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Synthesis of 3-Oxa-guaianolides from Santonin

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Abstract—This article reports on the transformation of santonin into two C_{10}-epimeric 3-oxa-guaianolides which are 8-deoxyderivatives of several natural 3-oxaguaianolides isolated from *Achillea* species. The synthesis involved the photochemical rearrangement of the eudesmane skeleton into a guaiane skeleton and the transformation of the cyclopentane ring into a furan moiety with the concomitant loss of C_3. Comparison of the NMR data of the synthetic products with those of the natural products confirms the β orientation of the hydroxyl group at C_{10} in the products isolated from *Achillea*.

Introduction

The aromatic furan ring, one of the most representative five-membered heterocycles, can be found in many important pharmaceuticals as well as in naturally occurring compounds of vegetable and marine origin, especially terpenoids.[1,2] For this reason, the synthesis of furans with different substitution patterns has attracted the interest of many synthetic chemists and many strategies for the construction of this moiety have been devised.[3]

In recent years several unusual 3-nor-guaianolides bearing a furan moiety, namely 3-oxa-guaianolides, were isolated from the flower heads of European *Achillea roseo-alba* and *A. collina*, and their structures described as 8α-acetoxy- (**2**) (achillicin), 8α-angeloxy- (**3**) and 8α-tigloxy-3-oxa-10-*epi*-artabsin (**4**).[4,5] Almost simultaneously, two 3-oxa-guaianolides were isolated also from *A. millefolium* growing in Mongolia and named 8-acetyl- (**6**) and 8-angeloylegelolide (**7**), which differed only in the configuration assignment of C_{10}.[6] The structure of the compounds **2**–**4** isolated from the European species was reinvestigated later[7] with the use of modern 2D NMR techniques and the stereochemistry of C_{10} corrected to the configuration with the hydroxyl group at C_{10} β-orientated—the same configuration as in artabsin (**10**)—thus establishing that the products isolated from *A. roseo-alba* and *A. collina* were identical to those isolated from *A. millefolium* and had structures such as **6**–**8** (Fig. 1).

In this article we report on the first synthetic approach to 10-hydroxy-3-oxaguaian-6,12-olides starting from santonin (**1**). We have prepared the corresponding 8-deoxyderivatives of the above mentioned natural products in both configurations at C_{10} **5** and **9** in a stereoselective and unambiguous way. These synthesis have allowed the comparison of the NMR data of the synthetic materials and the natural

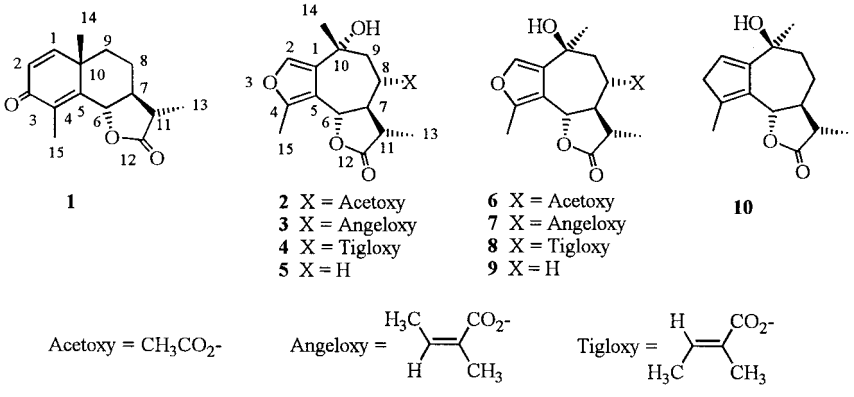

Figure 1.

Keywords: terpenes and terpenoids; lactones; *Achillea*; furans.

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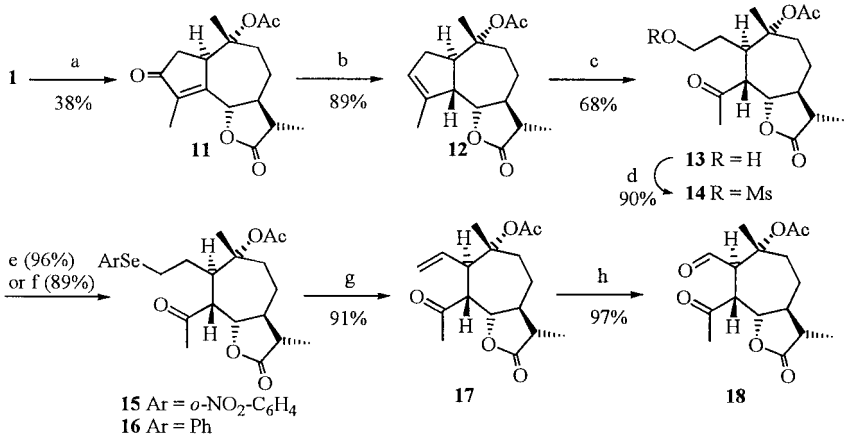


Scheme 1. (a) hν/AcOH; (b) 1. $TsNHNH_2$, 2. Catecholborane; (c) 1. O_3, 2. $NaBH_4$; (d) Mesyl chloride; (e) *o*-$NO_2C_6H_4SeCN$-Bu_3P; (f) NaPhSe; (g) H_2O_2; (h) 1. O_3, 2. Ph_3P.

products providing additional support to confirm the β-OH orientation of the hydroxyl group at C_{10}.

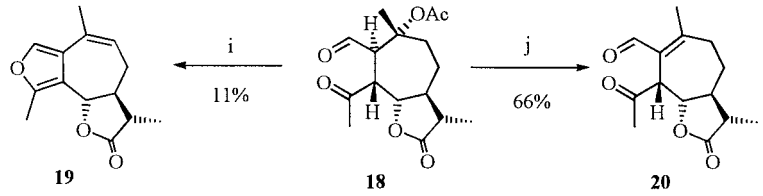
Results and Discussion

Santonin (**1**) was chosen as starting material in our synthetic scheme. The synthesis of 3-nor-guaianolides from this material required the transformation of the santonin carbon framework from eudesmane into guaiane, and the one carbon (C_3) degradation of the cyclopentane ring in the resulting guaiane with cleavage of the C_2–C_3 and C_3–C_4 bonds.

