Synthesis of Laurencione, a Labile Dihydro-3(2*H*)-furanone Derivative from the Red Alga *Laurencia spectabilis*

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The first total synthesis of laurencione, a naturally occurring dihydro-3(2*H*)-furanone derivative isolated from the red alga *Laurencia spectabilis*, is described. The synthesis is comprised (1) of conversion of γ-butyrolactone into α,α-dimethoxy-γ-butyrolactone, (2) addition of methyllithium across the lactone carbonyl, and (3) acid hydrolysis of the acetal moiety. An alternative synthesis consists of the acid-catalyzed conversion of 3,3-dimethoxy-2-hydroxy-2-methyltetrahydrofuran into laurencione methyl ether and subsequent acid-catalyzed hydrolysis. In addition, a convenient synthesis of the coffee and caramel flavor component 2-methyl-3(2*H*)-furanone has been developed by acid-catalyzed rearrangement of 2-methoxy-2-methyltetrahydrofuran-3-one.

Introduction

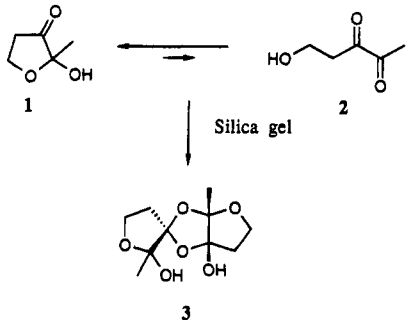
Laurencione is a major metabolite of the extract of the red alga *Laurencia spectabilis*, and to it has been attributed the structure of two interconverting forms, namely (±)-2-hydroxy-2-methyldihydrofuran-3(2*H*)-one (**1**) and 5-hydroxy-2,3-pentanedione (**2**) (ratio, 83:17 in $CDCl_3$; ^1H NMR) (Scheme 1).[1] Laurencione is a labile natural product, which dimerizes on silica gel to produce the spiroacetal **3**. It has been proposed that the latter racemic spiroacetal **3**, which has been isolated from *Laurencia pinnatifida*,[2] is an artifact of the extraction or chromatography and probably results from laurencione.[1] 5-Hydroxy-2,3-pentanedione (**2**) was recently found as a Strecker-type degradation product of xylose in the presence of α-amino acids.[3] However, this labile ω-hydroxy-α-dione was only characterized as the corresponding quinoxaline derivative, i.e. 2-(2-hydroxyethyl)-3-methylquinoxaline.[3]

In the present report, a straightforward synthesis of the labile laurencione is described.

Results and Discussion

The synthetic strategy for the synthesis of laurencione (**1** and **2**) was based on the α-functionalization of γ-butyrolactone and subsequent derivatization of the lactone carbonyl. Bromination of γ-butyrolactone (**4**) with bromine in the presence of red phosphorus afforded α-bromo-γ-butyrolactone (**5**),[4] which was reacted with sodium ethanethiolate in methanol to afford 3-(ethylthio)dihydrofuran-2-one (**6**) (Scheme 2). The latter compound has been described previously as a side product (22%) from the reaction of the dianion derived from α-mercapto-γ-butyrolactone and iodoethane, the major reaction product being α-ethyl-α-(ethylthio)-γ-butyrolactone.[5] The α-chlorination of lactone **6** was performed according to a well-established method for the chlorination of α-(thioalkyl)-carbonyl compounds.[6] Reaction of α-(ethylthio)-γ-butyrolactone (**6**) with a slight excess of *N*-chlorosuccinimide in carbon tetrachloride at 0 °C afforded α-chloro-α-(ethylthio)-γ-butyrolactone (**7**) in nearly quantitative yield. However, this compound appeared to be thermolabile as it was dehydrochlorinated upon simple evaporation under vacuum, applying mild heating, to give rise to the α,β-unsaturated lactone **9**. Attempts to utilize the latter compound in the synthesis of laurencione (**1** and **2**) failed. The reaction of α-(ethylthio)-α,β-unsaturated lactone **9** with dry hydrogen chloride in carbon tetrachloride did not give back the α-chloro-α-(ethylthio)-γ-butyrolactone (**7**), while the reaction of **9** with mercuric acetate in methanol did not convert it into α,α-dimethoxy-γ-butyrolactone (**8**). In order to avoid the undesirable dehydrochlorination of **7** into **9**, the freshly prepared solution of α-chloro-α-(ethylthio)-γ-butyrolactone (**7**) was dropped into a stirred suspension of mercuric acetate in absolute methanol, affording α,α-dimethoxy-γ-butyrolactone (**8**) in 69% yield after distillation in vacuo (Scheme 2). Previously, α,α-dimethoxy-γ-butyrolactones have been synthesized from α-(alkylthio)-γ-butyrolactones with thallium(III) nitrate in methanol.[7] This novel α,α-dimethoxy-γ-butyrolactone (**8**) was reacted with 1 molar equiv of methyllithium in diethyl ether at 0 °C for 30 min under a nitrogen atmosphere to afford

