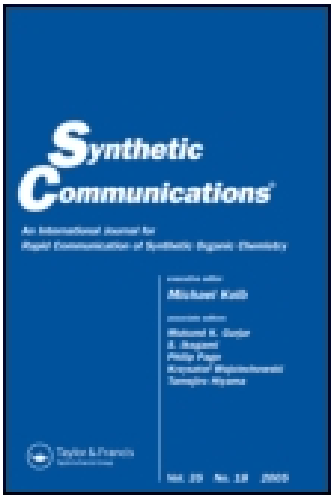

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Efficient Approach to 4-Benzyl-5,5-dimethyldihydrofuranones: Total Synthesis of (±)-Solafuranone

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Abstract: A six-step general and very efficient synthesis of 4-(arylmethyl)-5,5-dialkyl-dihydrofuranones starting from corresponding aryl aldehyde has been developed. Solafuranone, a novel furanone isolated from the Chinese folk medicine *Solanum indicum*, has been accomplished starting from 2,6-dimethylbenzaldehyde in six steps in an overall yield of 70%. Contrary to expectations, solafuranone and its analogue failed to exhibit any significant cytotoxicity against A549 (lung adenocarcinoma) and HL60 (leukemia cells) cell lines.

Keywords: cytotoxicity, dihydrofuranone, lycifuranones A and B, solafuranone, *Solanum indicum*

The Chinese folk medicine *Solanum indicum*, a plant grown widely in Taiwan, has the property of *jie du* (eliminating toxins) and is used as treatment for swelling. It has been widely used in folk medicine as an analgesic for toothache, rhinitis, and breast cancer.[1] In a search for antitumor constituents from *S. indicum*, Syu and coworkers have investigated the ethanolic extract of dried plants and fractionated based on the bioassay. The fraction that showed cytotoxicity against OVCAR-3 cells was further chromatographed and isolated two compounds, previously known spirosesquiterpene solavetivone **1** and a new novel dihydrofuranone, solafuranone **2a**, whose structure was

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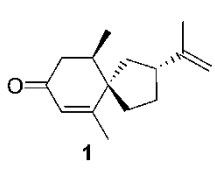
established from its spectral data and single crystal X-ray diffraction analysis.[1] It was also postulated that solavetivone **1** might be biogenetically converted into solafuranone **2a**. Subsequently, isolation and structure elucidation of two more members of the solafuranone family, lycifuranone A **2b** and lycifuranone B **2c**, along with an acetal derivative of lycifuranone B, were reported from the roots of *Lycianthes marlipoensis*.[2] However, their biological efficacy has not been evaluated.



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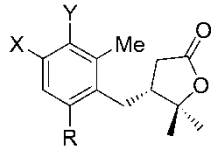
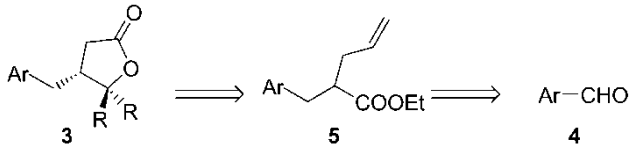


2a X=Y=H, R=Me
2b X=H, Y=OH, R=Me
2c X=Y=OH, R=CHO

As a part of our interest in the synthesis of bioactive natural products, recently, we reported an enantiospecific synthesis of solavetivone **1** from carvone.[3] Regarding the synthetic efforts toward solafuranones, there is only one report. Recently, Mahajan and coworkers reported the first synthesis of (±)-solafuranone **2a**.[4] In continuation of our interest in the synthesis of natural products and their analogues for investigating their theraupeutic potential, a short and efficient methodology was investigated for the synthesis of solafuranone and their analogues. Herein we describe results of our investigations.

We contemplated developing a general and efficient methodology for the synthesis of dihydrofuranones **3**, which could be applied to a variety of analogues of solafuranone, and aryl aldehyde **4** was considered as a possible starting material (Scheme 1). We thought that an aryl aldehyde **4** could be converted into 2-(arylmethyl)pent-4-enoate **5** in three steps, which could be transformed into target molecules **3** by a Grignard reaction followed by oxidative cleavage of the terminal olefin.

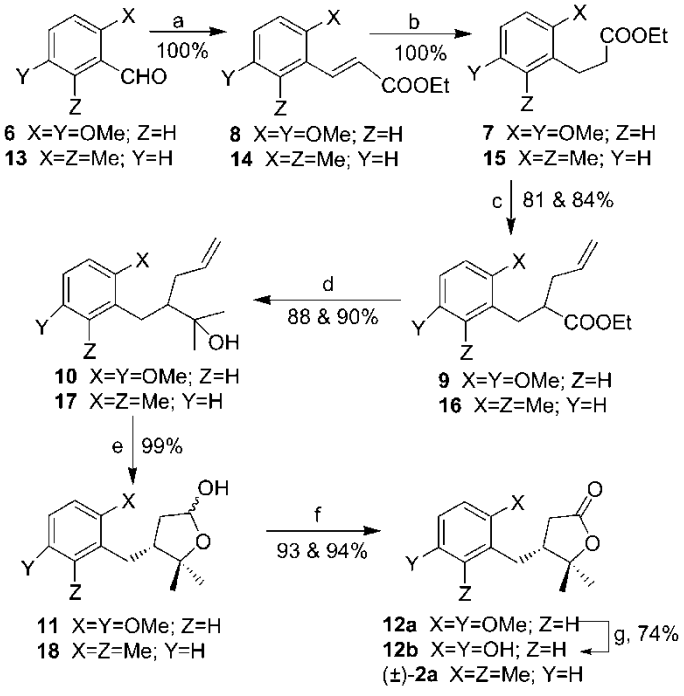
To test the feasibility of the strategy, 2,5-dimethoxybenzaldehyde **6** was chosen as a model substrate, because the hydroxy and alkoxy groups on aromatic ring are known to enhance the biological potential of a variety of aryl substituted butyrolactones (e.g., lignans).[5] The sequence is



