Structural Development of Benzhydrol-Type 1′-Acetoxychavicol Acetate (ACA) Analogs as Human Leukemia Cell-Growth Inhibitors Based on Quantitative Structure–Activity Relationship (QSAR) Analysis

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Benzhydrol-type analogs of 1′-acetoxychavicol acetate (ACA) were developed as inhibitors of human leukemia HL-60 cell growth based on quantitative structure–activity relationship (QSAR) analysis. An analog containing an anthracenyl moiety (8) was a potent inhibitor with the IC_{50} value of 0.12 μM.

Key words 1′-acetoxychavicol acetate; benzhydrol analog; HL-60; quantitative structure–activity relationship; molecular operating environment

1′-Acetoxychavicol acetate (ACA: **1**, Fig. 1) was first isolated from the rhizomes and seeds of Zingiberaceae plants, including *Languas garanga* and *Alpinia garanga*, which have been used as a ginger substitute and a stomach medicine in Southeast Asia.[1)] Recent studies have revealed that ACA (**1**) exhibits antitumor activities against a wide variety of cancers[2—6)] and anti-tumor-promoting activities towards estrogen-related endometrial carcinogenesis,[4)] azoxymethane-induced colonic aberrant crypt foci,[5)] phorbol ester-induced skin tumor promotion.[6)] Moreover, ACA (**1**) has been reported to elicit a variety of biological activities, including antioxidant, anti-inflammatory, and anti-human immunodeficiency virus (HIV) activity,[7—9)] induction of nitric oxide (NO) synthase gene expression,[8)] and inhibition of interferon-β production.[10)] We (Kizaki's group) have recently reported that ACA (**1**) induces the apoptosis of myeloid leukemia cells *in vitro* and *in vivo* through inhibition of NF-κB-related functions,[11,12)] suggesting ACA (**1**) is a candidate therapeutic agent for the treatment of myeloid leukemia. ACA (**1**) induces cell apoptosis through two different pathways in myeloid leukemia cells, *i.e.*, through generation of reactive oxygen species (ROS) and through activation of the Fas-pathway.[11)] ACA (**1**) also inhibited the cellular growth of myeloma cells in association with the down-regulation of NF-κB activity, affecting both the caspase 8 and 9 pathways.[13)]

Azuma *et al.* recently reported structure–activity relationship studies of ACA (**1**) for apoptotic activity towards human leukemia HL-60 cells,[14)] showing that (i) the two acetyl groups and the unsaturated double bond between the Cβ and Cγ positions of ACA (**1**) are essential for the activity, and (ii) the configuration at the α-position of ACA (**1**) does not affect the activity. Based on these results, we synthesized several ACA (**1**) analogs and examined their cell-growth-inhibitory activity using human leukemia HL-60 cells. Compound **2** (Fig. 1), a benzhydrol diacetate derivative, possessed moderate HL-60 cell-growth-inhibitory activity with an IC_{50} value of 3.5 μM, *i.e.*, it is slightly less potent than ACA (**1**, IC_{50}=2.0 μM). This led us to plan detailed structure–activity relationship studies of benzhydrol analogs developed from **2** as a lead compound.

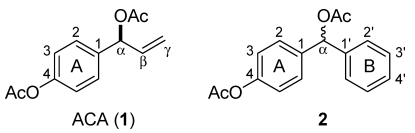

Fig. 1. Structures of ACA (**1**) and **2**

Here we describe structural development of benzhydrol-type potent HL-60 cell-growth inhibitors, guided by quantitative structure–activity relationship (QSAR) analysis.

Chemistry The synthesis of compound **2** and its analogs is outlined in Charts 1—3. Briefly, the hydroxyl group of 4-hydroxybenzaldehyde (**9**) was protected with *tert*-butyldimethylchlorosilane (TBS-Cl), followed by treatment with appropriate Grignard or aryllithium reagents (generated from aryl bromide by treatment with *n*-butyllithium) to afford the intermediates **11a**—**d**. Deprotection of the TBS group was performed with tetra-*n*-butylammonium fluoride (TBAF), and then acetylation with acetic anhydride afforded **3a**—**d**. On the other hand, protection of the hydroxyl group of 4-bromophenol (**14**) with TBS-Cl, followed by treatment with *n*-butyllithium, gave aryllithium species, which were quenched with various benzaldehydes to give intermediates **11e**—**h** and **13a**. Deprotection of the TBS group with TBAF, and successive acetylation with acetic anhydride afforded **3e**—**h** and **5a**. Sulfoxide **3j** and sulfone **3k** were prepared from **3c**. Oxidation of **3c** with 1 or 2 eq of *m*-chloroperbenzoic acid gave **3j** and **3k**, respectively. Compounds **3i** and **4a**—**g** were synthesized by our method using $^{t}Bu_4ZnLi_2$.[15,16)] As shown in Chart 2, iodobenzenes **16a**—**h** were treated with $^{t}Bu_4ZnLi_2$ (prepared from $ZnCl_2$ and $^{t}BuLi$), and the resulting organozincate intermediates were quenched with 4-*tert*-butyldimethylsilyloxybenzaldehyde (**10**) to afford intermediates **11i** and **12a**—**g**. Finally, deprotection of the TBS group with TBAF and subsequent acetylation with acetic anhydride gave **3i** and **4a**—**g**, respectively.

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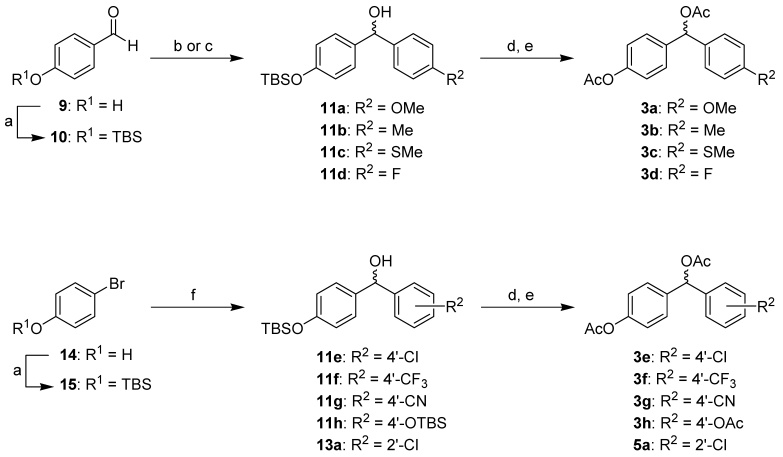
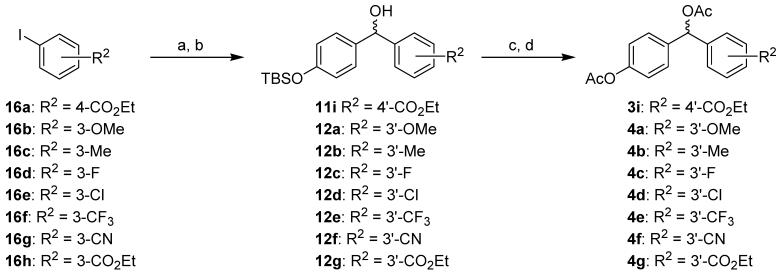
# Equal contribution with corresponding author.