Scheme 1



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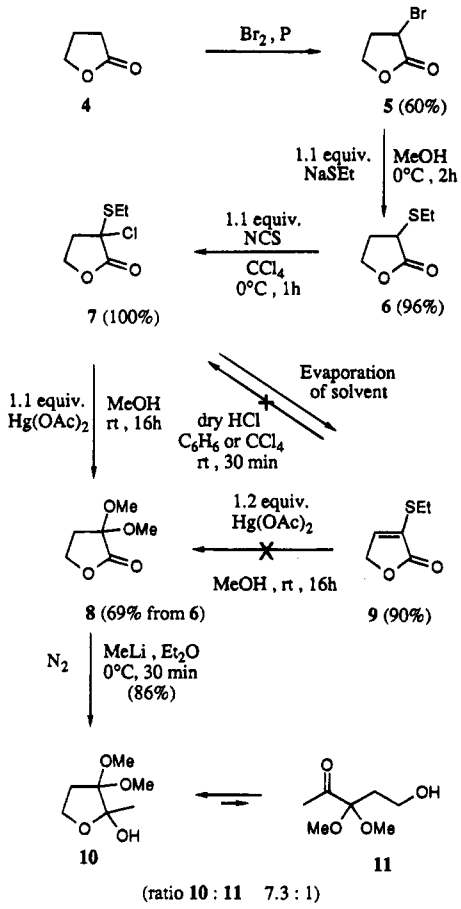
Scheme 2



