First total synthesis of Saurufuran B *via* regioselective alkylation

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Saurufuran B (**1**), a furanditerpene isolated from the root of *Saururus chinensis*, was prepared in a highly efficient manner by regioselective alkylation from (*E, E*)-farnesol (**8**) and the readily available citraconic anhydride (**5**).

Keywords: Saurufuran B, first total syntheses, regioselective alkylation

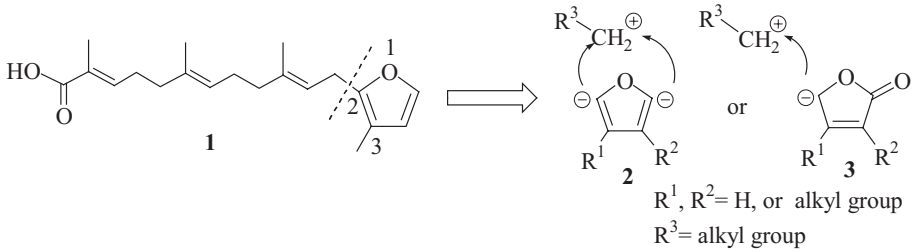
Saurufuran B[1] (**1**) is a naturally occurring furanoditerpene. It is a bioactive constituent of the root of *Saururus chinensis*, which is widely spread in southern Korea and China and is used in folk medicine for the treatment of inflammation, tumors, jaundice and gonorrhea. Structurally, this molecule is characterised by bearing an alkyl group and a methyl group at the C2 and C3 position of a furan.

In designing a synthesis of Saurufuran B (**1**), not only do we wish to minimise the number of linear steps from commercially available starting materials, but also design a route that is flexible and can be adapted to analogue synthesis. Since alkyl furans are important intermediates in organic synthesis,[2] considerable effort has been devoted to developing synthetic methods for their construction. Relatively few simple, general methods are available for the synthesis of these molecules.[3] The most straightforward way for synthesising alkylated furans is the direct coupling of a furan nucleophile with an alkyl electrophile. For example, coupling of the hypothetical C5-carbanion of an alkyl-substituted but-2-en-4-olides **3** or the C2-carbanions of an alkyl-substituted furan **2** with different electrophilic reagents gives rise to 2-alkylated furans, as the disconnection analysis shows (Scheme 1). However, direct deprotonation of an alkyl-substituted furan **2** normally generates two isomeric carbanions and alkylation with different electrophilic reagents gives both C2- and C5-substituted products. A similar complication is encountered when the lithium enolate obtained from alkyl-substituted but-2-en-4-olides **3** is alkylated with electrophiles. The furanoid carbanion can be alkylated at both C3- and C5- positions and generates a pair of isomers. Therefore the appropriate selection of reaction and conditions are required for a controlled coupling.

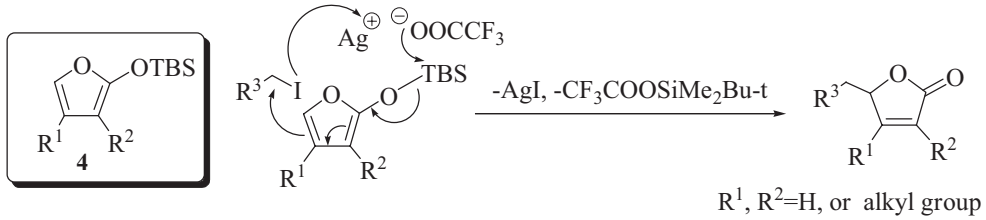
Jefford's method[4] for constructing substituted 2-furanones could be arranged to ensure the desired C5-regioselectivity on alkylation. Thus, we settled on a strategy that attaches each side chain to the substituted furan *via* a Lewis acid catalysed regioselective alkylation. We planned to synthesise the target molecule **1** with (*E, E*)-farnesol (**8**) and commercially available and inexpensive citraconic anhydride (**5**) as starting materials. Alkyl-substituted of 2-(*tert*-butyl-dimethylsiloxy)-furan **4**, which can be prepared from **5**, may be considered as the synthetic equivalent of the γ anion **3** of furan-2 (5*H*)-one (Scheme 2). The clear strategy that emerged from our retrosynthetic analysis enabled us to embark on the synthetic phase of the investigation. We now describe the application of this method to the first total synthesis of Saurufuran B.