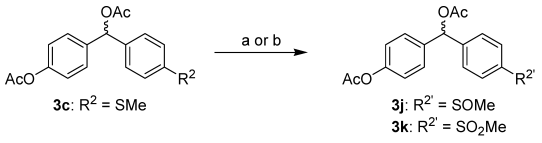
Reagents and conditions: (a) TBSCl, imidazole, DMF; (b) ArMgX, THF; (c) ArBr, *n*-BuLi, THF; (d) TBAF, THF; (e) Ac_2O, pyridine; (f) ArCHO, *n*-BuLi, THF.

Chart 1



Reagents and conditions: (a) *t*-Bu_4ZnLi_2, THF; (b) **10**, THF; (c) TBAF, THF; (d) Ac_2O, pyridine.

Chart 2



Reagents and conditions: (a) *m*CPBA (1 eq.), Et_2O; (b) *m*CPBA (2 eq.), Et_2O.

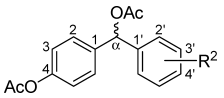
Chart 3

Results and Discussion

Biological Evaluation of Synthetic Compounds The HL-60 cell-growth-inhibitory activity of the 20 prepared compounds was evaluated by calculating IC_{50} values from viability data of test compound-treated HL-60 cells, and the results are shown in Table 1. The IC_{50} values of the 20 compounds were rather similar (2.1—7.7 μM) and no apparent electronic substituent effects were observed. Reproducibility of the assay results was good. Therefore, we judged that the IC_{50} values described in Table 1 are reliable, which led us to explore the QSAR of the 20 compounds. The QSAR analysis was performed by using the QSAR applications of the molecular operating environment (MOE 2006)[17] with the genetic algorithm analysis applying all descriptors of MOE (184 kinds). The correlation plot between pIC_{50} values obtained from observed IC_{50} values and calculated pIC_{50} values according to Eq. 1 is displayed in Fig. 2.

$$pIC_{50}(\mu M) = 0.885856 + 3.36049 \times (BCUT\_SMR\_2) + (-0.010704) \times (PEOE\_VSA\_PNEG) + 7.87731 \times (b\_1rotR) + 0.743102 \times (petitjeanSC) \quad (1)$$

Table 1. Cell-Growth-Inhibitory Activities of Benzhydrol Diacetate Analogs



	R^2	IC_{50} (μM)		R^2	IC_{50} (μM)
2	H	3.5	**3j**	4′-SOMe	3.9
3a	4′-OMe	4.5	**3k**	4′-SO_2Me	5.1
3b	4′-Me	2.7	**4a**	3′-MeO	2.4
3c	4′-SMe	2.1	**4b**	3′-Me	5.7
3d	4′-F	3.9	**4c**	3′-F	5.7
3e	4′-Cl	3.8	**4d**	3′-Cl	3.8
3f	4′-CF_3	5.4	**4e**	3′-CF_3	7.7
3g	4′-CN	4.8	**4f**	3′-CN	4.6
3h	4′-OAc	3.8	**4g**	3′-CO_2Et	3.5
3i	4′-CO_2Et	2.1	**5a**	2′-Cl	3.8

The meanings of the parameters of Eq. 1 are as follows: (i) BCUT[18]_SMR[19]_2: descriptor of molar refraction and coupling matrix, (ii) PEOE[20]_VSA[21]_PNEG: surface area of negative charge moiety, (iii) b_1rotR: rate of rotatable single bond, and (iv) PetitjeanSC[22]: (diameter-radius)/radius.

The BCUT_SMR_2, b_1rotR, and petitjeanSC parameters indicate that cell-growth-inhibitory activity tends to rise in proportion to the bulkiness of the functional group on the phenyl (B) ring. In addition, the negative coefficient of the PEOE_VSA_PNEG parameter suggests that compounds pos-

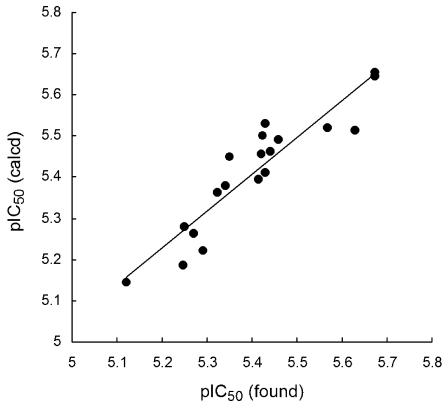
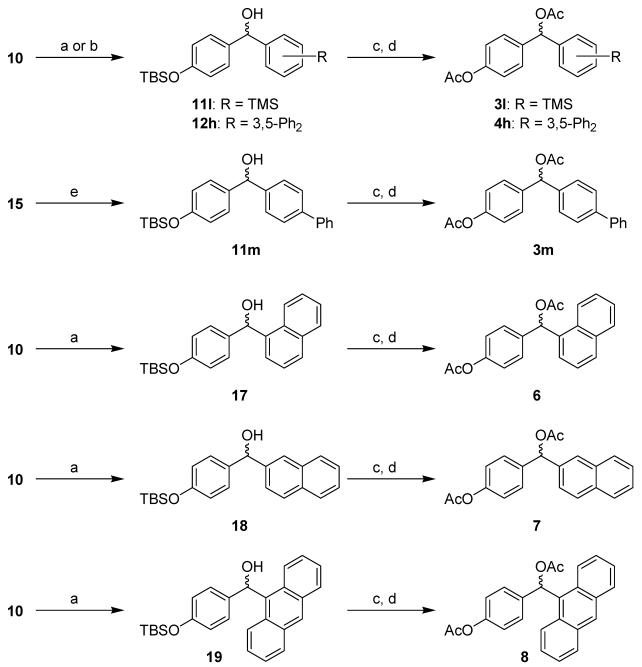


Fig. 2. Correlation of Observed and Calculated (with Eq. 1) pIC_{50} Values for 20 Benzhydrol Diacetate Analogs



Reagents and conditions: (a) ArBr, *n*-BuLi, THF; (b) ArBr, Mg, Et_2O, THF; (c) TBAF, THF; (d) Ac_2O, pyridine; (e) ArCHO, *n*-BuLi, THF.

