Synthesis of γ-Hydroxybutenolides Applying Crossed Aldol Condensation in the Presence of a Bulky Lewis Acid and Their Anti-tumor Activity

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An improved synthesis of γ-hydroxybutenolides 1a—d was achieved *via* crossed aldol condensation between aldehydes 2a—d and the protected γ-hydroxy-β-methylbutenolides 3 or 4 using the bulky Lewis acid, aluminum tris(2,6-diphenylphenoxide) (ATPH). Using this same methodology, the γ-hydroxybutenolides 17a—d having various heteroaromatic rings were synthesized and their anti-tumor activities were evaluated.

Key words γ-hydroxybutenolide; crossed aldol condensation; bulky Lewis acid; anti-tumor activity

In the course of synthetic work to develop novel anti-tumor retinoidal compounds, we synthesized[1] γ-hydroxybutenolides **1a**—**d** (Fig. 1) containing conjugated double bond structures of various length. Biological activity measurements of these compounds revealed that only compound **1c** had promising properties. The compound **1c** is the equivalent of a formyl carboxylic acid **1c′**, which has a structure similar to that of retinoic acid having a formyl group at the C-13 position. In human promyelocytic leukemia (HL-60) cells, only **1c** showed both differentiation- and apoptosis-inducing activities in a manner different from retinoic acid.[1] Indeed its apoptosis-inducing potency at 10^{-6} M was almost compatible to that of staurosporine, a well-known potent inducer of apoptosis in HL-60 cells.[2]

The earlier procedure[1,3] for the synthesis of γ-hydroxybutenolides has been unsatisfactory, because the harsh conditions employed in the final step resulted in a low yield. Furthermore it was difficult to purify the desired products from the reaction mixture due to the generation of by-products.

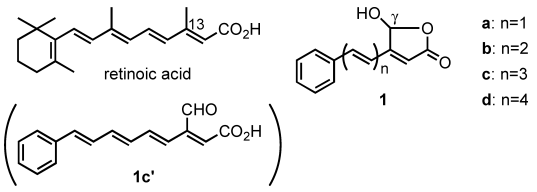

Fig. 1. Structure of Retinoic Acid and γ-Hydroxybutenolides **1a**—**d**

Herein, we describe an improved procedure, suitable for the synthesis of not only γ-hydroxybutenolides **1a**—**d** but also their analogues **17a**—**d** having various heteroaromatic rings. The anti-tumor activities of these analogues are also reported.

Results and Discussion

Improved Synthesis of γ-Hydroxybutenolides 1a—d Recently, Yamamoto and his coworkers reported[4] that vinylogous crossed aldol condensation between α,β-unsaturated esters and aldehydes in the presence of the bulky Lewis acid, aluminum tris(2,6-diphenylphenoxide) (ATPH), and lithium 2,2,6,6-tetramethylpiperidide (LTMP) regioselectively gave γ-addition products. In order to synthesize γ-hydroxybutenolides **1a**—**d** effectively, we applied this method for the condensation of aldehydes **2a**—**d** with the protected γ-hydroxy-β-methylbutenolides **3** or **4** (Chart 1).

The preparation of compounds **3** and **4** was initiated by the Emmons–Horner reaction of pyruvic aldehyde dimethyl acetal with triethyl phosphonoacetate in the presence of NaH to give an isomeric mixture ($E:Z=15:1$) of the ester **5** (94%). Treatment of **5** with 6 M hydrochloric acid under reflux afforded the γ-hydroxy-β-methylbutenolide **6**[5] (quant.), which was then protected with the triethylsilyl (TES) or *tert*-butyldimethylsilyl (TBS) group by the usual method to give the corresponding ethers **3** (86%) and **4** (64%), respectively.

According to Yamamoto's procedure,[4] precomplexation of a solution of benzaldehyde **2a** (1.0 eq) and the triethylsilyloxy (TESO)-butenolide **3** (2.0 eq) in toluene with ATPH (3.3

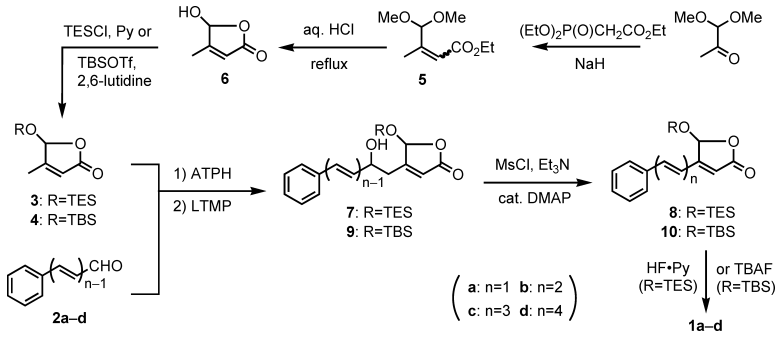

Chart 1. Synthesis of γ-Hydroxybutenolides **1a**—**d**

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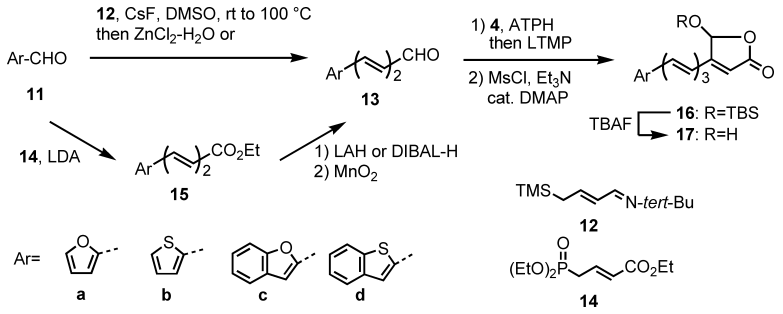

Chart 2. Synthesis of γ-Hydroxybutenolides **17a**—**d**

eq) followed by treatment with a solution of LTMP (2.3 eq) in tetrahydrofuran (THF) at −78 °C provided the desired aldol adduct **7a** in good yield (89%). On the other hand, this aldol reaction in the absence of ATPH resulted in a complex mixture, thus illustrating that ATPH gives some influences in this reaction. Dehydration[6] of **7a** by treatment with methanesulfonyl chloride (MsCl), triethylamine and a catalytic amount of 4-dimethylaminopyridine (DMAP) gave compound **8a** (76%), which was then desilylated with hydrogen fluoride pyridine (Py) complex, affording the γ-hydroxybutenolide **1a** (95%). Compounds **1b** and **1c** were similarly prepared by condensation of aldehydes **2b** and **2c**[7] with the TESO-butenolide **3** followed by dehydration (**8b**: 42%, **8c**: 21%) and subsequent desilylation (**1b**: 79%, **1c**: 72%). However, increasing the number of conjugated double bonds of aldehydes **2a**—**c** tended to decrease the yield of **1**, probably due to instability of the TES group. Thus, highly conjugated aldehydes **2c**[7] and **2d**[7] were condensed with the *tert*-butyldimethylsilyloxy (TBSO)-butenolide **4** instead of the TESO-butenolide **3** and subsequently dehydrated to afford compounds **10c** (45%) and **10d** (41%), respectively. Although the TBS groups of these compounds were resistant to treatment with hydrogen fluoride pyridine complex and aqueous hydrogen fluoride, they could be effectively deprotected by use of tetrabutylammonium fluoride (TBAF) at low temperature (−50 °C), leading to the desired γ-hydroxybutenolides **1c** (90%) and **1d** (95%), respectively.

The total yields from aldehydes **2a**—**d** to γ-hydroxybutenolides **1a** (65%, lit.[3]: 31%), **1b** (33%, lit.[3]: 13%), **1c** (41%, lit.[1]: 32%) and **1d** (39%, lit.[1]: 11%) have been improved. By this method, final products **1a**—**d** were conveniently purified by washing of the crude solids with a mixed solvent of diethyl ether and *n*-hexane.

Synthesis of γ-Hydroxybutenolides 17a—d To develop more effective anti-tumor γ-hydroxybutenolides, we next synthesized compounds **17a**—**d**. Various heteroaromatic rings were substituted for the benzene ring in **1c** as shown in Chart 2.