86% of an equilibrium mixture of 2-hydroxy-3,3-dimethoxy-2-methyltetrahydrofuran (**10**) and 5-hydroxy-3,3-dimethoxy-2-pentanone (**11**). In $CDCl_3$ solution was observed an 88:12 equilibrium mixture (^1H NMR) of compounds **10** and **11**. Stirring of the equilibrium mixture in $CDCl_3$ with trace amounts of potassium carbonate resulted in deuteration of the methyl group. This process leading to 2-(trideuteriomethyl)tetrahydrofuran **10-d_4** went fast to completion after a period of 10 min (Scheme 3), after which no ring-opened isomer could be detected by ^1H NMR spectroscopy. The reaction of **10** and **11** with trimethylsilyl iodide (2.5 equiv) in chloroform (rt, 2 h) or trifluoroacetic acid (2.3 equiv) in chloroform (0 °C, 5–20 h) afforded only very complex reaction mixtures. Reaction of the equilibrium mixture of compounds **10** and **11** with *p*-toluenesulfonic acid in 50% aqueous acetone at room temperature for 3 h afforded laurencione (**1** and **2**) in 42% yield (Scheme 3). When the equilibrium mixture of **10** and **11** was reacted with p-toluenesulfonic acid in dry acetone at room temperature for 5 h, 2-methoxy-2-methyldihydro-3(2*H*)-furanone (**12**) was formed in 58% yield. The 2-methoxy substituent resulted from the hydrolysis of the dimethyl acetal function in **10** and **11**. The same reaction was observed on treatment of **10** and **11** with trifluoroacetic acid in chloroform at room temperature for 1 h. Efforts were undertaken to convert 2-methoxy-2-methyldihydro-3(2*H*)-furanone (**12**) into laurencione (**1** and **2**). The reaction of compound **12** with boron tribromide in dichloromethane at −78 °C for 30 min delivered only tars.[8] The reaction of compound **12** with 1 equiv of *p*-toluenesulfonic acid in benzene under reflux for 1 h or the reaction with 2 N aqueous hydrogen chloride under reflux for 1 h gave rise to the formation of 2-methyl-3(2*H*)-furanone (**13**) in 22–60% yield. Compound **13** has been identified previously in the volatile flavor fraction of coffee and caramel,[9,10] while it has been found in models of Maillard reactions[11] and as a thermal degradation product of thiamin.[12] The formation of this rearranged unsaturated 3(2*H*)-furanone derivative **13** can be explained by acid-catalyzed expulsion of the 2-methoxy substituent to form the oxonium ion **16** which is more stable in its enol form **17**. Deprotonation of oxonium ion **17** produces furan derivative **18** which tautomerizes to **13** (Scheme 4). However, the reaction of 2-methoxy-2-methyldihydro-3(2*H*)-furanone (**12**) with *p*-toluenesulfonic acid in 50% aqueous acetone at room temperature for 3 h afforded laurencione (**1** and **2**) in 42% yield, completing a second synthetic approach to this marine natural product. The same reaction for a period of 16 h at room temperature gave a complex reaction mixture. The identification of laurencione, which is always complicated by the presence of both isomers **1** and **2**, was performed by comparison with spectroscopic data from the literature[1] and by conversion into the known diacetate **14** (Scheme 3).[1]

Experimental Section

^1H NMR spectra were recorded at 60 and 270 MHz, while ^{13}C NMR spectra were obtained at 67.8 MHz. Mass spectra were obtained at 70 eV using the GC–MS technique or the direct inlet system.

α-Bromo-γ-butyrolactone (**5**) was prepared by reaction of γ-butyrolactone (**4**) with bromine in the presence of red phosphorus.[4]

Synthesis of α-(Ethylthio)-γ-butyrolactone (6). A solution of 2 N sodium ethylthiolate in methanol was prepared by addition of 7.44 g (0.12 mol) of ethanethiol to a solution of 55 mL of 2 N sodium methoxide (0.11 mol) in methanol at 0 °C. After the solution was stirred for 2 min at this temperature, 16.5 g (0.10 mol) of α-bromo-γ-butyrolactone (**5**) was added dropwise while the mixture was stirred. Stirring was continued for 30 min at 0 °C and then for 2 h at room temperature. The reaction mixture was poured in 300 mL of water, and extraction was performed three times with dichloromethane. The combined extracts were dried ($MgSO_4$) and evaporated in vacuo to give an oil which consisted of almost pure α-(ethylthio)-γ-butyrolactone (**6**) (purity > 97%, ^1H NMR, GC), which could be used as such in the next experiment, i.e. the conversion into α,α-dimethoxy-γ-butyrolactone (**8**) (vide infra). Vacuum distillation of the crude α-sulfenylated γ-butyrolactone **6** provided 14.0 g (96%) of the pure compound **6**: bp 65–75 °C/0.1 mmHg; ^1H NMR ($CDCl_3$, 270 MHz) δ 1.30 (3H, t, J = 7.4 Hz), 2.07–2.2 (1H, m), 2.60–2.90 (3H, m), 3.58 (1H, dxd, J = 4.95 Hz, J = 8.57 Hz), 4.28–4.46 (2H, m); ^{13}C NMR ($CDCl_3$) δ 14.20, 25.30, 29.99, 39.07, 66.88, 175.61 (*C*=O). For the IR and mass spectrum, see ref 5.

