of the epoxide followed by hydrolysis would form solandelactones. Formation of the alcohols epimeric at C-11 suggests a non-enzymatic process for the hydrolysis.[19] Solandelactone I (**9**) might be formed by the same ring-opening and hydrolysis at C-13. However, the expected 13-epimer has not

been isolated from this work.[6,18]

Cyclopropyl containing oxylipins have been reported to inhibit 5-lipoxygenase or PLA_2. Considering the biogenetic origin of these compounds analogous to that of prostaglandins, these bioactivities against enzymes participating in the arachidonic acid cascade are expected.[7,16] In our measurement, however, solandelactones exhibited none of these activities. This may be due to the presence of an additional C_2 unit in solandelactones. On the other hand, at the concentration of 100 μg/ml, solandelactones C (**3**), D (**4**), and G (**7**) inhibited Farnesyl Protein Transferase by 69, 89, and 61%, respectively.

EXPERIMENTAL

General. NMR spectra were recorded in $CDCl_3$ solutions on a 500-MHz Varian Unity spectrometer. All chemical shifts were recorded with respect to internal Me_4Si. Infrared spectra were recorded on a Matteson GALAXY spectrophotometer. Mass measurements were supplied by Mass Spectrometry Facility, Department of Chemistry, University of California, Riverside. Optical rotations were measured on a JASCO digital polarimeter with a 5-cm microcell. Circular Dichroic measurements were obtained on a JASCO polarimeter with a 0.5 ml microcell. HPLC was performed using a Spectra-Physics Isochrom pump, Shodex RI detector, and YMC ODS semi-preparative column (1 cm x 25 cm). GC spectra were recorded on a Hewlett-Packard 5890 Analytical Gas Chromatograph using SP™-1 column and N_2 as carrier gas. All solvents used were spectral grade or were distilled from glass prior to use.

Collection, Extraction and Isolation. *Solanderia secunda*[4] was collected by hand using SCUBA at 15-25 m depth in January 1990, along the offshore of Jaeju Island, Korea. The collection was frozen immediately and kept in freezer until chemically investigated. The hydroid (5 kg) was defrosted, dried under shade, and repeatedly extracted with CH_2Cl_2 (5 L x 3) and MeOH (5 L x 2). The combined extracts (10.7 g) were subject to silica vacuum flash chromatography using sequential mixtures of n-hexane and EtOAc as eluents. The fractions eluted with 55 to 80% EtOAc in hexane were combined and separated by reversed-phase HPLC (50% CH_3CN in water for **1** - **4**, 42% CH_3CN in water for **5** - **9**).

Solandelactone A (1): oil (22.4 mg, 0.22 % of the crude extract); $[\alpha]^{25}_D$ + 0.5° (c 0.8, MeOH); HRDCIMS: $(M + H)^+$ obsd 365.2687, $C_{22}H_{37}O_4$ requires 365.2692; LRMS: *m/z* (relative intensity) 365 (5), 347 (60), 329 (53), 235 (48), 217 (33), 199 (16), 191 (10), 171 (14), 95 (33), 55 (100); IR (KBr) 3400, 2930, 2870, 1730, 1460, 1240, 1130, 1050 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.78 (2H, m, H-12, -13), 5.59 (1H, dtt, 10.8, 7.3, 1.5, H-17), 5.37 (1H, dtt, 10.8, 7.3, 1.5, H-16), 4.18 (1H, dt, 4.4, 6.4, H-14), 4.09 (1H, dt, 6.4, 7.8, H-7), 3.64 (1H, dd, 7.8, 3.4, H-11), 2.44 (2H, m, H-2), 2.32 (2H, m, H-15), 2.05 (2H, brdt, 6.8, 6.8, H-18), 1.85 (4H, m, H-3, -6), 1.68 (2H, m, H-4), 1.53 (2H, m, H-5), 1.34 (2H, m, H-19), 1.28 (4H, m, H-20, -21), 1.15 (1H, m, H-8), 0.98 (1H, m, H-10), 0.88 (3H, t, 7.1, H-22), 0.68 (1H, ddd, 8.8, 5.4, 5.4, H-9), 0.60 (1H, ddd, 8.3, 5.4, 5.4, H-9).

Solandelactone B (2): oil (19.5 mg, 0.19 % of the crude extract), $[\alpha]^{25}_D$ +6.5° (c 0.8, MeOH); HRDCIMS: $(M + H)^+$ obsd 365.2690, $C_{22}H_{37}O_4$ requires 365.2692; LRMS: *m/z* (relative intensity) 365 (13), 349 (18), 347 (100), 329 (73), 235 (44), 217 (24), 199 (12), 189 (10), 167 (11), 137 (25), 95 (30), 55 (79); IR (KBr) 3400, 2930, 2850, 1730, 1450, 1240, 1130, 1060 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.75 (2H, m, H-12, -13), 5.57 (1H, dtt, 10.7, 7.1, 1.5, H-17), 5.37 (1H, dtt, 10.7, 7.1, 1.5, H-16), 4.16 (1H, dt, 3.9, 6.3, H-14), 4.05 (1H,

dt, 6.4, 6.8, H-7), 3.66 (1H, dd, 7.8, 4.9, H-11), 2.43 (2H, m, H-2), 2.34 (1H, ddd, 14.6, 7.8, 6.3, H-15), 2.28 (1H, ddd, 14.6, 7.1, 6.3, H-15), 2.05 (2H, brdt, 7.3, 7.3, H-18), 1.86 (2H, m, H-3), 1.79 (2H, m, H-6), 1.70 (2H, m,, H-4), 1.53 (2H, m, H-5), 1.36 (2H, m, H-19), 1.29 (4H, m, H-20, -21), 1.05 (1H, m, H-8), 0.99 (1H, m, H-10), 0.89 (3H, t, 7.1, H-22), 0.71 (2H, m, H-9).