Chart 4

sessing a substituent with a negative charge on a phenyl (B) ring would show reduced cell-growth-inhibitory activity.

Based on this information, we designed compounds with 4-trimethylsilylphenyl (**3l**), 4-phenylphenyl (**3m**), 3,5-diphenylphenyl (**4h**), 1-naphthyl (**6**), 2-naphthyl (**7**), and 9-anthracenyl (**8**) moieties. All of them, except for **3l**, were prepared using the same procedure as shown in Chart 1 (Chart 4). For **3l**, we adopted Grignard reaction instead, because of the low yield with our standard method.

As expected, all the newly synthesized compounds showed the same or higher cell-growth-inhibitory activity than **2** (Table 2). The compounds bearing a phenyl group(s) on the phenyl (B) ring, such as **3m** and **4h**, showed more potent activity than **2** (**3m**: $IC_{50}=1.7\,\mu M$; **4h**: $IC_{50}=1.1\,\mu M$). Compounds **6**—**8** also exhibited higher inhibitory activity than **2**. The 1-naphthyl derivative (**6**) showed far more potent activity than the regioisomeric 2-naphthyl derivative (**7**). Especially, **6** and **8** were found to have activity an order of magnitude

Table 2. Cell-Growth-Inhibitory Activities of Newly Synthesized Benzhydrol Diacetate Analogs

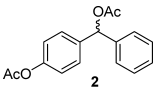
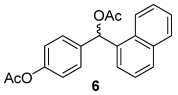
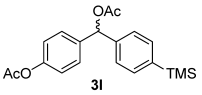
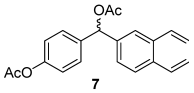
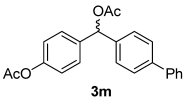
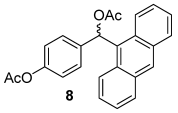
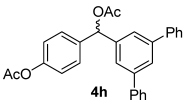
Compound	IC_{50} (μM)	Compound	IC_{50} (μM)
 **2**	3.5	 **6**	0.29
 **3l**	4.0	 **7**	2.2
 **3m**	1.7	 **8**	0.12
 **4h**	1.1		

Table 3. Comparison of Cell-Growth-Inhibitory Activity of the Enantiomers of **3m** towards HL-60 Cells

	Cell growth-inhibition rate (%)[a]
rac-**3m**	82.4
Enantiomer of **3m**_1	83.3
Enantiomer of **3m**_2	80.1

a) At 3.0 μM.

higher than that of **2**, with IC_{50} values of 0.29 and 0.12 μM, respectively. The compounds with a trimethylsilyl group at the 4′-position on the phenyl (B) ring, **3l**, and with a 2-naphthyl group, **7**, possessed the same or slightly higher activity than **2**. These results suggest that (i) compounds bearing a substituent which maintains the π-conjugated system on the phenyl (B) ring tend to show higher cell-growth-inhibitory activity; (ii) the introduction of a substituent on the phenyl (B) ring at a *meta*-position(s) is better than that at the *para*-position; (iii) the π-conjugated system between the phenyl (B) ring and its substituent should preferably consist of a ring-fused structure.

According to Azuma's report,[14] the enantiomers of ACA (**1**) showed the same cell-growth-inhibitory activity towards HL-60 cells. We also compared the cell-growth-inhibitory activities of the enantiomers of our compound **3m**. Separation of the enantiomers of **3m** was performed by chiral HPLC using DAICEL CHIRALPAK AD-H. As shown in Table 3, the enantiomers of **3m** exhibited similar cell-growth-inhibitory activities. We confirmed that racemization of the enantiomers of **3m** did not occur under the experimental conditions (data not shown). This result suggests that the activities of the enantiomers of **3m** are essentially the same.

In conclusion, we have developed analogs of ACA (**1**) with potent cell-growth-inhibitory activity, based on QSAR analysis. Compound **8** was 16 to 17 times more potent than ACA (**1**, $IC_{50}=2.0\,\mu M$), having the IC_{50} value of 0.12 μM. Further structural development and biological studies are in progress.

Experimental

General ^{1}H-NMR spectra were recorded on a JEOL JNM-GX500 (500 MHz), JNM-AL400 (400 MHz), JNM-AL-300 (300 MHz) spectrometer. Chemical shifts are expressed in δ (ppm) values with tetramethylsilane (TMS) as an internal reference. High-resolution mass spectra (HR-MS) were recorded on a JEOL JMS-DX303 spectrometer with *m*-nitrobenzyl alcohol. Flash column chromatography was performed on silica gel 60 (Kanto Kagaku, 40—100 μm).

4-(*tert*-Butyldimethylsilyloxy)benzaldehyde (10) To a solution of *p*-hydroxybenzaldehyde (536 mg, 4.39 mmol) and imidazole (398 mg, 5.85 mmol) in DMF (10 ml) was added *tert*-butyldimethylchlorosilane (740 mg, 5.06 mmol) at room temperature. The mixture was stirred overnight at room temperature, brine was added, and the whole was extracted with ethyl acetate. The organic layer was dried over $MgSO_4$, and concentrated. The residue was purified by column chromatography (ethyl acetate/hexane=1/10) to give **10** (926 mg, 89%) as a pale yellow oil: ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 9.89 (1H, s), 7.78 (2H, d, J=8.5 Hz), 6.92 (2H, d, J=8.5 Hz), 0.97 (9H, s), 0.18 (6H, s).

4-(*tert*-Butyldimethylsilyloxy)-α-(4′-methoxyphenyl)benzyl Alcohol (11a) [Typical Procedure A] To a solution of **10** (482 mg, 2.04 mmol) in dry THF (5.0 ml) was added dropwise *p*-methoxyphenylmagnesium bromide (1.0 M in THF, 2.5 ml, 2.50 mmol) at −78 °C. The mixture was stirred for 3 h at −78 °C, dil. HCl was added, and the whole was extracted with ethyl acetate. The organic layer was dried with $MgSO_4$, and concentrated. The residue was purified by column chromatography (ethyl acetate/hexane=1/5) to give **11a** (266 mg, 34%) as a pale yellow oil: ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 7.33 (2H, d, J=8.5 Hz), 7.27 (2H, d, J=8.5 Hz), 6.93 (2H, d, J=8.5 Hz), 6.86 (2H, d, J=8.5 Hz), 5.80 (1H, s), 3.85 (3H, s), 1.05 (9H, s), 0.26 (6H, s).