Synthesis of α,α-Dimethoxy-γ-butyrolactone (8). A stirred solution of 1.46 g (0.01 mol) of α-(ethylthio)-γ-butyrolactone (**6**) in 150 mL of carbon tetrachloride was treated with 1.47 g (0.011 mol) of *N*-chlorosuccinimide at 0 °C. After stirring for 1 h at this temperature, the reaction mixture was filtered, and the solvent was evaporated in vacuo with mild heating to afford 1.30 g (90%) of almost pure α-ethylthio-α,β-unsaturated γ-butyrolactone **9** (purity > 96%).

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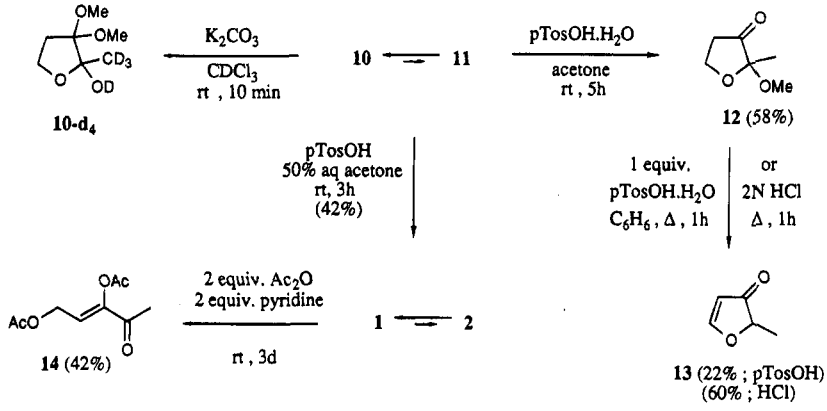
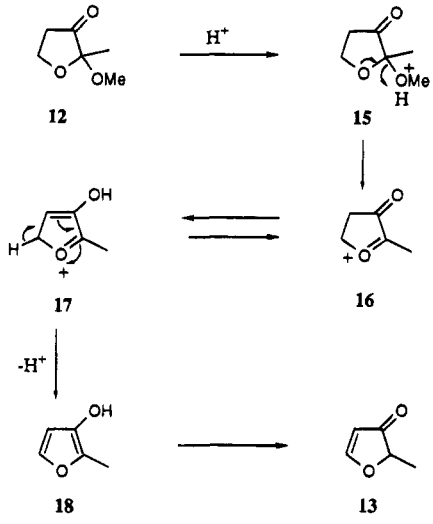
Scheme 3



Scheme 4



α-Ethylthio-α,β-unsaturated γ-butyrolactone 9: ^{1}H NMR ($CDCl_3$, 60 MHz) δ 1.05 (3H, t, J = 7.3 Hz), 2.99 (2H, q, J = 7.3 Hz), 4.98 (2H, d, J = 2 Hz), 7.20 (1H, t, J = 3 Hz).

When the reaction mixture was monitored by ^{1}H NMR before evaporation of the solvent, the intermediate and labile α-chloro-α-(ethylthio)-γ-butyrolactone (**7**) was identified as the sole reaction product.

α-Chloro-α-(ethylthio)-γ-butyrolactone (7): ^{1}H NMR (CCl_4, 60 MHz) δ 1.33 (3H, t, J = 7.3 Hz), 2.6–3.3 (4H, m), 4.3–4.6 (2H, m).

In order to avoid the undesirable 1,2-dehydrochlorination of compound **7**, the following straightforward one-pot procedure to α,α-dimethoxy-γ-butyrolactone (**8**) was followed.