With this aim (Scheme 1), santonin (**1**) was transformed into guaianolide **12** as has been described previously, in two steps involving photochemical rearrangement of santonin to *O*-acetylisophotosantonin (**11**), and reduction of the tosylhydrazone of the resulting enone with catecholborane.[8] The occurrence of the C_3–C_4 double bond in compound **12** should allow the cleavage of the C_3–C_4 bond by ozonolysis. On the other hand it was considered convenient that, after ozonolysis, both carbon atoms C_3 and C_4 resulted in a different functionalization in order to make easier further selective elaboration of the C_2–C_3 fragment leading to the cleavage of this bond. Therefore compound **12** was subjected to ozonolysis in dichloromethane–methanol followed by careful reduction with sodium borohydride. In this way reduction was achieved up to the alcohol at the less substituted carbon C_3 while C_4 remained as a ketone giving hydroxyketone **13** in 68% yield. The following steps were addressed to the elimination of the hydroxyl group at C_3, which would permit removal of C_3 from the molecule, by ozonolysis of the resulting C_2–C_3 double bond. Elimination was carried out in two steps via arylselenide **15**. Treatment of compound **13** with *o*-nitrophenylselenocyanate and tri-*n*-butylphosphine in THF–pyridine gave compound **15** in 96% yield, which upon treatment with H_2O_2 followed by spontaneous elimination of the resulting selenoxide gave alkene **17** in 91% yield.[9,10] Alternatively, compound **17** was also prepared via a different selenide **16** in a one step longer sequence which uses diphenyldiselenide instead of the more toxic and expensive *o*-nitrophenylselenocyanate. Thus, the C_3-hydroxyl in compound **13** was transformed into its mesylate **14** in 90% yield which was then treated with sodium phenylselenolate to give phenylselenide **16** in 89% yield.[11,12] The oxidative elimination of this selenide yielded 90% of alkene **17** with identical features to the compound obtained from **15**. With compound **17** in our hands we undertook the cleavage of the C_2–C_3 double bond by ozonolysis. The outcome of this reaction was very dependent on the work up of the ozonolysis mixture. Ozonization in dichloromethane–methanol followed by reduction with Zn[13] or dimethyl sulfide[14] gave the desired ketoaldehyde **18** in moderate yield (52 and 64%, respectively) together with by-products resulting from methanol addition. Ozonization in dichloromethane followed by cleavage of the ozonide with triethylamine[15] resulted in a similar yield (52%) of the expected product.[15] Finally, compound **18** was obtained in very high yield (97%) when the ozonide prepared in dichloromethane was reduced with triphenylphosphine.[16]

Although 1,4-dicarbonyl compounds, such as **18**, have been traditionally considered as the direct precursors for furans,[17] it was fairly foreseeable that the tertiary acetoxy group at C_{10} may cause difficulties during the cyclization to the furan moiety. Indeed, it was observed that upon treatment with *p*-toluenesulfonic acid in benzene compound **18** led to alkenefuran **19**[†] in very low yield besides polymeric material (Scheme 2). On the other hand, when the reaction was attempted using silica gel, basic or acidic aluminum oxide as dehydrating agents, compound **20**, resulting from acetic acid elimination, was obtained in fair yields (ca. 65%). We assumed that the conjugation of the resulting double bond with the aldehyde carbonyl was the cause of the easy elimination of the acetoxy group. The solution to this problem consisted of the reduction of the aldehyde group which made necessary an oxidative step later on in the synthetic sequence (Scheme 3). The selective reduction of the aldehyde group occurred with concomitant cyclization to hemiacetal **21**. The best yield (95%) was obtained

[†] Compound **19.** ^{1}H NMR ($CDCl_3$) δ 7.24 (1H, s, H-1), 5.41 (1H, brd, J=6.5 Hz, H-9), 5.02 (1H, d, J=8.8 Hz, H-6), 2.61 (1H, dd, J=6.5, 16.8 Hz, H-8), 2.4–2.1 (3H, m, H-7, H-8, H-11), 2.38 (3H, s, H-15), 1.95 (3H, s, H-14), 1.24 (3H, d, J=7.0 Hz, H-13); ^{13}C NMR δ 178.5 (s, C-12), 148.3 (s, C-4), 138.8 (d, C-2), 126.6, 123.5 (s, C-1, C-10), 122.8 (d, C-9), 115.3 (s, C-5), 79.3 (d, C-6), 48.3 (d, C-7), 41.3 (d, C-11), 31.7 (t, C-8), 23.7, 23.6 (q, C-14, C-15), 13.3 (q, C-13).



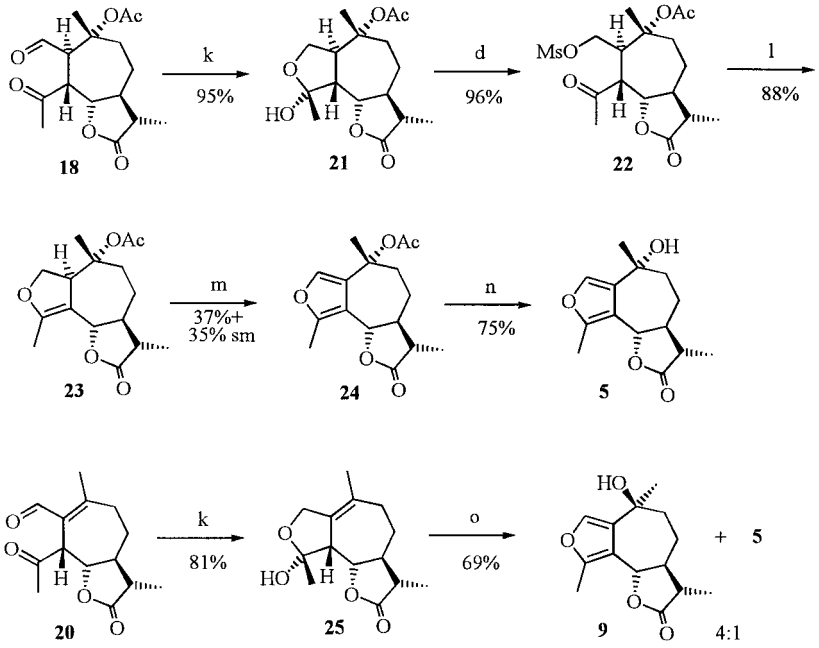
Scheme 2. (i) TsOH; (j) Al_2O_3.

with $LiAlH_4$ at low temperature, which proved better than $NaBH_4$ in CH_2Cl_2–MeOH (40%) and sodium triacetoxyborohydride in benzene (48%).[18] The stereochemistry of C_4 was determined by NOE experiments. NOE between H_6 and H_5 indicated the β disposition of H_5; irradiation of H_{15} gave NOEs with H_5 and the C_4–OH group, and also NOEs were observed with H_1, $H_{2\alpha}$, and H_{15} upon irradiation of the C_4–OH signal at δ 2.63. These experiments indicated the *trans* junction of the dihydrofuran and the cycloheptane ring in the molecule and the β orientation of the methyl group at C_4.

The elimination of the hydroxyl group at C_4 was attempted via its conversion into a mesylate. Unexpectedly, treatment of compound **21** with mesyl chloride in pyridine gave 96% of a compound that was identified as the C_2-mesylate **22**. Compound **22** is probably formed through the equilibrium between the hemiacetal and hydroxyketone forms of **21**. Anyway, this fact did not cause any setback since treatment of mesylate **22** with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in toluene gave the desired dihydrofuran **23** in 88% yield, via an intramolecular *O*-alkylation of the ketone enolate.

For the construction of the furan moiety the dehydrogenation of the dihydrofuran ring in reaction conditions compatible with the tertiary acetoxy group at C_{10} was required. Quite surprisingly, not many methods to achieve this transformation can be found in the literature. NiO_2[19] or sulfur[20] have been used, but they require strong conditions and do not give good results. Softer conditions have been described with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ).[21] However treatment of compound **23** with DDQ at 40°C gave rise to untreatable mixtures. As an alternative, we attempted the allylic oxidation of the $\Delta^{4,5}$ double bond with SeO_2 which was also unsuccessful. Finally it was possible to obtain the furan ring by methylene blue sensitized photooxygenation.[10,12] Photooxygenation of alkenes in these conditions leads to allylic hydroperoxides with migration of the double bond. In our case, probably this reaction gave a $\Delta^{1,5}$-4-hydroperoxyderivative which eliminated hydrogen peroxide during column chromatography to give the desired furan **24** with a moderate yield (37%) together with 35% of recovered starting material **23**.