Dienals **13a**—**d** were prepared from commercially available aldehydes **11a**—**d**. According to the literature,[7] 2-furanal **11a** was treated with γ-trimethylsilyl (TMS) crotonaldimine **12** in the presence of cesium fluoride in DMSO at rt, followed by heating at 100 °C. Subsequent hydrolysis by aqueous zinc chloride afforded the dienal **13a** (56%; lit.[7]: 94%). The same reaction of the 2-thienyl aldehyde **11b** with TMS-aldimine **12** resulted in a complex mixture. Thus, the 2-thieny dienal **13b** was synthesized *via* the ester **15b**. Emmons–Horner reaction of the aldehyde **11b** with triethyl 4-phosphonocrotonate **14** in the presence of lithium diisopropylamide (LDA) gave the dienoate **15b** (72%), which was reduced with lithium aluminum hydride (LAH) and subsequently oxidized with manganese dioxide to provide the dienal **13b** (86%). The 2-benzofuranyl and 2-benzothienyl aldehydes **11c** and **11d** were similarly transformed into dienals **13c** (61%) and **13d** (66%) in 3 steps, except that diisobutylaluminum hydride (DIBAL-H) served as the reducing agent instead of LAH.

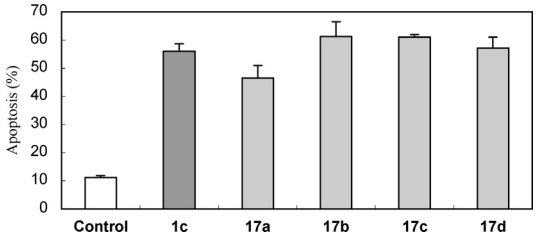

Fig. 2. Percentage of Apoptosis Peak in Culture of HL-60 Cells Treated with Vehicle or Butenolides **1c** and **17a**—**d** at 10^{-6} M

Condensation of these dienals with the TBSO-butenolide **4** under the conditions described by Yamamo followed by dehydration gave compounds **16a**—**d** (**16a**: 43%, **16b**: 35%, **16c**: 35%, **16d**: 25%), which were then deprotected to afford the desired γ-hydroxybutenolides **17a**—**d** (**17a**: 85%, **17b**: 64%, **17c**: 78%, **17d**: 79%), respectively.

Anti-tumor Activities of γ-Hydroxybutenolides 17a—d in HL-60 Cells Previously we reported[1] that of the four γ-hydroxybutenolides **1a**—**d** only **1c** was active for inducing differentiation and apoptosis in HL-60 cells. This finding suggested that the length of the conjugated system was related to the expression of the activity. As shown in Fig. 2, all γ-hydroxybutenolides **17a**—**d** induced apoptosis in HL-60 cells in a manner similar to **1c**, suggesting that the length of conjugated triene-double bonds between the butenolide ring and the aromatic ring is significant for the expression of inductive activities.

The expressions of cell surface antigen CD11b, a marker of granulocyte/monocyte/macrophage differentiation,[8] and of CD14 antigen, marker of monocyte-associated antigen,[9] were measured to evaluate the differentiation-inducing activity of these novel γ-hydroxybutenolides. All of these compounds induced both CD11b and CD14 expression as effectively as compound **1c** did (Fig. 3). Interestingly, compounds **17b**, **c**, and **d** showed fairly stronger differentiation-inducing activity than did **1c**. Thus, additional modifications of the benzene ring on the γ-hydroxybutenolide **1c** may lead to development of effective cancer chemotherapeutic agents. Fur-

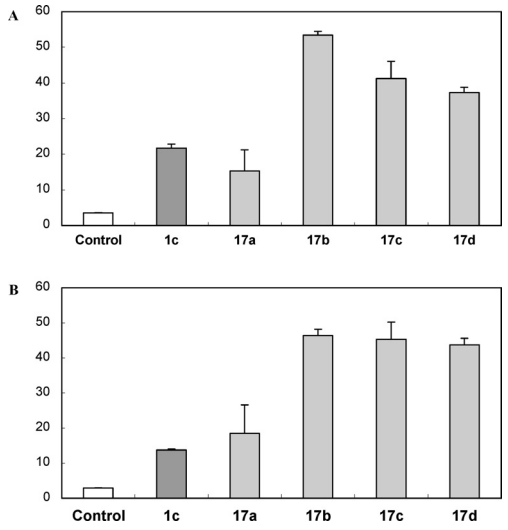

Fig. 3. Cell Surface CD11b Antigen (A)- and CD14 Antigen (B)-Positive Cell Number in Culture of HL-60 Cells Treated with Vehicle or Butenolides **1c** and **17a**—**d** at 10^{-6} M

ther modifications are currently in progress.

Experimental

General Melting points (mp) are measured on a micro melting point apparatus (Yanagimoto) and are uncorrected. UV–VIS spectra were recorded on a JASCO Ubest-55 instrument. IR spectra were measured on a Perkin Elmer FT-IR spectrometer, model Paragon 1000. ^{1}H- and ^{13}C-NMR spectra were determined on a Varian Gemini-300 or a Varian VXR-500 superconducting FT-NMR spectrometer, for deuteriochloroform solutions unless otherwise stated (tetramethylsilane as internal reference). Mass spectra were taken on a Hitachi M-4100 spectrometer.

CC was performed on silica gel (Merck Art. 7734). Short-column chromatography (SCC) was conducted on silica gel (Merck Art. 7739) under reduced pressure. PHPLC was carried out on a Shimadzu LC-6A with a UV–VIS detector.

All operations were carried out under nitrogen or argon. Evaporation of the extract or the filtrate was carried out under reduced pressure. Ether refers to diethyl ether, and hexane to *n*-hexane.

Ethyl 4,4-Diemthoxy-3-methylbut-2-enoate 5 A solution of the triethyl phosphonoacetate in dry THF (20 ml) was added dropwise to a stirred suspension of NaH (63% oil dispersion; 3.80 g, 100 mmol) in dry THF (80 ml) at 0 °C. After being stirred at 0 °C for 20 min, a solution of pyruvic aldehyde dimethyl acetal (8.00 g, 13 mmol) in dry THF (20 ml) was added dropwise to it. The reaction mixture was then warmed to rt and stirring was continued for 4 h. The reaction was quenched by addition of saturated aq. NH_4Cl and the mixture was extracted with ether. The extracts were washed with brine, dried and evaporated to give a residue, which was purified by CC (acetone–hexane, 3 : 17) to afford the etser **5** (12.0 g, 94%; *E* : *Z*, *ca.* 15 : 1) as a pale yellow oil; IR ($CHCl_3$) cm^{-1}: 1714 (conj. C=O), 1661 (C=C); ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.29 (3H, t, J=7 Hz, $CH_2C\underline{H}_3$), 1.90 (3/16H, s, *Z*-3-Me), 2.11 (45/16H, s, *E*-3-Me), 3.31 (90/16H, s, *E*-OMe×2), 3.43 (6/16H, s, *Z*-OMe×2), 4.18 (2H, q-like, J=7 Hz, $C\underline{H}_2CH_3$), 4.61 (15/16H, s, *E*-4-H), 5.80 (1/16H, s, *Z*-2-H), 5.95 (1/16H, s, *Z*-4-H), 6.03 (15/16H, s, *E*-2-H); MS *m/z*: 189.1120 [Calcd for $C_9H_{17}O_4$ requires (MH^+) 189.1126].

5-Hydroxy-4-methyl-2(5*H*)-furanone 6 According the reported procedure,[5] the ester **5** (4.50 g, 23.8 mmol; *E* : *Z*, *ca.* 15 : 1) was boiled under reflux with 6 M hydrochloric acid (50 ml) in the presence of catalytic amount of iodine (5 mg) for 3 h; every 45 min, about 5 ml was distilled form the mixture to remove the alcohols formed. The resulting mixture was concentrated under reduced pressure to give a residue, which was purified by CC (acetone–hexane, 1 : 7 to 3 : 7) to provide the hydroxybutenolide **6** (2.73 g, quant.) as a pale yellow oil. IR and ^{1}H-NMR data were identical with those reported.[5]

5-Triethylsilyloxy-4-methyl-2(5*H*)-furanone 3 To a solution of the hydroxybutenolide **6** (1.36 g, 11.9 mmol) and Py (1.93 ml, 23.9 mmol) in dry CH_2Cl_2 (20 ml) was added chlorotriethylsilane (TESCl) (2.40 ml, 14.3 mmol) at 0 °C. The mixture was stirred at 0 °C for 1 h, poured into chilled water and extracted with ether. The extracts were washed successively with aq. 5% HCl, saturated aq. $NaHCO_3$ and brine. Evaporation of the dried solution gave a residue, which was purified by CC (ether–hexane, 1 : 4) to afford the TES ether **3** (2.23 g, 82%) as a colorless oil; IR ($CHCl_3$) cm^{-1}: 1774 (C=O), 1659 (C=C); ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.72 (6H, q, J=8.5 Hz, $SiC\underline{H}_2CH_3$×3), 1.00 (9H, t, J=8.5 Hz, $CH_2C\underline{H}_3$×3), 2.05 (3H, s, 4-Me), 5.80 and 5.90 (each 1H, s, 3-H, 5-H); MS *m/z*: 229.1265 [Calcd for $C_{11}H_{21}O_3Si$ (MH^+) 229.1258].