To an ice-cold solution of 14.2 g (0.097 mol) of 3-(ethylthio)-γ-butyrolactone in 80 mL of dry carbon tetrachloride was added 14.24 g (0.1067 mol) of *N*-chlorosuccinimide, and the mixture was stirred at 0 °C for 1 h. The reaction mixture was then filtered and washed with dry carbon tetrachloride, and the combined filtrates were added to a suspension of 33.8 g (0.1067 mol) of mercuric acetate in 260 mL of absolute methanol. The mixture was stirred at room temperature for 16 h and then filtered. The solvents were evaporated in vacuo, and the residual oil was treated with 10% aqueous $NaHCO_3$. This mixture was filtered, and the precipitate was washed with dichloromethane and aqueous $NaHCO_3$. The combined filtrates were extracted thoroughly with dichloromethane and diethyl ether. The combined extracts were then dried ($MgSO_4$), and after evaporation of the solvents in vacuo, 14.2 g of crude product was distilled in vacuo to give 9.83 g (69%) of α,α-dimethoxy-γ-butyrolactone, bp 70–80 °C/0.3 mmHg.

α,α-Dimethoxy-γ-butyrolactone (8): ^{1}H NMR ($CDCl_3$, 270 MHz) δ 2.44 (2H, t, J = 6.6 Hz), 4.39 (2H, t, J = 6.6 Hz), 3.45 (6H, s); ^{13}C NMR ($CDCl_3$) δ 33.46, 50.98, 64.99, 98.70, 170.04; IR (NaCl) 2840 (OMe), 1782 cm^{-1} (C=O); mass spectrum *m/z* (relative intensity, no M$^+$) 115 (22, M$^+$ − OMe), 102 (45), 88 (50), 86 (7), 84 (10), 72 (18), 59 (88), 58 (33), 57 (66), 49 (15), 44 (40), 43 (100). Anal. Calcd: C, 49.31; H, 6.90, 49.31% C, 6.90% H; Found: C, 49.21; H, 6.98%.

Reaction of α,α-Dimethoxy-γ-butyrolactone (8) with Methyllithium. A solution of 0.88 g (0.006 mol) of α,α-dimethoxy-γ-butyrolactone (**8**) in 8 mL of dry diethyl ether was treated dropwise by syringe with 3.76 mL of 1.6 M methyllithium (0.006 mol) in diethyl ether at 0 °C under a nitrogen atmosphere. The mixture was stirred at this temperature for 30 min, then poured in water, and extracted three times with diethyl ether. The combined extracts were dried ($MgSO_4$), and the solvent was evaporated in vacuo. The residual oil (0.84 g, 86%) consisted of almost pure 2-hydroxy-3,3-dimethoxy-2-methyltetrahydrofuran (**10**), which occurred as a 7.3:1 equilibrium mixture with 5-hydroxy-3,3-dimethoxy-2-pentanone (**11**) (^{1}H NMR, $CDCl_3$). This labile equilibrium mixture of compounds **10** and **11** was used as such in the final step leading to laurencione (vide infra). Purification could be performed by flash chromatography (silica gel; ethyl acetate: hexane, 3:7), affording 0.70 g (72%) of a mixture of **10** and **11** (ratio, 7.3:1).

2-Hydroxy-3,3-dimethoxy-2-methyltetrahydrofuran (10): ^{1}H NMR ($CDCl_3$, 270 MHz) δ 1.46 (3H, s), 2.17 (2H, t, J = 6.3 Hz), 3.31 and 3.37 (each 3H, each s), 4.10 (1H, broad s), 3.81 and 3.88 (each 1H, each m); ^{13}C NMR ($CDCl_3$) δ 22.73, 30.91, 49.79, 49.94, 62.42, 103.41, 106.48; IR (NaCl; from equilibrium mixture) 3400 (OH, broad), 2835 cm^{-1} (OMe); mass spectrum *m/z* (relative intensity, no M$^+$) 119 (17), 114 (7), 113 (15), 112 (42), 111 (15), 102 (12), 101 (12), 99 (10), 97 (10), 83 (7), 75 (5), 73 (5), 72 (5), 71 (5), 70 (5), 69 (5), 59 (15), 57 (30), 55 (15), 53 (12), 43 (100).

