Synthesis of Elemane Bis-Lactones from Santonin – Synthesis of the Reported Structure of *seco*-Isoerivanin Pseudo Acid and Formal Synthesis of (+)-8-Deoxyvernolepin

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Dedicated to the memory of the late Prof. Joaquin de Pascual Teresa

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The synthesis of the reported structure for *seco*-isoerivanin pseudo acid (**1**) and of an elemane bis-lactone **5** from santonin (**4**) through a common vinylic precursor **12** is described. Compound **5** is a known intermediate in a previous synthesis of the antitumor compound (+)-8-deoxyvernolepin (**3**). The vinyl group of **12** underwent a regio- and diastereoselective *anti* addition of an external electrophile and an intramolecular condensation to yield either the selenolactone **13** or the hydroxylactone **17**. The lactones **13** and **17** served as key intermediates in the total synthesis of **1** and **5** respectively. A revision of the structure of *seco*-isoerivanin pseudo acid to the C-10 epimer is suggested on the basis of comparison between the spectral data of the natural and synthetic products.

Introduction

Sesquiterpenes and, in particular, sesquiterpene lactones make up a group of natural compounds that show a wide variety of biological properties. These properties range from compounds of medical interest, such as some antitumor drugs, to products of agrochemical application, with antifeedant or herbicidal activities. The interest in this type of products is manifested by the increasing number of articles dealing with their isolation and synthesis that appear in the scientific literature.[1]

Further to their practical application, the unique structures shown by some of the members of the sesquiterpene family have also attracted the attention of synthetic organic chemists. For instance, the occurrence of a second lactone ring on the carbon skeleton is a structural feature only present in a small number of sesquiterpene lactones, which in general have only one lactone ring.

As an example we can mention bis-lactone **1**, named *seco*-isoerivanin pseudo acid, whose isolation from *Artemisia judaica* has been reported.[2] This compound shows a unique structural feature consisting of a hemiacetal δ-lactone moiety between a carboxylate group on C-3 and a ketone hydrate on C-1.

Other examples are the potent antitumor compound vernolepin (**2**),[3] isolated from *Vernonia hymenolepis,* and the unnatural (+)-8-deoxyvernolepin (**3**) which shows even more potent activity against in vitro CCRF-CEM tumor cell cultures than does natural vernolepin.[4] This biological activity has aroused much attention among organic chemists, who have devised several synthetic approaches to these compounds, most of them using santonin (**4**) as starting material (Figure 1).[5] In all of them, the required oxyfunctionalization of the angular methyl group is achieved by photochemical remote oxidation from 2β-[5c] and 6β-[5a] alkoxy radicals; and in a very recent approach, from a hydroxymethyl radical in bis-lactone **5**.[6] In this article we would like to report the synthesis of compounds **1** and **5** by means of an unusual lactonization reaction of compound **12** upon treatment with an electrophilic reagent.[7] The synthesis of compound **5** constitutes a formal synthesis of (+)-8-deoxyvernolepin (**3**).

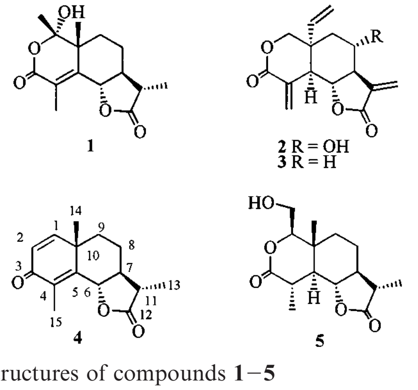

Figure 1. Structures of compounds **1**−**5**

Results and Discussion

The synthesis of compound **1** was elaborated first. Keto ester **16** was considered as the immediate precursor of compound **1** in the synthetic scheme.

The synthesis of compound **16** from santonin (**4**) required cleavage of the C(2)−C(3) bond in a way designed to preserve the C(4)−C(5) double bond present in santonin and in compound **16**.

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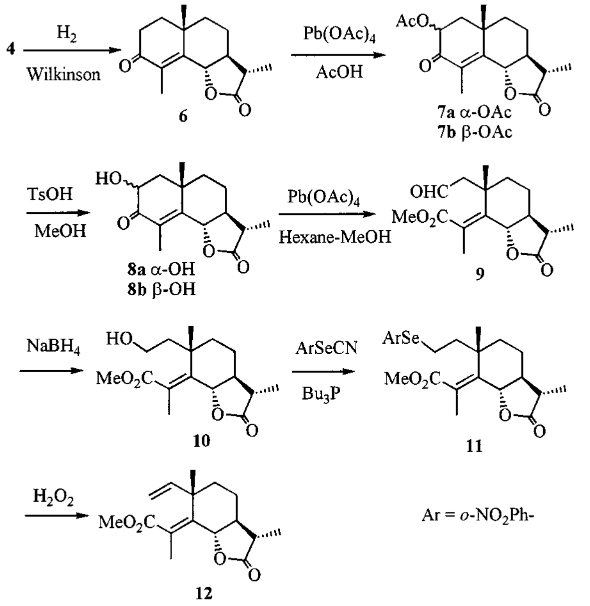
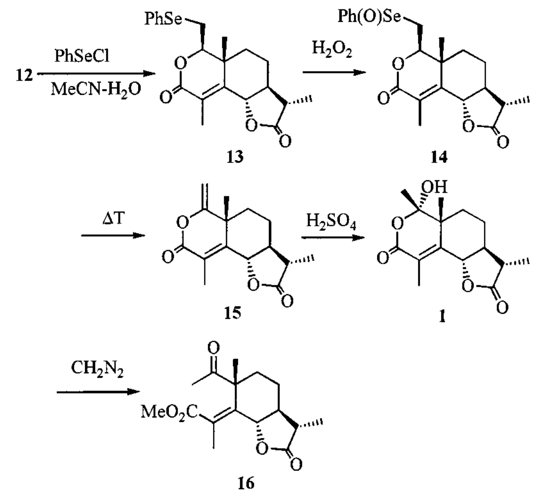


Scheme 1



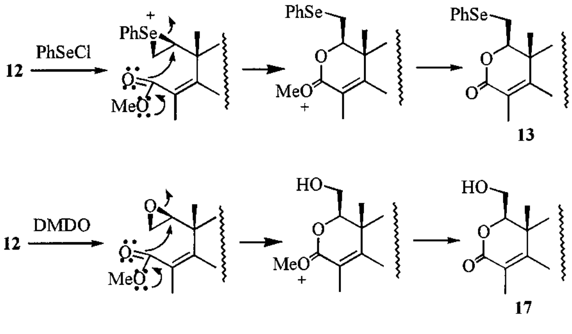
Scheme 2

With this aim (Scheme 1), dihydrosantonin (**6**), obtained quantitatively from santonin by selective hydrogenation with Wilkinson catalyst[8] was treated with lead tetraacetate (LTA)[5e] to give the acetoxylated products **7a** and **7b** in 65% yield. During this reaction some santonin (13%) was also recovered, probably as a result of partial elimination in the acetoxylated products. In order to cleave the C(2)−C(3) bond, the mixture of acetates **7a** and **7b** was subjected to methanolysis with methanol containing a catalytic amount of TsOH to afford hydroxy ketones **8a** and **8b** in 95% yield. Treatment of these compounds with LTA in hexane/methanol[9] brought about cleavage of the C(2)−C(3) bond yielding aldehyde ester **9**. This was very unstable and so was immediately reduced with sodium borohydride to give alcohol **10** in 67% overall yield for the two steps.