A mixture of furan derivatives **7m** and **7n** were easily prepared by using a known two-step procedure[5,6] that begins with citraconic anhydride. (Scheme 3) Separation of the two isomers was delayed to a later stage because of their similar boiling points.

Acetylation of farnesol **8** under the usual acetic anhydride/pyridine conditions[7] quantitatively generated farnesylacetate, which was regioselectively oxidised by catalytic amounts of selenium dioxide in the presence of *tert*-butyl hydroperoxide[8] in dichloromethane to produce the primary alcohol **9** as the major product. The primary alcohol **9** was converted to the *tert*-butyldimethylsilyl (TBS) ether **10** in the presence of triethylamine and *tert*-butyldimethylsilyl chloride in dichloromethane at room temperature.[9] The acetate of **10** was hydrolysed using potassium carbonate in methanol to give the corresponding allylic alcohol[10], which was converted to allylic iodide **11** by triphenylphosphine, imidazole and iodine in ether-acetonitrile following the procedure of Corey[11] (Scheme 4).



Scheme 1



Scheme 2

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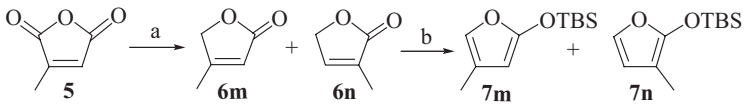
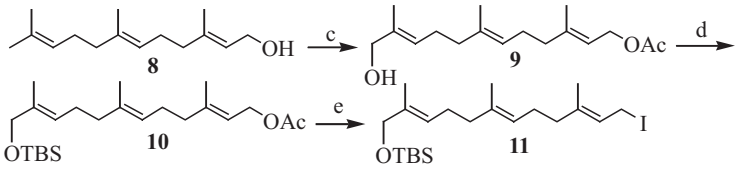


Scheme 3 Reagents and conditions: (a) $NaBH_4$, THF, Ref. 5; (b) TBDMSOTf (1.1 equiv), TEA (1.4 equiv), CH_2Cl_2, 0–25°C, 24 h, 84%, (**7m**:**7n** = 85:15).[6] TBDMSOTf = *tert*-butyl-dimethylsilyl trifluoromethanesulfonate; TEA = triethylamine.



Scheme 4 Reagents and conditions: (c) i. Ac_2O, Pyridine, DMAP (Cat.); ii. *t*-BuOOH, SeO_2; (d) TBDMSCl, Et_3N, DMAP; (e) i. K_2CO_3, CH_3OH; ii. Ph_3P (1.5equiv), Imidazole (1.5equiv), I_2 (2.5equiv), CH_3CN–Et_2O (2/3), rt, 30 min. DMAP = 4-dimethylamion-pyridine.

Our route for preparing the butenolides **12m** and **12n**, entails regioselective alkylation of 2-(*tert*-butyldimethylsiloxy)-4-methylfuran (**7m**) or 2-(*tert*-butyldimethylsiloxy)-3-methylfuran (**7n**) at the C5 position. In order to bring about such an alkylation, care should be taken so that the acid-sensitive furan is not compromised. To this end, a stoichiometric amount of silver trifluoroacetate was used to facilitate the coupling between **11** and a mixture of **7m** and **7n** under mild conditions. The coupling proceeded smoothly in the presence of silver trifluoroacetate and **12m** and **12n** were generated as the major products in a total yield of 73% (Scheme 5). The two isomers can be readily separated by silica gel flash chromatography at this stage.

The conversion of the α, β-unsaturated γ-lactone to a furan involves partial reduction of the lactone followed by dehydration of the resulting hemiacetal intermediate. Initial attempts at the partial reduction of the unsaturated lactone with alcohol-treated lithium aluminum hydride[12] (LAH) were not successful and the starting material was recovered. Fortunately, diisobutylaluminiumhydride[13] (DIBAL) proved to be a superior reagent and the furan derivative **13m** was isolated after acidic work-up of the hemiacetal intermediate. After cleavage of the silyl ether group[14] of **13m** with tetrabutylammonium fluoride, the resulting alcohol **14m** was oxidised under Swern conditions[15] to afford the aldehyde **15m**. Further oxidation to the methyl ester was performed according to the procedure developed by Corey.[16] Thus, exposure of **15m** to a mixture of sodium cyanide and manganese dioxide in methanol at room temperature gave the corresponding methyl ester **16m**. Finally, saponification of **16m** with lithium hydroxide in acetone produced Saurufuran B (**1**) in 78% yield[17] (Scheme 6).