5-Hydroxy-3,3-dimethoxy-2-pentanone (11): ^{1}H NMR ($CDCl_3$, 270 MHz) δ 2.25 (3H, s), 2.07 (2H, t, J = 6.0 Hz), 3.62 (2H, t, J = 6.0 Hz), 3.26 (6H, s), the OH signal probably resonates at the same position as the hydroxyl resonance of the isomer **10**; ^{13}C NMR ($CDCl_3$) δ 26.79, 35.40, 49.47, 57.20, 207.29; IR (NaCl) 1738 cm^{-1} (C=O).

Deuteration of 2-Hydroxy-3,3-dimethoxy-2-methyltetrahydrofuran (10). A solution of 0.32 g (0.002 mol) of the equilibrium mixture of compounds **10** and **11** in 0.6 mL of $CDCl_3$ was treated with 0.028 g (0.0002 mol) of potassium carbonate and stirred at room temperature for 10 minutes. The decanted solution was investigated by ^{1}H NMR spectroscopy, revealing that a complete deuteration of the 2-methyl group and the hydroxyl group had occurred.

2-Deuteroxy-2-D$_3$-methyl-3,3-dimethoxytetrahydrofuran (10-d$_4$): ^{1}H NMR ($CDCl_3$, 270 MHz) δ 2.16 (2H, t, J = 6.9 Hz), 3.33 (6H, s), 3.81 (2H, t, J = 6.9 Hz); ^{13}C NMR ($CDCl_3$) δ 22.87, 31.59, 49.68, 61.53, 106.23, the signal of the other acetal carbon (C-2 or C-3) was not visible (probably overlap); IR (NaCl) no specific absorption bands, only a very weak absorption of 1730 cm^{-1} is visible, although ^{13}C NMR spectroscopy did not detect the carbonyl resonance; mass spectrum *m/z* (relative intensity, no M$^+$) 148 (4), 147 (6), 146 (5), 145 (4), 120 (8), 119 (8), 118 (8), 117 (8), 116 (5), 115 (5), 114 (11), 113 (23), 112 (30), 111 (19), 110 (8), 103 (5), 102 (30), 101 (10), 100 (6), 99 (9), 98 (8), 97 (8), 89 (15), 87 (7), 86 (8), 85 (15), 73

(18), 70 (8), 59 (27), 58 (8), 59 (19), 55 (18), 54 (12), 46 (12), 45 (40), 44 (100), 43 (38).

Synthesis of Laurencione (1 and 2) from Acetals 10 and 11. To a stirred solution of 0.48 g (0.003 mol) of a 7.3:1 equilibrium mixture of compounds **10** and **11** in 15 mL of 50% aqueous acetone was added 0.57 g (0.003 mol) of *p*-toluenesulfonic acid monohydrate, and the solution was stirred for 3 h at room temperature. The reaction mixture was extracted with diethyl ether, dried ($MgSO_4$, −20 °C), and evaporated in vacuo without heating to leave an oil consisting mostly (>90%) of laurencione **1** and **2**. Flash chromatographic separation (silica gel; EtOAc:hexane, 1:1) afforded 0.21 g (60%) of laurencione as an equilibrium mixture of **1** and **2** (ratio, 87:13 in $CDCl_3$) (reported ratio, 83:17).[1] Laurencione **1** and **2** exhibited in all aspects the same spectral data (^1H NMR, ^{13}C NMR, IR, and MS) as the reported natural product.[1]