The elimination of the hydroxyl group was achieved in two steps following the procedure described by Grieco et al..[10] The sequence involves transformation of the hydroxyl group into an *o*-nitrophenyl selenide **11** in 85% yield by treatment with *o*-nitrophenyl selenocyanate and tri-*n*-butylphosphane, followed by spontaneous elimination of the corresponding selenoxide upon treatment with H_2O_2 to give compound **12** in 89% yield.

With alkene **12** available, we attempted different methods to oxidize the vinyl group into a ketone. Alkene **12** was subjected to modified Wacker procedures without success.[11] Other procedures for the hydration of the vinyl group, such as solvomercuration,[12] were equally unsuccessful, and therefore compound **16** could not be prepared from **12**.

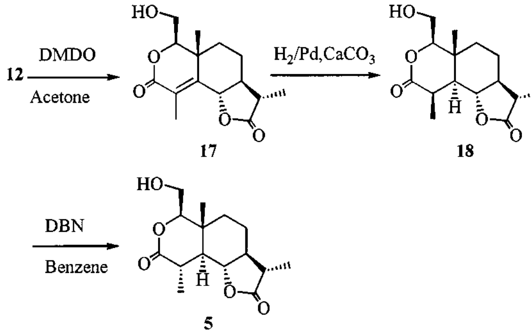
To overcome this problem, we planned a new strategy consisting of the introduction of a hydroxyl group on C-1 and a potential leaving group on C-2, which after lactonization and elimination would yield the vinyl lactone **15**, synthetically equivalent to a carbonyl group on C-1. With this aim (Scheme 2), alkene **12** was subjected to phenylselenohydroxylation by treatment with PhSeCl in aqueous acetonitrile.[13] This resulted in a spontaneous lactonization to give a bis-lactone **13**, with total regio- and diastereoselectivity. The configuration at C-1 was determined from a NOE observed between 1-H (δ = 4.18) and 9α-H (δ = 1.21). The cyclohexane ring in this molecule is in a chair conformation with 6-H, 7-H, 8β-H, 9α-H and the 10-Me group in axial positions as deduced from the coupling constants in the ^{1}H NMR spectrum. On the other hand, the δ−lactone ring must be in a flattened chair conformation because of the α,β-unsaturated lactone moiety. The observed NOE is in good agreement with a 1,3-diaxial interaction between 1-H and 9α-H, and therefore 1-H must be of α orientation, in an axial or pseudoaxial disposition. The high diastereoselectivity observed in this reaction can be explained considering the approach of PhSe$^+$ as external electrophile from the *re* side of the vinyl group,[14] this being the group eclipsed with the 10-Me group in the most favored conformation,[15] followed by an intramolecular condensation in a 6-*exo-tet* process as depicted in Scheme 3. In this conformation the *si* attack is hindered by the ester group.



Scheme 3. Lactonization of compound **12**

Elimination of the phenyl selenide was achieved by its conversion into the corresponding phenyl seleniumoxide **14** upon treatment with H_2O_2. Despite the fact that elimination of selenoxides normally occurs at room temperature, in this case elimination was only observed after heating at benzene reflux temperature to give the corresponding enol lactone **15** in 93% yield. Finally, hydration of the double bond was carried out by treatment with 50% H_2SO_4 to afford the desired product **1** as a single epimer in 86% yield. The configuration at C-1 was assigned on the basis of a NOE ($CDCl_3$) observed between 2-H (δ = 1.57) and 14-H (δ = 1.30). The synthetic material obtained in this way showed spectral data consistent with its structure. However these spectral data did not coincide with those reported in the literature for the natural epimer mixture isolated from *Artemisia judai*ca.[2] Significant differences were found between almost all signals in the ^{1}H NMR spectra (C_6D_6) of both materials: δ = 3.87−3.86 (dq, ^1J = 1.5, 11.0 Hz, 6-H), 2.14−2.11 (s, 15-H), 1.47−1.44 (s, 2-H), 1.41−1.13 (s, 14-H) and 0.95−0.91 (d, ^1J = 7 Hz, 13-H) for the natural epimer mixture, and δ = 3.72 (dq, ^1J = 2.0, 11.6 Hz, 6-H), 2.42 (d, ^1J = 2.0 Hz, 15-H), 1.36 (s, 2-H), 0.87 (d, ^1J = 6.8, 13-H) and 0.76 (s, 14-H) for our synthetic material.

Since natural *seco*-isoerivanin pseudo acid was isolated in very small amount as a mixture of two C-1 epimers and its structure was assigned by its chemical transformation into a methyl ester whose structure was supposed to be that of compound **16**,[2] we subjected our synthetic material **1** to esterification under the same conditions reported by those authors. Thus, by treatment of compound **1** with an ethereal solution of diazomethane we obtained a material that was characterized as methyl ester **16**. The ^{1}H NMR spectrum of the product obtained in this way matched with that of natural *seco*-isoerivanin pseudo acid methyl ester, except for the signals corresponding to 14-H and 8-H. These appeared at δ = 1.52 and 1.80 in the natural ester, and at δ = 1.42 and 1.51 in the synthetic product. These results indicated that the structures of both methyl esters, although different, were very similar to each other. Given the structural simplicity of **16** and the coincidence of the coupling patterns of the signals in the ^{1}H NMR spectra of both compounds, we believe that the difference between them, and hence between natural *seco*-isoerivanin pseudo acid and our synthetic bis-lactone **1**, should lie in the configuration at C-10. Consequently, we suggest the C-10 epimer of our synthetic materials **1** and **16** as the revised structures for natural *seco*-isoerivanin pseudo acid and its methyl ester respectively.