Preparation of Compounds 8a—c *via* the Aldol Reaction between the TESO-Butenolide 3 and Aldehydes 2a—c To a solution of 2,6-diphenylphenol (2.44 g, 9.9 mmol) in dry toluene (10 ml) was added Me_3Al (2.0 M in toluene; 1.65 ml, 3.3 mmol) at rt. The resulting pale yellow solution was stirred for a further 30 min and then cooled to −78 °C. To this ATPH solution was added a solution of the butenolide **3** (456 mg, 2 mmol) and the aldehyde **2a** (106 mg, 1.0 mmol) in dry toluene (2 ml) at −78 °C and the mixture was stirred for a further 20 min. Then an LTMP solution, prepared from 2,2,6,6-tetramethylpiperidine (0.39 ml, 2.3 mmol) and *n*-BuLi (1.59 M in hexane; 1.45 ml, 2.3 mmol) in dry THF (12 ml) at −78 °C with stirring, was transferred by a steel cannula to the reaction mixture at −78 °C. After being stirred at this temperature for 1 h, the reaction was quenched with saturated aq. NH_4Cl. The resulting suspension was filtered through a Celite and the filtrate was extracted with ether. The extracts were washed with brine, dried and evaporated. To this residue was added hexane and the resulting precipitates of 2,6-diphenylphenol were filtered off. The filtrate was concentrated to give a residue, which was purified by short CC (AcOEt–hexane, 1 : 4 to 2 : 3) to provide the aldol adduct **7a** (298 mg, 89%; diastereomeric ratio, *ca.* 3 : 2) as a pale yellow oil; IR ($CHCl_3$) cm^{-1}: 3602, 3468 (OH), 1762 (C=O), 1651 (C=C); ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.72 (6H, q, J=7.5 Hz, $SiC\underline{H}_2CH_3$×3), 1.00 (9H, t, J=7.5 Hz, $CH_2C\underline{H}_3$×3), 2.40 (1H, br s, OH), *ca.* 2.78 (2/5H), 2.79 (6/5H, d, J=6 Hz), 2.88 (2/5H, dd, J=8, 15.5 Hz) (1′-H_2), 4.98 (1H, t-like, J=6 Hz, 2′-H), 5.81 (2/5H), 5.90 (3/5H), 5.93 (2/5H), 5.97 (3/5H) (each s, 3-H, 5-H), 7.36 (5H, s-like, Ar-H); MS *m/z*: 334.1608 [Calcd for $C_{18}H_{26}O_4Si$ (M^+) 334.1599].

Subsequently, MsCl (0.10 ml, 1.34 mnol) was added to a solution of the above aldol adduct **7a** (298 mg, 0.89 mmol), Et_3N (0.37 ml, 2.67 mmol) and DMAP (4 mg, 0.04 mmol) in dry CH_2Cl_2 (5 ml) at 0 °C. After being stirred at 0 °C for 30 min, the reaction mixture was diluted with AcOEt. The organic layer was washed successively with aq. 5% HCl, saturated aq. $NaHCO_3$ and brine. Evaporation of the dried solution gave a residue, which was purified by short CC (AcOEt–hexane, 1 : 9) to provide the dehydrated product **8a** (215 mg, 76%; 68% from **2a**) as a pale yellow oil; UV λ_{max} (EtOH) nm: 315; IR ($CHCl_3$) cm^{-1}: 1793, 1760 (split) (C=O), 1633, 1596 (C=C); ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.77 (6H, q, J=8 Hz, $SiC\underline{H}_2CH_3$×3), 1.03 (9H, t, J=8 Hz, $CH_2C\underline{H}_3$×3), 6.00 (1H, s, 3-H), 6.33 (1H, s, 5-H), 6.94 (1H, d, J=16.5 Hz, 1′-H), 7.19 (1H, d, J=16.5 Hz, 2′-H), 7.36—7.51 (5H, m, Ar-H); MS *m/z*: 316.1493 [Calcd for $C_{18}H_{24}O_3Si$ (M^+) 316.1493].

Compounds **8b** (42% from **2b**) and **8c** (21% from **2c**) were similarly prepared by the reaction of the TESO-butenolide **3** with the aldehyde **2b** or **2c**[7] and subsequent dehydration of the resulting aldol adducts **7b** (diastereomeric ratio, *ca.* 3 : 2) and **7c** (diastereomeric ratio, *ca.* 1 : 1).

5-Triethylsilyloxy-4-[(3*E*)-2-hydroxy-4-phenylbut-3-enyl]-2(5*H*)-furanone **7b**: Pale yellow oil; IR ($CHCl_3$) cm^{-1}: 3602, 3467 (OH), 1797, 1763 (split) (C=O), 1651, 1600 (C=C); ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.74 (6H, q, J=7.5 Hz, $SiC\underline{H}_2CH_3$×3), 1.00 (9H, t, J=7.5 Hz, $CH_2C\underline{H}_3$×3), 2.25 (1H, m, OH), 2.70 (2H, m, 1′-H_2), 4.59 (1H, m, 2′-H), 5.97 (2/5H, d-like, J=0.5 Hz), 5.99 (3/5H, d-like, J=0.5 Hz), 6.03 (3/5H, s), 6.04 (2/5H, s) (3-H, 5-H), 6.21 (2/5H), 6.24 (3/5H) (each dd, J=6.5, 16 Hz, 3′-H), 6.64 (1H, d, J=16 Hz, 4′-H), 7.26—7.40 (5H, m, Ar-H); MS *m/z*: 360.1749 [Calcd for $C_{20}H_{28}O_4Si$ (M^+) 360.1755].

5-Triethylsilyloxy-4-[(1*E*,3*E*)-4-phenylbuta-1,3-dienyl]-2(5*H*)-furanone **8b**: Pale yellow oil; UV λ_{max} (EtOH) nm: 344; IR ($CHCl_3$) cm^{-1}: 1758 (C=O), 1612 (C=C); ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.76 (6H, q, J=7.5 Hz, $SiC\underline{H}_2CH_3$×3), 1.02 (9H, t, J=7.5 Hz, $CH_2C\underline{H}_3$×3), 5.92 (1H, s, 3-H), 6.27 (1H, s, 5-H), 6.48 (1H, d, J=15 Hz, 1′-H), 6.79 (1H, d, J=15 Hz, 4′-H), 6.89 (1H, dd, J=10, 15 Hz, 3′-H), 6.99 (1H, dd, J=10, 15 Hz, 2′-H), 7.30—7.49 (5H, m, Ar-H); MS *m/z*: 342.1650 [Calcd for $C_{20}H_{26}O_3Si$ (M^+) 342.1651].

5-Triethylsilyloxy-4-[(3*E*,5*E*)-2-hydroxy-6-phenylhexa-3,5-dienyl]-2(5*H*)-furanone **7c**: Pale yellow oil; UV λ_{max} (EtOH) nm: 208, 280 (sh), 287; IR ($CHCl_3$) cm^{-1}: 3602, 3458 (OH), 1794, 1764 (C=O), 1650 (C=C); ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.73 (6H, q, J=8 Hz, $SiC\underline{H}_2CH_3$×3), 1.00 (9H, t, J=8 Hz, $CH_2C\underline{H}_3$×3), 2.05, 2.12 (each 1/2H, br s, OH), 2.66 (2H, m,

1′-H_2), 4.52 (1H, m, 2′-H), 5.82, 5.84 (each 1/2H, dd, J=4.5, 15 Hz, 3′-H), 5.96, 5.98 (each 1/2H, d-like, J=1 Hz, 3-H), 6.03, 6.04 (each 1/2H, s, 5-H), 6.44 (1H, dd, J=10.5, 15 Hz, 4′-H), 6.59 (1H, d, J=15.5 Hz, 6′-H), 6.75 (1H, dd-like, J=10.5, 15.5 Hz, 5′-H), 7.22—7.42 (5H, m, Ar-H); MS *m/z*: 386.1925 [Calcd for $C_{22}H_{30}O_4Si$ (M^+) 386.1912].