Synthesis of Laurencione Methyl Ether (12). (a) A solution of 0.26 g (0.0016 mol) of the equilibrium mixture of compounds **10** and **11** in 5 mL of dry acetone was treated with 0.30 g (0.0016 mol) of *p*-toluenesulfonic acid monohydrate, and the solution was stirred for 5 h at room temperature. The reaction mixture was poured into water and extracted with diethyl ether. The combined extracts were dried ($MgSO_4$) and evaporated to leave 0.12 g (58%) of crude laurencione methyl ether (**12**) (purity > 95%, GC). An analytical sample was obtained by preparative gas chromatography: ^1H NMR ($CDCl_3$, 270 MHz) δ 1.37 (3H, s), 2.40−2.66 (2H, m), 3.29 (3H, s), 4.10−4.25 (2H, m); ^{13}C NMR ($CDCl_3$) δ 16.08, 33.58, 48.91, 61.85, 99.17, 208.57; IR (NaCl) 1762 cm^{-1} (C=O); Mass spectrum *m/z* (relative intensity, no M^+) 102 (21), 99 (17), 98 (8), 84 (10), 49 (10), 43 (100). (b) A solution of 0.63 g (0.0038 mol) of the equilibrium mixture of compounds **10** and **11** in 10 mL of chloroform was treated with 1.01 g (0.009 mol) of trifluoroacetic acid. The solution was stirred for 1 h at room temperature. ^1H NMR analysis showed laurencione methyl ether (**12**) to be present as the sole reaction product next to methanol, trifluoroacetic acid, and methyl trifluoroacetate.

Synthesis of Laurencione 1 and 2 from Laurencione Methyl Ether (12). To a stirred solution of 0.43 g (0.0033 mol) of laurencione methyl ether (**12**) in 7 mL of acetone and 7 mL of water was added 0.627 g (0.0033 mol) of *p*-toluenesulfonic acid monohydrate. The solution was stirred at room temperature for 3 h, after which time 30 mL of diethyl ether was added. The organic phase was isolated, and a second extraction with diethyl ether was performed. The organic phases were dried ($MgSO_4$), and the solvent was evaporated in vacuo to afford 0.16 g (42%) of laurencione as a 5:1 equilibrium mixture ($CDCl_3$, ^1H NMR) of compounds **1** and **2**, respectively. All spectroscopic data (^1H NMR, ^{13}C NMR, IR, and MS) of **1** and **2** were identical with the data of the reported natural product.[1]

Conversion of Laurencione Methyl Ether (12) into 2-Methyl-3(2*H*)-furanone (13). To a solution of 1.30 g (0.01 mol) of laurencione methyl ether (**12**) in 15 mL of benzene were added 0.9 mL of water and 1.90 g (0.01 mol) of *p*-toluenesulfonic acid monohydrate. The mixture was refluxed for 1 h. It was then cooled, diluted with water, and extracted with dichloromethane. After drying ($MgSO_4$), the solvents were removed in vacuo, affording 0.59 g (60%) of crude compound **13**. An analytically pure sample of compound **13** was obtained by preparative gas chromatography. The spectroscopic data (^1H NMR, IR, and MS) matched completely the data of the known compound **13**.[12,13]

Synthesis of 3,5-Diacetoxy-3-penten-2-one (14). To 0.116 g (0.001 mol) of an equilibrium mixture of laurencione **1** and **2** were added 0.204 g (0.002 mol) of acetic anhydride and 0.158 g (0.002 mol) of pyridine. The mixture was left at room temperature for 3 days, after which time it was treated with water. Extraction was performed with dichloromethane, which was washed with 0.2 N hydrogen chloride. The extract was dried ($MgSO_4$) and evaporated to afford 0.084 g (42%) of 3,5-diacetoxy-3-penten-2-one (**14**) (purity > 95%, ^1H NMR), which exhibited the same spectroscopic data (^1H NMR, ^{13}C NMR, IR, and MS) as the known compound.[1]

Acknowledgment. We are indebted to the Belgian National Fund for Scientific Research for financial support.

Supporting Information Available: Full NMR data (^1H and ^{13}C NMR) for compounds **8**, **10**, **11**, **10-d$_4$**, and **12** based on 2-D COSY, HETCOR, and DEPT experiments (1 page). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordening information.

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