The final transformation of compound **24** into **5** required the hydrolysis of the acetate group. This step was complicated by the tendency of C_{10} in compound **5** to epimerize in aqueous acids. This fact was observed in preliminary assays of acetate hydrolysis in aqueous media and was confirmed in an independent experiment, as we will see below. Since one of the objectives of this work was to prepare both epimers at C_{10} in an unambiguous way, the use of aqueous acid during reaction or work up had to be avoided. With this purpose we decided to remove the acetate group not by hydrolytic but by reductive procedures. Compound **24** was treated with an excess of Red-Al® in order to ensure



Scheme 3. (d) Mesyl chloride; (k) $LiAlH_4$; (l) DBU; (m) 1. O_2, hν, methylene blue, 2. SiO_2; (n) 1. Red-Al®, 2. NMO, TPAP; (o) 1. OsO_4, 2. 2 M HCl

Table 1. Comparative ^{1}H NMR δ values of compounds **5**–**9**

H	**5**[a]	**9**[a]	**6**[a,b]	**7**[a,b]	**8**[a,b]
2	7.27	7.17	7.18	7.19	7.19
6	4.98	5.30	5.41	5.45	5.45
14	1.45	1.63	1.65	1.66	1.64
15	2.36	2.38	2.39	2.39	2.39

[a] δ registered using TMS as internal standard. We have registered the ^{1}H NMR of compounds **5** and **9** using TMS as internal standard for a more accurate comparison with the natural products ^{1}H NMR spectra.
[b] Taken from Refs. 4 and 6.

complete reduction of the acetate group. This treatment also brought about the reduction of the lactone ring to give a mixture of lactols which were subjected to reoxidation with 4-methylmorpholine *N*-oxide (NMO) and tetra-*n*-propylammonium perruthenate (TPAP) without separation.[22] In this way we obtained a compound in 75% yield for the two steps. The NMR data obtained for this compound were in good agreement with the expected for a 10-hydroxy-3-oxaguaian-6,12-olide and it was assigned structure **5**. The α orientation of the hydroxyl group was determined by the stereochemistry of C_{10} in *O*-acetylisophotosantonin (**11**) which is perfectly known and does not change along the synthetic sequence.

The tendency of compound **5** to epimerize in aqueous acid was confirmed in the following way. Compound **5** was stirred in 2 M HCl for 2 min and then extracted with ethyl acetate. The extract was analyzed by ^{1}H NMR and contained ca. 54% of **5**, 18% of **9** and 9% of **19**.

For the synthesis of the 3-oxaguaianolide with the β-OH group **9**, the epimerization of C_{10} was required. Although this compound can be obtained directly from **5** by epimerization in acidic media we envisaged a shorter procedure for its synthesis (Scheme 3). The starting point was compound **20** obtained as mentioned above. Selective reduction of the aldehyde group with $LiAlH_4$ gave hemiacetal **25** in 81% yield. The orientation of the C_4–OH group in this compound was determined from the NOEs observed between H_5 and H_6, and H_5 and H_{15} signals. Compound **25** was subsequently subjected to hydroxylation of the double bond with osmium tetroxide[23] followed by work up with 2 M HCl which brought about dehydration and aromatization of the triols resulting from hydroxylation. In this way we obtained two hydroxy furans in 60% and 15% yield respectively after column chromatography. The minor product showed spectral data identical to furan **5** obtained as described above and it was assigned the structure with the C_{10} α-OH group. On the other hand, the ^{1}H and ^{13}C NMR spectra of the major product were consistent with a 10-hydroxy-3-oxaguaian-6,12-olide and it was assigned the epimeric structure **9** with the C_{10} β-OH group. The most significant differences in the ^{1}H NMR spectra of both epimers correspond to the chemical shifts of H_2 and H_6 which are differently influenced in each epimer by the spatial proximity of the hydroxyl group at C_{10} which causes a deshielding effect. This effect is experienced by H_2 in compound **5** where this hydroxyl group is α-orientated and by H_6 in compound **9** which has the C_{10} hydroxyl group with β configuration. Thus, H_2 appears at δ 7.27 in compound **5** and at δ 7.17 in compound **9**, while H_6 appears at δ 4.98 in compound **5** and at δ 5.30 in **9**.

On the other hand, the resonance frequency of H_{14} will be also affected because of the magnetic anisotropy due to the furan ring, depending on its orientation (α or β).[24] In compound **9**, H_{14} with an α orientation is held in the deshielding zone and it is expected that it resonates at higher δ value than in compound **5** where this methyl group is out of this zone. The observed values are 1.45 and 1.63 ppm in compounds **5** and **9**, respectively.

Following this reasoning, a comparative study of the ^{1}H NMR data of the oxaguaianolides isolated from *Achillea* sp. and of our synthetic materials can be applied to determine the stereochemistry of C_{10} in these natural products. This comparison is feasible since the 8-acyloxy groups present in the natural products are far away enough from H_2, H_6, and H_{14}; and therefore will not have a noticeable effect on their NMR chemical shifts. The δ values for these protons and H_{15} in the ^{1}H NMR spectra of compounds **5**, **9**, and of the three natural oxa-guaianolides are shown in Table 1. A good agreement between the δ corresponding to H_2, H_6 and H_{14} is observed for compounds **6**–**8** and **9**, while they differ significantly from the observed in compound **5**. This agreement is in accordance with the expected results according to the reasoning above and therefore constitutes additional evidence for the β-orientation of the C_{10}–OH group in the natural products **6**–**8**.

Experimental

General

All melting points are uncorrected. Column chromatography was performed on silica gel (Merck, silica gel 60, 230–400 mesh). Commercial reagents and solvents were analytical grade or were purified by standard procedures, prior to use.[25] All reactions involving air or moisture sensitive materials were carried out under argon atmosphere. Specific rotations were measured in $CHCl_3$. IR were recorded as liquid film in NaCl for oils and as KBr discs for solids. NMR were run in $CDCl_3$ at 399.94 MHz for ^{1}H and at 50.3, 75.43, or 100.58 MHz for ^{13}C NMR, and referenced to the solvent as internal standard (δ_H=7.24 ppm) except for compounds **5** and **9** (TMS as internal standard). The carbon type was determined by DEPT experiments. Mass spectra were run by electron impact at 70 eV or chemical ionization using methane as ionizing gas.