5-Triethylsilyloxy-4-[(1*E*,3*E*,5*E*)-6-phenylhexa-1,3,5-trienyl]-2(5*H*)-furanone **8c**: Pale yellow oil; UV λ_{max} (EtOH) nm: 374; IR ($CHCl_3$) cm^{-1}: 1789, 1758 (split) (C=O), 1627, 1598 (C=C); ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 0.60 (2H, q, J=8 Hz, C$\underline{H}_2$CH$_3$), 0.76 (4H, q-like, J=8 Hz, SiC$\underline{H}_2$CH$_3$×2), 0.97 (3H, t, J=8 Hz, CH$_2$C$\underline{H}_3$), 1.02 (6H, t, J=8 Hz, CH$_2$C$\underline{H}_3$×2), 5.89 (1H, s, 3-H), 6.25 (1H, s, 5-H), 6.40 (1H, d, J=15.5 Hz, 1′-H), 6.45 (1H, dd, J=11, 15 Hz, 3′-H), 6.63 (1H, dd, J=10.5, 15 Hz, 4′-H), 6.73 (1H, d, J=15.5 Hz, 6′-H), 6.89 (1H, dd, J=10.5, 15.5 Hz, 5′-H), 6.91 (1H, dd, J=11, 15.5 Hz, 2′-H), 7.27 (1H, t, J=7.5 Hz, 4″-H), 7.34 (2H, t, J=7.5 Hz, 3″-H, 5″-H), 7.43 (2H, d, J=7.5 Hz, 2″-H, 6″-H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 4.95 (SiCH$_2$×2), 5.81 (SiCH$_2$), 6.59 (CH$_2$CH$_3$), 6.62 (CH$_2$CH$_3$×2), 97.58 (C5), 115.22 (C3), 121.37 (C1′), 126.80 (C2″, C6″), 128.20, 128.45 (C5′, C4″), 128.80 (C3″, C5″), 131.83 (C3′), 136.39 (C6′), 136.68 (C1″), 139.35 (C4′), 139.88 (C2′), 162.09 (C4), 170.89 (C2); MS *m/z*: 368.1817 [Calcd for $C_{22}H_{28}O_3Si$ (M^+) 368.1806].

Desilylation of Compounds 8a—c HF·Py (0.5 ml) was added to a solution of the TES ether **8a** (173 mg, 0.55 mmol) in dry THF (5 ml) at 0 °C. After being stirred at 0 °C for 5 min, the reaction mixture was diluted with AcOEt. The organic layer was washed with brine, dried and evaporated to give a crude product, which was washed with a combined solution of ether and hexane (1 : 1) to afford the γ-hydorxybutenolide **1a** (105 mg, 95%) as colorless solids. Compounds **8b** and **8c** were similarly desilylated to provide γ-hydoroxybutenolides **1b** (79%) and **1c** (72%), respectively. These spectral data were in accordance with those reported.[1,3,10]

5-Hydroxy-4-[(1*E*)-2-phenylethenyl]-2(5*H*)-furanone **1a**: Colorless solid; UV λ_{max} (EtOH) nm: 313; UV λ_{max} (MeOH) nm (ε): 314 (32700); IR (KBr) cm^{-1}: 3226 (OH), 1735 (C=O), 1630, 1594 (C=C); ^{1}H-NMR (300 MHz, DMSO-d_6) δ: 6.23 (1H, s, 3-H), 6.40 (1H, s, 5-H), 7.17, 7.27 (each 1H, d, J=16.5 Hz, 1′-H, 2′-H), 7.36—7.47 (3H, m, 3″-H, 4″-H, 5″-H), 7.63 (1H, dd, J=1.5, 8 Hz, 2″-H, 6″-H), 7.94 (1H, br s, OH); ^{1}H-NMR (300 MHz, acetone-d_6) δ: 6.13 (1H, s, 3-H), 6.47 (1H, d-like, J=8.5 Hz, 5-H), 6.87 (1H, d, J=8.5 Hz, OH), 7.21, 7.40 (each 1H, d, J=16.5 Hz, 1′-H, 2′-H), 7.36—7.46 (3H, m, 3″-H, 4″-H, 5″-H), 7.65 (2H, m, 2″-H, 6″-H); MS *m/z*: 202.0627 [Calcd for $C_{12}H_{10}O_3$ (M^+) 202.0629].

5-Hydroxy-4-[(1*E*,3*E*)-4-phenylbuta-1,3-dienyl]-2(5*H*)-furanone **1b**: Pale yellow solid; UV λ_{max} (MeOH) nm (ε): 340 (47700); IR (KBr) cm^{-1}: 3287 (OH), 1752, 1736 (split) (C=O), 1610 (C=C); ^{1}H-NMR (300 MHz, DMSO-d_6) δ: 6.19 (1H, s, 3-H), 6.33 (1H, d, J=8.5 Hz, 5-H), 6.63 (1H, d, J=15 Hz, 1′-H), 6.95 (1H, d, J=15.5 Hz, 4′-H), 7.08 (1H, dd, J=10.5, 15.5 Hz, 3′-H), 7.15 (1H, dd, J=10.5, 15 Hz, 2′-H), 7.32 (1H, t-like, J=7.5 Hz, 4″-H), 7.39 (2H, t-like, J=7.5 Hz, 3″-H, 5″-H), 7.58 (2H, d-like, J=7.5 Hz, 2″-H, 6″-H), 7.91 (1H, d, J=8.5 Hz, OH); MS *m/z*: 228.0792 [Calcd for $C_{14}H_{12}O_3$ (M^+) 228.0785].

5-Hydroxy-4-[(1*E*,3*E*,5*E*)-6-phenylhexa-1,3,5-trienyl]-2(5*H*)-furanone **1c**: Yellow solid; UV λ_{max} (EtOH) nm: 368; UV λ_{max} (THF) (ε): 368 (61000); IR (KBr) cm^{-1}: 3285 (OH), 1736 (C=O), 1624, 1597 (C=C); ^{1}H-NMR (500 MHz, DMSO-d_6) δ: 6.13 (1H, s, 3-H), 6.29 (1H, d, J=8.5 Hz, 5-H), 6.54 (1H, d, J=15.5 Hz, 1′-H), 6.59 (1H, dd, J=11, 15 Hz, 3′-H), 6.77 (1H, dd, J=11, 15 Hz, 4′-H), 6.81 (1H, d, J=15.5 Hz, 6′-H), 7.00 (1H, dd, J=11, 15.5 Hz, 2′-H), 7.08 (1H, dd, J=11, 15.5 Hz, 5′-H), 7.27 (1H, t, J=7.5 Hz, 4″-H), 7.35 (2H, t, J=7.5 Hz, 3″-H, 5″-H), 7.52 (2H, d, J=7.5 Hz, 2″-H, 6″-H), 7.85 (1H, d, J=8.5 Hz, OH); ^{13}C-NMR (125 MHz, DMSO-d_6) δ: 97.64 (C5), 115.34 (C3), 122.04 (C1′), 126.71 (C2″, C6″), 128.24 (C4″), 128.76 (C5′), 128.79 (C3″, C5″), 132.40 (C3′), 135.57 (C6′), 136.60 (C1″), 139.12 (C4′), 139.73 (C2′), 162.05 (C4), 170.86 (C2); MS *m/z*: 254.0942 [Calcd for $C_{16}H_{14}O_3$ (M^+) 254.0942].