In summary, a simple and convenient preparation of Saurufuran B from citraconic anhydride and (*E, E*)-farnesol has been accomplished by making use of a Lewis acid-catalysed regioselective alkylation. The spectroscopic properties of synthetic compound **1** were identical to those reported for Saurufuran B. The details of the biological activities of Saurufuran B will be given elsewhere.

Experimental

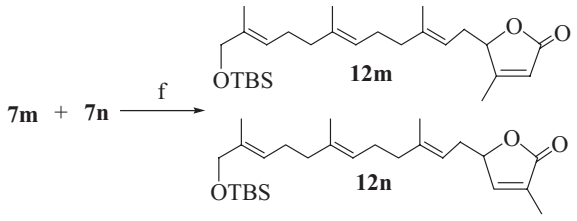
IR spectra were obtained on a NICOLET NEXUS 670 FT-IR spectrometer. ^1H NMR and ^{13}C NMR spectra were recorded on a BRUKER AM-400 and VARIAN MECURY PLUS 300 spectrometer in $CDCl_3$ using TMS as an internal reference, and *J* values were given in Hz. Mass spectra (EI) were run on a HP5988A mass spectrometer and signals were given in *m/z* with relative intensity (%) in brackets. HRMS were determined on a BRUKER DALTONICS APEXII 47e Fourir Transfer spectrometer with either of EI, CI, FAB or SIMS ionisation methods or ZAB-HS instrument. Flash chromatography was performed with silica gel, using petroleum ether (PE) and diethyl ether (Et) mixtures as eluent except otherwise stated. All anhydrous solvents were freshly purified by standard techniques just before use. Reactions were carried out in an argon atmosphere when necessary, and monitored by thin layer chromatography (TLC) on silica gel plate (GF_{254}). Organic extracts were washed with brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure on a rotary evaporator. Purification of products was performed by Flash Column Chromatography (FCC) on silica gel (200~300 mesh) and neutral aluminum oxide purchased from Qing Dao Marine Chemical Co. (Qingdao, China).

Tert-butyl-dimethyl-(4-methyl-furan-2-yloxy)-silane (**7m**) and *tert*-butyl-di-methyl-(3- methyl-furan-2-yloxy)-silane (**7n**) were synthesised by the reported method.[5,6]

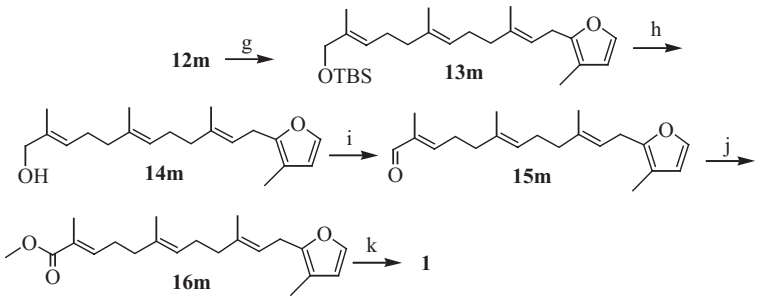
(2E, 6E, 10E)-12-(tert-Butyl-dimethyl-silanyloxy)-3, 7, 11-trimethyl-dodeca-2, 6, 10-trien-1-ol: A stirred solution of the acetate **10** (602 mg, 1.53 mmol) in methanol (3 ml) was treated with powered dry K_2CO_3 (150 mg, 1.09 mmol). The resulting mixture was stirred at room temperature for 5 h. The mixture was filtered and the solvent was evaporated *in vacuo* to give an oily residue, which was taken in ether (10 ml) and washed with water, brine, and dried. After the solvent was removed under reduced pressure, the residue was subjected to chromatographic purification to provide the primary alcohol (506 mg, 94%) as colourless oil.