***O*-Acetylisophotosantonin (11).** A solution of santonin (**1**) (9.5 g, 38.6 mmol) in 140 mL of glacial acetic acid was irradiated under argon with a 150 W medium-pressure mercury lamp housed in an refrigerated quartz immersion tube until complete reaction of santonin as determined by ^{1}H NMR analysis of an aliquot. The acetic acid was evaporated under reduced pressure with the help of hexane and the resulting oil dissolved in 16 mL of hot methanol and then left overnight at −20°C. Filtration afforded 4.5 g (38%) of compound **11**: mp 176–177°C (MeOH) [lit. 175–178°C (MeOH)];[26] $[\alpha]_D^{22}$=+49 (*c* 1.0, $CHCl_3$) [lit. $[\alpha]_D^{24}$=+48.8 ($CHCl_3$)];[26] IR (KBr) ν_{max} 1775, 1736, 1699, 1235 cm^{-1}; ^{1}H NMR δ 4.77 (1H, d, *J*=10.5 Hz, H-6), 4.13 (1H, dd, *J*=3.3, 8.0 Hz, H-1), 2.60 (1H, td, *J*=4.4, 13.8 Hz, H-9),

2.48 (1H, dd, J=8.0, 19.5 Hz, H-2), 2.37 (1H, dd, J=3.3, 19.5 Hz, H-2′), 2.30 (1H, dq, J=6.6, 11.8 Hz, H-11), 2.20–2.15 (2H, m, H-7, H-9′), 2.03 (1H, dt, J=4.4, 16.4 Hz, H-8), 1.97 (3H, s, OAc), 1.87 (3H, t, J=1.5 Hz, H-15), 1.42 (1H, dddd, J=2.8, 13.0, 13.8, 15.4 Hz, H-8′), 1.26 (3H, d, J=6.6 Hz, H-13), 1.06 (3H, s, H-14); ^{13}C NMR δ 206.5 (s, C-3), 176.8 (s, C-12), 169.9 (s, CH_3CO), 160.8 (s, C-5), 142.6 (s, C-4), 85.2 (s, C-10), 80.8 (d, C-6), 47.8 (d, C-7), 46.9 (d, C-1), 40.9 (d, C-11), 37.6 (t, C-9), 36.5 (t, C-2), 24.9 (t, C-8), 21.9 (q, CH_3CO), 19.6 (q, C-14), 12.1 (q, C-13), 9.1 (q, C-15).

10α-Acetoxy-1,7αH,5,6,11β*H*-guaia-3-en-6,12-olide (12). A solution of compound **11** (3.02, 9.85 mmol) and *p*-toluenesulfonylhydrazine (2.42 g, 12.9 mmol) in 10 mL of absolute ethanol was heated at 80–85°C under argon for 1 h. After this time the solvent was evaporated under vacuum and the resulting yellow solid dissolved in 30 mL of chloroform, cooled at 0°C and treated with 20 mL of an 1 M solution of catecholborane in THF (20 mmol) under argon. The resulting mixture was stirred for 1 h at 0°C and at room temperature for two additional hours. After this time, sodium acetate trihydrate (10 g, 73 mmol) was added and the mixture refluxed under argon for 1 h. Then it was filtered, concentrated and the residue chromatographed on silica gel with 8:2 hexane–EtOAc to give 2.55 g (89%) of compound **12**: mp 114–116°C ($CHCl_3$) [lit. 116–117°C];[8] $[\alpha]_D^{22}=-33$ (c 0.8, $CHCl_3$) [lit. $[\alpha]_D^{24}=-35$ ($CHCl_3$)];[8] IR (KBr) ν_{max} 1768, 1739 cm^{-1}; HRMS (EI) m/z 232.1456 (M^+-CH_3COOH, 100, $C_{15}H_{20}O_2$ required 232.1463), 217 (37), 159 (31), 105 (22); ^{1}H NMR δ 5.34 (1H, br m, H-3), 4.24 (1H, dd, J=9.0, 10.0 Hz, H-6), 3.27 (1H, dt, J=9.0, 10.0 Hz, H-1), 2.97 (1H, t, J=9.0, H-5), 2.44 (1H, td, J=10.0, 3.2 Hz, H-9), 2.3–2.1 (4H, m, 2H-2, H-7, H-11), 1.96 (3H, s, OAc overlapped with H-9′), 1.86 (3H, s, H-15 overlapped with H-8), 1.35 (3H, s, H-14 overlapped with H-8′), 1.21 (3H, d, J=6.4 Hz, H-13); ^{13}C NMR δ 178.5 (s, C-12), 170.3 (s, CH_3CO), 139.1 (s, C-4), 125.4 (d, C-3), 86.7 (s, C-10), 82.9 (d, C-6), 49.0, 48.6, 47.7 (d, C-1, C-5, C-7), 42.3 (d, C-11), 37.7 (t, C-2), 32.4 (t, C-9), 22.4 (d, C-8), 22.4 (q, CH_3CO), 21.2 (q, C-15), 16.9 (q, C-14), 12.1 (q, C-13).

Hydroxy ketone 13. Ozone enriched oxygen was bubbled through a solution of compound **12** (1.52 g, 5.19 mmol) in 415 mL of 1:1 MeOH–CH_2Cl_2 at −78°C until the appearance of a blue color in the solution. The excess ozone was removed with an argon purge. A fivefold excess of $NaBH_4$ (0.21 g, 5.5 mmol, total 27.5 mmol) was added at intervals of 15 min at −78°C. After the last addition, the reaction flask was transferred to an ice bath and stirred for 45 min. The reaction was quenched with 200 mL of std aqueous NH_4Cl. The organic layer was separated and the aqueous layer concentrated to half volume and extracted twice with dichloromethane (2×100 mL). The combined organic layers were dried, concentrated and chromatographed on silica gel (1:1 hexane–EtOAc) to give 1.15 g (68%) of compound **13**: mp 141–143°C (hexane–EtOAc); $[\alpha]_D^{19}=-53$ (c 1.0, $CHCl_3$); IR (KBr) ν_{max} 3496, 1765, 1739, 1695 cm^{-1}; HRMS (CI) m/z 327.1802 (M^++1, 0.6, $C_{17}H_{27}O_6$ required 327.1808), 309 (29), 267 (100), 249 (34), 207 (36); ^{1}H NMR δ 4.25 (1H, dd, J=4.2, 10.5 Hz, H-6), 3.79 (2H, m, 2H-3), 3.19 (1H, t, J=4.2 Hz, H-5), 2.87 (1H, dq, J=5.5, 10.5 Hz, H-7), 2.76 (1H, m, H-1), 2.31 (1H, m, H-9), 2.22 (3H, s, H-15), 2.16 (1H, dq, J=1 0.5, 6.8 Hz, H-11), 1.89 (3H, s, OAc overlapped with H-9′), 1.81 (1H, m, H-8), 1.55 (3H, s, H-14), 1.32 (1H, m, H-8′), 1.22 (3H, d, J=6.8 Hz, H-13); ^{13}C NMR δ 207.1 (s, C-4), 178.7 (s, C-12), 169.8 (s, CH_3CO), 86.5 (s, C-10), 79.1 (d, C-6), 60.8 (t, C-3), 52.3 (d, C-7), 44.5, 43.6 (d, C-1, C-5), 41.4 (C-11), 31.8, 31.2 (t, C-2, C-9), 30.1 (q, C-15), 25.5 (q, CH_3CO), 25.3 (t, C-8), 21.8 (q, C-14), 13.2 (q, C-13).