5-*tert*-Butyldiemthylsilyloxy-4-methyl-2(5*H*)-furanone 4 To a solution of the hydroxybutenolide **6** (6.00 g, 53 mmol) and 2,6-lutidine (18.4 ml, 156 mmol) in dry CH_2Cl_2 (20 ml) was added *tert*-butyldimethylsilyl trifluoromethanesulfonate (TBSOTf) (18.1 ml, 78 mmol) at 0 °C. The mixture was stirred at 0 °C for 2 h, poured into chilled water and extracted with ether. The extracts were washed successively with aq. 5% HCl, saturated aq. $NaHCO_3$ and brine. Evaporation of the dried solution gave a residue, which was purified by CC (acetone–hexane, 17 : 83) to afford the TBS ether **4** (7.68 g, 64%) as colorless solids; IR ($CHCl_3$) cm^{-1}: 1771 (C=O), 1659 (C=C); ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.19, 0.22 (each 3H, s, SiMe×2), 0.93 (9H, s, *tert*-Bu), 2.05 (3H, s, 4-Me), 5.81, 5.89 (each 1H, s, 3-H, 5-H); MS *m/z*: 229.1251 [Calcd for $C_{11}H_{21}O_3Si$ (MH^+) 229.1258].

Preparation of Compounds 10c, d *via* the Aldol Reaction between the TBSO-Butenolide 4 and Aldehydes 2c, d In the same manner as described for the preparation of compounds **8a**—**c** *via* the aldol reaction between the TESO-butenolide **3** and aldehydes **2a**—**c**, compounds **10c** (45% from **2c**) and **10d** (41% from **2d**) were similarly prepared by the reaction of the TBSO-butenolide **4** with the aldehyde **2c**[7] or **2d**[7] and subsequent dehydration.

5-*tert*-Butyldimethylsilyloxy-4-[(1*E*,3*E*,5*E*)-6-phenylhexa-1,3,5-trienyl]-2(5*H*)-furanone **10c**: Yellow solid; UV λ_{max} (EtOH) nm 374; IR ($CHCl_3$) cm^{-1}: 1760 (C=O), 1627, 1598, 1588 (C=C); ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.22, 0.28 (each 3H, s, SiMe×2), 0.95 (9H, s, *tert*-Bu), 5.89 (1H, s, 3-H), 6.25 (1H, s, 5-H), 6.40 (1H, d, J=15.5 Hz, 1′-H), 6.45 (1H, dd, J=11, 15 Hz, 3′-H), 6.62 (1H, dd, J=10.5, 15 Hz, 4′-H), 6.73 (1H, d, J=15.5 Hz, 6′-H), 6.90 (2H, dd-like, J=10.5, 15.5 Hz, 2′-H, 5′-H), 7.25—7.38 (3H, m, 3″-H, 4″-H, 5″-H), 7.44 (2H, d, J=8 Hz, 2″-H, 6″-H); MS *m/z*: 368.1814 [Calcd for $C_{22}H_{28}O_3Si$ (M^+) 368.1806].

5-*tert*-Butyldimethylsilyloxy-4-[(1*E*,3*E*,5*E*,7*E*)-8-phenylocta-1,3,5,7-tetraenyl]-2(5*H*)-furanone **10d**: Yellow solid; UV λ_{max} (EtOH) nm: 396; IR ($CHCl_3$) cm^{-1}: 1753 (C=O), 1618, 1599 (C=C); ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 0.21, 0.27 (each 3H, s, SiMe×2), 0.94 (9H, s, *tert*-Bu), 5.87 (1H, s, 3-H), 6.23 (1H, s, 5-H), 6.37 (1H, d, J=16 Hz, 1′-H), 6.38 (1H, dd, J=11, 15 Hz, 3′-H), 6.45 (1H, dd, J=11, 15 Hz, 5′-H), 6.54 (1H, dd, J=11, 15 Hz, 4′-H), 6.58 (1H, dd, J=10.5, 15 Hz, 6′-H), 6.66 (1H, d, J=15.5 Hz, 8′-H), 6.88 (2H, dd-like, J=10.5, 15.5 Hz, 7′-H, 2′-H), 7.25 (1H, t, J=7.5 Hz, 4″-H), 7.33 (2H, t, J=7.5 Hz, 3″-H, 5″-H), 7.42 (2H, d, J=7.5 Hz, 2″-H, 6″-H); MS *m/z*: 394.1962 [Calcd for $C_{24}H_{30}O_3Si$ (M^+) 394.1969].

Desilylation of Compounds 10c and 10d TBAF (1.0 M in THF; 0.55 ml, 0.55 mmol) was added to a stirred solution of the TBS ether **10c** (201 mg, 0.55 mmol) in dry THF (5 ml) at −50 °C and the mixture was stirred for a further 5 min. The reaction was quenched by addition of aq. 3% HCl and the mixture was extracted with AcOEt. The extracts were washed with brine, dried and evaporated to give a crude product, which was washed with a combined solution of ether and hexane (1 : 1) to afford the γ-hydorxybutenolide **1c** (125 mg, 90%) as yellow solids. Spectral properties of this compound were identical with those of the compound prepared by desilylation of the TES ether **8c**. The compounds **10d** was similarly desilylated to provide the γ-hydroxybutenolide **1d** (95%) as yellow solids. Spectral data were in accordance with those previously reported.[1]

5-Hydroxy-4-[(1*E*,3*E*,5*E*,7*E*)-8-phenylocta-1,3,5,7-tetraenyl]-2(5*H*)-furanone **1d**: UV λ_{max} (EtOH) nm (ε): 392 (66500); IR (nujol) cm^{-1}: 3269, 3165 (OH), 1737, 1710 (split) (C=O); ^{1}H-NMR (300 MHz, DMSO-d_6) δ: 6.12 (1H, s, 3-H), 6.29 (1H, br s, 5-H), 6.53 (1H, d, J=15.5 Hz, 1′-H), 6.49—6.60 (2H, m, 3′-H, 5′-H), 6.67 (1H, dd, J=10.5, 15 Hz, 6′-H), 6.72 (1H, dd, J=11, 15 Hz, 4′-H), 6.74 (1H, d, J=15.5 Hz, 8′-H), 6.99 (1H, dd, J=11, 15.5 Hz, 2′-H), 7.06 (1H, dd, J=10.5, 15.5 Hz, 7′-H), 7.26 (1H, t, J=7.5 Hz, 4″-H), 7.35 (2H, t, J=7.5 Hz, 3″-H, 5″-H), 7.51 (2H, d, J=7.5 Hz, 2″-H, 6″-H), 7.86 (1H, br s, OH); MS *m/z*: 280.1108 [Calcd for $C_{18}H_{16}O_3$ (M^+) 280.1099].

Ethyl (2*E*,4*E*)-5-(2-Thienyl)penta-2,4-dienoate 15b *n*-BuLi (1.60 M in hexane; 22.3 ml, 35.6 mmol) was added to a stirred solution of diisopropylamine (4.98 ml, 35.6 mmol) in dry THF (12 ml) at −30 °C and the mixture was stirred for a further 15 min. To this LDA solution was added dropwise a solution of triethyl 4-phosphonocrotonate **14** (8.70 g, 34.8 mmol) in dry THF (5 ml). The mixture was stirred at −30 °C, after which a solution of the aldehyde **11b** (3.00 g, 26.8 mmol) in dry THF was added dropwise at the same temperature and stirring was continued for a further 20 min. After being quenched with saturated aq. NH_4Cl, the mixture was extracted with ether. The extracts were washed with brine, dried and evaporated to give a residue, which was purified by CC (ether–hexane, 1 : 3) to afford the etser **15b** (4.00 g, 72%) as colorless crystals; mp 65—66 °C (ether–hexane); UV λ_{max} (EtOH) nm: 337; IR ($CHCl_3$) cm^{-1}: 1698 (conj. C=O), 1619 (C=C); ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.31 (3H, t, J=7 Hz, CH$_2$C$\underline{H}_3$), 4.22 (2H, q, J=7 Hz, C$\underline{H}_2$CH$_3$), 5.95 (1H, d, J=15 Hz, 2-H), 6.66 (1H, dd, J=11.5, 15 Hz, 4-H), 7.01 (1H, dd, J=3.5, 5 Hz, 4′-H), 7.01 (1H, d, J=15 Hz, 5-H), 7.11 (1H, d, J=3.5 Hz, 3′-H), 7.28 (1H, d, J=5 Hz, 5′-H), 7.38 (1H, dd, J=11.5, 15 Hz, 3-H); MS *m/z*: Found: 208.0570 [Calcd for $C_{11}H_{12}O_2S$ (M^+) 208.0557]. *Anal*. Calcd for $C_{11}H_{12}O_2S$: C, 63.43; H, 5.81. Found: C, 63.40; H, 5.96.

