Available online at www.sciencedirect.com
ScienceDirect
Bioorganic & Medicinal Chemistry
Bioorganic & Medicinal Chemistry 16 (2008) 4272–4285

Co-existence of α-glucosidase-inhibitory and liver X receptor-regulatory activities and their separation by structural development

Kosuke Dodo,[a,*] Atsushi Aoyama,[a] Tomomi Noguchi-Yachide,[a] Makoto Makishima,[b] Hiroyuki Miyachi[a] and Yuichi Hashimoto[a]

[a]*Institute of Molecular and Cellular Biosciences, University of Tokyo, 1-1-1, Yayoi, Bunkyo-ku, Tokyo 113-0032, Japan*
[b]*Department of Biochemistry, Nihon University School of Medicine, 30-1 Oyaguchi-kamicho, Itabashi-ku, Tokyo 173-8610, Japan*

Received 29 October 2007; revised 18 February 2008; accepted 26 February 2008
Available online 29 February 2008

Abstract—Liver X receptors (LXR), which were originally reported as oxysterol-activated nuclear receptors, were recently found to recognize glucose as a physiological ligand. On this basis, we have already developed novel LXR antagonists based upon α-glucosidase inhibitors derived from thalidomide. Here, to clarify the relationship between α-glucosidase inhibition and LXR modulation, we investigate the α-glucosidase-inhibitory activity of typical LXR ligands and the LXR-modulating activity of typical α-glucosidase inhibitors. Although there were some exceptions, co-existence of LXR-regulatory and α-glucosidase-inhibitory activities seemed to be rather general among the examined compounds. The LXR ligands were found to be non-competitive α-glucosidase inhibitors, suggesting that it might be possible to separate the two activities. To test this idea, we focused on riccardin C, a naturally occurring LXR ligand, which we found here to be a potent α-glucosidase inhibitor as well. Structural development of riccardin C afforded novel LXR antagonists lacking α-glucosidase-inhibitory activity, **19c** and **19f**, and a LXRα-selective antagonist, **22**.

1. Introduction

Liver X receptors (LXRα and LXRβ) are members of the nuclear receptor superfamily, and function as heterodimers with retinoid-X receptor (RXR) to control the transcription of genes regulating cholesterol efflux and fatty acid biosynthesis, such as ATP-binding cassette ABCA-1, CYP7A, and sterol responsive element binding protein (SREBP-1).[1–4] ABCA1 is required for efflux of cholesterol from cells to lipid-poor apoA-I protein and HDL particles. Activation of LXRs also results in inhibition of the expression of genes encoding inflammatory factors, including tumor necrosis factor (TNF)-α, IL-1β, and IFNF.[5] Physiological ligands of LXR have been believed to be oxysterols, including 24(*S*),25-epoxycholesterol and 22-(*R*)-hydroxycholesterol (HC) (Fig. 1), which are the intermediates of bile acid biosynthesis.[1,2] Therefore, LXRs have been thought to work as sensors of cholesterol metabolites and to regulate several important lipids, including cholesterol and bile acid. Generally, the ligands of nuclear receptors have been considered to be hydrophobic compounds, including steroids and retinoids. However, Mitro et al. recently reported that glucose and its derivatives act as LXR ligands.[6] LXRs have also been reported to regulate the expression of several genes involved in glucose metabolism, which implies that LXRs may function as a global sensor of metabolism and regulate both sugar and lipid metabolism. An undesirable effect observed with oxysterol-type LXR agonists, including 24(*S*),25-epoxycholesterol and 22-(*R*)-hydroxycholesterol (HC), was a significant increase in serum and liver triglyceride levels via the upregulation of SREBP-1c and other lipogenic genes in the liver.