4-(*tert*-Butyldimethylsilyloxy)-α-(4′-fluorophenyl)benzyl Alcohol (11d) Prepared from **10** and *p*-fluorophenylmagnesium bromide by typical procedure A (50%): Yellow oil; ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 7.34 (2H, t, J=7.0 Hz), 7.19 (2H, d, J=8.5 Hz), 7.01 (2H, t, J=7.0 Hz), 6.80 (2H, d, J=8.5 Hz), 5.77 (1H, s), 0.97 (9H, s), 0.18 (6H, s).

4-(*tert*-Butyldimethylsilyloxy)-α-(4′-methylphenyl)benzyl Alcohol (11b) [Typical Procedure B] To a solution of *p*-bromotoluene (500 ml, 4.20 mmol) in dry THF (5.0 ml) was added *n*-butyllithium (1.65 M in THF, 1.25 ml, 2.06 mmol) at −78 °C. Then, **10** (505 mg, 2.1 mmol) was added dropwise. The mixture was stirred for 3 h at −78 °C, saturated aqueous NH_4Cl solution was added and the whole was extracted with ethyl acetate. The organic layer was dried with $MgSO_4$, and concentrated. The residue was purified by column chromatography (ethyl acetate/hexane=1/6) to give **11b** (335 mg, 41%) as a pale yellow oil: ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 7.25 (2H, d, J=8.0 Hz), 7.21 (2H, d, J=8.5 Hz), 7.14 (2H, d, J=8.0 Hz), 6.79 (2H, d, J=8.5 Hz), 5.77 (1H, s), 2.33 (3H, s), 0.97 (9H, s), 0.18 (6H, s).

4-(*tert*-Butyldimethylsilyloxy)-α-(4′-methylsulfanylphenyl)benzyl Alcohol (11c) Prepared from **10** and *p*-bromophenyl methyl sulfide by typical procedure B (57%): Yellow oil; ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 7.28 (2H, d, J=8.0 Hz), 7.21 (2H, d, J=7.0 Hz), 7.19 (2H, d, J=7.0 Hz), 6.79 (2H, d, J=8.0 Hz), 5.74 (1H, s), 2.47 (3H, s), 0.98 (9H, s), 0.19 (6H, s).

4-(*tert*-Butyldimethylsilyloxy)-1-bromobenzene (15) Prepared from *p*-bromophenol by means of a procedure similar to that **10**. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 7.31 (2H, d, J=8.5 Hz), 6.71 (2H, d, J=8.5 Hz), 0.97 (9H, s), 0.18 (6H, s); FAB-MS *m*/*z*: 286 $(M)^+$.

4-(*tert*-Butyldimethylsilyloxy)-α-(4′-chlorophenyl)benzyl Alcohol (11e) Prepared from **15** and *p*-chlorobenzaldehyde by typical procedure B (40%): Yellow oil; ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 7.64 (4H, s), 7.10 (2H, d, J=8.5 Hz), 6.75 (2H, d, J=8.5 Hz), 5.76 (1H, s), 0.97 (9H, s), 0.18 (6H, s).

4-(*tert*-Butyldimethylsilyloxy)-α-(4′-trifluoromethylphenyl)benzyl Alcohol (11f) Prepared from **15** and *p*-trifluoromethylbenzaldehyde by typical procedure B (50%): Colorless oil; ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 7.59 (2H, d, J=8.5 Hz), 7.50 (2H, d, J=8.5 Hz), 7.19 (2H, d, J=8.5 Hz), 6.81 (2H, d, J=8.0 Hz), 5.83 (1H, s), 0.97 (9H, s), 0.18 (6H, s).

4-(*tert*-Butyldimethylsilyloxy)-α-(4′-cyanophenyl)benzyl Alcohol (11g) Prepared from **15** and *p*-cyanobenzaldehyde by typical procedure B (51%): Colorless oil; ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 7.62 (2H, d, J=8.5 Hz), 7.50 (2H, d, J=8.0 Hz), 7.16 (2H, d, J=8.5 Hz), 6.81 (2H, d, J=8.5 Hz), 5.81 (1H, s), 0.97 (9H, s), 0.18 (6H, s).

4-(*tert*-Butyldimethylsilyloxy)-α-(4′-*tert*-butyldimethylsilyloxy)phenylbenzyl Alcohol (11h) Prepared from **10** and **15** by typical procedure B (26%): Colorless oil; ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 7.20 (2H, d, J=9.0 Hz), 6.79 (2H, d, J=9.0 Hz), 5.74 (1H, d), 0.97 (18H, s), 0.18 (12H, s).

4-(*tert*-Butyldimethylsilyloxy)-α-(2′-chlorophenyl)benzyl Alcohol (13a) Prepared from **15** and *o*-chlorobenzaldehyde by typical procedure B (66%): Yellow oil; ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 7.62 (2H, t, J=8.0 Hz), 7.32 (2H, d, J=8.5 Hz), 7.30 (2H, t, J=8.5 Hz), 7.23 (2H, d, J=8.5 Hz), 7.22 (2H, t, J=8.5 Hz), 6.15 (1H, s), 0.97 (9H, s), 0.18 (6H, s).

4-(*tert*-Butyldimethylsilyloxy)-α-(3′-methoxyphenyl)benzyl Alcohol (12a) [Typical Procedure C] 3-Iodoanisole (473 mg, 2.00 mmol) was added dropwise to a solution of ^{t}Bu$_4$ZnLi$_2$ (2.20 mmol) in THF at −78 °C, and the solution was warmed to 0 °C, and stirred for 2 h. Then, 0.74 ml of **10** (3 mmol) added. The mixture was allowed to warm to room temperature, stirred for 15 h, quenched by adding saturated aqueous NH_4Cl solution and 2 N HCl, and extracted with Et_2O. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography (ethyl acetate/hexane=1 : 5) to give **12a** as a colorless oil (366 mg, 49%): ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.25—7.20 (3H, m), 6.94—6.92 (2H, m), 6.80—6.77 (3H, m), 5.76 (1H, s), 3.78 (3H, s), 0.97 (9H, s), 0.18 (6H, s).