(2*E*,4*E*)-5-(2-Thienyl)penta-2,4-dienal 13b A solution of the ester **15b** (1.90 g, 9.13 mmol) in dry ether (15 ml) was added dropwise to a stirred suspension of LAH (0.26 g, 6.85 mmol) in dry ether (50 ml) at 0 °C and the mixture was stirred at 0 °C for 5 min. After the excess of LAH was decomposed addition of water, the mixture was extracted with ether. The extracts were dried and evaporated to give a crude alcohol, which without purification was dissolved in a mixture of ether and hexane (*ca.* 1 : 1) and shaken

with active MnO_2 (30 g) at rt for 5 h. The mixture was filtered through Celite. Evaporation of the filtrate gave a residue, which was purified by CC (acetone–hexane, 1 : 4) to provide the dienal **13b** (1.20 g, 86%) as yellow solids. ^{1}H-NMR data were accordance with those reported[7]; UV λ_{max} (EtOH) nm: 350; IR ($CHCl_3$) cm^{-1}: 1673 (conj. C=O), 1616 (C=C); ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 6.21 (1H, dd, J=8, 15 Hz, 2-H), 6.77 (1H, dd, J=11, 15 Hz, 4-H), 7.04 (1H, dd, J=3, 5 Hz, 4′-H), 7.12 (1H, d, J=15 Hz, 5-H), 7.18 (1H, d, J=3 Hz, 3′-H), 7.18 (1H, dd, J=11, 15 Hz, 3-H), 7.34 (1H, d, J=5 Hz, 5′-H), 9.58 (1H, d, J=8 Hz, CHO); MS m/z: 164.0279 [Calcd for C_9H_8OS (M^+) 164.0296].

Ethyl (2*E*,4*E*)-5-(2-Benzofuranyl)penta-2,4-dienoate 15c According to the procedure for the preparation of the ester **15b**, Emmons–Horner reaction between the aldehyde **11c** (930 mg, 6.58 mmol) and the phosphonate **14** followed by purification by CC (acetone–hexane, 1 : 4) provided the ester **15c** (1.72 g, 82%) as pale yellow crystals; mp 47—48 °C (ether–hexane); UV λ_{max} (EtOH) nm: 345; IR ($CHCl_3$) cm^{-1}: 1703 (conj. C=O), 1622, 1611 (C=C); ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.31 (3H, t, J=7.5 Hz, $CH_2C\underline{H}_3$), 4.23 (2H, q, J=7.5 Hz, $C\underline{H}_2CH_3$), 6.04 (1H, d, J=15.5 Hz, 2-H), 6.71 (1H, s, 3′-H), 6.72 (1H, d, J=15.5 Hz, 5-H), 7.00 (1H, dd, J=11.5, 15.5 Hz, 4-H), 7.19 (1H, t-like, J=7.5 Hz, 5′-H), 7.28 (1H, t-like, J=7.5 Hz, 6′-H), 7.40 (1H, dd, J=11.5, 15.5 Hz, 3-H), 7.43 (1H, d, J=7.5 Hz, 7′-H), 7.51 (1H, d, J=7.5 Hz, 4′-H); MS m/z: 242.0934 [Calcd for $C_{15}H_{14}O_3$ (M^+) 242.0942]. *Anal*. Calcd for $C_{15}H_{14}O_3$: C, 74.36; H, 5.82. Found: C, 74.46; H, 5.85.

(2*E*,4*E*)-5-(2-Benzofuranyl)penta-2,4-dienal 13c DIBAL-H (1.0 M in hexane; 6.57 ml, 6.57 mmol) was added to a solution of the ester **15c** (1.06 g, 4.38 mmol) in dry CH_2Cl_2 (20 ml) at 0 °C and the mixture was further stirred for 5 min. The excess of DIBAL-H was destroyed by an addition of moist silica gel (SiO_2–H_2O, 10 : 1), and the mixture was filtered through Celite. The filtrate was dried and evaporated to give a crude alcohol, which without purification was dissolved in THF and shaken with active MnO_2 (15 g) at rt for 5 h. The mixture was filtered through Celite. Evaporation of the filtrate gave the crude product, which was recrystallized from AcOEt–ether–hexane to afford the dienal **13c** (643 mg, 74%) as pale yellow crystals; mp 87—88 °C; UV λ_{max} (EtOH) nm: 356; IR ($CHCl_3$) cm^{-1}: 1671 (conj. C=O), 1620, 1607 (C=C); ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 6.32 (1H, dd, J=8, 14.5 Hz, 2-H), 6.84 (1H, s, 3′-H), 6.87 (1H, d, J=14 Hz, 5-H), 7.14 (1H, dd, J=11, 14 Hz, 4-H), 7.23 (1H, td, J=1, 7.5 Hz, 5′-H), 7.23 (1H, dd, J=11, 14.5 Hz, 3-H), 7.34 (1H, td, J=1, 7.5 Hz, 6′-H), 7.50 (1H, dd, J=1, 7.5 Hz, 7′-H), 7.56 (1H, br d, J=7.5 Hz, 4′-H), 9.63 (1H, d, J=8 Hz, CHO); MS m/z: 198.0682 [Calcd for $C_{13}H_{10}O_2$ (M^+) 198.0681]. *Anal*. Calcd for $C_{13}H_{10}O_2$: C, 78.77; H, 5.09. Found: C, 78.79; H, 5.28.

Ethyl (2*E*,4*E*)-5-(2-Benzo[*b*]thieny)penta-2,4-dienoate 15d According to the procedure for the preparation of the ester **15b**, the aldehyde **11d** (3.00 g, 18.5 mmol) was condensed with the phosphonate **14** to give solids, which was recrystallized from MeOH to afford the ester **15d** (4.28 g, 90%) as orange crystals; mp 94—95 °C; UV λ_{max} (EtOH) nm: 344; IR ($CHCl_3$) cm^{-1}: 1703 (conj. C=O), 1621, 1590 (C=C); ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.32 (3H, t, J=7 Hz, $CH_2C\underline{H}_3$), 4.23 (2H, q, J=7 Hz, $C\underline{H}_2CH_3$), 6.00 (1H, d, J=15.5 Hz, 2-H), 6.71 (1H, dd, J=11, 15 Hz, 4-H), 7.09 (1H, dd, J=0.6, 15 Hz, 5-H), 7.29 (1H, s, 3′-H), 7.33 (2H, m, Ar-H), 7.41 (1H, ddd, J=0.6, 11, 15.5 Hz, 3-H), 7.68—7.79 (2H, m, Ar-H); MS m/z: 258.0714 [Calcd for $C_{15}H_{14}O_2S$ (M^+) 258.0714]. *Anal*. Calcd for $C_{15}H_{14}O_2S$: C, 69.74; H, 5.46; S, 12.39. Found: C, 69.76; H, 5.48; S, 12.44.

(2*E*,4*E*)-5-(2-Benzo[*b*]thieny)penta-2,4-dienal 13d In the same manner as described for the preparation of the dienal **13c**, reduction of the above ester **15d** (1.50 g, 5.81 mmol) with DIBAL-H followed by oxidation with MnO_2 gave solids, which was recrystallized from AcOEt–hexane to afford the aldehyde **13d** (913 mg, 73%) as orange crystals; mp 135—136 °C; UV λ_{max} (EtOH) nm: 357; IR ($CHCl_3$) cm^{-1}: 1678 (conj. C=O), 1616, 1588 (C=C); ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 6.26 (1H, dd, J=8, 15.5 Hz, 2-H), 6.81 (1H, dd, J=11, 15.5 Hz, 4-H), 7.20 (1H, d, J=15.5 Hz, 5-H), 7.20 (1H, dd, J=11, 15.5 Hz, 3-H), 7.31—7.38 (2H, m, Ar-H), 7.36 (1H, s, 3′-H), 7.70—7.81 (2H, m, Ar-H) 9.60 (1H, d, J=8 Hz CHO); MS m/z: 214.0448 [Calcd for $C_{13}H_{10}OS$ (M^+) 214.0452]. *Anal*. Calcd for $C_{13}H_{10}OS$: C, 72.87; H, 4.70; S, 14.96. Found: C, 72.63; H, 4.86; S, 15.06.