3 **5** **4**

Scheme 1.

depicted in Scheme 2. First the aldehyde **6** was converted into 3-arylpropionate **7**. Thus, the Horner–Wadsworth–Emmons reaction of the aldehyde **6** with triethyl phosphonoacetate and sodium hydride in THF at room temperature quantitatively furnished the cinnamate **8**, which on hydrogenation with 10% palladium on carbon as the catalyst in methanol at one atmosphere pressure of hydrogen furnished the propionate **7** in quantitative yield. Generation of the lithium enolate with lithium diisopropylamide (LDA) at $-70^{\circ}C$ followed by reacting with allyl bromide transformed the propionate **7** into the pentenoate **9** in 81% yield. Reaction of the pentenoate **9** with an excess of methylmagnesium iodide in ether at room temperature furnished the tertiary alcohol **10** in 88% yield. Ozonolytic cleavage of the terminal olefin in hexenol **10** in methanol–methylene chloride at $-70^{\circ}C$ followed by reductive workup with dimethyl sulfide generated the hemi acetal **11** in quantitative yield, which on oxidation with a mixture of pyridinium chlorochromate (PCC) and silica gel in methylene chloride at room temperature



Scheme 2. Reagents and conditions: (a) NaH, $(EtO)_2P(O)CH_2COOEt$, THF, rt, 6 h; (b) 10% Pd/C, EtOH, 1 atm. H_2, 4 h; (c) LDA, THF, $-70^{\circ}C \rightarrow$ rt, $CH_2{=}CHCH_2Br$, 10 and 11 h; (d) MeMgI, Et_2O, $0^{\circ}C \rightarrow$ rt, 4 and 5 h; (e) O_3/O_2, CH_2Cl_2-MeOH (5:1), $-70^{\circ}C$, Me_2S, rt, 10 and 4 h; (f) PCC, silica gel, CH_2Cl_2, rt, 2 h; (g) BBr_3, CH_2Cl_2, $0^{\circ}C$, 4 h.

furnished the dihydrofuranone **12a** in 93% yield. The structure of the dihydrofuranone **12a** was established from its spectral data. Presence of a carbonyl absorption band at 1774 cm^{-1} in the IR spectrum due to a typical γ-butyrolactone revealed the formation of the product **12a**. In the ^1H NMR spectrum presence of three signals, a doublet of doublet (δ 6.68) and two doublets (6.74 and 6.63), due to the 1,2,5-trisubstituted aromatic group, two singlets at 3.78 and 3.75 due to two methoxy groups, and two singlets at 1.42 and 1.37 ppm due to two tertiary methyl groups established the structure of the product. It was further confirmed by the presence of a lactone carbon signal at δ 175.1 ppm in the fifteen-line ^{13}C NMR spectrum of the lactone **12a**. Boron tribromide–mediated demethoxylation of the lactone **12a** in methylene chloride for 4 h furnished the diol **12b**.

After successfully demonstrating the strategy for the efficient conversion of the aryl aldehyde **6** in to the dihydrofuranone **12** (in six steps for an overall yield of 65%), it has been extended for the total synthesis of the novel furanone, solafuranone **2a**, starting from 2,6-dimethylbenzaldehyde **13**. Thus, Horner–Wadsworth–Emmons reaction of the aldehyde **13** with triethyl phosphonoacetate and sodium hydride followed by catalytic hydrogenation of the cinnamate **14** furnished the 3-arylpropionate **15** in quantitative yield. Allylation of the ester **15** with LDA and allyl bromide in THF generated the pentenoate **16** in 84% yield, which on Grignard reaction with an excess of methylmagnesium iodide furnished the tertiary alcohol **17** in 90% yield. Ozonolytic cleavage of the terminal olefin in the hexenol **17** in methanol–methylene chloride followed by reductive workup with dimethyl sulfide generated the hemiacetal **18**, which on oxidation with a mixture of PCC and silica gel furnished solafuranone **2a** in 94% yield. Synthetic solafuranone **2a** exhibited ^1H and ^{13}C NMR spectral data in acetone-d_6 identical to that reported for the natural product.