^1H NMR (400 MHz, $CDCl_3$) δ_{ppm} 5.44–5.38 (m, 2H), 5.12 (t, *J* = 6.8 Hz, 1H), 4.16 (d, *J* = 6.8 Hz, 2H), 4.01 (s, 2H), 2.18–2.00 (m, 8H), 1.69 (s, 3H), 1.61 (s, 3H), 1.60 (s, 3H), 0.91 (s, 9H), 0.07 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.77, 135.41, 135.18, 124.26, 123.29, 123.04, 68.61, 59.40, 39.50, 39.33, 31.64, 28.03, 26.25, 26.11, 25.95 (3C), 18.42, 16.28, –5.27 (2C); IR (film, cm^{-1}): 3339, 2929, 2856, 1465, 1382, 1253; EIMS (*m/z*,%): 334 (M^+, 0.01), 159 (20), 135 (15), 107 (24), 93 (39), 75 (100), 41 (32).

*(2E, 6E, 10E)-tert-Butyl-(12-iodo-2, 6, 10-trimethyl-dodeca-2, 6, 10-trienyloxy)-dimethy-silane (***11**): A stirred clear solution of alcohol prepared above (560 mg, 1.6 mmol), triphenylphosphine



Scheme 5 Reagents and conditions: (f) CF_3COOAg (0.8 eq), **7m** + **7n** (1.2 eq), **11** (1.0 eq), CH_2Cl_2, –78°C, 3.5 h, 73%, (**12m**: **12n** = 88: 12)



Scheme 6 Reagents and conditions: (g) DIBAL, THF, –20 °C, 3.5 h, 73%; (h) *n*-Bu_4NF, THF, rt, 10 h, 98%; (i) $(COCl)_2$ (1.1eq), DMSO (2.4eq), Et_3N (5.0eq), CH_2Cl_2, –78 °C, 30 min, 93%; (j) NaCN (5.0eq), MnO_2 (20eq), CH_3COOH (1.5eq), CH_3OH; rt, 12 h, 78%; (k) LiOH, CH_3COCH_3, rt, 3 h, 78%.

(625 mg, 2.4 mmol) and imidazole (162 mg, 2.4 mmol) in a mixture of acetonitrile (2 ml) and ether (3 ml) was treated with iodine crystals (505 mg, 4.0 mmol) portionwise at 0°C over 5 minutes. The resulting mixture was allowed to warm to room temperature and stirred for 30 min. Ether (20 ml) was added and the mixture was filtered; the filtrate was washed with saturated sodium thiosulfate, copper sulfate aqueous solution, water, brine, and dried. After evaporation of the solvent under reduced pressure at 30 °C, the crude iodide **11** was taken up in anhydrous methylene chloride (2 ml) and immediately used in the subsequent procedure without further purification.

*(2E, 6E, 10E)-5-[12-(tert-Butyl-dimethyl-silanyloxy)-3,7,11-trimethyl-dodeca-2, 6, 10-trienyl]-4-methyl-5H-furan-2-one (***12m***) and (2E, 6E, 10E)-5-[12-(tert-butyl-dimethyl-silanyloxy)-3, 7, 11-trimethyl-dodeca-2, 6, 10-trienyl]-3-methyl-5H-furan-2-one (***12n***)*: A stirred suspension of freshly prepared silver trifluoroacetate (CF_3COOAg) (281 mg, 1.3 mmol) in methylene chloride (20 ml), was treated with a mixture of the above prepared iodide **11** and furansilane **7m** + **7n** (370 mg, 1.9 mmol) in dichloromethane (2 ml) dropwise at –78 °C. The resulting mixture was stirred at the same temperature for 3.5 h, then quenched with saturated ammonium chloride aqueous (5 ml) and warmed to room temperature. The mixture was filtered through *Celite* and the solvent was removed *in vacuo*. The residue was taken up in ether and washed with water, brine, and dried. After the solvent was removed *in vacuo* the residue was purified by flash column chromatography to provide two isomers **12m** (441 mg) **and 12n** (60 mg)**,** respectively. (total 73% yield).