Scheme 4

For the synthesis of compound **5** (Scheme 4), a known intermediate in a recent synthetic approach to (+)-8-deoxyvernolepin (**3**), we devised a modification of the above lactonization reaction that allowed the introduction of a hydroxyl group on C-2 instead of PhSe. This consisted of epoxidation of the vinyl group. However, compound **12** was difficult to epoxidize and resisted treatment with *m*-chloroperoxybenzoic acid and dimethyldioxirane (DMDO) generated in situ in a biphasic system.[16] Epoxidation finally succeeded by treatment with a solution of DMDO in acetone.[17] The resulting epoxide, observed by TLC, underwent spontaneous lactonization to compound **17** on standing after concentration of the reaction mixture or during column chromatography on silica gel, this process following a similar stereochemical pathway to the reaction with PhSeCl (Scheme 3). The configuration at C-1 in this compound was ascertained by a strong NOE found between 1-H (δ = 4.14) and 9α-H (δ = 1.48), taking into account the same conformational considerations as in compound **13**. Hydrogenation of the C(4)−C(5) double bond was first achieved on 5% Pd/C to give a mixture of the *trans*- and *cis*-decalin isomers in 7:3 approximate ratio as determined from the 14-H NMR signals, which appeared at δ = 1.08 for the *trans* compound and at δ = 1.02 for the *cis* compound. The ratio was improved by performing the hydrogenation on 5% Pd/$CaCO_3$, affording a ca. 9:1 mixture from which pure **18** was isolated in 82% yield after crystallization from hexane-EtOAc. Compound **18** was assigned the *trans*-decalin-like structure with the 4-Me group β axial, which is expected from the preferential *syn* hydrogenation from the α side of the molecule. The *trans* junction was inferred from the coupling constant $^1J_{5,6}$ = 11.0 Hz (ax-ax) which indicated that 5-H and 6-H were in an *anti* diaxial orientation. The β axial disposition of the 4-Me group was confirmed by a NOE between 14-H (δ 1.08) and 15-H (δ 1.46). Finally, integration of our sequence into the formal synthesis of 8-deoxyvernolepin required epimerization at C-4 to give compound **5**. This step was brought about by treatment of bislactone **18** with DBN in boiling benzene. Epimerization at C-4 was revealed by the upfield shift of 4-H in the ^{1}H NMR spectra from δ = 3.08 in compound **18** to δ = 2.64 in compound **5**, and the change in the $^1J_{4,5}$ values from 8.0 Hz (ax-eq) in compound **18** to 11.6 Hz (ax-ax) in compound **5**. In the same way, the downfield shift of the 4-Me group from δ 1.46 in compound **18** to δ = 2.15 in compound **5** was observed. Transformation of compound **5** into **3** has been described elsewhere,[6] and therefore the method described here for the preparation of compound **5** constitutes a formal synthesis of (+)-8-deoxyvernolepin (**3**).

Conclusion

In summary, an appropriate procedure for the preparation of sesquiterpenes bearing a δ-lactone moiety on the A ring, such as **1** and **3**, has been developed. The key step involves the stereoselective addition of an electrophile to the vinyl group in compound **12**, followed by spontaneous lactonization. Reaction of **12** with PhSeCl yields the phenylselenolactone **13**, while reaction with DMDO affords the hydroxylactone **17**. Oxidative elimination of the phenylselenenyl group in **13** permits the construction of an enol lactone moiety in **15** and its hydration gives a ketone hydrate lactone moiety in **1**. These procedures should be of general application for the preparation of these particular types of lactones. On the other hand, compound **17** allows the synthesis of the antitumor compound (+)-8-deoxyvernolepin. Finally, we suggest a revision of the structure of natural *seco*-isoerivanin pseudo acid isolated from *Artemisia judaica* to the corresponding C-10 epimer.

Experimental Section

General Remarks: All melting points are uncorrected. − Column chromatography was performed on silica gel (Merck, silica gel 60, 230−400 mesh). − IR spectra were recorded as liquid film in NaCl for oils and as KBr discs for solids. − Commercial reagents and solvents were analytical grade or were purified by standard procedures prior to use.[18] All reactions involving air- or moisture-sensitive materials were carried out under argon atmosphere. − Specific rotations were measured in $CHCl_3$. − NMR spectra were run in $CDCl_3$, unless otherwise noted, at 399.94 MHz for ^1H and at 50.3, 75.43, or 100.58 MHz for ^{13}C NMR. Signal assignation in the ^1H NMR spectra was achieved by extensive ^1H-^1H decoupling experiments. Heteronuclear ^1H-^{13}C NMR correlation experiments were performed for compounds **1**, **5** and **18**. The carbon type was determined by DEPT experiments. − Mass spectra were performed using electron impact at 70 eV or chemical ionization with methane as the ionizing gas.

Dihydrosantonin (6): Dihydrosantonin (4.0 g, 100%) was obtained by hydrogenation of santonin (4.0 g) with Wilkinson's catalyst as described by Piers and Cheng.[8]

2-Acetoxy-3-oxo-7α*H*,6,11β*H*-eudesm-4-en-6,12-olide (7): A solution of dihydrosantonin **6** (500 mg, 2.02 mmol) in acetic acid (21 mL) was treated with LTA (1.21 g, 3.27 mmol) under argon at 80 °C for 20 h. After this time, the reaction mixture was allowed to cool to room temperature and diluted with ethyl acetate, washed with aqueous saturated $NaHCO_3$ and brine, dried (Na_2SO_4), and concentrated in vacuo. Flash chromatography of the resulting oil with hexane−diethyl ether mixtures (60% to 80% gradient elution) afforded 30 mg (6%) of the starting material **6**, 404 mg (65%) of **7** and 63 mg (13%) of santonin (**5**). According to ^1H NMR analysis, **7** was composed of a ca. 1:1 mixture of two epimers (**7a** and **7b**). Analytical samples of both compounds were obtained by HPLC separation.

Compound 7a:[19] M.p. 122−124 °C. − $[\alpha]_D^{24} = +50$ ($c = 0.4$). − IR (KBr): ṽ = 1783 cm^{-1}, 1743, 1691. − MS; *m/z* (%): 306 (23), [M$^+$], 305 (78) [M$^+$ − H], 291 (6) [M$^+$ − CH_3], 246 (89) [M$^+$ − CH_3COOH], 202 (100). − HRMS; 306.1466 $C_{17}H_{22}O_5$ required 306.1467. − ^1H NMR: δ = 1.26 (d, ^1J = 6.8 Hz, 3 H, 13-H), 1.47 (s, 3 H, 14-H), 1.54 (m, 1 H, 9α-H), 1.60 (m, 1 H, 8βH), 1.79 (dt, ^1J = 2.8, 13.6 Hz, 1 H, 8α-H), 1.92 (dq, ^1J = 3.2, 11.6 Hz, 1 H, 7-H), 2.01 (d, ^1J = 1.6 Hz, 3 H, 15-H), 2.1 (m, 3 H, 1α-H overlapped with 1β-H and 9β-H), 2.17 (s, 3 H, CH_3), 2.33 (dq, ^1J = 6.8, 12.0 Hz, 1 H, 11-H), 4.68 (dq, ^1J = 1.6, 11.6 Hz, 1 H, 6-H), 5.49 (t, ^1J = 10.8 Hz, 1 H, 2-H). − ^{13}C NMR: δ = 11.4 (q), 12.5(q), 20.8 (q), 24.3 (t), 24.7 (q), 39.3 (s), 41.1 (d), 42.2 (t), 43.6 (t), 52.7 (d), 70.4 (d), 81.4 (d), 127.2 (s), 151.9 (s), 170.3 (s), 177.4 (s), 194.1 (s).