Because solafuranone **2a** was obtained from the fraction that exhibited activity against the human ovarian cancer cell line OVCAR-3, after successfully developing an efficient approach to solafuranone **2a** and its analogues **12a** and **12b** containing two oxygen substituents on the aromatic ring, preliminary investigations were carried out to test their biological activity. The dihydrofuranones **2a**, **12a**, and **12b** were tested for cytotoxicity on A549 (lung adenocarcinoma) and HL60 (leukemia cells) using [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide] (MTT) assay. After incubation of the cells in up to 40-μM concentration for 72 h, there was no change in the cell viability or growth kinetics observed in comparison with DMSO (vehicle)–treated cells. However, it is not clear whether the compounds **2a**, **12a**, and **12b** are inactive because of their racemic nature. Further investigations are in progress.

In conclusion, we have developed a six-step efficient methodology for the synthesis of 4-(arylmethyl)-5,5-dialkyldihydrofuranones. Employing the strategy, solafuranone **2a**, a natural dihydrofuranone, was obtained starting from 2,6-dimethylbenzaldehyde **13**, in six steps in an overall yield of more than 70%. Because the methodology is quite general, it is ideally suited for

generation of a library of dihydrofuranones (having diversification at two places, aryl group and Grignard reagent) to evaluate their biological potential and is being investigated currently.

EXPERIMENTAL

Melting points were recorded using a Mettler FP1 melting-point apparatus in capillary tubes and are uncorrected. IR spectra were recorded on Jasco FTIR 410 spectrophotometer. ^{1}H (300-MHz) and ^{13}C (75-MHz) NMR spectra were recorded on JNM λ-300 spectrometer. Unless otherwise specified, a 1:1 mixture of $CDCl_3$ and CCl_4 was used as solvent for preparing the NMR samples. The chemical shifts (δ ppm) and coupling constants (Hz) are reported in the standard fashion with reference to either internal tetramethylsilane (for ^{1}H) or the central line (77.0 ppm) of $CDCl_3$ (for ^{13}C). In the ^{13}C NMR spectra, the nature of the carbons (C, CH, CH_2, or CH_3) was determined by recording the DEPT-135 spectra and is given in parentheses. High-resolution mass spectra (HRMS) were recorded using a Micromass Q-TOF micromass spectrometer using electrospray ionization.

Ethyl *E*-3-(2,5-Dimethoxyphenyl)prop-2-enoate (8)

A suspension of sodium hydride (241 mg, 60% dispersion in oil, 6.0 mmol) in hexanes under nitrogen atmosphere was magnetically stirred for 10 min, and the solvent was syringed out. The oil-free NaH was then suspended in dry THF (3 ml) and cooled in an ice bath. Triethyl phosphonoacetate (1.19 ml, 6.0 mmol) was added dropwise, and the reaction mixture was stirred for 30 min at room temperature. To the reaction mixture, a solution of the aldehyde **6** (500 mg, 3.01 mmol) in dry THF (2 ml) was added dropwise and stirred for 6 h at rt. The reaction was then quenched by careful addition of saturated aqueous NH_4Cl solution and extracted with ether (4 × 4 ml). The combined ether extract was washed with brine and dried (Na_2SO_4). Evaporation of the solvent and purification of the residue over a silica-gel column using ethyl acetate–hexane (1:20) as eluent furnished the cinnamate **8** (710 mg, 100%) as oil. IR (neat): ν_{max}/cm^{-1} 1714, 1633, 1496. ^{1}H NMR (300 MHz, $CDCl_3 + CCl_4$): δ 7.91 (1H, d, *J* 16.2 Hz, H-3), 7.00 (1H, d, 2.4 Hz, H-6′), 6.84 (1H, dd, *J* 8.7 and 2.4 Hz, H-4′), 6.79 (1H, d, *J* 8.7 Hz, H-3′), 6.44 (1H, d, *J* 16.2 Hz, H-2), 4.24 (2H, q, *J* 7.2 Hz, OCH_2CH_3), 3.82 (3H, s) and 3.75 (3H, s) [2 × OCH_3], 1.33 (3H, t, *J* 7.2 Hz, OCH_2CH_3). ^{13}C NMR (75 MHz, $CDCl_3 + CCl_4$): δ 166.8 (C, OC=O), 153.5 (C), 152.6 (C), 139.6 (CH, C-3), 124.0 (C, C-1′), 118.9 (CH, C-2), 116.8 (CH), 113.1 (CH), 112.2 (CH), 60.0 (CH_2, OCH_2CH_3), 55.8 (CH_3) and 55.4 (CH_3) [2 × OCH_3], 14.4 (CH_3, OCH_2CH_3). HRMS: m/z calcd. for $C_{13}H_{16}O_4Na$ (M + Na): 259.0946. Found: 259.0945.

Ethyl 3-(2,5-Dimethoxyphenyl)propinoate (7)