Solandelactone C (3): oil (4.1 mg, 0.04 % of the crude extract), $[\alpha]^{25}_D$ +2.9° (c 0.2, MeOH); HRDCIMS: $(M + NH_4)^+$ obsd 380.2809, $C_{22}H_{38}NO_4$ requires 380.2801 LRMS: *m/z* (relative intensity) 380 (2), 214 (25), 197 (16), 141 (11), 132 (10), 125 (14), 115 (24), 81 (27), 45 (100); IR (KBr) 3400, 2930, 2860, 1735, 1360, 1250, 1050, 990 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.81 (1H, dd, 15.6, 5.0, H-13), 5.77 (1H, dd, 15.6, 4.4, H-12), 5.57 (1H, dtt, 11.2, 7.3, 1.5, H-19), 5.41 (2H, m, H-16, -20), 5.30 (1H, dtt, 10.7, 7.3, 1.5, H-17), 4.20 (1H, dt, 3.9, 6.6, H-14), 4.09 (1H, dt, 6.4, 7.6, H-7), 3.65 (1H, dd, 7.6, 4.4, H-11), 2.81 (2H, dd, 7.3, 7.3, H-18), 2.44 (2H, m, H-2), 2.36 (2H, m, H-15), 2.07 (2H, brdq, 7.6, 7.6, H-21), 1.85 (4H, m, H-3, -6), 1.69 (2H, m, H-4), 1.55 (2H, m, H-5), 1.16 (1H, m, H-8), 0.99 (1H, m, H-10), 0.98 (3H, t, 7.6, H-22), 0.68 (1H, ddd, 8.8, 5.4, 5.4, H-9), 0.60 (1H, ddd, 8.8, 5.4, 5.4, H-9).

Solandelactone D (4): oil (4.9 mg, 0.05 % of the crude extract), $[\alpha]^{25}_D$ +5.7° (c 0.2, MeOH); HRDCIMS: $(M + NH_4)^+$ obsd 380.2817, $C_{22}H_{38}NO_4$ requires 380.2801; LRMS: *m/z* (relative intensity) 380 (19), 306 (5), 214 (28), 132 (19), 97 (16), 59 (41), 44 (100); IR (KBr) 3400, 2930, 2860, 1735, 1460, 1250, 1130 1050 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.76 (2H, m, H-12, -13), 5.56 (1H, dtt, 12.2, 7.4, 1.4, H-19), 5.41 (2H, m, H-16, -20), 5.30 (1H, dtt, 12.2, 7.5, 1.4, H-17), 4.19 (1H, dt, 4.2, 6.0, H-14), 4.05 (1H, dt, 6.6, 7.5, H-7), 3.66 (1H, dd, 8.0, 4.5, H-11), 2.81 (2H, dd, 7.4, 7.4, H-18), 2.43 (2H, m, H-2), 2.35 (2H, m, H-15), 2.07 (2H, brdq, 7.5, 7.5, H-21), 1.86 (2H, m, H-3), 1.79 (2H, m, H-6), 1.69 (2H, m, H-4), 1.53 (2H, m, H-5), 1.06 (1H, m, H-8), 0.99 (1H, m, H-10), 0.98 (3H, t, 7.5, H-22), 0.71 (2H, m, H-9).

Solandelactone E (5): oil (35.1 mg, 0.35 % of the crude extract), $[\alpha]^{25}_D$ +2.0° (c 0.7, MeOH); HRDCIMS: $(M + NH_4)^+$ obsd 380.2785, $C_{22}H_{38}NO_4$ requires 380.2801; LRMS: *m/z* (relative intensity) 380 (17), 362 (20), 345 (61), 327 (32), 233 (10), 212 (32), 182 (13), 128 (28), 96 (26), 44 (100); IR (KBr) 3400, 2930, 2860, 1745, 1330, 1220, 1050, 970 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.78 (3H, m, H-4, -12, -13), 5.76 (1H, m, H-5), 5.58 (1H, brdt, 11.1, 7.3, H-17), 5.38 (1H, brdt, 11.1, 6.8, H-16), 4.18 (1H, dt, 5.5, 6.8, H-14), 4.05 (1H, ddd, 10.3, 7.3, 1.0, H-7), 3.66 (1H, dd, 7.3, 4.4, H-11), 2.86 (1H, m, H-3), 2.73 (1H, ddd, 13.2, 5.9, 2.9, H-2), 2.63 (1H, ddd, 14.2, 10.5, 6.4, H-6), 2.32 (2H, m, H-15), 2.30 (1H, m, H-2), 2.26 (1H, ddd, 14.2, 7.8, 1.5, H-6), 2.12 (1H, m, H-3), 2.05 (2H, dt, 7.3, 7.3, H-18), 1.36 (2H, m, H-19), 1.28 (4H, m, H-20, -21), 1.14 (1H, m, H-8), 1.01 (1H, m, H-10), 0.89 (3H, t, 6.8, H-22), 0.74 (1H, ddd, 8.8, 5.4, 4.9, H-9), 0.60 (1H, ddd, 8.3, 5.4, 5.3, H-9).