Ethyl 4-{1′-Hydroxy-1′-[(4″-*tert*-butyldimethylsilyloxy)phenyl]methyl}-benzoate (11i) Prepared from **16a** and **10** typical procedure C (45%): Colorless oil; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.25—7.20 (3H, m), 6.94—6.92 (2H, m), 6.80—6.77 (3H, m), 5.76 (1H, s), 3.78 (3H, s), 0.97 (9H, s), 0.18 (6H, s).

4-(*tert*-Butyldimethylsilyloxy)-α-(3′-methylphenyl)benzyl Alcohol (12b) Prepared from **16b** and **10** by typical procedure C (51%): Colorless oil; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.23—7.16 (5H, m), 7.08—7.05 (1H, m), 6.79 (2H, d, J=6.6 Hz), 5.75 (1H, d, J=3.3 Hz), 2.33 (3H, s), 2.12 (2H, d, J=6.6 Hz), 0.97 (9H, s), 0.18 (6H, s).

4-(*tert*-Butyldimethylsilyloxy)-α-(3′-fluorophenyl)benzyl Alcohol (12c) Prepared from **16c** and **10** by typical procedure C (49%): Pale yellow oil; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.25—7.20 (3H, m), 6.94—6.92 (2H, m), 6.80—6.77 (3H, m), 5.76 (1H, s), 3.78 (3H, s), 0.97 (9H, s), 0.18 (6H, s).

4-(*tert*-Butyldimethylsilyloxy)-α-(3′-chlorophenyl)benzyl Alcohol (12d) Prepared from **16d** and **10** by typical procedure C (43%): Pale yellow oil; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.27—7.24 (1H, m), 7.19 (2H, d, J=8.4 Hz), 7.13—7.08 (1H, m), 6.93 (1H, dt, J=2.7, 8.6 Hz), 6.80 (2H, d, J=8.4 Hz), 5.76 (1H, d, J=3.3 Hz), 2.21 (1H, d, J=3.3 Hz), 0.97 (9H, s), 0.18 (6H, s).

4-(*tert*-Butyldimethylsilyloxy)-α-(3′-trifluoromethylphenyl)benzyl Alcohol (12e) Prepared from **16e** and **10** by typical procedure C (52%): Colorless oil; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.68 (1H, s), 7.52—7.51 (2H, m), 7.44 (1H, d, J=7.2 Hz), 7.19 (2H, d, J=8.4 Hz), 6.81 (2H, d, J=8.4 Hz), 5.82 (1H, d, J=3.3 Hz), 2.26 (1H, d, J=3.3 Hz), 0.97 (9H, s), 0.18 (6H, s).

4-(*tert*-Butyldimethylsilyloxy)-α-(3′-cyanophenyl)benzyl Alcohol (12f) Prepared from **16f** and **10** by typical procedure C (55%): Yellow oil; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.69 (1H, s), 7.59 (1H, d, J=7.6 Hz), 7.53 (1H, d, J=8.0 Hz), 7.42 (1H, t, J=7.6 Hz), 7.17 (2H, d, J=8.4 Hz), 6.81 (2H, d, J=8.4 Hz), 5.78 (1H, s), 2.36 (1H, s), 0.97 (9H, s), 0.19 (6H, s).

Ethyl 3-{1′-Hydroxy-1′-[(4″-*tert*-butyldimethylsilyloxy)phenyl]methyl}-benzoate (12g) Prepared from **16h** and **10** typical procedure C (51%): Colorless oil; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 8.07 (1H, s), 7.93 (1H, d, J=8.0 Hz), 7.55 (1H, d, J=8.0 Hz), 7.39 (1H, t, J=7.6 Hz), 7.20 (2H, d, J=8.0 Hz), 6.79 (2H, d, J=8.0 Hz), 5.83 (1H, d, J=2.8 Hz), 4.36 (2H, q, J=7.2 Hz), 2.29 (1H, d, J=2.8 Hz), 1.38 (3H, t, J=7.2 Hz), 0.97 (9H, s), 0.18 (6H, s).

4-(*tert*-Butyldimethylsilyloxy)-α-(3′,5′-diphenyl)benzyl Alcohol (12h) Prepared from **10** and 1-bromo-3,5-diphenylbenzene[23,24] by typical procedure B (30%): Colorless oil; ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 7.72 (1H, s), 7.63 (2H, d, J=7.0 Hz), 7.60 (2H, s), 7.45 (4H, t, J=7.0 Hz), 7.37 (2H, t, J=7.0 Hz), 7.30 (2H, d, J=8.5 Hz), 6.82 (2H, d, J=8.5 Hz), 5.93 (1H, s), 0.98 (9H, s), 0.19 (6H, s).

4-(*tert*-Butyldimethylsilyloxy)-α-(4′-phenyl)benzyl Alcohol (11m) Prepared from **15** and 1-bromo-4-phenylbenzene by typical procedure B (44%): Pale yellow oil; ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 7.58 (2H, d, J=7.0 Hz), 7.56 (2H, d, J=7.0 Hz), 7.45—7.41 (4H, m), 7.34 (1H, t, J=7.0 Hz), 7.26 (2H, d, J=8.0 Hz), 6.81 (2H, d, J=8.0 Hz), 5.84 (1H, s), 0.98 (9H, s), 0.19 (6H, s).

4-(*tert*-Butyldimethylsilyloxy)-α-(1′-naphthyl)benzyl Alcohol (17) Prepared from **10** and 1-bromonaphthalene by typical procedure B (49%): Colorless oil; ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 7.99 (1H, d, J=8.0 Hz), 7.86 (1H, d, J=8.0 Hz), 7.81 (1H, d, J=8.0 Hz), 7.68 (1H, d, J=8.0 Hz), 7.45 (1H, t, J=8.0 Hz), 7.45 (1H, t, J=8.0 Hz), 7.42 (1H, t, J=8.0 Hz), 7.25 (2H, d, J=8.5 Hz), 6.79 (2H, d, J=8.5 Hz), 6.50 (1H, s), 0.97 (9H, s), 0.17 (6H, s).

4-(*tert*-Butyldimethylsilyloxy)-α-(2′-naphthyl)benzyl Alcohol (18) Prepared from **15** and 2-naphthylaldehyde by typical procedure B (96%): Colorless oil; ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 7.89 (1H, s), 7.83 (1H, t, J=8.5 Hz), 7.82 (1H, t, J=8.5 Hz), 7.79 (1H, d, J=8.5 Hz), 7.50—7.44 (2H,

m), 7.42(1H, t, J=8.0 Hz), 7.42 (1H, d, J=8.5 Hz), 7.25 (2H, d, J=8.5 Hz), 6.80 (2H, d, J=8.5 Hz), 5.96 (1H, s), 0.97 (9H, s), 0.18 (6H, s).