Compound 7b:[19] M.p. 116−118 °C. − $[\alpha]_D^{23} = -157$ ($c = 1.4$). − IR (KBr): ṽ = 1782 cm^{-1}, 1735, 1698. − MS; *m/z* (%): 306 (12) [M$^+$], 305 (55) [M$^+$ − H], 291 (8) [M$^+$ − CH_3], 246 (100) [M$^+$ − CH_3COOH], 202 (88). − HRMS; 306.1456 $C_{17}H_{22}O_5$ required 306.1467. − ^1H NMR: δ = 1.24 (d, ^1J = 6.8 Hz, 3 H, 13-H), 1.28 (s, 3 H, 14-H), 1.6−1.8 (m, 3 H, 8α-H overlapped with 8β-H and 9α-H). − 1.07−1.95 (m, 4 H, 1α-H overlapped with 1β-H and 7-H, 9β-H), 2.00 (d, ^1J = 1.2 Hz, 3 H, 15-H), 2.16 (s, 3 H, CH_3), 2.36 (dq, ^1J = 6.8, 11.8 Hz, 1 H, 11-H), 4.80 (br d, ^1J = 10.8 Hz, 1 H, 6-H), 5.32 (dd, ^1J = 7.2, 12.4 Hz, 1 H, 2-H). − ^{13}C NMR: δ = 11.7 (q), 12.5(q), 20.8 (q), 23.7 (q), 28.8 (t), 37.4 (t), 39.5 (s), 40.6 (t), 41.2 (d), 54.2 (d), 70.0 (d), 81.2 (d), 125.6 (s), 153.1 (s), 170.3 (s), 177.4 (s), 194.1 (s).

2-Hydroxy-3-oxo-7α*H*,6,11β*H*-eudesm-4-en-6,12-olide (8): The mixture of acetates **7a** and **7b** (389 mg, 1.27 mmol) was dissolved in methanol (31 mL) and a catalytic amount of TsOH was added. After refluxing for 5 h, the reaction mixture was diluted with water and extracted with three portions of ethyl acetate. The combined organic layers were washed with saturated aqueous $NaHCO_3$ and brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was chromatographed (hexane-ethyl acetate) to give a ca. 1:1 mixture of two epimeric alcohols **8a** and **8b** (319 mg, 95%). Analytical samples of both compounds were obtained by HPLC.

Compound 8a: [19] M.p. 123−125 °C. − $[\alpha]_D^{23} = +36$ ($c = 1.1$). − IR (KBr): ṽ = 1782, 1735, 1698 cm^{-1}. − MS; *m/z* (%): 264 (100) [M$^+$], 261 (4), 260 (2), 246 (2) [M$^+$ − H_2O], 219 (8) [M$^+$ − C_2H_5O]. − HRMS; 264.1370 $C_{15}H_{20}O_4$ required 264.1362. − ^1H NMR: δ = 1.26 (d, ^1J = 6.8 Hz, 3 H, 13-H), 1.44 (s, 3 H, 14-H), 1.54 (dq, ^1J = 4.4, 13.2 Hz, 1 H, 8β-H), 1.67 (dt, ^1J = 2.8, 11.6 Hz, 1 H, 9α-H), 1.77 (br t, ^1J = 12.0 Hz, 1 H, 1α-H), 1.92 (dq, ^1J = 3.6, 11.6 Hz, 1 H, 7-H), 2.05 (d, ^1J = 1.6 Hz, 3 H, 15-H), 2.16 (dd, 1 H, ^1J = 5.6, 12.0 Hz, 1β-H), 2.35 (dq, ^1J = 6.8, 12.0 Hz, 1 H, 11-H), 3.64 (br. s, 1 H, OH), 4.32 (dd, ^1J = 5.6, 14.0 Hz, 1 H, 2-H), 4.67 (dq, ^1J = 1.6, 11.6 Hz, 1 H, 6-H). − ^{13}C NMR: δ = 11.4 (q), 12.4 (q), 24.3 (t), 24.6 (q), 38.9 (s), 41.1 (d), 42.4 (t), 46.4 (t), 52.8 (d), 68.5 (d), 81.6 (d), 126.0 (s), 153.6 (s), 177.4 (s), 200.6 (s).

Compound 8b:[19] M.p. 135−137 °C. − $[\alpha]_D^{23} = -204$ ($c = 1.1$). − IR (KBr): ṽ = 1782 cm^{-1}, 1735, 1698. − MS; *m/z* (%): 264 (100) [M$^+$], 246 (4) [M$^+$ − H_2O], 219 (6) [M$^+$ − C_2H_5O], 202 (5) [M$^+$ − H_2O − CO_2]. − HRMS; 264.1359 $C_{15}H_{20}O_4$ required 264.1362. − ^1H NMR: δ = 1.24 (d, ^1J = 7.2 Hz, 3 H, 13-H), 1.26 (s, 3 H, 14-H), 1.65−1.80 (m, 3 H, 7-H overlapped with 8-H, and 9-H), 1.95−2.05 (m, 2 H, 8-H overlapped with 9-H), 2.04 (d, ^1J = 1.6 Hz, 3 H, 15-H), 2.15 (dd, ^1J = 6.0, 13.2 Hz, 1 H, 1-H), 2.39 (dq, ^1J = 7.2, 11.7 Hz, 1 H, 11-H), 4.18 (dd, ^1J = 6.0, 14.4 Hz, 1 H, 2-H), 4.83 (dq, ^1J = 1.6, 9.6 Hz, 1 H, 6-H). − ^{13}C NMR: δ = 11.6 (q), 12.5 (q), 23.6 (t), 29.0 (q), 37.1 (t), 39.1 (s), 41.1 (d), 43.2 (t), 54.3 (d), 67.9 (d), 81.3 (d), 124.2 (s), 154.7 (s), 177.4 (s), 200.5 (s).