Preparation of Compounds 16a—d In the same manner as described for the preparation of compounds **8a**—**c** *via* the aldol reaction between the TESO-butenolide **3** and aldehydes **2a**—**c**, compounds **16a** (43% from **13a**[7]), **16b** (35% from **13b**), **16c** (35% from **13c**) and **16d** (79% from **13d**) were similarly prepared by the reaction of the TBSO-butenolide **4** with aldehydes **13a**—**d** and subsequent dehydration.

5-*tert*-Butyldimethylsilyloxy-4-[(1*E*,3*E*,5*E*)-6-(2-furanyl)hexa-1,3,5-trienyl]-2(5*H*)-furanone **16a**: Orange solid; UV λ_{max} (EtOH) nm: 393; IR ($CHCl_3$) cm^{-1}: 1751 (C=O), 1618, 1581 (C=C); ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 0.21, 0.27 (each 3H, s, SiMe×2), 0.94 (9H, s, *tert*-Bu), 5.88 (1H, s, 3-H), 6.23 (1H, s, 5-H), 6.37 (1H, d, J=3.5 Hz, 3″-H), 6.38 (1H, d, J=15.5 Hz, 1′-H), 6.42 (1H, dd, J=2, 3.5 Hz, 4″-H), 6.43 (1H, dd, J=11, 14.5 Hz, 3′-H), 6.50 (1H, d, J=16 Hz, 6′-H), 6.54 (1H, dd, J=11, 14.5 Hz, 4′-H), 6.78 (1H, dd, J=11, 16 Hz, 5′-H), 6.88 (1H, dd, J=11, 15.5 Hz, 2′-H), 7.41 (1H, d, J=2 Hz, 5″-H); MS m/z: 358.1599 [Calcd for $C_{20}H_{26}O_4Si$ (M^+) 358.1596].

5-*tert*-Butyldimethylsilyloxy-4-[(1*E*,3*E*,5*E*)-6-(2-thienyl)hexa-1,3,5-trienyl]-2(5*H*)-furanone **16b**: Orange solid; UV λ_{max} (EtOH) nm: 392; IR ($CHCl_3$) cm^{-1}: 1759 (C=O), 1624, 1581 (C=C); ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.21, 0.27 (each 3H, s, SiMe×2), 0.94 (9H, s, *tert*-Bu), 5.88 (1H, s, 3-H), 6.23 (1H, s, 5-H), 6.37 (1H, d, J=16 Hz, 1′-H), 6.41 (1H, dd, J=11, 15 Hz, 3′-H), 6.55 (1H, dd, J=10, 15 Hz, 4′-H), 6.68 (1H, dd, J=10, 15 Hz, 5′-H), 6.86 (1H, d, J=15 Hz, 6′-H), 6.89 (1H, dd, J=11, 16 Hz, 2′-H), 6.70 (1H, dd, J=3.5, 5 Hz, 4″-H), 7.05 (1H, d, J=3.5 Hz, 3″-H), 7.24 (1H, d, J=5 Hz, 5″-H); MS m/z: 374.1371 [Calcd for $C_{20}H_{26}O_3SSi$ (M^+) 374.1370].

4-[(1*E*,3*E*,5*E*)-6-(2-Benzofuranyl)hexa-1,3,5-trienyl]-5-*tert*-butyldimethylsilyloxy-2(5*H*)-furanone **16c**: Orange solid; UV λ_{max} (EtOH) nm: 401; IR ($CHCl_3$) cm^{-1}: 1757 (C=O), 1625, 1578 (C=C); ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.22, 0.28 (each 3H, s, SiMe×2), 0.93 (9H, s, *tert*-Bu), 5.91 (1H, s, 3-H), 6.25 (1H, s, 5-H), 6.43 (1H, d, J=15.5 Hz, 1′-H), 6.51 (1H, dd, J=10.5, 14.5 Hz, 3′-H), 6.61 (1H, dd, J=10, 14.5 Hz, 4′-H), 6.62 (1H, d, J=15.5 Hz, 6′-H), 6.69 (1H, s, 3″-H), 6.90 (1H, dd, J=10.5, 15.5 Hz, 2′-H), 7.05 (1H, dd, J=10, 15.5 Hz, 5′-H), 7.21 (1H, t-like, J=7.5 Hz, 5″-H), 7.29 (1H, t-like, J=7.5 Hz, 6″-H), 7.44 (1H, d, J=7.5 Hz, 7″-H), 7.53 (1H, d, J=7.5 Hz, 4″-H); MS m/z: 408.1766 [Calcd for $C_{24}H_{28}O_4Si$ (M^+) 408.1755].

4-[(1*E*,3*E*,5*E*)-6-(2-Benzo[*b*]thienyl)hexa-1,3,5-trienyl]-5-*tert*-butyldimethylsilyloxy-2(5*H*)-furanone **16d**: Orange solid; UV λ_{max} (EtOH) nm: 397; IR ($CHCl_3$) cm^{-1}: 1757 (C=O), 1624, 1579 (C=C); ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.22, 0.28 (each 3H, s, SiMe×2), 0.94 (9H, s, *tert*-Bu), 5.90 (1H, s, 3-H), 6.24 (1H, s, 5-H), 6.41 (1H, d, J=15.5 Hz, 1′-H), 6.48 (1H, dd, J=10.5, 14 Hz, 3′-H), 6.59 (1H, dd, J=10.5, 14 Hz, 4′-H), 6.74 (1H, dd, J=10.5, 15 Hz, 5′-H), 6.90 (1H, dd, J=10.5, 15.5 Hz, 2′-H), 6.95 (1H, d, J=15 Hz, 6′-H), 7.24 (1H, s, 3″-H), 7.32 (2H, m, Ar-H), 7.67—7.78 (2H, m, Ar-H); MS m/z: 424.1541 [Calcd for $C_{24}H_{28}O_3SSi$ (M^+) 424.1527].

Desilylation of Compounds 16a–d In the same manner as described for the desilylation of compounds **10c** and **10d**, compounds **16a**—**d** were treated with TBAF to give compounds **17a** (85%), **17b** (64%), **17c** (79%) and **17d** (79%), as orange solids, respectively.

4-[(1*E*,3*E*,5*E*)-6-(2-Furanyl)hexa-1,3,5-trienyl]-5-hyxroxy-2(5*H*)-furanone **17a**: UV λ_{max} (EtOH) nm: 391; λ_{max} (MeOH) nm (ε): 350 (48400); IR (KBr) cm^{-1}: 3343 (OH), 1752, 1736 (split) (C=O), 1616, 1576 (C=C); ^{1}H-NMR (500 MHz, DMSO-d_6) δ: 6.12 (1H, s, 3-H), 6.28 (1H, d, J=8.5 Hz, 5-H), 6.51 (1H, d, J=15.5 Hz, 1′-H), 6.54 (1H, dd, J=1.5, 3.5 Hz, 4″-H), 6.58 (1H, dd, J=11.5, 14 Hz, 3′-H), 6.59 (1H, d, J=3.5 Hz, 3″-H), 6.67 (1H, d, J=15 Hz, 6′-H), 6.73 (1H, dd, J=11, 14 Hz, 4′-H), 6.78 (1H, dd, J=11, 15 Hz, 5′-H), 6.97 (1H, dd, J=11.5, 15.5 Hz, 2′-H), 7.70 (1H, d, J=1.5 Hz, 5″-H), 7.84 (1H, d, J=8.5 Hz, 5-OH); ^{13}C-NMR (125 MHz, DMSO-d_6) δ: 97.62 (C5), 110.78 (C3″), 112.41 (C4″), 115.19 (C3), 121.84 (C1′), 122.85 (C6′), 126.66 (C5′), 132.27 (C3′), 138.63 (C4′), 139.69 (C2′), 143.85 (C5″), 152.40 (C2″), 162.03 (C4), 170.85 (C2); MS m/z: 244.0757 [Calcd for $C_{14}H_{12}O_4$ (M^+) 244.0735].