4-(*tert*-Butyldimethylsilyloxy)-α-(9′-anthracenyl)benzyl Alcohol (19) Prepared from **10** and 9-bromoanthracene by typical procedure B (34%): Yellow oil; ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 8.47 (1H, s), 8.37 (2H, d, J=8.5 Hz), 8.02 (2H, d, J=8.5 Hz), 7.44 (2H, t, J=8.5 Hz), 7.40 (2H, t, J=8.5 Hz), 7.35 (1H, s), 7.22 (2H, d, J=8.5 Hz), 6.74 (2H, d, J=8.5 Hz), 0.96 (9H, s), 0.16 (6H, s).

4-(*tert*-Butyldimethylsilyloxy)-α-(4′-trimethylsilylphenyl)benzyl Alcohol (11l) To a solution of magnesium (200 mg, 7.5 mmol) activated with iodine (5.0 mg) in Et_2O was added dropwise **10** (342 mg, 1.50 mmol) at room temperature. This solution was added dropwise to a solution of **1** (236 mg, 1.0 mmol) in dry THF (3.0 ml) at −78 °C. The mixture was stirred for 1.5 h at −78 °C, brine was added and the whole was extracted with ethyl acetate. The organic layer was dried over $MgSO_4$, and concentrated. The residue was purified by column chromatography (ethyl acetate : hexane = 1 : 10) to give **11l** (198 mg, 52%) as a pale yellow oil: ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 7.49 (2H, d, J=8.0 Hz), 7.35 (2H, d, J=8.0 Hz), 7.22 (2H, d, J=8.5 Hz), 6.79 (2H, d, J=8.5 Hz), 5.78 (1H, d, J=3.5 Hz), 2.12 (1H, d, J=3.5 Hz) 0.97 (9H, s), 0.25 (9H, s). 0.18 (6H, s); HR-FAB-MS *m/z*: 356.1455 (Calcd for $C_{20}H_{24}O_4Si$: $(M)^+$, 356.1444).

4-Acetoxy-a-(4′-methoxyphenyl)benzyl Acetate (3a) [Typical Procedure D] To a solution of **11a** (192 mg, 0.58 mmol) in dry THF (5.0 ml) was added TBAF (1.0 M in THF, 0.5 ml, 0.500 mmol) at 0 °C. The reaction mixture was stirred for 1 h at the same temperature, then concentrated under reduced pressure. The residue was taken up in pyridine (4.0 ml) and acetic anhydride (500 μl, 1.47 mmol) was added to the solution at room temperature. The mixture was stirred for 3 h at room temperature, NH_4Cl aq. was added and the whole was extracted with ethyl acetate. The organic layer was dried with $MgSO_4$, and concentrated. The residue was purified by column chromatography (ethyl acetate/hexane=1/4) to give **3a** (27.0 mg, 51%) as a colorless oil: ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 7.27 (2H, d, J=8.0 Hz), 7.25 (2H, t, J=8.5 Hz), 7.01 (2H, d, J=8.0 Hz), 6.96 (2H, t, J=8.5 Hz), 6.80 (1H, s), 2.22 (3H, s), 2.09 (3H, s); HR-FAB-MS *m/z*: 302.0989 (Calcd for $C_{17}H_{16}FO_4$: $(M)^+$, 302.0954).

4-Acetoxy-α-(4′-methylphenyl)benzyl Acetate (3b) Prepared from **11b** by typical procedure D (21%): Colorless oil; ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 7.46 (2H, d, J=8.0 Hz), 7.56 (2H, d, J=7.5 Hz), 7.48 (2H, d, J=7.5 Hz), 7.39 (2H, d, J=8.0 Hz), 7.19 (1H, s), 2.67 (3H, s), 2.63 (3H, s), 2.37 (3H, s); HR-FAB-MS *m/z*: 298.1169 (Calcd for $C_{18}H_{18}O_4$: $(M)^+$, 298.1205).

4-Acetoxy-α-(4′-methylsulfanylphenyl)benzyl Acetate (3c) Prepared from **11c** by typical procedure D (87%): Yellow oil; ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 7.32 (2H, d, J=8.5 Hz), 7.25 (2H, d, J=8.5 Hz), 7.21 (2H, d, J=8.5 Hz), 7.05 (2H, d, J=8.5 Hz), 6.84 (1H, s), 2.47 (3H, s), 2.29 (3H, s), 2.15 (3H, s); FAB-MS *m/z*: 330.0891 (Calcd for $C_{18}H_{18}O_4S$: $(M)^+$, 330.0926).

4-Acetoxy-α-(4′-fluorophenyl)benzyl Acetate (3d) Prepared from **11d** by typical procedure D (81%): Colorless oil; ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 7. 27 (2H, d, J=8.0 Hz), 7.25 (2H, dd, J=8.5, 5.5 Hz [with H-F coupling]), 7.01 (2H, d, J=8.0 Hz), 6.96 (2H, dd, J=8.5, 8.5 Hz [with H-F coupling]), 6.80 (1H, s), 2.22 (3H, s), 2.09 (3H, s); HR-FAB-MS *m/z*: 302.0989 (Calcd for $C_{17}H_{16}O_4F$: $(M)^+$, 302.0954).

4-Acetoxy-α-(4′-chlorophenyl)benzyl Acetate (3e) Prepared from **11e** by typical procedure D (79%): Colorless oil; ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 7.31 (4H, d, J=8.5 Hz), 7.26 (2H, d, J=8.5 Hz), 7.06 (2H, d, J=8.5 Hz), 6.84 (1H, s), 2.29 (3H, s), 2.15 (3H, s,); HR-FAB-MS *m/z*: 318.0609 (Calcd for $C_{17}H_{15}ClO_4$: $(M)^+$, 318.0659).

4-Acetoxy-α-(4′-trifluoromethylphenyl)benzyl Acetate (3f) Prepared from **11f** by typical procedure D (94%): Colorless oil; ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 7.60 (2H, d, J=8.0 Hz), 7.46 (2H, d, J=8.0 Hz), 7.33 (2H, d, J=8.0 Hz), 7.07 (2H, d, J=8.0 Hz), 6.90 (1H, s), 2.29 (3H, s), 2.17 (3H, s); HR-FAB-MS *m/z*: 352.0895 (Calcd for $C_{18}H_{15}F_3O_4$: $(M)^+$, 352.0922).