Solandelactone F (6): oil (42.0 mg, 0.42 % of the crude extract), $[\alpha]^{25}_D$ +3.0° (c 1.0, MeOH); HRDCIMS: $(M + NH_4)^+$ obsd 380.2812, $C_{22}H_{38}NO_4$ requires 380.2801; LRMS: *m/z* (relative intensity) 380 (13), 362 (13), 345 (100), 327 (51), 233 (15), 107 (10), 96 (15), 81 (26), 55 (16); IR (KBr) 3400, 2930, 2860, 1740, 1330, 1220, 1060, 970 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.79 (3H, m, H-4, -12, -13), 5.73 (1H, m, H-5), 5.58 (1H, brdt, 11.0, 7.3, H-17), 5.37 (1H, brdt, 11.0, 7.1, H-16), 4.17 (1H, dt, 5.3, 6.8, H-14), 4.01 (1H, ddd, 10.3, 8.1, 1.7, H-7), 3.67 (1H, dd, 6.3, 4.9, H-11), 2.84 (1H, m, H-3), 2.73 (1H, ddd, 13.2, 5.9, 2.9, H-2), 2.57 (1H, ddd, 14.0, 10.3, 6.4, H-6), 2.33 (2H, m, H-15), 2.30 (1H, m, H-2), 2.19 (1H, ddd, 14.0, 8.1, 1.7, H-6), 2.12 (1H, m, H-3), 2.04 (2H, dt, 7.3, 7.3, H-18), 1.35 (2H, m, H-19), 1.29 (4H, m, H-20, -21), 1.02 (2H, m, H-8, -10), 0.89 (3H, t, 7.1, H-22), 0.78 (1H, ddd, 8.3, 5.4, 5.4, H-9), 0.70 (1H, ddd, 8.4, 5.4, 5.4, H-9).

Solandelactone G (7): oil (19.2 mg, 0.19 % of the crude extract), $[\alpha]^{25}_D$ +3.7° (c 0.8, MeOH);

HRDCIMS: $(M - H)^+$ obsd 359.2217, $C_{22}H_{31}O_4$ requires 359.2222; LRMS: *m/z* (relative intensity) 359 (3), 343 (5), 268 (9), 233 (15), 228 (38), 212 (59), 149 (14), 132 (31), 96 (59), 44 (100); IR (KBr) 3400, 2930, 2870, 1740, 1450, 1380, 1250, 1040 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.79 (3H, m, H-4, -12, -13), 5.74 (1H, m, H-5), 5.57 (1H, dtt, 10.7, 7.3, 1.5, H-19), 5.41 (1H, m, H-16, -20), 5.30 (1H, dtt, 10.7, 6.8, 1.5, H-17), 4.20 (1H, dt, 5.9, 4.9, H-14), 4.01 (1H, ddd, 10.0, 8.3, 1.9, H-7), 3.67 (1H, dd, 7.8, 4.9, H-11), 2.85 (1H, m, H-3), 2.81 (2H, dd, 7.1, 7.1, H-18), 2.74 (1H, ddd, 13.7, 5.9, 2.9, H-2), 2.57 (1H, ddd, 14.0, 10.3, 6.4, H-6), 2.33 (1H, ddd, 13.7, 4.9, 1.5, H-2), 2.32 (2H, m, H-15), 2.26 (1H, ddd, 14.0, 7.8, 1.5, H-6), 2.12 (1H, m, H-3), 2.07 (2H, brdq, 7.6, 7.6, H-21), 1.14 (1H, m, H-8), 1.01 (1H, m, H-10), 0.98 (3H, t, 7.6, H-22), 0.74 (1H, ddd, 8.8, 5.1, 5.1, H-9), 0.60 (1H, ddd, 8.8, 5.1, 5.1, H-9).

Solandelactone H (8): oil (16.8 mg, 0.17 % of the crude extract), $[\alpha]^{25}_D$ +2.4° (c 0.5, MeOH); HRDCIMS: $(M - H)^+$ obsd 359.2239, $C_{22}H_{31}O_4$ requires 359.2222; LRMS: *m/z* (relative intensity) 359 (1), 268 (1), 233 (7), 149 (11), 137 (16), 126 (24), 109 (25), 97 (37), 44 (100); IR (KBr) 3400, 2930, 2870, 1730, 1450, 1380, 1250, 1050, 990 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.79 (3H, m, H-4, -12, -13), 5.74 (1H, m, H-5), 5.57 (1H, dtt, 10.7, 7.3, 1.5, H-19), 5.41 (2H, m, H-16, -20), 5.29 (1H, dtt, 10.8, 7.3, 1.5, H-17), 4.19 (1H, dt, 6.8, 5.1, H-14), 4.01 (1H, ddd, 10.2, 8.0, 1.9, H-7), 3.67 (1H, dd, 6.8, 4.9, H-11), 2.85 (1H, m, H-3), 2.81 (2H, dd, 7.3, 7.3, H-18), 2.73 (1H, ddd, 13.2, 5.9, 2.9, H-2), 2.58 (1H, ddd, 14.0, 10.2, 6.8, H-6), 2.36 (2H, m, H-15), 2.30 (1H, ddd, 13.2, 11.7, 4.9, H-2), 2.19 (1H, ddd, 14.0, 8.0, 1.9, H-6), 2.12 (1H, m, H-3), 2.07 (2H, brdq, 7.3, 7.6, H-21), 1.03 (2H, m, H-8, -10), 0.98 (3H, t, 7.6, H-22), 0.78 (1H, ddd, 8.1, 5.4, 5.3, H-9), 0.70 (1H, ddd, 8.1, 5.4, 5.3, H-9).