To 10% Pd-C (50 mg), a solution of the cinnamate **8** (700 mg, 2.966 mmol) in methanol (5 ml) was added. The reaction mixture was stirred for 4 h at rt in an atmosphere of hydrogen, created by evacuative replacement of air (balloon), and then the catalyst was filtered off. Evaporation of the solvent furnished the saturated ester **7** (705 mg, 100%) as oil. IR (neat): ν_{max}/cm^{-1} 1734, 1502, 1224. ^{1}H NMR (300 MHz, $CDCl_3 + CCl_4$): δ 6.70 (1H, d, J 9.0 Hz, H-3′), 6.69 (1H, brs, H-6′), 6.64 (1H, dd, J 9.0 and 2.7 Hz, H-4′), 4.10 (2H, q, J 7.2 Hz, OCH_2CH_3), 3.76 (3H, s) and 3.72 (3H, s) ($2 \times OCH_3$), 2.87 (2H, t, J 7.8 Hz), 2.55 (2H, t, J 7.8 Hz), 1.23 (3H, t, J 7.2 Hz, OCH_2CH_3). ^{13}C NMR (75 MHz, $CDCl_3 + CCl_4$): δ 172.8 (C, OC=O), 153.5 (C), 151.7 (C), 130.0 (C, C-1′), 116.3 (CH), 111.5 (CH), 110.9 (CH), 60.1 (CH_2, OCH_2CH_3), 55.6 (CH_3), 55.4 (CH_3), 34.3 (CH_2), 26.3 (CH_2), 14.3 (CH_3, OCH_2CH_3). HRMS: m/z calcd. for $C_{13}H_{18}O_4Na$ (M + Na): 261.1103. Found: 261.1096.

Ethyl 2-(2,5-Dimethoxybenzyl)pent-4-enoate (9)

To a cold (−70°C), magnetically stirred solution of LDA [prepared from diisopropylamine (0.35 ml, 2.52 mmol) and ^{n}BuLi (1.7 M in hexane, 1.38 ml, 2.35 mmol)] in dry THF (3 ml), a solution of the ester **7** (200 mg, 0.84 mmol) in dry THF (1 ml) was added and the resulting reaction mixture stirred for 45 min at the same temperature. The enolate thus formed was treated with allyl bromide (0.22 ml, 2.52 mmol) and stirred for 10 h at rt. It was then diluted with water and extracted with ether (3×5 ml). The combined ether extract was washed with 3 N aq. HCl followed by brine and dried (Na_2SO_4). Evaporation of the solvent and purification of the residue over a silica-gel column using ethyl acetate–hexane (1:50) as eluent furnished the ester **9** (190 mg, 81%) as oil. IR (neat): ν_{max}/cm^{-1} 1732, 1502, 1224. ^{1}H NMR (300 MHz, $CDCl_3 + CCl_4$): δ 6.80–6.50 (3H, m, Ar-H), 5.74 (1H, ddt, J 17.4, 10.2 and 6.9 Hz, CH=CH_2), 5.05 (1H, d, J 17.4 Hz), and 5.00 (1H, d, J 10.2 Hz), (CH=CH_2), 4.03 (2H, q, J 7.2 Hz, OCH_2CH_3), 3.77 (3H, s), and 3.71 (3H, s) [$2 \times OCH_3$], 3.00–2.80 (3H, m), 2.50–2.20 (2H, m), 1.14 (3H, t, J 7.2 Hz, OCH_2CH_3). ^{13}C NMR (75 MHz, $CDCl_3 + CCl_4$): δ 174.8 (C, OC=O), 153.3 (C), 151.9 (C), 135.5 (CH, CH=CH_2), 128.7 (C), 117.0 (CH), 116.7 (CH_2, CH=CH_2), 111.8 (CH), 110.9 (CH), 59.9 (CH_2, OCH_2CH_3), 55.7 (CH_3), 55.4 (CH_3), 45.1 (CH, C-2), 36.4 (CH_2), 33.0 (CH_2), 14.3 (CH_3, OCH_2CH_3). HRMS: m/z calcd. for $C_{16}H_{22}O_4Na$ (M + Na): 301.1416. Found: 301.1402.

3-(2,5-Dimethoxybenzyl)-2-methylhex-5-en-2-ol (10)

To a cold (0°C), magnetically stirred solution of methylmagnesium iodide (2.16 mmol) [prepared from magnesium (52 mg, 2.16 mmol), methyl iodide

(0.16 ml, 2.59 mmol), and a catalytic amount of iodine in 3 ml of dry ether], a solution of the ester **9** (60 mg, 0.22 mmol) in dry ether (2 ml) was added. The reaction mixture was slowly warmed up to rt and stirred for 4 h. It was then poured into cold saturated aq. NH_4Cl solution and extracted with ether (3×3 ml). The ether extract was washed with brine and dried (Na_2SO_4). Evaporation of the solvent and purification of the residue on a silica-gel column using ethyl acetate–hexane (1:7) as eluent furnished the tertiary alcohol **10** (50 mg, 88%) as oil. IR (neat): ν_{max}/cm^{-1} 3454, 1500, 1223. ^1H NMR (300 MHz, $CDCl_3 + CCl_4$): δ 6.72 (1H, d, *J* 9.0 Hz, H-3′), 6.70 (1H, d, *J* 3.0 Hz, H-6′), 6.64 (1H, dd, *J* 9.0 and 3.0 Hz, H-4′), 5.79 (1H, ddt, *J* 17.4, 10.2 and 6.9 Hz, H-5), 5.00 (1H, d, *J* 17.1 Hz), and 4.94 (1H, d, *J* 10.2 Hz) [H-6], 3.79 (3H, s) and 3.74 (3H, s) [$2 \times OCH_3$], 2.90 (1H, dd, *J* 13.5 and 4.2 Hz), 2.40 (1H, dd, *J* 13.5 and 8.4 Hz), 2.40–1.98 (3H, m), 1.93–1.80 (1H, m), 1.23 (3H, s), and 1.21 (3H, s) [$2 \times$ *tert*-CH_3]. ^{13}C NMR (75 MHz, $CDCl_3 + CCl_4$): δ 153.5 (C), 151.6 (C), 139.0 (CH, C-5), 131.3 (C), 117.5 (CH), 115.6 (CH_2, C-6), 111.2 (CH), 111.0 (CH), 74.0 (C, C-2), 55.8 (CH_3), 55.5 (CH_3), 50.0 (CH, C-3), 35.3 (CH_2), 30.6 (CH_2), 27.9 (CH_3), 27.0 (CH_3). HRMS: m/z calcd. for $C_{16}H_{24}O_3Na$ (M + Na): 287.1623. Found: 287.1627.