Aldehyde 9: To a solution of compounds **8a** and **8b** (43 mg, 0.16 mmol) in methanol (1.7 mL) at 0 °C under argon was added LTA (152 mg, 0.33 mmol). After stirring at this temperature for 5 min and at room temperature for 25 min, the mixture was diluted with ethyl acetate. Usual workup and flash chromatography with hexane − ethyl acetate (20% to 40% gradient elution) yielded 26 mg (54%) of compound **9** as a colorless oil. − $[\alpha]_D^{19} = +8$ ($c = 0.8$). − IR (NaCl): ṽ = 2741 cm^{-1}, 1782, 1722. − MS; *m/z* (%): 295 (16) [M$^+$ + 1], 294 (18), 277 (93) [M$^+$ +1 − H_2O], 263 (100) [M$^+$ +1 − CH_3OH], 235 (67) [M$^+$ +1 − CH_3CO − CO], 217 (38). − HRMS; 294.1483 $C_{16}H_{22}O_5$ required 294.1467. − ^1H NMR: δ = 1.23 (d, ^1J = 7.2 Hz, 3 H, 13-H), 1.32 (s, 3 H, 14-H), 2.11 (d, ^1J = 2.0 Hz, 3 H, 15-H), 2.25 (dq, ^1J = 7.2, 11.5 Hz, 1 H, 11-H), 2.68 (dd, ^1J = 2.2, 16.8 Hz, 1 H, 1-H), 2.74 (dd, ^1J = 2.2, 16.8 Hz, 1 H, 1′-H), 3.71 (s, 3 H, CH_3O), 4.71 (dq, ^1J = 2.0, 11.6 Hz, 1 H, 6-H), 9.70

(t, ^1J = 2.2 Hz, 1 H, 2-H). − ^{13}C NMR: δ = 12.3 (q), 19.2 (q), 22.7 (t), 27.5 (q), 36.4 (t), 40.1 (s), 41.6 (d), 48.1(d), 52.0 (q), 52.7 (t), 81.0 (d), 126.7 (s), 136.5 (s), 172.7 (s), 177.9 (s), 201.1 (s).

Hydroxy Ester 10: (a) A solution of aldehyde **9** (22 mg, 0.08 mmol) in methanol (1.4 mL) was cooled to 0 °C and treated with $NaBH_4$ (1.5 mg, 0.04 mmol). The mixture was stirred at 0 °C for 25 min and quenched with saturated aqueous NH_4Cl. Usual workup and chromatography (1:1 hexane − ethyl acetate) afforded 20 mg (88%) of compound **10** as a colorless oil: $[\alpha]_D^{20}$ = +5 (*c* = 0.9). − IR (NaCl): ṽ = 3500 cm^{-1}, 1776, 1726. − MS; *m*/*z* (%): 296 (26) [M$^+$], 278 (5) [M$^+$ − H_2O], 264 (92) [M$^+$ − CH_3OH], 252 (100) [M$^+$ − CH_3CO]. − HRMS; 296.1626 $C_{16}H_{24}O_5$ required 296.1624. − ^{1}H NMR: δ = 1.15 (s, 3 H, 14-H), 1.22 (d, 3 H, ^1J = 7.2 Hz, 13-H), 1.40−1.65 (m, 3 H, 8β-H overlapped with 9α-H, 9β-H), 1.81 (dd, ^1J = 7.0, 14.0 Hz, 1 H, 1-H), 1.90−2.10 (m, 2 H, 7-H overlapped with 8α-H), 2.09 (d, ^1J = 1.6 Hz, 3 H, 15-H), 2.23 (dq, ^1J = 7.2, 12.0 Hz, 1 H, 11-H), 3.69 (t, ^1J = 7.2 Hz, 2 H, 2-H), 3.75 (s, 3 H, CH_3O), 4.71 (dq, ^1J = 1.6, 11.5 Hz, 1 H, 6-H). − ^{13}C NMR: δ = 12.3 (q), 19.4 (q), 22.3 (t), 27.4 (q), 34.6 (t), 40.8 (s), 41.9 (d), 42.4 (t), 46.9 (d), 52.0 (q), 59.3 (t), 80.9 (d), 126.4 (s), 138.5 (s), 173.3 (s), 178.3 (s).

(b) (Without purification of aldehyde **9**). A solution of compounds **7a** and **7b** (800 mg, 3.03 mmol) in 24 mL of hexane − methanol (3:1) was cooled to 0 °C. LTA (2.11 g, 4.52 mmol) was added and the mixture was stirred at 0 °C for 15 min and at room temperature for 25 min. The usual workup gave a colorless oil that was immediately reduced with $NaBH_4$ as described previously to give 603 mg (67%) of compound **10**.

***o*-Nitrophenyl Selenide 11:** To a solution of compound **10** (450 mg, 1.52 mmol) and *o*-nitrophenyl selenocyanate (570 mg, 2.46 mmol) in THF−pyridine 1:1 (16 mL) at room temperature under argon, was added (by syringe) tri-*n*-butylphosphane (0.6 mL, 2.38 mmol). The reaction mixture was stirred for 1 h. After solvent removal, the residue was chromatographed on silica gel with hexane-ethyl acetate (30% to 40% gradient elution) to yield 520 mg (84%) of **11** as a yellow oil: $[\alpha]_D^{19}$ = −67 (*c* = 2.4). − IR (NaCl): ṽ = 1780 cm^{-1}, 1721, 1512, 1332. − ^{1}H NMR: δ = 1.22 (d, ^1J = 7.2 Hz, 3 H, 13-H), 1.23 (s, 3 H, 14-H), 1.60 (m, 3 H, 8β-H overlapped with 9α-H and 9β-H), 1.90−2.10 (m, 3 H, 1-H overlapped with 7-H and 8α-H), 2.10 (d, ^1J = 1.6 Hz, 3 H, 15-H), 2.18−2.25 (m, 2 H, 1′-H overlapped with 11-H), 2.90 (m, 2 H, 2-H), 3.69 (s, 3 H, CH_3O), 4.73 (dq, ^1J = 1.6, 11.5 Hz, 1 H, 6-H), 7.32 (dt, ^1J = 1.0, 9.0 Hz, 1 H, Ar-H), 7.53 (m, 2 H, Ar-H), 8.29 (dd, ^1J = 1.0, 9.0 Hz, 1 H, Ar-H). − ^{13}C NMR: δ = 12.3 (q), 19.5 (q), 21.1 (t), 26.7 (t), 26.3 (q), 33.8 (t), 38.0 (t), 41.8 (d), 42.2 (s), 46.9 (d), 51.9 (q), 80.6 (d), 125.4 (d), 126.3 (d), 127.4 (s), 128.9 (d), 133.2 (s), 133.5 (d), 137.5 (s), 146.7 (s), 172.6 (s), 177.9 (s).