Solandelactone I (9): oil (9.8 mg, 0.10 % of the crude extract), $[\alpha]^{25}_D$ -37.7° (c 0.3, MeOH); HRDCIMS: $(M + NH_4)^+$ obsd 382.2973, $C_{22}H_{40}NO_4$ requires 382.2957; LRMS: *m/z* (relative intensity) 382 (46), 347 (11), 242 (18), 223 (16), 158 (60), 126 (14), 96 (19), 81 (22), 45 (100); IR (KBr) 3400, 2930, 2860, 1730, 1240, 1050, 970 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.57 (1H, dtt, 9.8, 7.3, 1.5, H-17), 5.56 (1H, dd, 15.1, 6.3, H-12), 5.42 (1H, dtt, 9.8, 7.8, 1.5, H-16), 5.37 (1H, dd, 15.1, 8.3, H-11), 4.12 (1H, dt, 6.3, 7.6, H-7), 3.92 (1H, dd, 6.3, 6.3, H-13), 3.49 (1H, ddd, 7.8, 6.3, 4.8, H-14), 2.44 (2H, m, H-2), 2.25 (2H, m, H-15), 2.04 (2H, dt, 6.8, 7.1, H-18), 1.87 (2H, m, H-3), 1.82 (2H, m, H-6), 1.70 (1H, m, H-4), 1.56 (1H, m, H-4), 1.54 (2H, m, H-5), 1.41 (1H, m, H-10), 1.35 (2H, m, H-19), 1.30 (2H, m, H-20), 1.27 (2H, m, H-21), 1.14 (1H, m, H-8), 0.90 (1H, ddd, 8.3, 5.4, 5.4, H-9), 0.89 (3H, t, 6.8, H-22), 0.71 (1H, ddd, 8.3, 5.4, 5.4, H-9) ; ^{13}C NMR ($CDCl_3$) δ 176.62 (C, C-1), 135.62 (CH, C-11), 133.55 (CH, C-17), 127.60 (CH, C-12), 124.42 (CH, C-16), 81.29 (CH, C-7), 75.10 (CH, C-13), 74.29 (CH, C-14), 37.13 (CH_2, C-6), 32.69 (CH_2, C-2), 31.50 (CH_2, C-20), 31.07 (CH_2, C-15), 29.24 (CH_2, C-3), 29.06 (CH_2, C-19), 27.36 (CH_2, C-18), 26.46 (CH_2, C-4), 24.86 (CH, C-8), 24.15 (CH_2, C-5), 22.62 (CH_2, C-21), 19.24 (CH, C-10), 14.03 (CH_3, C-22), 12.16 (CH_2, C-9).

Solandelactone A diacetate (10). To a stirred solution of 1.5 mg of **1** in 0.3 mL of dry pyridine was added 0.2 mL of acetic anhydride. The mixture was stirred at room temperature for 1 hr. After removing the pyridine and excess acetic anhydride under vacuum, the residue was purified by reversed-phase HPLC (100% CH_3CN) to give 1.3 mg of **10**: oil, HRDCIMS: $(M + H)^+$ obsd 449.2898, $C_{26}H_{41}O_6$ requires 449.2903; LRMS: *m/z* (relative intensity) 449 (14), 389 (100), 337 (27), 329 (37), 235 (22), 217 (18), 137 (10), 109 (11), 81 (31); ^1H NMR ($CDCl_3$) δ 5.71 (1H, m, H-13), 5.69 (1H, m, H-12), 5.51 (1H, dtt, 11.2, 7.3, 1.5, H-17), 5.28 (1H, dtt, 11.2, 7.3, 1.5, H-16), 5.27 (1H, m, H-14), 4.83 (1H, ddd, 8.3, 3.2, 1.5, H-11), 4.05 (1H, dt, 5.4, 8.1, H-7), 2.43 (3H, m, H-2, -15), 2.34 (1H, m, H-15), 2.07 (3H, s, Ac), 2.05 (3H, s, Ac), 2.01 (2H, brdt, 6.4, 7.8, H-18), 1.86 (2H, m, H-3), 1.79 (2H, m, H-6), 1.70 (1H, m, H-4), 1.56 (1H, m, H-4), 1.53 (2H, m, H-5), 1.34 (2H, m, H-19),

1.29 (4H, m, H-20, -21), 1.21 (1H, m, H-8), 1.04 (1H, m, H-10), 0.89 (3H, t, 7.1, H-22), 0.74 (1 H, ddd, 8.3, 5.4, 5.4, H-9), 0.60 (1H, ddd, 8.3, 5.4, 5.4, H-9).

Solandelactone B diacetate (11). Prepared as described for the formation of **10**: oil, HRDCIMS: $(M + NH_4)^+$ obsd 466.3151, $C_{26}H_{44}NO_6$ requires 466.3169; LRMS: *m/z* (relative intensity) 466 (24), 389 (9), 337 (2), 214 (5), 126 (6), 98 (11), 86 (10), 77 (16), 60 (49), 45 (100); ^{1}H NMR ($CDCl_3$) δ 5.68 (1H, dd, 15.6, 5.4, H-13), 5.64 (1H, dd, 15.6, 5.4, H-12), 5.50 (1H, dtt, 10.7, 7.3, 1.5, H-17), 5.28 (1H, dtt, 10.7, 7.3, 1.5, H-16), 5.25 (1H, m, H-14), 4.88 (1H, dd, 7.3, 5.4, H-11), 4.06 (1H, dt, 6.8, 7.1, H-7), 2.42 (2H, m, H-2), 2.41 (1H, m, H-15), 2.32 (1H, m, H-15), 2.06 (3H, s, Ac), 2.05 (3H, s, Ac), 2.01 (2H, brdt, 6.8, 7.3, H-18), 1.86 (2H, m, H-3), 1.78 (2H, brdt, 5.9, 6.1, H-6), 1.69 (1H, m, H-4), 1.55 (1H, m, H-4), 1.52 (2H, m, H-5), 1.34 (2H, m, H-19), 1.29 (4H, m, H-20, -21), 1.04 (2H, m, H-8, -10), 0.89 (3H, t, 6.8, H-22), 0.74 (1H, ddd, 8.3, 5.4, 5.4, H-9), 0.70 (1H, ddd, 8.3, 5.4, 5.4, H-9).