4-(2,5-Dimethoxybenzyl)-5,5-dimethyltetrahydrofuran-2-ol (11)

A precooled (−70°C) mixture of ozone in oxygen was passed through a cold (−70°C) solution of the hexenol **10** (40 mg, 0.15 mmol) and a catalytic amount of $NaHCO_3$ in methanol (2 ml) and CH_2Cl_2 (8 ml) for 40 s. The reaction mixture was flushed off with oxygen, and dimethyl sulfide (0.11 ml, 1.52 mmol) was added to the reaction mixture. It was then slowly warmed up to rt and magnetically stirred for 10 h. Evaporation of the solvent under reduced pressure and purification of the residue on a silica-gel column using ethyl acetate–hexane (1:3) as eluent furnished a diastereomeric mixture of the lactol **11** (40 mg, 99%) as a colorless solid, which was recrystallized from a mixture of CH_2Cl_2 and hexane. Mp: 112–114°C. IR (neat): ν_{max}/cm^{-1} 3392, 1500, 1223. ^1H NMR (300 MHz, $CDCl_3 + CCl_4$): δ 6.80–6.40 (3H, m, Ar-H), 5.36 (1H, d, *J* 4.2 Hz, H-2), 3.76 (3H, s) and 3.73 (3H, s) [$2 \times OCH_3$], 3.63 (1H, brs, OH), 2.75–2.05 (4H, m), 2.00–1.60 (1H, m), 1.34 and 1.29 (3H, s), and 1.10 and 1.23 (3H, s) ($2 \times$ *tert*-CH_3). ^{13}C NMR (75 MHz, $CDCl_3 + CCl_4$): δ 153.5 and 153.4 (C), 151.7 and 151.6 (C), 130.3 (C), 116.7 (CH), 111.2 and 111.0 (CH), 111.1 (CH), 97.3 and 96.4 (CH), 84.1 and 83.2 (C), 55.6 (CH_3) and 55.5 (CH_3) ($2 \times OCH_3$), 45.8 and 48.7 (CH), 39.4 and 39.7 (CH_2), 30.5 and 30.8 (CH_2), 29.5 and 28.0 (CH_3), 23.5 and 23.7 (CH_3). HRMS: m/z calcd. for $C_{15}H_{22}O_4Na$ (M + Na): 289.1416. Found: 289.1408.

4-(2,5-Dimethoxylbenzyl)-5,5-dimethyldihydro-2(3*H*)-furanone (12a)

To a magnetically stirred solution of the lactol **11** (25 mg, 0.09 mmol) in 1 ml of dry CH_2Cl_2, a homogeneous mixture of PCC (101.3 mg, 0.47 mmol) and

silica gel (101 mg) were added and stirred vigorously for 2 h at rt. The reaction mixture was then filtered through a small silica-gel column and eluted the column with an excess of CH_2Cl_2. Evaporation of the solvent and purification of the residue over a silica-gel column using ethyl acetate–hexane (1:20 to 1:10) as eluent furnished the lactone **12a** (23 mg, 93%) as an oil. IR (neat): ν_{max}/cm^{-1} 1774, 1500. ^1H NMR (300 MHz, $CDCl_3 + CCl_4$): δ 6.74 (1H, d, J 8.7 Hz, H-3′), 6.68 (1H, dd, J 8.7 and 3.0 Hz, H-4′), 6.63 (1H, d, J 3.0 Hz, H-6′), 3.78 (3H, s) and 3.75 (3H, s) [2 × OCH_3], 2.76 (1H, d, J 8.4 Hz), 2.70–2.48 (2H, m), 2.48–2.20 (2H, m), 1.42 (3H, s) and 1.37 (3H, s) (2 × *tert*-CH_3). ^{13}C NMR (75 MHz, $CDCl_3 + CCl_4$): δ 175.1 (C, OC═O), 153.5 (C), 151.4 (C), 128.5 (C, C-1′), 116.8 (CH), 111.5 (CH), 111.1 (CH), 86.2 (C, C-5), 55.6 (CH_3) and 55.5 (CH_3) [2 × OCH_3], 45.8 (CH, C-4), 34.8 (CH_2), 30.5 (CH_2), 27.4 (CH_3) and 21.9 (CH_3) [2 × *tert*-CH_3]. HRMS: m/z calcd. for $C_{15}H_{20}O_4Na$ (M + Na): 287.1259. Found: 287.1255.