Alkene 12: A solution of compound **11** (580 mg, 1.42 mmol) in THF was treated with 30% aqueous hydrogen peroxide (0.5 mL, 4.89 mmol) at 0 °C for 7 h, and at room temperature for 2 h. After this time, the reaction mixture was extracted with ethyl acetate, washed with 3% aqueous Na_2SO_3 and brine, dried (Na_2SO_4), and concentrated. Chromatography with hexane − ethyl acetate yielded 351 mg (89%) of compound **12** as a white solid: m.p. 96−97 °C. − $[\alpha]_D^{19}$ = +48 (*c* = 1.2). − IR (KBr): ṽ = 1776 cm^{-1}, 1726. − MS; *m*/*z* (%): 278 (100) [M$^+$], 264 (11) [M$^+$ − CH_2] , 263 (12) [M$^+$ − CH_3], 246 (9) [M$^+$ − CH_3OH], 233 (11) [M$^+$ − C_2H_5O], 202 (19). − HRMS; 278.1514 $C_{16}H_{22}O_4$ required 278.1518. − ^{1}H NMR: δ = 1.23 (d, ^1J = 6.8 Hz, 3 H, 13-H), 1.31 (s, 3 H, 14-H), 1.4−1.6 (m, 2 H, 2 8-H), 1.66 (dt, 1 H, ^1J = 5.0, 12.0 Hz, 3 H, 9α-H), 1.80−2.00 (m, 2 H, 7-H overlapped with 9β-H), 2.08 (d, ^1J = 2 Hz, 3 H, 15-H), 2.26 (dq, ^1J = 6.8, 12.0 Hz, 1 H, 11-H), 3.56 (s, 3 H, CH_3O), 4.69 (dq, ^1J = 2.0, 11.5 Hz, 1 H, 6-H), 5.01 (d, ^1J = 17.4 Hz, 1 H, 2-H), 5.02 (d, ^1J = 10.4 Hz, 1 H, 2′-H), 5.91 (dd, ^1J = 10.4, 17.4 Hz, 1 H, 1-H). − ^{13}C NMR: δ = 12.2 (q), 18.4 (q), 23.2 (q), 23.9 (t), 39.9 (t), 40.9 (d), 45.1 (s), 50.8 (q), 82.1 (d), 112.3 (t),126.0 (s),135.2 (s), 145.2 (d), 172.4 (s), 178.7 (s).

Phenylselenolactone 13: Phenylselenenyl chloride (110 mg, 0.57 mmol) was added to a solution of compound **12** (103 mg, 0.37 mmol) in 1.14 mL of aqueous acetonitrile (5:1 acetonitrile/water) and the solution was stirred at room temperature for 2 h. After this time, water was added and the mixture extracted with ethyl acetate. The organic layer was washed with brine, dried and concentrated. Chromatography with hexane/ethyl acetate (20% to 40% gradient elution) gave 144 mg (93%) of compound **13** as a yellow oil: $[\alpha]_D^{21}$ = −18 (*c* = 1.6). − IR (NaCl): ṽ = 1782 cm^{-1}, 1712. − ^{1}H NMR: δ = 1.17 (s, 3 H, 14-H), 1.21 (ddd, ^1J = 5.2, 12.0, 13.2 Hz, 1 H, 9α-H) 1.24 (d, ^1J = 6.8 Hz, 3 H, 13-H), 1.55 (dq, ^1J = 3.6, 12.0 Hz, 1 H, 8β-H), 1.75 (td, ^1J = 3.6, 13.2 Hz, 1 H, 9β-H), 1.80 (dq, ^1J = 3.0, 12.0 Hz, 1 H, 7-H), 1.99 (m, 1 H, 8α-H), 2.12 (d, ^1J = 2.0 Hz, 3 H, 15-H), 2.32 (dq, ^1J = 6.8, 12.0 Hz, 1 H, 11-H), 2.97 (dd, ^1J = 2.0, 12.8 Hz, 1 H, 2-H), 3.09 (dd, ^1J = 10.0, 12.8 Hz, 1 H, 2′-H), 4.18 (dd, ^1J = 2.0, 10.0 Hz, 1 H, 1-H), 4.56 (dq, ^1J = 2.0, 12.0 Hz, 1 H, 6-H), 7.26 (m, 3 H, Ar-H), 7.53 (dd, ^1J = 3.0, 6.5 Hz, 2 H, Ar-H). − ^{13}CNMR: δ = 12.3 (q), 13.2 (q), 18.1 (q), 23.7 (t), 26.8(t), 35.9 (t), 40.8 (d), 41.0 (s), 51.2 (d), 80.5 (d), 84.0 (d), 121.2 (s), 127.5 (d), 129.2 (d), 129.6 (d), 133.0 (s), 133.4 (d), 149.5 (s), 165.1 (s), 177.2 (s).

Enol Lactone 15: A solution of compound **13** (234 mg, 0.56 mmol) in THF (4.2 mL) was treated with 30% H_2O_2 (0.32 mL, 3.13 mmol) at 0 °C for 2 h. The usual workup and chromatography with hexane/ethyl acetate (6:4) and dichloromethane/methanol (9:1) gave 225 mg (93%) of selenoxide **14**: IR (NaCl) 1780, 1709 cm^{-1}. − ^{1}H NMR: δ = 1.15 (s, 3 H, 14-H), 1.27 (d, ^1J = 6.8 Hz, 3 H, 13-H), 2.17 (d, ^1J = 2.0 Hz, 3 H, 15-H), 2.33 (dq, ^1J = 6.8, 11.5 Hz, 1 H, 11-H), 2.67 (dd, ^1J = 1.0, 11.5 Hz, 1 H, 2-H), 3.12 (t, ^1J = 11.5 Hz, 1 H, 2′-H), 4.56 (dq, ^1J = 2.0, 12.0 Hz, 1 H, 6-H), 4.74 (dd, ^1J = 1.0, 11.5 Hz, 1 H, 1-H), 7.55 (m, 3 H, Ar-H), 7.76 (dd, ^1J = 3.0, 6.5 Hz, 2 H, Ar-H).

A solution of the resulting selenoxides **14** (219 mg, 0.50 mmol) was refluxed in benzene (13.5 mL) for 30 min. After evaporation of the solvent, the remaining residue was flash chromatographed (6:4 hexane-ethyl acetate) to give 118 mg (90%) of compound **15**: m.p. 116−118 °C. − $[\alpha]_D^{21}$ = +281 (*c* = 0.9). − IR (KBr): ṽ = 1772 cm^{-1}, 1727, 1651. − MS; *m*/*z* (%): 262 (100) [M$^+$], 261 (3), 259 (4), 217 (7) [M$^+$ − C_2H_5O]. − HRMS; 262.12053 $C_{15}H_{18}O_4$ required 262.1205. − ^{1}H NMR: δ = 1.27 (d, ^1J = 6.8 Hz, 3 H, 13-H), 1.47 (s, 3 H, 14-H), 1.63 (dq, ^1J = 3.5, 12.4 Hz, 1 H, 8β-H), 1.80−1.93 (m, 2 H, 7-H overlapped with 9β-H), 2.02−2.20 (m, 2 H, 9α-H overlapped with 8α-H), 2.14 (d, ^1J = 2.0 Hz, 3 H, 15-H), 2.36 (dq, ^1J = 6.8, 12.5 Hz, 1 H, 11-H), 4.43 (d, ^1J = 2.8 Hz, 1 H, 2-H), 4.64 (dq, ^1J = 2.0, 11.5 Hz, 1 H, 6-H), 4.79 (d, ^1J = 2.8 Hz, 1 H, 2′-H). − ^{13}C NMR: δ = 12.3 (q), 13.0 (q), 23.6 (t), 27.8 (q), 36.1 (t),40.5 (s), 40.8 (d), 51.0(d), 80.3 (d), 94.4 (t), 113.5 (s), 120.1 (s), 148.1 (s), 160.9 (s), 177.1 (s).