Solandelactone E diacetate (12). Prepared as described for the formation of **10**: oil, ^{1}H NMR ($CDCl_3$) δ 5.75 (1H, m, H-4), 5.70 (1H, m, H-5), 5.68 (2H, m, H-12, -13), 5.49 (1H, brdt, 11.2, 7.3, H-17), 5.27 (1H, brdt, 11.2, 7.1, H-16), 5.26 (1H, m, H-14), 4.80 (1H, dd, 8.6, 2.6, H-11), 3.94 (1H, ddd, 10.7, 8.1, 1.7, H-7), 2.82 (1H, m, H-3), 2.70 (1H, ddd, 13.2, 5.9, 2.9, H-2), 2.56 (1H, ddd, 14.1, 10.3, 6.4, H-6), 2.36 (2H, m, H-15), 2.27 (1H, ddd, 13.2, 11.7, 4.9, H-2), 2.16 (1H, ddd, 14.1, 7.8, 1.5, H-6), 2.10 (1H, m, H-3), 2.01 (2H, dt, 7.3, 7.3, H-18), 2.05 (3H, s, Ac), 2.04 (3H, s, Ac), 1.32 (2H, quin, 7.3, H-19), 1.27 (4H, m, H-20, -21), 1.18 (1H, m, H-8), 1.03 (1H, m, H-10), 0.87 (3H, t, 7.1, H-22), 0.78 (1H, ddd, 8.8, 5.4, 5.4, H-9), 0.60 (1H, ddd, 8.8, 5.4, 5.4, H-9); ^{13}C NMR ($CDCl_3$) δ 176.78 (C, C-1), 170.07 (C x 2, Ac), 133.30 (CH, C-17), 132.84 (CH, C-4), 130.50 (CH, C-12), 129.49 (CH, C-13), 127.93 (CH, C-5), 123.15 (CH, C-16), 80.51 (CH, C-7), 75.81 (CH, C-11), 73.07 (CH, C-14), 37.77 (CH_2, C-2), 34.17 (CH_2, C-6), 32.30 (CH_2, C-15), 31.53 (CH_2, C-20), 29.23 (CH_2, C-19), 27.42 (CH_2, C-18), 24.47 (CH_2, C-3), 22.60 (CH_2, C-21), 21.27 (CH_3, Ac), 21.24 (CH_3, Ac), 21.14 (CH, C-10), 20.93 (CH, C-8), 14.10 (CH_3, C-22), 8.75 (CH_2, C-9).

Solandelactone F diacetate (13). Prepared as described for the formation of **10**: oil, ^{1}H NMR ($CDCl_3$) δ 5.76 (1H, m, H-4), 5.72 (1H, m, H-5), 5.66 (2H, m, H-12, -13), 5.48 (1H, brdt, 10.8, 6.6, H-17), 5.26 (1H, brdt, 10.8, 6.8, H-16), 5.24 (1H, dt, 6.4, 6.4, H-14), 4.84 (1H, dd, 7.8, 5.4, H-11), 3.97 (1H, ddd, 10.2, 8.3, 1.5, H-7), 2.82 (1H, m, H-3), 2.70 (1H, ddd, 13.2, 6.3, 2.9, H-2), 2.54 (1H, ddd, 14.1, 9.8, 6.4, H-6), 2.35 (2H, m, H-15), 2.27 (1H, ddd, 13.2, 11.7, 4.9, H-2), 2.14 (1H, ddd, 14.1, 8.3, 1.5, H-6), 2.10 (1H, m, H-3), 1.99 (2H, dt, 6.6, 6.6, H-18), 2.05 (3H, s, Ac), 2.03 (3H, s, Ac), 1.32 (2H, quin, 7.3, H-19), 1.27 (4H, m, H-20, -21), 1.05 (1H, m, H-10), 0.99 (1H, m, H-8), 0.87 (3H, t, 6.8, H-22), 0.74 (1H, ddd, 8.3, 5.4, 5.4, H-9), 0.71 (1H, ddd, 8.3, 5.4, 5.4, H-9); ^{13}C NMR ($CDCl_3$) δ 176.74 (C, C-1), 170.12 (C, Ac), 170.08 (C, Ac), 133.36 (CH, C-17), 132.87 (CH, C-4), 130.50 (CH, C-12), 129.49 (CH, C-13), 127.91 (CH, C-5), 123.16 (CH, C-16), 80.42 (CH, C-7), 75.55 (CH, C-11), 73.07 (CH, C-14), 37.70 (CH_2, C-2), 34.17 (CH_2, C-6), 32.26 (CH_2, C-15), 31.50 (CH_2, C-20), 29.19 (CH_2, C-19), 27.39 (CH_2, C-18), 24.43 (CH_2, C-3), 22.56 (CH_2, C-21), 21.25 (CH_3, Ac), 21.21 (CH_3, Ac), 20.87 (CH, C-8), 19.97 (CH, C-10), 14.06 (CH_3, C-22), 9.57 (CH_2, C-9).