4-(2,5-Dihydoxylbenzyl)-5,5-dimethyldihydro-2(3H)-furanone (12b)

A solution of BBr_3 (1 *M* in CH_2Cl_2, 0.85 ml, 0.85 mmol) was added dropwise to a solution of the ether **12a** (40 mg, 0.17 mmol) in CH_2Cl_2 (3 ml) at 0°C; the reaction mixture slowly warmed up to rt and stirred for 4 h at rt. It was quenched with saturated aqueous $NaHCO_3$ solution and extracted with CH_2Cl_2 (3 × 5 ml). The combined organic layer was washed with brine and dried (Na_2SO_4). Evaporation of the solvent and purification of the residue over a silica-gel column using ethyl acetate–hexane (1:2) as eluent furnished the phenol **12b** (30 mg, 74%) as yellow color oil. IR (neat): ν_{max}/cm^{-1} 3371, 1739, 1506. ^1H NMR (300 MHz, D_2O): δ 6.50 (1H, d, J 8.4 Hz), 6.64–6.40 (2H, m), 2.70–2.20 (5H, m), 1.28 (3H, s) and 1.25 (3H, s) [2 × *tert*-CH_3]. ^{13}C NMR (75 MHz, D_2O): δ 181.0 (C, OC═O), 149.7 (C), 147.9 (C), 128.7 (C), 118.0 (CH), 117.7 (CH), 115.0 (CH), 90.8 (C, C-5), 45.8 (CH, C-4), 35.3 (CH_2), 30.0 (CH_2), 27.1 (CH_3) and 21.7 (CH_3) [2 × *tert*-CH_3]. HRMS: m/z calcd. for $C_{13}H_{16}O_4Na$ (M + Na): 259.0946. Found: 259.0958.

Ethyl *E*-3-(2,6-Dimethylphenyl)prop-2-enoate (14)

A suspension of sodium hydride (210 mg, 60% dispersion in oil, 5.25 mmol) in hexanes under nitrogen atmosphere was magnetically stirred for 10 min, and the solvent was syringed out. The oil-free NaH was then suspended in dry THF (2 ml) and cooled in an ice bath. Triethyl phosphonoacetate (0.98 ml, 4.95 mmol) was added dropwise, and the reaction mixture was stirred for 30 min at room temperature. To the reaction mixture, a solution of the

aldehyde **13** (220 mg, 1.64 mmol) in dry THF (1 ml) was added dropwise and stirred for 6 h at rt. The reaction was then quenched by careful addition of saturated aqueous NH_4Cl solution and extracted with ether (4 × 4 ml). The combined ether layer was extracted with brine and dried (Na_2SO_4). Evaporation of the solvent and purification of the residue over a silica-gel column using ethyl acetate–hexane (1:20) as eluent furnished the cinnamate **14** (334 mg, 100%) as oil. IR (neat): ν_{max}/cm^{-1} 1716, 1639, 1174. ^{1}H NMR (300 MHz, $CDCl_3 + CCl_4$): δ 7.80 (1H, d, *J* 16.5 Hz, H-3), 7.20–6.90 (3H, m, Ar-H), 6.03 (1H, d, *J* 16.5 Hz, H-2), 4.26 (2H, q, *J* 7.2 Hz, OCH_2CH_3), 2.34 (6H, s, 2 × $ArCH_3$), 1.34 (3H, t, *J* 7.2 Hz, OCH_2CH_3). ^{13}C NMR (75 MHz, $CDCl_3 + CCl_4$): δ 166.3 (C, OC=O), 143.2 (CH, C-3), 136.4 (2 C, C, C-2′ and 6′), 134.0 (C, C-1′), 128.2 (3 C, CH), 123.9 (CH, C-4′), 60.3 (CH_2, OCH_2CH_3), 21.1 (2 C, CH_3, 2 × $ArCH_3$), 14.4 (CH_3, OCH_2CH_3). HRMS: *m*/*z* calcd. for $C_{13}H_{16}O_2Na$ (M + Na): 227.1048. Found: 227.1044.

Ethyl 3-(2,6-Dimethylphenyl)propinoate (15)

To 10% Pd-C (25 mg), a solution of the cinnamate **14** (300 mg, 1.47 mmol) in ethanol (3 ml) was added. The reaction mixture was stirred for 4 h at rt in an atmosphere of hydrogen, created by evacuative replacement of air (balloon), and then the catalyst was filtered off. Evaporation of the solvent furnished the saturated ester **15** (302 mg, 100%) as oil. IR (neat): ν_{max}/cm^{-1} 1736, 1180, 769. ^{1}H NMR (300 MHz, $CDCl_3 + CCl_4$): δ 6.95 (3 H, brs, Ar-H), 4.14 (2H, q, *J* 7.2 Hz, OCH_2CH_3), 2.94 (2H, t, *J* 8.1 Hz), 2.40 (2H, t, *J* 8.1 Hz), 2.32 (6H, s, 2 × CH_3), 1.27 (3H, t, *J* 7.2 Hz, OCH_2CH_3). ^{13}C NMR (75 MHz, $CDCl_3 + CCl_4$): δ 172.7 (C, OC=O), 137.1 (C, C-1′), 135.9 (2 C, C, C-2′ and 6′), 128.3 (2 C, CH, C-3′ and 5′), 126.2 (CH, C-4′), 60.3 (CH_2, OCH_2CH_3), 33.5 (CH_2), 25.1 (CH_2), 19.8 (2 C, CH_3), 14.4 (CH_3, OCH_2CH_3). HRMS: *m*/*z* calcd. for $C_{13}H_{18}O_2Na$ (M + Na): 229.1204. Found: 229.1212.