4-Acetoxy-α-(4′-cyanophenyl)benzyl Acetate (3g) Prepared from **11g** by typical procedure D (39%): Colorless oil; ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 7.64 (2H, d, J=8.5 Hz), 7.45 (2H, d, J=8.5 Hz), 7.31 (2H, d, J=8.5 Hz), 7.08 (2H, d, J=8.5 Hz), 6.87 (1H, s), 2.29 (3H, s), 2.17 (3H, s); HR-FAB-MS *m/z*: 3091036 (Calcd for $C_{18}H_{15}NO_4$: $(M)^+$, 309.1001).

4-Acetoxy-α-(4′-acetoxyphenyl)benzyl Acetate (3h) Prepared from **11h** by typical procedure D (82%): Colorless oil; ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 7.32 (2H, d, J=8.5 Hz), 7.24 (2H, d, J=8.5 Hz), 7.21 (2H, d, J=8.5 Hz), 7.05 (2H, d, J=8.5 Hz), 6.84 (1H, s), 2.47 (3H, s), 2.29 (3H, s), 2.14 (3H, s); HR-FAB-MS *m/z*: 342.1103 (Calcd for $C_{19}H_{18}O_6$: $(M)^+$, 342.1103).

4-Acetoxy-α-(2′-chlorophenyl)benzyl Acetate (5a) Prepared from **13a** by typical procedure D (94%): Colorless oil; ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 7.47 (1H, d, J=7.5 Hz), 7.35 (2H, d, J=8.5 Hz), 7.27 (1H, t, J=7.5 Hz), 7.23 (1H, d, J=8.5 Hz), 7.22 (1H, t, J=7.5 Hz), 7.03 (2H, d, J=7.5 Hz), 2.26 (3H, s), 2.13 (3H, s); HR-FAB-MS *m/z*: 318.0682 (Calcd for $C_{17}H_{15}ClO_4$: $(M)^+$, 318.0659).

Ethyl 4-{1′-Acetoxy-1′-[(4″-acetoxyphenyl)methyl]benzoate (3i) Prepared from ethyl **11i** by typical procedure D (48%): Colorless viscous oil; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.02 (2H, d, J=8.4 Hz), 7.41 (2H, d, J=8.4 Hz), 7.33 (2H, d, J=8.4 Hz), 7.06 (2H, d, J=8.4 Hz), 6.90 (1H, s), 4.37 (2H, q, J=6.9 Hz), 2.28 (3H, s), 2.17 (3H, s), 1.38 (3H, t, J=6.9 Hz); HR-FAB-MS *m/z*: 356.1288 (Calcd for $C_{20}H_{20}O_6$: $(M)^+$, 356.1260).

4-Acetoxy-α-(3′-methoxyphenyl)benzyl Acetate (4a) Prepared from **12a** by typical procedure D (48%): Colorless oil; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.34 (2H, d, J=8.4 Hz), 7.28—7.23 (1H, m), 7.05 (2H, d, J=8.4 Hz), 6.92—6.80 (4H, m), 3.78 (3H, s), 2.28 (3H, s), 2.15 (3H, s); HR-FAB-MS *m/z*: 314.1162 (Calcd for $C_{18}H_{18}O_5$: $(M)^+$, 314.1154).

4-Acetoxy-α-(3′-methylphenyl)benzyl Acetate (4b) Prepared from **12b** by typical procedure D (59%): Colorless oil; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.34 (2H, d, J=8.4 Hz), 7.22—7.20 (1H, m), 7.14—7.03 (5H, m), 6.84 (1H, s), 2.33 (3H, s), 2.28 (3H, s), 2.15 (3H, s); HR-FAB-MS *m/z*: 298.1231 (Calcd for $C_{18}H_{18}O_4$: $(M)^+$, 298.1205).

4-Acetoxy-α-(3′-fluorophenyl)benzyl Acetate (4c) Prepared from **12c** by typical procedure D (38%): Colorless oil; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.35—7.26 (3H, m), 7.11—7.04 (4H, m), 7.01—6.95 (1H, m), 6.85 (1H, s), 2.29 (3H, s), 2.16 (3H, s); HR-FAB-MS *m/z*: 302.0982 (Calcd for $C_{17}H_{15}FO_4$: $(M)^+$, 302.0954).

4-Acetoxy-α-(3′-chlorophenyl)benzyl Acetate (4d) Prepared from **12d** by typical procedure D (87%): Colorless oil; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.34—7.31 (3H, m), 7.27—7.26 (2H, m), 7.21—7.19 (1H, m), 7.07 (2H, d, J=8.7 Hz), 6.82 (1H, s), 2.28 (3H, s), 2.16 (3H, s); HR-FAB-MS *m/z*: 318.0694 (Calcd for $C_{17}H_{15}ClO_4$: $(M)^+$, 318.0659).

4-Acetoxy-α-(3′-trifluoromethylphenyl)benzyl Acetate (4e) Prepared from **12e** by typical procedure D (33%): Colorless oil; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.62 (1H, s), 7.57—7.43 (3H, m), 7.34 (2H, d, J=8.7 Hz), 7.08 (2H, d, J=8.7 Hz), 6.91 (1H, s), 2.29 (3H, s), 2.18 (3H, s); HR-FAB-MS *m/z*: 352.0954 (Calcd for $C_{18}H_{15}F_3O_4$: $(M)^+$, 352.0922).

4-Acetoxy-α-(3′-cyanophenyl)benzyl Acetate (4f) Prepared from **12f** by typical procedure D (74%): Colorless oil; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.66 (1H, s), 7.60—7.53 (2H, m), 7.47—7.42 (1H, m), 7.32 (2H, d, J=8.4 Hz), 7.09 (2H, d, J=8.4 Hz), 6.86 (1H, s), 2.30 (3H, s), 2.18 (3H, s); HR-FAB-MS *m/z*: 309.1017 (Calcd for $C_{18}H_{15}NO_4$: $(M)^+$, 309.1001).

Ethyl 3-{1′-Acetoxy-1′-[(4″-acetoxyphenyl)methyl]benzoate (4g) Prepared from **12g** by typical procedure D (48%): Colorless oil; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.04 (1H, s), 7.97 (1H, d, J=7.2 Hz), 7.52—7.50 (1H, m), 7.41 (1H, t, J=7.5 Hz), 7.34 (2H, d, J=8.4 Hz), 7.06 (2H, d, J=8.4 Hz), 6.90 (1H, s), 4.37 (2H, q, J=7.2 Hz), 2.28 (3H, s), 2.14 (3H, s), 1.39 (3H, t, J=7.2 Hz); HR-FAB-MS *m/z*: 356.1253 (Calcd for $C_{20}H_{20}O_6$: $(M)^+$, 356.1260).