***p*-Bromobenzoylation of solandelactone E (5).** To a stirred solution of 4.5 mg of **5** in 10 mL of a mixture of CH_2Cl_2 and pyridine (v:v = 12.5:1) was added 37 mg of *p*-bromobenzoyl chloride. The mixture was stirred under N_2 at room temperature for 2 days. After removing the solvent under vacuum, the residue was subject to silica HPLC (30% EtOAc in hexane) to yield 5.9 mg of pure **14** and 2.8 mg of a mixture of monobenzoates. The mixture was finally purified by reversed-phase HPLC (15% aqueous CH_3CN) to yield 1.0 mg of **15** and 1.2 mg of **16**.

Bis(*p*-bromobenzoyl)solandelactone E (14): oil, ^{1}H NMR ($CDCl_3$) δ 7.88 (2H, d, 8.3, Ar), 7.87 (2H, d, 8.3, Ar), 7.57 (2H, d, 8.3, Ar), 7.56 (2 H, d, 8.3, Ar), 5.87 (2H, m, H-12, -13), 5.73 (1H, brdt, 11.2, 6.6, H-4), 5.63 (1H, dd, 11.2, 8.1, H-5), 5.53 (1H, m, H-14), 5.48 (1H, dtt, 11.2, 7.3, 1.5, H-16), 5.33 (1H, dtt, 11.2, 7.1, 1.5, H-17), 5.07 (1H, dd, 8.3, 2.4, H-11), 3.94 (1H, ddd, 10.3, 8.8, 2.0, H-7), 2.81 (1H, m, H-3), 2.68 (1H, ddd, 13.2, 5.9, 2.9, H-2), 2.50 (2H, m, H-15), 2.47 (1H, m, H-6), 2.26 (1H, ddd, 13.2, 11.7, 4.9, H-2), 2.09 (1H, ddd, 10.3, 8.1, 2.0, H-6), 2.07 (1H, m, H-3), 1.98 (2H, m, H-18), 1.27 (2H, quin, 7.3, H-19), 1.25 (1H, m, H-8), 1.23 (4H, m, H-20, -21), 1.16 (1H, m, H-10), 0.84 (1H, ddd, 8.8, 5.1, 5.1, H-9), 0.84 (3H, t, 6.8, H-22), 0.69 (1H, ddd, 8.8, 5.1, 5.1, H-9).

11-(*p*-Bromobenzoyl)solandelactone E (15): oil, ^{1}H NMR ($CDCl_3$) δ 7.89 (2H, d, 8.5, Ar), 7.58 (2H, d, 8.5, Ar), 5.85 (1H, dd, 15.6, 5.7, H-13), 5.81 (1H, dd, 15.6, 5.4, H-12), 5.74 (1H, m, H-4), 5.66 (1H, m, H-5), 5.56 (1H, brdt, 10.7, 7.3, H-16), 5.33 (1H, brdt, 10.7, 7.8, H-17), 5.03 (1H, dd, 8.3, 5.4, H-11), 4.18 (1H, m, H-14), 3.95 (1H, brdd, 8.5, 8.5, H-7), 2.80 (1H, m, H-3), 2.69 (1H, ddd, 13.2, 5.4, 2.9, H-2), 2.51 (1H, m, H-6), 2.28 (2H, m, H-15), 2.27 (1H, m, H-2), 2.12 (1H, ddd, 14.1, 8.3, 1.5, H-6), 2.08 (1H, m, H-3), 2.01 (2H, m, H-18), 1.32 (2 H, quin, 7.1, H-19), 1.26 (4H, m, H-20, -21), 1.25 (1H, m, H-8), 1.16 (1H, m, H-10), 0.86 (3H, t, 7.1, H-22), 0.84 (1H, ddd, 8.3, 5.4, 5.4, H-9), 0.69 (1H, ddd, 8.3, 5.4, 5.4, H-9).

14-(*p*-Bromobenzoyl)solandelactone E (16): oil, UV (MeOH) λmax 245 nm (ε 21600); CD (MeOH) 242.3 nm (Δε +10.67); ^{1}H NMR ($CDCl_3$) δ 7.88 (2H, d, 8.5, Ar), 7.56 (2H, d, 8.5, Ar), 5.86 (1H, dd, 15.6, 6.1, H-13), 5.79 (1H, dd, 15.6, 5.4, H-12), 5.76 (1H, m, H-4), 5.70 (1H, m, H-5), 5.52 (1H, m, H-14), 5.50 (1H, brdt, 10.7, 7.3, H-16), 5.36 (1H, brdt, 10.7, 7.3, H-17), 4.00 (1H, ddd, 8.3, 8.3, 1.5, H-7), 3.69 (1H, dd, 7.3, 5.4, H-11), 2.82 (1H, m, H-3), 2.71 (1H, ddd, 13.2, 5.9, 2.9, H-2), 2.60 (1H, m, H-6), 2.51 (2H, m, H-15), 2.28 (1H, m, H-2), 2.21 (1H, ddd, 13.7, 8.3, 1.5, H-6), 2.10 (1H, m, H-3), 2.02 (2H, m, H-18), 1.32 (2H, quin, 7.0, H-19), 1.24 (4H, m, H-20, -21), 1.11 (1H, m, H-8), 0.97 (1H, m, H-10), 0.85 (3H, t, 6.8, H-22), 0.72 (1H, ddd, 8.8, 5.4, 5.4, H-9), 0.59 (1H, ddd, 8.8, 5.4, 5.4, H-9).