Ethyl 2-(2,6-Dimethylbenzyl)pent-4-enoate (16)

To a cold (−70°C) magnetically stirred solution of LDA [prepared from diisopropylamine (0.46 ml, 3.26 mmol) and ^{n}BuLi (2.3 *M* in hexane, 1.27 ml, 2.91 mmol)] in dry THF (4 ml), a solution of the ester **15** (240 mg, 1.16 mmol) in dry THF (2 ml) was added, and the resulting reaction mixture was stirred for 45 min at the same temperature. The enolate thus formed was treated with allyl bromide (0.30 ml, 3.49 mmol) and stirred for 11 h at rt. It was then diluted with water and extracted with ether (3 × 5 ml). The combined ether extract was washed with 3 *N* aq. HCl followed by brine and dried (Na_2SO_4). Evaporation of the solvent and purification of the residue over a silica-gel column using ethyl acetate–hexane

(1:50) as eluent furnished the ester **16** (240 mg, 84%) as oil. IR (neat): ν_{max}/cm^{-1} 1732, 1163, 769. ^{1}H NMR (300 MHz, $CDCl_3 + CCl_4$): δ 6.95 (3H, brs, Ar-H), 5.72 (1H, ddt, *J* 17.1, 10.2, and 6.9 Hz, H-3), 5.05 (1H, d, *J*, 17.1 Hz) and 5.01 (1H, d, *J*, 10.2 Hz) [H-4], 4.01 (2H, q, *J*, 7.2 Hz, OCH_2CH_3), 2.99 (1H, dd, *J* 14.1 and 7.2 Hz), 2.82 (1H, dd, *J* 14.1 and 7.2 Hz), 2.76–2.60 (1H, m), 2.58–2.45 (1H, m), 2.40–2.10 (1H, m), 2.32 (6H, s, 2 × $ArCH_3$), 1.10 (3H, t, *J* 7.2 Hz, OCH_2CH_3). ^{13}C NMR (75 MHz, $CDCl_3 + CCl_4$): δ 175.0 (C, OC═O), 136.6 (2 C, C, C-2′ and 6′), 135.9 (C, C-1′), 135.5 (CH, C-3), 128.4 (2 C, CH, C-3′ and 5′), 126.2 (CH, C-4′), 117.0 (CH_2, C-4), 60.1 (CH_2, OCH_2CH_3), 45.1 (CH, C-2), 36.3 (CH_2), 32.1 (CH_2), 20.4 (2 C, CH_3), 14.2 (CH_3, OCH_2CH_3). HRMS: *m*/*z* calcd. for $C_{16}H_{22}O_2Na$ (M + Na): 269.1517. Found: 269.1529.

3-(2,6-Dimethylbenzyl)-2-methylhex-5-en-2-ol (17)

To a cold (0°C), magnetically stirred solution of methylmagnesium iodide (9.1 mmol) [prepared from magnesium (218 mg, 9.1 mmol), methyl iodide (0.66 ml, 10.58 mmol), and a catalytic amount of iodine in 3 ml of dry ether] was added a solution of the ester **16** (186 mg, 0.76 mmol) in dry ether (2 ml). The reaction mixture was slowly warmed up to rt and stirred for 5 h. It was then poured into saturated aq. NH_4Cl solution and extracted with ether (3 × 3 ml). The ether extract was washed with brine and dried (Na_2SO_4). Evaporation of the solvent and purification of the residue on a silica-gel column using ethyl acetate–hexane (1:10 to 1:5) as eluent furnished the tertiary alcohol **17** (157 mg, 90%) as oil. IR (neat): ν_{max}/cm^{-1} 3452, 767. ^{1}H NMR (300 MHz, $CDCl_3 + CCl_4$): δ 6.98 (3 H, brs, Ar-H), 5.72–5.52 (1H, m, H-5), 4.87 (1H, d, *J* 18.0 Hz) and 4.82 (1H, d, *J* 9.9 Hz) [H-6], 2.87 (1H, dd, *J* 13.5 and 4.2 Hz) and 2.58 (1H, dd, *J* 13.5 and 10.5 Hz) [$ArCH_2$], 2.35 (6H, s, 2 × $ArCH_3$), 2.25–2.15 (1H, m), 2.10–1.90 (2H, m), 1.70 (1H, s, OH), 1.32 (3H, s) and 1.29 (3H, s) [2 × *tert*-CH_3]. ^{13}C NMR (75 MHz, $CDCl_3 + CCl_4$): δ 139.9 (CH, C-5), 137.7 (C, C-1′), 136.6 (2 C, C, C-2′ and 6′), 128.4 (2 C, CH, C-3′ and 5′), 125.9 (CH, C-4′), 115.0 (CH_2, C-6), 74.5 (C, C-2), 48.9 (CH, C-3), 34.1 (CH_2), 30.3 (CH_2), 27.9 (CH_3) and 26.9 (CH_3) [2 × *tert*-CH_3], 20.9 (2 C, CH_3, 2 × $ArCH_3$). HRMS: *m*/*z* calcd. for $C_{16}H_{24}ONa$ (M + Na): 255.1725. Found: 255.1735.