Vinyl ketone 17. (a) *Via o-nitrophenylselenide **15***: To a solution of compound **13** (611 mg, 1.87 mmol) and *o*-nitrophenylselenocyanate (975 mg, 4.2 mmol) in 19 mL of 1:1 THF–pyridine was added via syringe n-Bu_3P (1.4 mL, 5.62 mmol) under argon. After 1 h, the reaction mixture was diluted with ethyl acetate (100 mL), washed with 2 M HCl (25 mL) and brine (25 mL), and dried with $MgSO_4$. After filtration and evaporation of the solvent under reduced pressure, the residue was chromatographed on silica gel (6:4 to 3:7 hexane–EtOAc) to give 910 mg (96%) of a yellow solid identified as compound **15**: mp 96–98°C (ether); $[\alpha]_D^{19}=+7$ (c 0.8, $CHCl_3$); IR (KBr) ν_{max} 1764, 1729, 1700 cm^{-1}; ^{1}H NMR δ 8.28 (1H, dd, J=1.2, 8.5 Hz, Ar), 7.53 (1H, td, J=8.5, 1.2 Hz, Ar), 7.44 (1H, dd, J=1.2, 8.5 Hz, Ar), 7.34 (1H, td, J=8.5, 1.2 Hz, Ar), 4.24 (1H, dd, J=5.5, 10.0 Hz, H-6), 3.20 (1H, t, J=5.5 Hz, H-5), 3.00 (2H, m, 2H-3), 2.76 (1H, m, H-1), 2.63 (1H, m, H-7), 2.24 (3H, s, H-15), 2.09 (4H, m, H-2, H-8, H-9, H-11), 1.91 (3H, s, OAc overlapped with H-9′), 1.61 (1H, m, H-2′), 1.51 (3H, s, H-14), 1.30 (1H, m, H-8′), 1.21 (3H, d, J=7.2 Hz, H-13); ^{13}C NMR δ 206.6 (s, C-4), 177.6 (s, C-12), 169.6 (s, CH_3CO), 146.0 (s, Ar), 133.8 (s, d, Ar), 132.2 (s, Ar), 128.8, 126.5, 125.8 (d, Ar), 86.5 (s, C-10), 79.7 (d, C-6), 52.6 (d, C-7), 48.6, 42.7, 42.5 (d, C-1, C-5, C-11), 33.7 (t, C-3), 31.8 (q, C-15), 29.4 (t, C-9), 25.7, 24.9 (t, C-2, C-8), 23.4 (q, CH_3CO), 22.1 (q, C-14), 13.0 (q, C-13).

To a solution containing compound **15** (2.25 g, 4.4 mmol) in 34 mL of THF cooled at −78°C was added 5 mL of 30% H_2O_2. The mixture was stirred at room temperature for 7 h and then diluted with 200 mL of EtOAc, washed with 50 mL of 8% aqueous $Na_2S_2O_3$ and 50 mL of brine. Removal of the solvent under reduced pressure and chromatography on silica gel (6:4 hexane–EtOAc) yielded 1.23 g (91%) of compound **17**: mp 144–146°C (hexane–EtOAc); $[\alpha]_D^{21}=-64$ (c 0.8, $CHCl_3$); IR (KBr) ν_{max} 1776, 1727 cm^{-1}; HRMS (CI) m/z 309.1701 (M^++1, 1.4, $C_{17}H_{25}O_5$ required 309.1702), 249 (100), 207 (48), 189 (15); ^{1}H NMR δ 5.69 (1H, ddd, J=10.0, 10.2, 16.5 Hz, H-2), 5.04 (1H, dd, J=1.5, 10.2 Hz, H-3), 4.96 (1H, dd, J=1.5, 16.5 Hz, H-3′), 4.28 (1H, dd, J=7.8, 10.6 Hz, H-6), 3.63 (1H, t, J=10.0 Hz, H-1), 3.28 (1H, dd, J=7.8, 10.0 Hz, H-5), 2.74 (1H, td, J=11.5, 4.1 Hz, H-9), 2.47 (1H, qd, J=10.6, 1.9 Hz, H-7), 2.15 (3H, s, H-15), 2.10 (1H, dq, J=7.2, 10.5 Hz, H-11), 1.95 (2H, m, H-8, H-9′), 1.85 (3H, s, OAc), 1.38, (3H, s, H-14), 1.26 (1H, m, H-8′), 1.21 (3H, d, J=7.2 Hz, H-13); ^{13}C NMR δ 207.0 (s, C-4), 177.3 (s, C-12), 169.7 (s, CH_3CO), 135.0 (d, C-2), 118.4 (t, C-3), 85.7 (s, C-10), 81.8 (d, C-6), 52.1, 50.9 (d, C-1, C-7), 44.4 (d, C-5), 41.6 (d, C-11), 37.2 (t, C-9), 34.3 (q, C-15), 26.9 (t, C-8), 22.4 (q, CH_3CO), 21.7 (q, C-14), 12.8 (q, C-13).

(b) *Via phenylselenide* ***16***: A solution of compound **13** (79 mg, 0.24 mmol) and triethylamine (48 μL, 0.35 mmol) in 1.2 mL of CH_2Cl_2 at 0°C was treated with mesyl chloride (22 μL, 0.28 mmol). After 85 min, the reaction mixture was diluted with 60 mL of EtOAc, washed with 20 mL of 2 M HCl and 20 mL of brine. Chromatography on silica gel with 8:2 hexane–EtOAc yielded 88 mg (90%) of mesylate **14**: ^{1}H NMR δ 4.35 (1H, dd, J=5.9, 10.0 Hz, H-6), 4.20 (2H, m, 2H-3), 3.17 (1H, t, J=5.9 Hz, H-5), 3.00 (3H, s, OMs), 2.6–2.4 (2H, m, H-1, H-7), 2.2–2.0 (4H, m, H-2, H-8, H-9, H-11) 2.25 (3H, s, H-15), 1.91 (3H, s, OAc overlapped with H-9′), 1.51 (3H, s, H-14 overlapped with H-2′), 1.25 (1H, m, H-8′), 1.17 (3H, d, J=6.9 Hz, H-13).

To a mixture of $NaBH_4$ (9.4 mg, 0.25 mmol) and diphenyldiselenide (45 mg, 0.14 mmol) under argon was added 0.5 mL of DMF via syringe. A rapid evolution of hydrogen took place and the mixture was decolorized. After evolution of hydrogen ceased, a solution of mesylate **14** (23 mg, 0.058 mmol) in 1 mL of DMF was injected and the mixture stirred for 2 h at room temperature. The reaction was quenched with water (10 mL) and extracted with EtOAc (3×20 mL). Chromatography of the extract allowed to obtain 24 mg (89%) of phenylselenide **16**. ^{1}H NMR (300 MHz) δ 7.50 (2H, m, Ar), 7.26 (3H, m, Ar), 4.17 (1H, dd, J=5.3, 10.4 Hz, H-6), 3.09 (1H, t, J=5.3 Hz, H-5), 3.1–2.9 (3H, m, H-1, 2H-3), 2.8–2.6 (2H, m, H-7, H-9), 2.15 (3H, s, H-15 overlapped with H-2, H-8, H-11), 1.86 (3H, s, OAc overlapped with H-9′), 1.62 (1H, m, H-2′), 1.46 (3H, s, H-14), 1.21 (4H, d, J=6.9 Hz, H-13, overlapped with H-8′).

Compound **16** (55 mg, 0.12) in THF was treated with 30% H_2O_2 for 16 h as described above for compound **15** to give 33 mg (90%) of **17**.