4-Acetoxy-α-(4′-trimethylsilylphenyl)benzyl Acetate (3l) Prepared from **11l** by typical procedure D (71%): Colorless oil; ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 7.49 (2H, d, J=8.0 Hz), 7.35 (2H, d, J=8.0 Hz), 7.31 (2H, d, J=8.0 Hz), 7.05 (2H, d, J=8.0 Hz), 6.86 (1H, s), 2.29 (3H, s), 2.15 (3H, s), 0.25 (9H, s); FAB-MS *m/z*: 356.1455 (Calcd for $C_{20}H_{24}O_4Si$: $(M)^+$, 356.1444).

4-Acetoxy-α-(3′,5′-diphenylphenyl)benzyl Acetate (4h) Prepared from **12h** by typical procedure D (75%): Colorless oil; ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 7.74 (1H, s), 7.62 (4H, d, J=7.0 Hz), 7.55 (2H, s), 7.46 (4H, t, J=7.0 Hz), 7.44 (2H, d, J=7.5 Hz), 7.38 (2H, t, J=7.0 Hz), 7.09 (2H, d, J=7.5 Hz), 7.02 (1H, s), 2.29 (3H, s), 2.02 (3H, s); HR-FAB-MS *m/z*: 436.1672 (Calcd for $C_{29}H_{24}O_4$: $(M)^+$, 436.1675).

4-Acetoxy-α-(4′-phenyl)benzyl Acetate (3m) Prepared from **12m** by typical procedure D (97%): Colorless oil; ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 7.56 (4H, d, J=7.5 Hz), 7.45—7.38 (6H, m), 7.35 (2H, t, J=7.5 Hz), 7.08 (2H, d, J=8.0 Hz), 6.93 (1H, s), 2.30 (3H, s), 2.17 (3H, s); HR-FAB-MS *m/z*: 360.1402 (Calcd for $C_{23}H_{20}O_4$: $(M)^+$, 360.1362).

4-Acetoxy-α-(1′-naphthyl)benzyl Acetate (6) Prepared from **17** by typical procedure D (99%): Colorless oil; ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 7.96 (4H, d, J=8.0 Hz), 7.87—7.84 (2H, m), 7.61 (1H, s), 7.58 (2H, d, J=8.0 Hz), 7.50—7.40 (3H, m), 7.36 (2H, d, J=8.5 Hz), 7.04 (2H, d, J=8.5 Hz), 2.28 (3H, s), 2.18 (3H, s). HR-FAB-MS: *m/z* 334.1208 (Calcd for $C_{21}H_{18}O_4$: $(M)^+$, 3334.1205).

4-Acetoxy-α-(2′-naphthyl)benzyl Acetate (7) Prepared from **18** by typical procedure D (95%): Colorless oil; ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 7.84—7.80 (4H, m), 7.51—7.46 (2H, m), 7.40—7.38 (3H, m), 7.06 (2H, d, J=7.5 Hz), 7.05 (1H, s), 2.29 (3H, s), 2.19 (3H, s); HR-FAB-MS *m/z*: 334.1202 (Calcd for $C_{21}H_{18}O_4$: $(M)^+$, 334.1205).

4-Acetoxy-α-(9′-anthracenyl)benzyl Acetate (8) Prepared from **19** by

typical procedure D (57%): Yellow oil; ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 8.52 (1H, s), 8.48 (1H, s), 8.37 (2H, d, J=9.0 Hz), 8.04 (2H, d, J=9.0 Hz), 7.46—7.44 (4H, m), 7.18 (2H, d, J=8.5 Hz), 6.98 (2H, d, J=8.5 Hz), 2.26 (3H, s), 2.15 (3H, s); HR-FAB-MS m/z: 384.1354 (Calcd for $C_{25}H_{20}O_4$: $(M)^+$, 384.1362).

4-Acetoxy-α-(4′-methylsulfinylphenyl)benzyl Acetate (3j) To a solution of **3c** (90.0 mg, 0.27 mmol) in Et_2O (3.0 ml) was added *m*-chloroperbenzoic acid (44.0 mg, 0.26 mmol) at 0 °C. The mixture was stirred for 18 h at room temperature, brine was added, and the whole was extracted with ethyl acetate. The organic layer was dried over $MgSO_4$, and concentrated. The residue was purified by column chromatography (ethyl acetate /hexane=1/1) to give **13** (2.5 mg, 3%) as a pale yellow oil: ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 7.63 (2H, d, J=8.0 Hz), 7.50 (2H, d, J=8.0 Hz), 7.34 (2H, d, J=8.0 Hz), 7.07 (2H, d, J=8.0 Hz), 6.90 (1H, s), 2.72 (3H, s), 2.29 (3H, s), 2.18 (3H, s); HR-FAB-MS m/z: 347.0993 (Calcd for $C_{18}H_{19}O_5S$: $(M+H)^+$, 347.0953).

4-Acetoxy-α-(4′-methylsulfonylphenyl)benzyl Acetate (3k) Prepared from **3c** by means of a procedure similar to that described for **3j**, using 2 eq of *m*-chloroperbenzoic acid (23%): Yellow oil; ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 7.90 (2H, d, J=8.5 Hz), 7.52 (2H, d, J=8.5 Hz), 7.31 (2H, d, J=8.5 Hz), 7.06 (2H, d, J=8.5 Hz), 6.88 (1H, s), 3.02 (3H, s), 2.27 (3H, s), 2.16 (3H, s); HR-FAB-MS m/z: 362.0834 (Calcd for $C_{18}H_{18}O_6S$: $(M)^+$, 362.0834).

Cell Culture HL-60 cells were maintained in RPMI 1640 medium containing 100 U/ml penicillin, 100 μg/ml streptomycin, and 10% heat-inactivated fetal bovine serum (FBS) in a humidified incubator at 37 °C under 5% CO_2/95% air.

Cell Growth Inhibition Assay HL-60 cells (1×10^5 cells/well) were suspended in fresh medium in a 24-well plate (1 ml/well) and treated with test compounds for 3 d. The cell-growth inhibitory activity was determined based on cell counts, compared with untreated controls.

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