12m: ^{1}H NMR (400 MHz, $CDCl_3$) δ_{ppm} 5.81 (s, 1H), 5.39–5.36 (m, 1H), 5.06–5.05 (m, 2H), 4.88 (t, *J* = 4.8 Hz, 1H), 4.01 (s, 2H), 2.67–2.63 (m, 1H), 2.38–2.34 (m, 1H), 2.14–1.98 (m, 8H), 2.05 (s, 3H), 1.68 (s, 3H), 1.64 (s, 3H), 1.60 (s, 3H), 0.91 (s, 9H), 0.07 (s. 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.14, 139.74, 124.66, 124.34, 123.96, 117.34, 116.15, 116.00, 109.80, 84.27, 68.67, 39.97. 39.71, 39.39, 31.70, 30.32, 26.49, 26.18 (3C), 25.97, 25.64, 23.35, 13.93, –5.25 (2C); IR (film, cm^{-1}): 2963, 2928, 2855, 1762, 1645, 1468, 1440, 1253, 1146, 1102, 1064, 838, 776; EIMS (*m/z*,%): 375 (M^+–57, 16.4), 135 (24), 107 (17), 97 (46), 93 (32), 81 (20), 79 (17), 77 (14.5), 75 (100), 69 (43), 55 (31), 41 (62); HRMS ($C_{26}H_{44}O_3Si$) *calcd.* 432.3060 *found* 432.3053.

12n: ^{1}H NMR (300 MHz, $CDCl_3$) δ_{ppm} 7.02 (d, *J* = 1.8 Hz, 1H), 5.39–5.37 (m, 1H), 5.14–5.09 (m, 2H), 4.86 (t, *J* = 6.9 Hz, 1H), 4.00 (s, 2H), 2.50–2.47 (m, 1H), 2.36–2.34 (m, 1H), 2.13–2.04 (m, 8H), 1.92 (s, 3H), 1.62 (s, 3H), 1.60 (br, s, 6H), 0.90 (s, 9H), 0.06 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.22, 148.53, 139.95, 135.33, 135.14, 134.27, 130.08, 124.21, 116.60, 80.80, 68.58, 39.66, 39.37, 32.14, 27.14, 26.44, 26.12, 25.94 (3C), 18.40, 15.97, 13.43, 10.67, –5.28 (2C); IR (film, cm^{-1}): 2955, 2929, 2856, 1762, 1465, 1254, 1102, 1064, 838, 776; EIMS (*m/z*,%): 375 (M^+–57, 2.7), 283 (1.1), 265 (1.1), 220 (1.3), 203 (4.4), 185 (1.7), 171 (7.4), 159 (15), 135 (13), 119 (11), 107 (24), 93 (32), 81 (23), 75 (100), 41 (29); HRMS ($C_{26}H_{44}O_3Si$) *calcd.* (M + NH_4) 450.3398 *found* 450.3395.

*(2E, 6E, 10E)-tert-Butyl-dimethyl-[2,6,10-trimethyl-12-(3-methyl-furan-2-yl)-dodeca-2,6,10-trienyloxy]-silane (***13m***)*: A toluene solution of diisobutylaluminum hydride (132 mg, 0.93 mmol) was added dropwise to a stirred solution of **12m** (200 mg, 0.46 mmol) in THF (2 ml) at –20°C in an argon atmosphere. The resulting mixture was stirred for an additional 3.5 h at ambient temperature. The progress of the reaction was monitored by thin layer chromatography and when complete, the reaction was quenched with 5% hydrogen chloride (1 ml) and warmed to room temperature. The mixture was extracted with diethyl ether and the extracts were washed with water, brine, and dried. The solvent was evaporated *in vacuo* and the residue was purified by flash column chromatography to give **13m** (140 mg, 73%).

^{1}H NMR (300 MHz, $CDCl_3$) δ_{ppm} 7.21 (d, *J* = 1.8 Hz, 1H), 6.15 (d, *J* = 1.8 Hz, 1H), 5.39–5.34 (m, 1 H), 5.26 (t, *J* = 6.6 Hz, 1H), 5.11–5.09 (m, 1H), 4.00 (s, 2H), 3.28 (d, *J* = 7.2 Hz, 2H), 2.17–1.96 (m, 8H), 1.96 (s, 3H), 1.71 (s, 3H), 1.59 (br, s, 6H), 0.91 (s, 9H), 0.06 (6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.08, 139.79, 136.50, 135.11, 134.92, 134.21, 124.40, 124.15, 119.91, 112.82, 68.66, 39.57, 39.35, 31.63, 26.43, 26.31, 26.13 (3C), 25.12, 18.42, 16.12, 13.43, 9.78, –5.26 (2C); IR (film, cm^{-1}): 2955, 2929, 2856, 1465, 1253, 1108, 1068, 837, 776; EIMS (*m/z*,%): 416 (M^+, 0.18), 359 (1.1), 284 (3.1), 198 (4.4), 189 (1.4), 173 (1.9), 161 (3.1), 95 (100), 75 (81); HRMS ($C_{26}H_{44}O_2Si$) *calcd*. 416.3111 *found* 416.3119.