***p*-Bromobenzoylation of solandelactone F (6)**. To a stirred solution of 4.3 mg of **6** in 10 mL of a mixture of CH_2Cl_2 and pyridine (v:v = 12.5:1) was added 33 mg of *p*-bromobenzoyl chloride. The mixture was stirred under N_2 at room temperature for 2 days. After removing the solvent under vacuum, the residue was subject to silica HPLC (30% EtOAc in hexane) to yield 2.3 mg of **17**, 2.9 mg of **18**, and 2.0 mg of **19**.

Bis(*p*-bromobenzoyl)solandelactone F (17): oil,^{1}H NMR ($CDCl_3$) δ 7.87 (2H, d, 8.3, Ar), 7.86 (2H, d, 8.3, Ar), 7.57 (2H, d, 8.3, Ar), 7.56 (2H, d, 8.3, Ar), 5.87 (1H, dd, 15.6, 5.4, H-13), 5.82 (1H, dd, 15.6, 5.4, H-12), 5.76 (1H, brdt, 11.2, 6.6, H-4), 5.66 (1H, dd, 11.2, 7.8, H-5), 5.51 (1H, m, H-14), 5.47 (1H, brdt, 10.7, 7.3, H-16), 5.33 (1H, brdt, 10.7, 7.3, H-17), 5.11 (1H, dd, 7.8, 5.4, H-11), 3.97 (1H, ddd, 10.5, 8.5, 1.5, H-7), 2.80 (1H, m, H-3), 2.69 (1 H, ddd, 13.2, 5.9, 2.9, H-2), 2.52 (1H, m, H-6), 2.49 (2H, m, H-15), 2.27 (1H, ddd, 13.2, 11.7, 4.9, H-2), 2.10 (1H, ddd, 14.2, 8.3, 1.5, H-6), 2.06 (1H, m, H-3), 1.98 (2H, m, H-18), 1.26 (2H, quin, 7.3, H-19), 1.23 (4H, m, H-20, -21), 1.17 (1H, m, H-10), 1.07 (1H, m, H-8), 0.84 (1H, ddd, 8.3, 5.1, 5.1, H-9), 0.84 (3H, t, 7.1, H-22), 0.79 (1H, ddd, 8.3, 5.1, 5.1, H-9).

11-(*p*-Bromobenzoyl)solandelactone F (18): oil, UV (MeOH) λmax 244 nm (ε 19000); CD (MeOH) 242.5 nm (Δε +7.13); ^{1}H NMR ($CDCl_3$) δ 7.89 (2H, d, 8.3, Ar), 7.57 (2H, d, 8.3, Ar), 5.84 (1H, dd, 15.5, 5.9, H-13), 5.77 (1H, dd, 15.5, 6.8, H-12), 5.75 (1H, m, H-4), 5.70 (1H, m, H-5), 5.55 (1H, brdt, 10.3, 7.3, H-16), 5.33 (1H, brdt, 10.3, 7.3, H-17), 5.15 (1H, dd, 6.8, 6.8, H-11), 4.16 (1H, m, H-14), 4.04 (1H, brdd, 9.0, 9.0, H-7), 2.82 (1H, m, H-3), 2.70 (1H, ddd, 13.2, 5.4, 2.4, H-2), 2.57 (1H, m, H-6), 2.29 (2H, m, H-15), 2.28 (1H, m, H-2), 2.17 (1H, brdd, 13.7, 8.3, H-6), 2.10 (1H, m, H-3), 2.00 (2H, m, H-18), 1.32 (2H, quin, 7.1, H-19), 1.25

(4H, m, H-20, -21), 1.21 (1H, m, H-10), 1.10 (1H, m, H-8), 0.85 (3H, t, 6.9, H-22), 0.80 (2H, m, H-9).

14-(*p*-Bromobenzoyl)solandelactone F (19): oil, UV (MeOH) λmax 245 nm (ε 19500); CD (MeOH) 241.8 nm (Δε +13.67); ^{1}H NMR ($CDCl_3$) δ 7.87 (2H, d, 8.3, Ar), 7.55 (2H, d, 8.3, Ar), 5.81 (2H, m, H-12, -13), 5.75 (1H, brdt, 11.2, 6.1, H-4), 5.66 (1H, 11.2, 7.3, H-5), 5.50 (2H, m, H-14, -16), 5.35 (1 H, brdt, 10.7, 7.3, H-17), 3.94 (1H, brdd, 9.0, 9.0, H-7), 3.63 (1H, dd, 6.8, 5.4, H-11), 2.80 (1H, m, H-3), 2.70 (1H, ddd, 13.2, 7.3, 1.5, H-2), 2.53 (1H, m, H-6), 2.50 (2H, m, H-15), 2.27 (1H, m, H-2), 2.13 (1H, ddd, 14.2, 8.3, 1.5, H-6), 2.10 (1H, m, H-3), 2.01 (2H, m, H-18), 1.29 (2H, quin, 7.0, H-19), 1.24 (4H, m, H-20, -21), 0.97 (2H, m, H-8, -10), 0.85 (3H, t, 6.6, H-22), 0.75 (1H, ddd, 8.3, 5.4, 5.4, H-9), 0.68 (1H, ddd, 8.3, 5.4, 5.4, H-9).