Dicarbonyl compound 18. A solution of compound **17** (1.10 g, 3.58 mmol) in 95 mL of dry dichloromethane was treated with ozone as described in the synthesis of **13**. The resulting solution was treated with Ph_3P (1.22 g, 5.66 mmol), the temperature was allowed to rise to room temperature and stirred for 5 h. After this time the solvent was removed and the residue chromatographed (6:4 to 4:6 hexane–EtOAc) to give 1.08 g (97%) of compound **18** as a white solid: mp 136–138°C (CH_2Cl_2–hexane); $[\alpha]_D^{21}$= −197 (c 1.2, $CHCl_3$); HRMS (CI) m/z 311.1491 (M^++1, 95, $C_{16}H_{23}O_6$ required 311.1495), 251 (100), 233 (86), 209 (62), 191 (76); IR (KBr) ν_{max} 1777, 1760, 1720, 1717 cm^{-1}; ^{1}H NMR δ 9.80 (1H, s, H-2), 4.29 (1H, m, H-6), 3.89 (1H, s, H-1), 3.88 (1H, d, J=2.0 Hz, H-5), 2.50 (1H, dt, J=4.5, 14.0 Hz, H-9), 2.32 (3H, s, H-15 overlapped with H-9′), 2.19 (1H, qd, J=10.5, 4.0 Hz, H-7), 2.12 (1H, dq, J=6.5, 10.5 Hz, H-11), 2.01 (4H, s, OAc overlapped with H-8), 1.50 (3H, s, H-14), 1.27 (1H, m, H-8′), 1.18 (3H, d, J=6.5 Hz, H-13); ^{13}C NMR δ 207.3 (s, C-4), 201.6 (s, C-2), 176.8 (s, C-12), 169.8 (s, CH_3CO), 86.4 (s, C-10), 80.7 (d, C-6), 58.6 (d, C-1), 46.4 (d, C-5), 44.6 (d, C-7), 41.4 (d, C-11), 38.2 (t, C-9), 33.5 (q, C-15), 26.4 (t, C-8), 22.3 (q, CH_3CO), 21.5 (q, C-14), 12.7 (q, C-13).

Dicarbonyl compound 20. A suspension of compound **18** (20 mg, 0.065 mmol) and 188 mg of aluminum oxide, activated, weakly acidic, in 2 mL of benzene was stirred at room temperature under argon for 6 h. The solvent was removed and the resulting powder was chromatographed on silica gel to give 3.3 mg (16%) of starting material and 10.6 mg (66%) of a product identified as **20**: mp 79–81°C (EtOAc); $[\alpha]_D^{25}$=−200 (c 1.0, $CHCl_3$); IR (KBr) ν_{max} 1784, 1707, 1661 cm^{-1}; HRMS (EI) m/z 250.1201 (M^+, 3, $C_{14}H_{18}O_4$ required 250.1205), 208 (68), 190 (73), 162 (57), 134 (100); ^{1}H NMR δ 10.07 (1H, s, H-2), 4.96 (1H, d, J=4.0 Hz, H-5), 3.85 (1H, dd, J=4.0, 10.8 Hz, H-6), 2.84 (1H, td, J=13.5, 2.0 Hz, H-9), 2.44 (1H, qd, J=10.8, 3.2 Hz, H-7), 2.33 (3H, s, H-15), 2.20 (3H, s, H-14 overlapped with H-9′ and H-11), 2.00 (1H, m, H-8), 1.31 (1H, m, H-8′), 1.21 (3H, d, J=6.9 Hz, H-13), ^{13}C NMR δ 205.6 (s, C-4), 189.2 (d, C-2), 177.1 (s, C-12), 165.4 (s, C-1), 133.0 (s, C-10), 81.7 (d, C-6), 48.8, 48.3 (d, C-5, C-7), 42.2 (d, C-11), 37.1 (t, C-9), 32.2 (q, C-15), 26.9 (t, C-8), 22.1 (q, C-14), 12.2 (q, C-13).

By the same procedure using aluminum oxide, activated, basic, Brockmann I, compound **20** was obtained in 66% yield.

By the same procedure using silica gel at benzene reflux temperature, compound **20** was obtained in 46–67% yield.

Hemiacetal 21. To a solution of compound **18** (150 mg, 0.48 mmol) in 14 mL of dry THF cooled at 0°C under argon was added $LiAlH_4$ (23 mg, 0.60 mmol) portionwise. The reaction mixture was stirred for 3 h and quenched with std aqueous NH_4Cl (5 mL) at this temperature. The temperature was allowed to rise to room temperature, 2 M HCl (5 mL) added and the mixture extracted with EtOAc (3×25 mL) and washed with brine (25 mL). Removal of the solvent under reduced pressure followed by chromatography (4:6 hexane–EtOAc) afforded 144 mg (95%) of compound **21**: mp 134–136°C (hexane–EtOAc); $[\alpha]_D^{25}$= −87 (c 1.0, $CHCl_3$); IR (KBr) ν_{max} 3471, 1772, 1729 cm^{-1}; HRMS (EI) m/z 297.1347 (M^+-CH_3, 7, $C_{15}H_{21}O_6$ required 297.1338), 209 (34), 192 (44), 164 (100), 119 (77); ^{1}H NMR δ 4.18 (1H, t, J=10.4 Hz, H-6), 4.00 (1H, t, J=7.5 Hz, H-2), 3.67 (1H, dd, J=7.5, 10.5 Hz, H-2′), 3.55 (1H, ddd, J=7.5, 10.5, 12.5 Hz, H-1), 2.63 (1H, br s, OH); 2.38 (1H, dt, J=13.5, 4.0 Hz, H-9), 2.27 (2H, dd, J=10.0, 12.5 Hz, H-5 overlapped with H-7), 2.19 (1H, td, J=13.5, 4.0 Hz, H-9), 2.11 (1H, dq, J=11.5, 7.0 Hz, H-11), 1.93 (3H, s, OAc, overlapped with H-8), 1.65 (3H, s, H-15), 1.38 (3H, s, H-14), 1.24 (1H, m, H-8′), 1.21 (3H, d, J=7.0 Hz, H-13); ^{13}C NMR δ 177.9 (s, C-12), 170.2 (s, CH_3CO), 105.0 (s, C-4), 84.8 (s, C-10), 80.9 (d, C-6), 67.6 (t, C-2), 48.1, 47.2, 47.1 (d, C-1, C-5, C-7), 41.7 (d, C-11), 38.2 (t, C-9), 27.5 (q, C-14), 26.0 (t, C-8), 22.3 (q, CH_3CO), 18.6 (q, C-15), 12.4 (q, C-13).

Dihydrofuran 23. A solution of compound **18** (148 mg, 0.47 mmol) and MsCl (357 μL, 4.60 mmol) in 10 mL of pyridine was stirred at 0°C for 1 h. After this time the mixture was diluted with 75 mL of EtOAc, washed with 25 mL of 2 M HCl and 25 mL of brine, and dried. Solvent removal and chromatography with 1:1 hexane–EtOAc gave 176 mg (96%) of mesylate **22**: $[\alpha]_D^{28}$=−90 (c 0.8, $CHCl_3$); IR (KBr) ν_{max} 1765, 1722 cm^{-1}, ^{1}H NMR (250 MHz) δ

4.5–4.1 (3H, m, H-6, 2H-2), 3.62 (1H, t, J=8.0 Hz, H-5), 3.17 (1H, m, H-1), 2.98 (3H, s, OMs), 2.41 (1H, dt, J=13.5, 4.0 Hz, H-9), 2.34 (3H, s, H-15), 2.3–1.9 (4H, m, H-7, H-11, H-8, H-9′), 1.99 (3H, s, OAc), 1.49 (3H, s, H-14), 1.25 (1H, m, H-8′), 1.17 (3H, d, J=6.6 Hz, H-13); ^{13}C NMR δ 208.0 (s, C-4), 176.9 (s, C-12), 169.8 (s, CH_3CO), 85.5 (s, C-10), 81.1 (d, C-6), 69.6 (t, C-2), 49.8 (d, C-7), 46.3, 44.2 (d, C-1, C-5), 41.3 (d, C-11), 38.2 (t, C-9), 37.3 (q, CH_3SO_2), 33.9 (q, C-15), 26.4 (t, C-8), 22.4 (q, CH_3CO), 21.6 (q, C-14), 12.7 (q, C-13).