*(2E, 6E, 10E)-2, 6, 10-Trimethyl-12-(3-methyl-furan-2-yl)-dodeca-2, 6, 10-trien-1-ol (***14m***)*: A solution of *n*-tetrabutylammonium fluoride in tetrahydrofuran (1M, 1 ml) at 0°C was added to a stirred solution of **13m** (160 mg, 0.38 mmol) in tetrahydrofuran (0.5 ml) was added dropwise. The resulting mixture was stirred at room temperature till the reaction was complete. Concentration of the reaction mixture under reduced pressure gave oily residue, which was taken in ether and washed with water, brine, and dried. Removal of the solvent with a rotary evaporator provided the crude oil, which was subjected to purification by flash column chromatography to afford **14m** (116 mg, 98%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ_{ppm} 7.21 (s, 1 H), 6.16 (s, 1H), 5.40–5.37 (m, 1 H), 5.26 (t, *J* = 6.8 Hz, 1H), 5.12–5.11 (m, 1H), 3.99 (s, 2H), 3.28 (d, *J* = 6.8 Hz, 2H), 2.18–1.94 (m, 8H), 1.98 (s, 3H), 1.71 (s, 3H), 1.66 (s, 3H), 1.63 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.11, 139.77, 136.43, 134.71, 134.67, 126.17, 125.17, 124.34, 120.01, 112.84, 69.04, 39.56, 39.26, 31.57, 26.43, 26.17, 25.16, 16.11, 13.66, 9.76; IR (film, cm^{-1}): 3398, 2925, 2859, 1448, 1380, 1069, 1012; EIMS (*m/z*,%): 302 (M^+, 1.4), 284 (4.1), 173 (3.7), 161 (3.8), 148 (28), 107 (21), 95 (100), 91 (22), 79 (21), 69 (31), 55 (29), 43 (87); HRMS ($C_{20}H_{30}O_2$) *calcd.* (M + Na) 325.2138 *found* 325.2141.

(2E, 6E, 10E)-2, 6, 10-Trimethyl-12-(3-methyl-furan-2-yl)-dodeca-2, 6, 10-trienal (**15m**): A solution of dimethyl sulfoxide (0.028 ml, 0.40 mmol) in dichloromethane (1 ml) at –78°C was added to a stirred solution of oxalyl chloride (0.016 ml, 0.18 mmol) in dichloromethane (1 ml) was added. The resulting mixture was stirred at the same temperature for 5 min, then the alcohol **14m** (49 mg, 0.16 mmol) was added dropwise within 5 min. After being stirred for additional 30 min at that temperature, triethylamine (0.12 ml, 0.83 mmol) was added and the mixture was stirred for another 5 min and then allowed to reach room temperature. Water (5 ml) was added and the aqueous phase was extracted with diethyl ether. The extracts were washed successively with dilute hydrogen chloride (1%), water, brine, dilute aqueous sodium carbonate (5%), water, and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography to give **15m** (45 mg, 93%) as a colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ_{ppm} 9.36 (s, 1H), 7.20 (s, 1 H), 6.47–6.42 (m, 1H), 6.15 (s, 1H), 5.25 (t, *J* = 6.9 Hz, 1H), 5.18–5.12 (m, 1H), 3.28 (d, *J* = 7.2 Hz, 2H), 2.25–1.96 (m, 8H), 1.96 (s, 3H), 1.74 (s, 3H), 1.70 (s, 3H), 1.61 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 195.36, 154.59, 154.23, 150.00, 139.77, 136.17, 133.45, 126.22, 125.32, 120.13, 112.81, 39.67, 39.37, 37.89, 30.23, 27.34,

26.28, 23.12, 16.13, 9.76; IR (film, cm^{-1}): 2924, 2857, 1687, 1644, 1446, 1083, 728; EIMS (*m/z*,%): 300 (M^+, 4.0), 265 (0.3), 207 (1.3), 175 (3.2), 161 (3.0), 149 (100), 95 (66), 55 (50), 41 (37); HRMS ($C_{20}H_{28}O_2$) *calcd*. 300.2089 *found* 300.2094.