Formation of bis(menthoxycarbonyl)solandelactone F (20). To a stirred solution of 7.6 mg of **6** in 0.6 mL of a mixture of toluene and pyridine (v:v = 2:1) was added 1 mL of (-)-menthoxycarbonyl (MC) chloride (0.11M solution in toluene). The mixture was stirred under N_2 at room temperature for 1.5 hr. After removing the solvent under vacuum, the mixture was dissolved in 5 mL of hexane and was subject to silica vacuum flash chromatography (1cm x 15 cm) by using sequential mixtures of hexane and EtOAc as eluents. The fraction eluted with 6% EtOAc in hexane contained 4.9 mg of pure **20** : oil, ^{1}H NMR ($CDCl_3$) δ 5.75 (2H, m), 5.69 (2H, m), 5.49 (1H, brdt, 18.1, 7.3), 5.28 (1H, brdt, 18.1, 7.6), 5.07 (1H, dd, 6.0, 6.0), 4.70 (1H, dd, 8.1, 5.1), 4.47 (2 H, m), 3.93 (1 H, brt, 9.3), 2.81 (1H, m), 2.70 (1H, ddd, 13.7, 5.9, 2.9), 2.54 (1H, ddd, 14.2, 10.3, 6.8), 2.40 (2H, m), 2.27 (1H, brdt, 12.5, 4.4), 2.17 (1H, brdd, 14.2, 7.8), 2.05-1.88 (7H, m), 1.66 (4H, m), 1.47-1.36 (4H, m), 1.31 (2H, quin, 7.3), 1.25 (4H, m), 1.09 (1H, m), 1.05-0.96 (5H, m), 0.92-0.83 (17H, m), 0.79 (2H, m), 0.75 (3H, d, 6.8).

Ozonolysis of bis(menthoxycarbonyl)solandelactone F (20). Ozone was bubbled into a stirred solution of 4.8 mg of **20** in 1 mL of $CHCl_3$ at -42 °C (CH_3CN and dry ice) for 5 min. The solution was further stirred at room temperature for 10 min. After removing the solvent by blowing with N_2, 1 mL of conc. acetic acid and 0.3 mL of H_2O_2 (35%) were added to the residue and stirred at 50 °C for 13 hr. After drying under vacuum, the residue was re-dissolved with 3 mL of dry THF and treated with diazomethane (formed *in situ* by addition of 10% NaOH solution to MNNG in diazomethane-generation apparatus) at 0 °C for 5 min. After drying under vacuum, the residue was subject to silica vacuum flash chromatography (1 cm x 15 cm) using sequential mixtures of hexane and EtOAc as eluents. Elution with 3% EtOAc in hexane yielded 0.5 mg of dimethyl-MC-*S*-malate (**24**): oil, ^{1}H NMR ($CDCl_3$) δ 5.39 (1H, dd, 6.8, 5.4), 4.55 (1H, ddd, 11.0, 11.0, 4.4), 3.76 (3H, s), 3.70 (3H, s), 2.90 (2H, m), 2.04 (1H, brd, 11.7), 2.00 (1H, heptet-d, 7.1, 2.4), 1.66 (2H, brd, 12.0), 1.46 (1H, m), 1.41 (1H, ddt, 11.7, 11.7, 3.2), 1.05 (1H, dd, 11.6, 11.6), 1.04 (1H, m), 0.90 (3H, d, 6.8), 0.89 (3H, d, 6.8), 0.85 (1H, m), 0.79 (3H, d, 6.8). GC analysis (170 °C) of dimethyl-MC-*S*-malate gave a peak at 23.917 min retention (standard *S*-malate: 24.039 min, *R*-malate: 24.296 min).

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10. The absolute configurations of constanolactones A and B were determined as 5*R*,6*R*,8*S*,9*S*,12*S* and 5*R*, 6*S*,8*S*,9*R*,12*S*, respectively by chemical and spectroscopic methods. The absolute stereochemistry of halichlactone was determined as 8*S*,9*R*,11*R*,12*R*,15*R* by total synthesis. See ref. 6 and 9.
11. To confirm the configuration of the cyclopropyl ring, we also performed NOESY experiments of **5** and **10** in which the key nOe interactions between the H-6 protons and the H-8 and H-10 protons were consistently observed.
12. 2*R* and 2*S* dimethyl-MC-malates were synthesized from dimethyl-*R* (*S*)-malates and (-)-MC chloride. ^{1}H NMR spectra of 2*R* and 2*S* dimethyl-MC-malates showed significantly differentiated chemical shifts for the H-7 and H-8 protons [2*R* derivative: δ 0.86 (H-7) and 1.90 (H-8); 2*S* derivative: δ 0.90 (H-7) and 2.00 (H-8)].
13. Constanolactone E (11*R*,12*S*); ^{1}H NMR δ 4.10 (dd, 6.8, 3.8, H-11), 3.66 (m, H-12); ^{13}C NMR δ 74.84 (C-11), 73.90 (C-12): constanolactone F (11*S*,12*S*); ^{1}H NMR δ 3.91 (t, 6.3, H-11), 3.48 (dd, 6.3, 5.7, H-12); ^{13}C NMR δ 75.13 (C-11), 74.20 (C-12). Solandelactone I; ^{1}H NMR δ 3.92 (t, 6.3, H-13), 3.49 (ddd, 7.8, 6.0, 4.8, H-14); ^{13}C NMR δ 75.10 (C-13), 74.29 (C-14): see ref.6.
14. Compound **9** was highly unstable. All of the efforts to convert **9** to derivatives for determination of stereochemistry at C-13 and C-14 resulted in decomposition of the reactant.
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19. The biogenetic origin and biosynthetic pathway of solandelactones are currently under investigation. The results will be published in due course.

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