A solution of the above mesylate (170 mg, 0.44 mmol) and DBU (68 μL, 0.45 mmol) in 45 mL of benzene was heated at reflux for 80 min. The usual work up and chromatography on silica gel with 1:1 hexane–EtOAc gave 113 mg (88%) of compound **23**: mp 134–136°C (hexane–EtOAc); $[\alpha]_D^{29}$= +71 (c 1.2, $CHCl_3$); HRMS (EI) m/z294.1482 (M^+, 2, $C_{16}H_{22}O_5$ required 294.1467), 234 (100), 219 (27), 190 (83), 161 (24); IR (KBr) ν_{max} 1764, 1722 cm^{-1}; ^{1}H NMR δ 4.61 (1H, d, J=10.8 Hz, H-6), 4.33 (2H, m, 2H-2), 3.98, (1H, t, J=8.4 Hz, H-1), 2.39 (1H, dt, J=13.5, 4.0 Hz, H-9), 2.20 (1H, dq, J=11.5, 6.8 Hz, H-11), 2.1–1.8 (3H, m, H-7, H-8, H-9), 1.97 (3H, s, OAc), 1.89 (3H, s, H-15), 1.31 (3H, s, H-14), 1.26 (1H, m, H-8), 1.22 (3H, d, J=6.8 Hz, H-13 overlapped with- H-8); ^{13}C NMR δ 178.4 (s, C-12), 170.3 (s, CH_3CO), 158.3 (s, C-4), 101.6 (s, C-5), 86.9 (s, C-10), 79.7 (d, C-6), 70.8 (t, C-2), 52.6, 49.8 (d, C-1, C-7), 41.8 (d, C-11), 37.9 (t, C-9), 24.1 (t, C-8), 22.5 (q, CH_3CO), 18.7 (q, C-14), 12.7, 12.3 (q, C-13, C-15).

Acetoxyfuran 24. Oxygen was gently bubbled through a solution of compound **23** (26 mg, 0.09 mmol) and methylene blue (2.4 mg) in absolute ethanol. The reaction tube was submerged in an ice bath and irradiated by two lamps (MAZDA, 400 W each) for 2 h. After this time, the solvent was removed under vacuum and the residue adsorbed on silica gel (500 mg). The resulting powder was placed on the top of a chromatography column for 3 h and the products eluted with 8:2 to 1:1 hexane–EtOAc mixtures to give 9.5 mg (37%) of compound **24** and 9 mg (35%) of starting material. Compound **24**: an oil, $[\alpha]_D^{26}$=−34 (c 1.0, $CHCl_3$); HRMS (EI) m/z 292.1316 (M^+, 80, $C_{16}H_{20}O_5$ required 292.1311), 250 (28), 232 (M^+−CH_3COOH, 100), 217 (29), 176 (22); IR (NaCl) ν_{max} 1787, 1766, 1728 cm^{-1}; ^{1}H NMR δ 7.24 (1H, s, H-2), 4.97 (1H, dq, J=10.5, 1.0 Hz, H-6), 2.36 (3H, d, J=1.0 Hz, H-15), 2.27 (1H, dq, J=11.0, 7.0 Hz, H-11), 2.20 (1H, m, H-9), 2.1–1.9 (3H, m, H-7, H-8, H-9′), 2.04 (3H, s, OAc), 1.75 (3H, s, H-14), 1.57 (1H, m, H-8′), 1.23 (3H, d, J=7.0 Hz, H-13); ^{13}C NMR δ 178.1 (s, C-12), 169.9 (s, CH_3CO), 148.2 (s, C-4), 137.9 (d, C-2), 128.5 (s, C-1), 114.5 (s, C-5), 81.5 (s, C-10), 78.5 (d, C-6), 51.0 (d, C-7), 41.6 (d, C-11), 36.1 (t, C-9), 26.2 (q, C-14), 25.6 (t, C-8), 22.4 (q, CH_3CO), 13.5 (q, C-15), 12.6 (q, C-13).

Hydroxyfuran 5. A solution of compound **24** (16.5 mg, 0.057 mmol) in 1.8 mL of dry THF was cooled at 0°C and treated with 60 μL (0.19 mmol) of a 65% solution of Red-Al® in toluene under argon. After 4 h, the reaction mixture was diluted with EtOAc (75 mL), washed with brine (15 mL) and dried with $MgSO_4$, and the solvent removed under reduced pressure. The resulting oil was diluted in CH_2Cl_2 and NMO (15.5 mg, 0.13 mmol) and TPAP (1.8 mg, 0.005 mmol) were added. The reaction mixture was stirred at room temperature for 30 min and then chromatographed on silica gel with 1:1 hexane–EtOAc to give 10.7 mg (75%) of compound **5**: mp 125–127°C (hexane–EtOAc); $[\alpha]_D^{28}$=−24 (c 0.3, $CHCl_3$); IR (KBr) ν_{max} 3473, 1770 cm^{-1}; HRMS (EI) m/z 250.1212 (M^+, 100, $C_{14}H_{18}O_4$ required 250.1205), 235 (86), 162 (89), 150 (58), 109 (28); ^{1}H NMR δ 7.27 (1H, s, H-2), 4.98 (1H, dq, J=1.2, 10.4 Hz, H-6), 2.36 (3H, d, J= 1.2 Hz, H-15), 2.31 (1H, dq, J=11.0, 6.8 Hz, H-11), 2.11 (1H, m, H-9), 2.00 (1H, m, H-8), 1.86 (1H, qd, J=10.4, 2.2 Hz, H-7), 1.81 (1H, td, J=12.8, 2.4, H-9′), 1.69 (1H, m, H-8′), 1.45 (3H, s, H-14), 1.25 (3H, d, J=6.8 Hz, H-13); ^{13}C NMR δ 178.0 (s, C-12), 147.6 (s, C-4), 136.4 (d, C-2), 132.2 (s, C-1), 114.1 (s, C-5), 79.5 (d, C-6), 72.3 (s, C-10), 52.4 (d, C-7), 42.5 (t, C-9), 41.2 (d, C-11), 28.6 (q, C-14), 26.4 (t, C-8), 13.4 (q, C-15), 12.5 (q, C-13).