*(2E, 6E, 10E)-2, 6, 10-Trimethyl-12-(3-methyl-furan-2-yl)-dodeca-2, 6, 10-trienoic acid methyl ester (***16m**): A mixture of **15m** (44 mg, 0.15 mmol), freshly prepared active manganese dioxide (255 mg, 2.9 mmol), acetic acid (14 mg, 0.23 mmol), and sodium cyanide (36 mg, 0.73 mmol) in methanol (1 ml) was stirred at room temperature for 12 h. The mixture was filtered and the solvent was evaporated before water was added. The resulting mixture was extracted with diethyl ether, washed with brine and dried over anhydrous sodium sulfate. After concentration under reduced pressure, the residue was purified with a flash column chromatography on silica gel to afforded **16m** (37 mg, 78%) as colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ_{ppm} 7.21 (s, 1 H), 6.75–6.72 (m, 1H), 6.16 (s, 1 H), 5.26 (t, *J* = 7.2 Hz, 1H), 5.15–5.11 (m, 1H), 3.72 (s, 3H), 3.28 (d, *J* = 7.2 Hz, 2H), 2.11–1.92 (m, 8H), 1.96 (s, 3H), 1.83 (s, 3H), 1.70 (s, 3H), 1.60 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.97, 159.30, 142.28, 139.76, 136.32, 133.97, 127.42, 125.86, 124.88, 120.11, 112.83, 51.63, 39.74, 39.46, 38.19, 30.57, 27.69, 26.43, 23.20, 16.09, 9.76; IR (film, cm^{-1}): 2925, 2858, 1716, 1437, 1269, 1122, 1085, 728; EIMS (*m/z*,%): 330 (M^+, 3.2), 182 (2.6), 175 (13.4), 161 (4.9), 149 (53), 135 (37.6), 121 (43), 105 (31.8), 95 (100), 86 (38.3), 79 (37.2), 55 (45.7), 49 (41.0), 41 (93.2); HRMS ($C_{21}H_{30}O_3$) *calcd*. (M + H) 331.2268 *found* 331.2270.

*(2E, 6E, 10E)-2, 6, 10-Trimethyl-12-(3-methyl-furan-2-yl)-dodeca-2, 6, 10-trienoic acid (***1**): To a solution of **16m** (18 mg, 0.05 mmol) in acetone (1 ml) was added aqueous lithium hydroxide (1M, 0.5 ml, 0.5 mmol) at 0 °C. The mixture was allowed to room temperature and stirred for 3 h. After dilution with diethyl ether (2 ml), the organic phase was acidified to pH≈4 with 5% aqueous hydrochloric acid. The extracts were washed with brine, water and dried. The solvent was evaporated *in vacuo* and the residue was purified by flash column chromatography on neutral aluminum oxide using pet. ether/acetate per 50 ml containing 1 drop of pyridine as eluent to give **1** (13 mg, 78%) as an oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ_{ppm} 7.21 (s, 1 H), 6.87 (m, 1H), 6.15 (s, 1 H), 5.26 (m, 1H), 5.13 (m, 1H), 3.28 (d, *J* = 7.2 Hz, 2H), 2.29–1.91 (m, 8H), 1.96 (s, 3H), 1.83 (s, 3H), 1.70 (s, 3H), 1.60 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.06, 150.15, 144.84, 139.78, 136.31, 133.88, 126.69, 125.09, 120.12, 113.41, 112.86, 39.44, 38.04, 27.50, 26.40, 25.16, 16.09, 15.95, 12.07, 9.75; IR (film, cm^{-1}): 3407, 2925, 2856, 1712, 1686, 1644, 1446, 1423, 1382, 1285, 1257, 1081, 890, 728; EIMS (*m/z*,%): 316 (M^+, 0.5), 248 (8.7), 233 (1.6), 191 (9.6), 149 (26.6), 135 (40.3), 95 (52.9), 43 (100), 55 (35.8); HRMS ($C_{20}H_{28}O_3$) *calcd*. 316.2038 *found* 316.2044.

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