4-(2,6-Dimethylbenzyl)-5,5-dimethyltetrahydrofuran-2-ol (18)

A precooled (−70°C) mixture of ozone in oxygen was passed through a cold (−70°C) solution of the olefin **17** (70 mg, 0.30 mmol) and a catalytic amount of $NaHCO_3$ in methanol (2 ml) and CH_2Cl_2 (8 ml) for 1 min. The reaction mixture was flushed off with oxygen, and dimethyl sulfide (0.11 ml, 1.51 mmol) was added to the reaction mixture. It was then slowly warmed

up to rt and magnetically stirred for 4 h. Evaporation of the solvent under reduced pressure and purification of the residue on a silica-gel column using ethyl acetate–hexane (1:10 to 1:3) as eluent first furnished the lactol **18** (70 mg, 99%) as colorless solid, which was recrystallized from a mixture of CH_2Cl_2 and hexane. Mp: 71–73°C. IR (neat): ν_{max}/cm^{-1} 3399, 1030, 769. ^1H NMR (300 MHz, $CDCl_3 + CCl_4$): δ 6.96 and 6.90 (3H, m, Ar-H), 5.32 (1H, d, J 4.8 Hz, H-2), 2.70–2.45 (4H, m), 2.31 and 2.30 (6H, s, 2 × $ArCH_3$), 2.20–1.90 (m) and 1.90–1.65 (m) [2H], 1.44 and 1.32 (3H, s), and 1.12 and 1.30 (3 H, s) [2 × *tert*-CH_3]. ^{13}C NMR (75 MHz, $CDCl_3 + CCl_4$): δ 137.2 (C), 135.8 (2 C, C), 128.4 (2 C, CH), 125.8 (CH), 96.1 and 97.1 (CH, C-2), 83.9 and 82.9 (C, C-5), 45.7 and 49.1 (CH, C-4), 38.8 and 39.3 (CH_2), 29.1 and 27.6 (CH_3), 28.8 and 29.0 (CH_2), 23.2 and 23.3 (CH_3), 20.3 (2 C, CH_3). HRMS: m/z calcd. for $C_{15}H_{22}O_2Na$ (M + Na): 257.1517. Found: 257.1528.

4-(2,6-Dimethylbenzyl)-5,5-dimethyldihydro-2(3H)-furanone (solafuranone 2a)

To a magnetically stirred solution of the lactol **18** (55 mg, 0.24 mmol) in 3 ml of dry CH_2Cl_2, a homogeneous mixture of PCC (253 g, 1.17 mmol) and silica gel (253 mg) was added which was stirred vigorously for 2 h at rt. The reaction mixture was then filtered through a small silica-gel column and eluted with an excess of CH_2Cl_2. Evaporation of the solvent and purification of the residue over a silica-gel column using ethyl acetate–hexane (1:20 to 1:10) as eluent furnished solafuranone[1] **2a** (51 mg, 94%). IR (neat): ν_{max}/cm^{-1} 1772, 1120, 771. ^1H NMR (300 MHz, acetone-d6): δ 7.01 (3H, brs, Ar-H), 2.90–2.70 (2H, m), 2.70–2.40 (2H, m), 2.40–2.10 (1H, m), 2.34 (6H, s, 2 × $ArCH_3$), 1.55 (3H, s) and 1.43 (3H, s) [2 × *tert*-CH_3]. ^1H NMR (300 MHz, $CDCl_3$): δ 7.02 (3H, brs, Ar-H), 2.85–2.65 (2H, m), 2.55–2.25 (3H, m), 2.32 (6H, s, 2 × $ArCH_3$), 1.56 (3H, s) and 1.43 (3H, s) [2 × *tert*-CH_3]. ^{13}C NMR (75 MHz, acetone-d6): δ 175.1 (C, OC═O), 137.2 (C, C-1′), 137.0 (2 C, C, C-2′ and 6′), 129.3 (2 C, CH, C-3′ and 5′), 126.9 (CH, C-4′), 86.6 (C, C-5), 46.3 (CH, C-4), 34.8 (CH_2), 29.1 (CH_2), 27.1 (CH_3) and 21.7 (CH_3) [2 × *tert*-CH_3], 20.4 (2 C, CH_3, 2 × $ArCH_3$). ^{13}C NMR (75 MHz, $CDCl_3$): δ 175.2 (C, OC═O), 135.9 (C, C-1′), 135.6 (2 C, C, C-2′ and 6′), 128.7 (2 C, CH, C-3′ and 5′), 126.3 (CH, C-4′), 86.5 (C, C-5), 45.7 (CH, C-4), 34.4 (CH_2), 28.5 (CH_2), 26.9 (CH_3) and 21.5 (CH_3) [2 × *tert*-CH_3], 20.2 (2 C, CH_3, 2 × $ArCH_3$). HRMS: m/z calcd. for $C_{15}H_{20}O_2Na$ (M + Na): 255.1361. Found: 255.1347.

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