5-Hydroxy-4-[(1*E*,3*E*,5*E*)-6-(2-thienyl)hexa-1,3,5-trienyl]-2(5*H*)-furanone **17b**: UV λ_{max} (EtOH) nm: 387; UV λ_{max} (MeOH) nm (ε): 389 (60700); IR (KBr) cm^{-1}: 3271 (OH), 1744 (C=O), 1619, 1577 (C=C); ^{1}H-NMR (500 MHz, DMSO-d_6) δ: 6.11 (1H, s, 3-H), 6.27 (1H, br s, 5-H), 6.50 (1H, d, J=15.5 Hz, 1′-H), 6.57 (1H, dd, J=11, 14 Hz, 3′-H), 6.71 (1H, dd, J=11, 14 Hz, 4′-H), 6.75 (1H, dd, J=11, 14.5 Hz, 5′-H), 6.97 (1H, dd, J=11, 15.5 Hz, 2′-H), 6.99 (1H, d, J=14.5 Hz, 6′-H), 7.05 (1H, dd, J=3.5, 5.5 Hz, 4″-H), 7.19 (1H, d, J=3.5 Hz, 3″-H), 7.50 (1H, d, J=5.5 Hz, 5″-H), 7.84 (1H, br s, 5-OH); ^{13}C-NMR (125 MHz, DMSO-d_6) δ: 97.69 (C5), 115.23 (C3), 121.84 (C1′), 126.59. (C5″), 127.70 (C3″), 128.03 (C5′), 128.27 (C4″), 128.52 (C6′), 132.07 (C3′), 138.61 (C4′), 139.72 (C2′), 141.86 (C2″), 162.01 (C4), 170.85 (C2); MS m/z: 260.0517 [Calcd for $C_{14}H_{12}O_3S$ (M^+) 260.0506].

4-[(1*E*,3*E*,5*E*)-6-(2-Benzofuranyl)hexa-1,3,5-trienyl]-5-hydroxy-2(5*H*)-furanone **17c**: UV λ_{max} (EtOH) nm: 398; UV λ_{max} (MeOH) nm (ε): 398 (61700); IR (KBr) cm^{-1}: 3246 (OH), 1747, 1719 (split) (C=O), 1613, 1573 (C=C); ^{1}H-NMR (500 MHz, DMSO-d_6) δ: 6.17 (1H, s, 3-H), 6.31 (1H, d, J=8.5 Hz, 5-H), 6.58 (1H, d, J=16 Hz, 1′-H), 6.72 (1H, dd, J=11, 15 Hz, 3′-H), 6.82 (1H, dd, J=11, 15 Hz, 4′-H), 6.85 (1H, d, J=15 Hz, 6′-H), 7.01 (1H, s, 3″-H), 7.02 (1H, dd, J=11, 16 Hz, 2′-H), 7.07 (1H, dd, J=11, 15 Hz,

5′-H), 7.24 (1H, t-like, J=7.5 Hz, 5″-H), 7.32 (1H, t-like, J=7.5 Hz, 6″-H), 7.54 (1H, d, J=7.5 Hz, 7″-H), 7.61 (1H, d, J=7.5 Hz, 4″-H), 7.88 (1H, d, J=8.5 Hz, 5-OH); ^{13}C-NMR (125 MHz, DMSO-d_6) δ: 97.58 (C5), 106.83 (C3″), 110.74 (C7″), 115.65 (C3), 121.20 (C4″), 122.45 (C6′), 122.73 (C1′), 123.18 (C5″), 125.23 (C6″), 128.60 (C3″a), 129.89 (C5′), 133.94 (C3′), 137.92 (C4′), 139.34 (C2′), 154.27, 154.38 (C2″, C7″a), 161.82 (C4), 170.72 (C2); MS m/z: 294.0913 [Calcd for $C_{18}H_{14}O_4$ (M^+) 294.0891].

4-[(1*E*,3*E*,5*E*)-6-(2-Benzo[*b*]thienyl)hexa-1,3,5-trienyl]-5-hydroxy-2(5*H*)-furanone **17d**: UV λ_{max} (EtOH) nm: 392; UV λ_{max} (MeOH) nm (ε): 391 (40500); IR (KBr) cm^{-1}: 3308 (OH), 1761 (C=O), 1622, 1577 (C=C); ^{1}H-NMR (500 MHz, DMSO-d_6) δ: 6.17 (1H, s, 3-H), 6.31 (1H, d, J=8.5 Hz, 5-H), 6.57 (1H, d, J=15.5 Hz, 1′-H), 6.69 (1H, dd, J=11, 14 Hz, 3′-H), 6.79 (1H, dd, J=10.5, 14 Hz, 4′-H), 6.84 (1H, dd, J=10.5, 14 Hz, 5′-H), 7.02 (1H, dd, J=11, 15.5 Hz, 2′-H), 7.15 (1H, d, J=14 Hz, 6′-H), 7.35 (2H, m, 6″-H, 5″-H), 7.49 (1H, s, 3″-H), 7.79 (1H, d-like, J=9 Hz, 4″-H), 7.88 (1H, d, J=8.5 Hz, 5-OH), 7.91 (1H, d-like, J=9 Hz, 7″-H); ^{13}C-NMR (125 MHz, DMSO-d_6) δ: 97.64 (C5), 115.63 (C3), 122.41 (C7″), 122.58 (C1′), 123.80 (C4″), 124.79 (C3″), 124.85, 125.31 (C5″, C6″), 128.83 (C6′), 130.68 (C5′), 133.40 (C3′), 138.08 (C4′), 138.55, 139.86 (C3″a, C7″a), 139.50 (C2′), 141.92 (C2″), 161.92 (C4), 170.81 (C2); MS m/z: 310.0685 [Calcd for $C_{18}H_{14}O_3S$ (M^+) 310.0663].

HL-60 Cells and Synchronization of Cell Cycle at S Phase by Excess Amounts of Thymidine HL-60 cells were maintained in continuous culture in RPMI-1640 medium (Nissui Seiyaku Co., Ltd., Tokyo, Japan) supplemented with 10% dextran-coated charcoal-treated fetal calf serum (FCS) (Gibco BRL, Grand Island, NY, U.S.A.), and kanamycin (0.06 mg/ml) (Sigma, St. Louis, MO, U.S.A.) at 37 °C in a humidified atmosphere of 5% CO_2 in air. The doubling time of HL-60 cells was approximately 24 h. For synchronization at S phase, cells (4×10^5 cells/ml) were cultured in 30 ml of RPMI-1640 medium supplemented with 2.5 mM thymidine. After washing with Ca, Mg-free phosphate-buffered saline (PBS) [PBS(−)]twice, the synchronization of cell cycle was repeated in the same manner, and the cells thus obtained were used in the biological assays.

Flow Cytometry Cells (10^5 cells/well) were placed in 24-well tissue culture plates and cultured for 24 h with each sample (10^{-6} M) in RPMI-1640 medium at 37 °C in a humidified atmosphere of 5% CO_2 in air. To reduce the effects of contact inhibition, control cells were adjusted to 60 to 70% confluency at the time of FACS analysis. Each group of cells was collected in PBS(−). Then, the cells were resuspended in PBS(−) containing 0.2% Triton-X and 1 μg/μl RNase, and incubated at 37 °C for 1 h. Cells were washed with PBS(−) and incubated with 0.5 ml of DNA-staining solution containing propidium iodide (50 μg/ml) at 4 °C for 20 min. The cells were analyzed with a flow cytometer euipped with an argon laser (488 nm, Becton Dickinson FACScan^{TM}) and cell cycle distribution was analyzed by ModiFiT LT (Verity).

Cell Surface Antigen Expression Analysis Cells (10^5 cells/well) were placed in 24-well tissue culture plates, and cultured for 24 h in RPMI-1640 medium with each sample (10^{-6} M) under the same conditions as described in the flow cytometry. Each group of cells was then collected and washed with PBS(−) once. Then, the cells (2×10^5 cells) were resuspended in 100 μl diluent solution containing 1% bovine serum albumin (BSA) and 1% sodium azide and incubated with 10 μl human monoclonal FITC conjugated CD 11b antibody and CD14 antibody (Sigma) for 30 min at room temperature. The cells were washed once with diluent solution and then fixed in 300 μl of PBS(−) containing 2% paraformaldehyde. Fluorescence was detected on a Becton Dickinson FACScan^{TM} at excitation wavelength of 490 nm and emission wavelength of 520 nm. Results were recorded as the mean fluorescence index, which is the product of the % fluorescence and the mean fluorescenced intensity, with 10^4 cells being counted per treatment.

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