Proposed Structure of *seco*-Isoerivanin Pseudo Acid (1): Compound **15** (60 mg, 0.23 mmol) was treated with 50% aqueous H_2SO_4 (2.4 mL) at room temperature for 45 min. The reaction mixture was extracted with ethyl acetate, and the organic layer was washed with water and brine, dried with Na_2SO_4, and concentrated. Chromatography with hexane/ethyl acetate afforded 55 mg (86%) of compound **1**: m.p. 188−190 °C. − $[\alpha]_D^{21}$ = +210 (*c* = 0.8). − IR (KBr):

$\tilde{\nu}$ = 3300 cm^{-1}, 1777, 1698. − MS; *m/z* (%): 280 (100) [M$^+$], 236 (7), 262 (9) [M$^+$ − H_2O], 207 (45) [M$^+$ − $C_3H_5O_2$]. − HRMS; 280.1306 $C_{15}H_{20}O_5$ required 280.1311. − ^{1}H NMR ($CDCl_3$): δ = 1.27 (d, ^1J = 6.8 Hz, 3 H, 13-H), 1.30 (s, 3 H, 14-H), 1.52 (dq, ^1J = 4.0, 12.0 Hz, 1 H, 8β-H), 1.57 (s, 3 H, 2-H), 1.70 (ddd, ^1J = 2.5, 4.0, 13.6 Hz, 1 H, 9β-H), 1.95 (dq, ^1J = 3.0, 12.0 Hz, 1 H, 7-H), 2.06 (m, 1 H, 8α-H), 2.14 (d, ^1J = 2.0 Hz, 3 H, 15-H), 2.19 (dt, ^1J = 5.2, 13.6 Hz, 1 H, 9α-H), 2.33 (dq, ^1J = 6.8, 12.0 Hz, 1 H, 11-H), 3.74 (s, 1 H, OH), 4.60 (dq, ^1J = 2.0, 12.0 Hz, 1 H, 6-H). − ^{13}C NMR (Cl_3CD): δ = 12.3 (q), 13.1 (q), 22.9 (q), 23.7 (t), 23.8 (q), 33.0 (t), 40.8 (d), 44.7 (s), 50.5 (d), 80.9 (d), 104.1 (s), 121.3 (s), 147.2 (s), 164.9 (s), 177.5 (s). − ^{1}H NMR (C_6D_6): δ = 0.56 (qd, ^1J = 13.0, 3.5 Hz, 1 H, 8β-H), 0.76 (s, 3 H, 14-H), 0.87 (d, ^1J = 6.8 Hz, 1 H, 13-H), 0.97 (ddd, ^1J = 2.5, 3.5, 13.0 Hz, 1 H, 9β-H), 1.19 (m, 1 H, 8α-H), 1.36 (s, 3 H, 2-H overlapped with 7-H), 1.48 (dq, ^1J = 6.8, 12.0 Hz, 1 H, 11-H), 1.81 (td, ^1J = 13.0, 5.2 Hz, 1 H, 9α-H), 2.42 (d, ^1J = 2.0 Hz, 3 H, 15-H), 3.72 (dq, ^1J = 11.6, 2.0 Hz, 1 H, 6-H), 4.69 (s, 1 H, OH),. − ^{13}C NMR (C_6D_6): δ = 12.1 (q), 13.4 (q), 22.6 (q), 23.3 (t), 23.3 (q), 32.7 (t), 40.4 (d), 44.5 (s), 49.8 (d), 80.3 (d), 103.9 (s), 121.4 (s), 147.5 (s), 165.1 (s), 176.4 (s).

Methyl Ester 16: To a solution of **1** (7.5 mg, 0.027 mmol) in diethyl ether (2 mL) was added ethereal diazomethane in excess and the reaction mixture was stirred for about 12 h. After solvent removal, the residue was chromatographed on silica gel with hexane/ethyl acetate to yield 7 mg (89%) of methyl ester **16** as a colorless oil with the following features: $[\alpha]_D^{21}$ = +210 (*c* = 0.8). − IR (KBr): $\tilde{\nu}$ = 1784 cm^{-1}, 1712. − MS; *m/z* (%): 294 (100) [M$^+$], 262 (5) [M$^+$ − CH_3OH], 249 (5) [M$^+$ − C_2H_5O], 218 (4). − HRMS; 294.1477 $C_{16}H_{22}O_5$ required 294.1467. − ^{1}H NMR: δ = 1.21 (d, ^1J = 6.8 Hz, 3 H, 13-H), 1.42 (s, 3 H, 14-H), 1.51 (m, 1 H, 8β-H),1.68 (dt, ^1J = 9.2, 16.4 Hz, 1 H, 9β-H), 1.85 (dt, ^1J = 8.0, 17.0 Hz, 1 H, 9α-H), 1.96 (dq, ^1J = 9.0, 17.0 Hz, 1 H, 8α-H), 2.09 (m, 1 H, 7-H), 2.14 (d, ^1J = 2.0 Hz, 3 H, 15-H), 2.22 (s, 3 H, 2-H), 2.26 (dq, ^1J = 6.8, 12.0 Hz, 1 H, 11-H), 3.67 (s, 3 H, CH_3O), 4.69 (dq, ^1J = 2.0, 12.0 Hz, 1 H, 6-H). − ^{13}C NMR: δ = 12.4 (q), 17.9 (q), 22.1 (t), 24.9 (q), 26.4 (q), 34.1 (q), 41.8 (d), 46.7 (d), 51.9 (q), 55.2 (s), 80.6 (d), 127.0 (s), 139.3 (s), 171.2 (s), 177.9 (s), 209.6 (s).