Hemiacetal 25. By the same procedure used in the synthesis of **21**, compound **20** (14 mg, 0.06 mmol) gave 11.4 mg (81%) of compound **25**: mp 127–128°C (EtOAc); $[\alpha]_D^{25}$= −143 (c 0.9, $CHCl_3$); IR (KBr) ν_{max} 3494, 1759 cm^{-1}; HRMS (EI) m/z 253.1448 (M^++1, 2, $C_{14}H_{21}O_4$ required 253.1440), 192 (100), 119 (99), 107 (58); ^{1}H NMR δ 4.69 (1H, dd, J=8.5, 10.5 Hz, H-6), 4.49 (1H, dd, J=1.5, 12.5 Hz, H-2), 4.32 (1H, dd, J=1.5, 12.5 Hz, H-2′), 3.25 (1H, d, J=10.5 Hz, H-5), 2.62 (1H, m, H-7), 2.34 (1H, m, H-9), 2.23 (1H, dq, J=11.0, 7.0 Hz, H-11), 2.10 (1H, qd, J=12.0, 4.8 Hz, H-8), 1.82 (1H, ddd, J=1.5, 6.0, 14.0 Hz, H-9′), 1.66 (3H, s, H-15), 1.63 (3H, d, J=1.5 Hz, H-14), 1.35 (1H, m, H-8′), 1.16 (3H, d, J=7.0 Hz, H-13); ^{13}C NMR δ 179.3 (s, C-12), 132.9 (s, C-10), 124.7 (s, C-1), 106.5 (s, C-4), 77.6 (d, C-6), 68.5 (t, C-2), 51.4 (d, C-7), 42.4, 42.3 (d, C-11, C-5), 30.2, 28.4 (t, C-8, C-9), 27.4 (q, C-14), 21.1 (q, C-15), 13.4 (q, C-13).

Hydroxyfuran 9. To a solution of compound **25** (34 mg, 0.14 mmol) in 1.3 mL of THF and 0.3 mL of pyridine cooled at 0°C was added OsO_4 (68 mg, 0.27 mmol) and the reaction mixture stirred at this temperature for 3 h. After this time, a mixture containing 12 mg of $NaHSO_3$, 1.9 mL of pyridine and 1.6 mL of water was added and stirring continued for 1 h at 0°C and for two additional hours at room temperature. Then, 2 M HCl (15 mL) was added and after 5 min the mixture extracted with CH_2Cl_2 (3×20 mL). The organic layer was washed with brine (20 mL), dried, and concentrated under reduced pressure. Chromatography of the residue with 7:3 to 1:1 mixtures of hexane–EtOAc eluted 18.5 mg (55%) of compound **9** and 4.5 mg (14%) of compound **5**. Compound **9**: mp 110–112°C (hexane–EtOAc); $[\alpha]_D^{27}$=−34 (c 1.6, $CHCl_3$); HRMS (EI) m/z 250.1212 (M^+, 41, $C_{14}H_{18}O_4$ required 250.1205), 232 (100), 217 (60), 162 (51), 150(38); IR (KBr) ν_{max} 3527, 1765 cm^{-1}; ^{1}H NMR δ 7.17 (1H, s, H-2), 5.30 (1H, qd, J=1.5, 10.5 Hz, H-6), 2.38 (3H, d, J=1.5 Hz, H-15), 2.34 (1H, dq, J=10.5, 7.2 Hz, H-11), 2.05 (1H, m, H-9), 1.5–1.9 (3H, m, H-7, H-8, H-9′), 1.63 (4H, s, H-14 overlapped with H-8′), 1.26 (3H, d, J=7.2 Hz, H-13); ^{13}C NMR δ 178.6 (s, C-12), 147.0 (s, C-4), 136.3 (d, C-2), 130.0 (s, C-1), 116.8 (s, C-5), 79.5 (d, C-6), 69.2 (s, C-10), 52.7 (d, C-7), 41.4 (d, C-11), 40.0 (t, C-9), 30.1 (q, C-14), 25.4 (t, C-8), 13.3 (q, C-15), 12.5 (q, C-13).

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References

1. Lipshutz, B. H. *Chem. Rev.* **1986**, *86*, 795–819.
2. Nakanishi, K. Natural Products Chemistry, Kondasha Ltd: Tokyo, 1974.
3. Hou, X. L.; Cheung, H. Y.; Hon, T. Y.; Kwan, P. L.; Lo, T. H.; Tong, S. Y.; Wong, H. N. C. *Tetrahedron* **1998**, *54*, 1955–2020.
4. Kastner, U.; Jurenitsch, J.; Baumann, A.; Robien, W.; Kubelka, W. *Pharm. Pharmacol. Lett.* **1991**, *1*, 55–56.
5. Kastner, U.; Glasl, S.; Jurenitsch, J.; Baumann, A.; Robien, W.; Kubelka, W. *Sci. Pharm.* **1992**, *60*, 163.
6. Ochir, G.; Budesinsky, M.; Motl, O. *Phytochemistry* **1991**, *30*, 4163–4165.
7. Schroeder, H.; Kastner, U.; Gargula, K.; Budesinsky, M.; Haslinger, E.; Jurenitsch, J.; Kubelka, W. *Phytochemistry* **1994**, *36*, 1449–1451.
8. Greene, A. E. *J. Am. Chem. Soc.* **1980**, *102*, 5337–5343.
9. Grieco, P. A.; Gilman, S.; Nishizawa, M. *J. Org. Chem.* **1976**, *41*, 1485–1486.
10. Blay, G.; Cardona, L.; García, B.; Pedro, J. R. *Can. J. Chem.* **1991**, *70*, 817–822.
11. Miyashita, M.; Suzuki, T.; Yoshikoshi, A. *J. Am. Chem. Soc.* **1989**, *111*, 3728–3734.
12. Blay, G.; Cardona, L.; García, B.; Pedro, J. R. *J. Org. Chem.* **1993**, *58*, 7204–7208.
13. Patel, D. V.; VanMiddlesworth, F.; Donaubauer, J.; Gannett, P.; Sih, C. J. *J. Am. Chem. Soc.* **1986**, *106*, 4603–4614.
14. Brunnelle, W. H.; Rafferty, M. A.; Hodges, S. L. *J. Org. Chem.* **1987**, *52*, 1603–1605.
15. Aurell, M. J.; Ceita, L.; Mestres, R.; Tortajada, A. *Tetrahedron* **1997**, *53*, 10883–10898.
16. Lorenz, O.; Parks, C. R. *J. Org. Chem.* **1965**, *30*, 1976–1981.
17. Joule, J. A.; Mills, K.; Smith, G. F. *Heterocyclic Chemistry*, 3rd ed.; Chapman & Hall: London, 1995; pp 290–300.
18. Cribble, G. W.; Ferguson, D. C. *J. Chem. Soc. Chem. Commun.* **1975**, 535–536.
19. Evans, D. L.; Minster, D. K.; Jordis, U.; Hecht, S. M.; Mazzu, A. L.; Meyers, A. I. *J. Org. Chem.* **1979**, *44*, 497–501.
20. Wynberg, H. *J. Am. Chem. Soc.* **1958**, *80*, 364–366.
21. Haefliger, W.; Kloppner, E. *Helv. Chim. Acta* **1982**, *65*, 1837–1852.
22. Griffith, W. P.; Ley, S. V.; Whitcombe, G. P.; White, A. D. *J. Chem. Soc. Chem. Commun.* **1987**, 1625–1627.
23. Ando, M.; Isogai, K.; Azami, H.; Hirato, N.; Yanagi, Y. *J. Nat. Prod.* **1991**, *54*, 1017–1024.
24. Abraham, R. J.; Fisher, J.; Loftus, P. *Introduction to NMR Spectroscopy*, Wiley: Chichester, 1988; pp 22–23.
25. Perrin, D. D.; Armarego, W. L. F. *Purification of Laboratory Chemicals*, 3rd ed.; Pergamon: Oxford, 1988.
26. Barton, D. H. R.; De Mayo, P.; Shafiq, M. *J. Chem. Soc.* **1957**, 929–935.