Hydroxy Bis-Lactone 17: Compound **12** (90 mg, 0.32 mmol) was dissolved in dichloromethane (2.4 mL) and 35 mL of a solution (ca. 0.07 M) of dimethyldioxirane in acetone was added at 0 °C. After stirring at room temperature for 3 days, the reaction mixture was concentrated and the residue was chromatographed on silica gel with hexane/ethyl acetate (50% to 90% gradient elution) to yield 75 mg (84%) of compound **17** as a colorless oil: $[\alpha]_D^{20}$ = +131 (*c* = 1.6). − IR (NaCl): $\tilde{\nu}$ = 3600 cm^{-1}, 1778, 1704. − MS; *m/z* (%): 281 (100) [M$^+$ +1], 263 (11) [M$^+$ +1 − H_2O], 250 (5) [M$^+$ +1 − CH_3O] , 249 (5) [M$^+$ +1 − CH_3OH], 235 (15). − HRMS; 280.1293 $C_{15}H_{20}O_5$ required 280.1310. − ^{1}H NMR: δ = 1.19 (s, 3 H, 14-H), 1.27 (d, ^1J = 6.4 Hz, 3 H, 13-H), 1.48 (dt, ^1J = 4.5, 12.5 Hz, 1 H, 9α-H), 1.59 (dq, ^1J = 3.0, 12.5 Hz, 1 H, 8β-H), 1.84 (td, ^1J = 3.0, 12.5 Hz, 1 H, 9β-H), 1.89 (dq, ^1J = 2.8, 12.0 Hz, 1 H, 7-H), 2.07 (m, 1 H, 8α-H), 2.15 (d, ^1J = 2.0 Hz, 3 H, 15-H), 2.36 (dq, ^1J = 6.5, 12.0 Hz, 1 H, 11-H), 3.75 (dd, ^1J = 2.4, 12.0 Hz, 1 H, 2-H), 3.86 (dd, ^1J = 8.0, 12.0 Hz, 1 H, 2-H), 4.14 (dd, ^1J = 2.4, 8.0 Hz, 1 H, 1-H), 4.59 (dq, ^1J = 2.0, 12.0 Hz, 1 H, 6-H). − ^{13}C NMR: δ = 12.3 (q), 13.2 (q), 19.1 (q), 23.8 (t), 35.8 (t), 39.4 (s), 40.8 (t), 51.4 (t), 60.5 (t), 80.3 (d), 84.8 (d), 121.4 (s), 150.0 (s), 165.2 (s), 177.1 (s).

Hydroxy Bis-Lactone 18: Compound **17**(20 mg, 0.22 mmol) was hydrogenated over 10% Pd/C (20 mg) in absolute ethanol (3.3 mL). The reaction mixture was stirred for 1 day. After this time, the mixture was filtered through a short pad of silica gel, concentrated, and the residue recrystallized from ethyl acetate-hexane to yield 50 mg (82%) of **18** as a white solid: m.p. 154−155 °C. − $[\alpha]_D^{21}$ = +84 (*c* = 1.0). − IR (KBr): $\tilde{\nu}$ = 3400 cm^{-1}, 1764, 1722. − MS; *m/z* (%): 283 (8) [M$^+$ + 1], 265 (7) [M$^+$ +1 − H_2O], 252 [M$^+$ + 1 − CH_3O], 251 (100) [M$^+$ + 1 − CH_3OH] , 237 (9) [M$^+$ + 1 − H_2O − C_2H_4], 223 (20). − HRMS; 283.1543 $C_{15}H_{23}O_5$ (M$^+$ + 1) required 283.1545. − ^{1}H NMR: δ = 1.08 (s, 3 H, 14-H), 1.25 (d, ^1J = 7.2 Hz, 3 H, 13-H), 1.37 (dt, ^1J = 3.6, 13.4 Hz, 1 H, 9α-H), 1.46 (d, ^1J = 8.0 Hz, 3 H, 15-H), 1.45−1.70 (m, 2 H, 7-H overlapped with 8β-H), 1.72 (dt, ^1J = 2.8, 13.4 Hz, 1 H, 9β-H), 1.97 (dq, ^1J = 2.8, 13.4 Hz, 1 H, 8α-H), 2.15 (dd, ^1J = 8.0, 11.0 Hz, 1 H, 5-H), 2.36 (dq, ^1J = 7.2, 12.4 Hz, 1 H, 11-H), 3.08 (m, ^1J = 8.0 Hz, 1 H, 4-H), 3.78 (m, 2 H, 2-H), 3.94 (t, ^1J = 11.0 Hz, 1 H, 6-H), 4.18 (dd, ^1J = 4.0, 7.5 Hz, 1 H, 1-H). − ^{13}C NMR: δ = 12.4 (q), 14.8 (q), 14.8 (q), 22.8 (t), 35.0 (d),35.7 (t), 37.2 (s), 40.9 (d), 46.8 (d), 52.3 (d), 61.0 (t), 78.4 (d), 90.0 (d), 173.1 (s), 178.5 (s).

Hydroxy Bis-Lactone 5: A solution containing compound **18** (6 mg, 0.021 mmol) and DBN (1.5 μL, 0.021 mmol) in benzene (1 mL) was stirred for 19 hours at 60 °C. Then the reaction mixture was diluted with dichloromethane, washed with 1M HCl and brine, dried (Na_2SO_4), and concentrated to yield 5 mg (83%) of **5** as a colorless oil: . − $[\alpha]_D^{23}$ = +31 (*c* = 0.5). − IR (NaCl): $\tilde{\nu}$ = 3400 cm^{-1}, 1775, 1722. − MS; *m/z* (%): 283 (8) [M$^+$ + 1], 265 (54) [M$^+$ +1 − H_2O], 251 (46) [M$^+$ + 1 − CH_3OH], 247 (23), 237 (45). − HRMS; 283.1545 $C_{15}H_{23}O_5$ (M$^+$ + 1) required 283.1545. − ^{1}H NMR: δ = 1.03 (s, 3 H, 14-H), 1.24 (d, ^1J = 6.8 Hz, 3 H, 13-H), 1.38 (dt, ^1J = 3.9, 12.9 Hz, 1 H, 9α-H), 1.48−1.57 (m, 1 H, 8β-H), 1.53 (d, ^1J = 7.2 Hz, 3 H, 15-H), 1.63 (dq, ^1J = 2.6, 12.0 Hz, 1 H, 7-H), 1.72−1.76 (m, 1 H, 9β-H), 1.75 (t, ^1J = 10.8 Hz, 1 H, 5-H), 1.81 (br s, 1 H, OH), 1.97 (dq, ^1J = 3.4, 11.6 Hz, 1 H, 8α-H), 2.29 (dq, ^1J = 6.8, 12.4 Hz, 1 H, 11-H), 2.64 (dq, ^1J = 7.2, 10.8 Hz, 1 H, 4-H), 3.77 (m, 2 H, 2-H), 3.81 (t, ^1J = 10.6 Hz, 1 H, 6-H), 4.19 (dd, ^1J = 4.6, 6.2 Hz, 1 H, 1-H). − ^{13}C NMR: δ = 12.4 (q), 13.6 (q), 18.3 (q), 22.9 (t), 34.4 (t), 37.7 (s), 38.0 (d), 40.6 (d), 51.2 (d), 52.1 (d), 61.1 (t), 81.6 (d), 88.9 (d), 172.8 (s), 178.4 (s).

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