Various attempts have been made to develop non-steroidal LXR agonists and to find LXR antagonists. Typical LXR agonists include T0901319[4] and GW3965,[7] as well as the natural ligands 24(*S*),25-epoxycholesterol, and

Keywords: Liver X receptor; Glucosidase; Antagonist; Inhibitor; Structural development.
* Corresponding author. Tel.: +81 3 5841 7849; fax: +81 3 5841 8495; e-mail: dodo@iam.u-tokyo.ac.jp

0968-0896/$ - see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bmc.2008.02.078

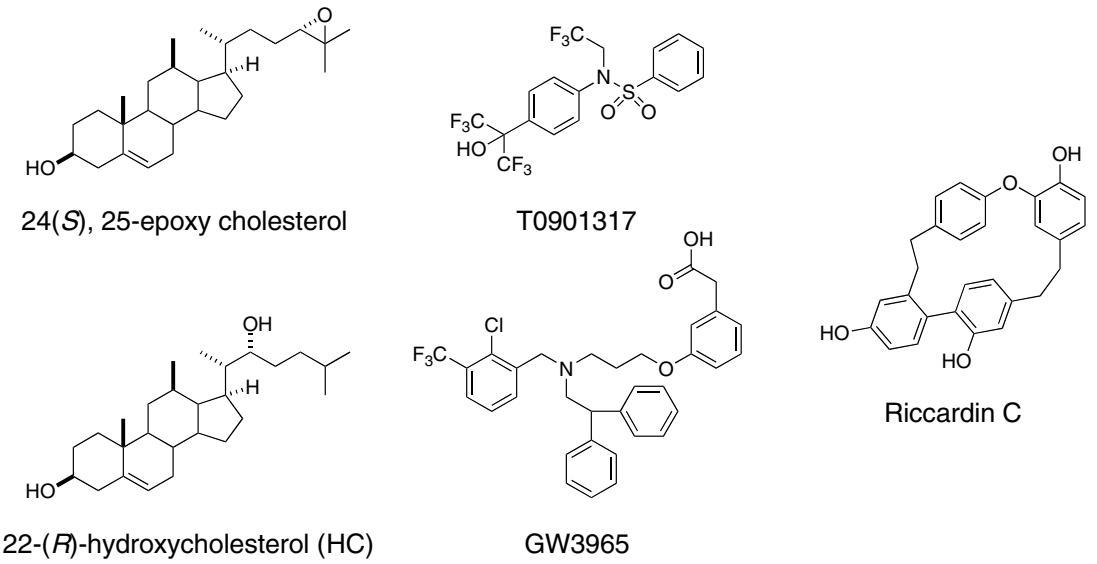


Figure 1. Structures of various LXR ligands.

22-(*R*)-hydroxycholesterol (HC) (Fig. 1). The natural product riccardin C (Fig. 1) has been reported to be an agonist for LXRα and an antagonist for LXRβ.[8]

In the previous studies,[9,10] we found that a competitive α-glucosidase inhibitor derived from thalidomide can act as a LXR antagonist, indicating that LXR ligands and α-glucosidase inhibitors share some common properties as glucose mimics. We were therefore interested in clarifying the relationship between the α-glucosidase-inhibitory activity and the LXR-modulating activity in typical α-glucosidase inhibitors and LXR ligands. Moreover, to obtain more specific LXR ligands, we set out to separate the LXR-modulating activity from the α-glucosidase-inhibitory activity.

2. Results and discussion

We first tested the α-glucosidase-inhibitory activity of typical LXR ligands with very different structures, that is, 22-(*R*)-hydroxycholesterol (HC) as a physiological LXR ligand, T0901317[4] and GW3965[7] as synthetic LXR agonists, and the natural product riccardin C as a LXR agonist/antagonist,[8] using *p*-nitrophenyl-α-D-glucopyranoside as a substrate, as reported previously.[9] The LXR ligands examined were found to possess moderate to potent α-glucosidase-inhibitory activity, with the exception of 22-(*R*)-hydroxycholesterol (HC) (Table 1). Though the number of compounds examined is too few to allow any definitive conclusion, it appeared that LXR-modulating activity has some relationship with α-glucosidase inhibition. In other words, LXRs and α-glucosidase may recognize some common structure, at least in the cases of the examined typical LXR ligands with α-glucosidase-inhibitory activity. Notably, GW3965 and riccardin C showed potent α-glucosidase-inhibitory activity with IC_{50} values of 4.8 and 9.9 μM, respectively, being far more potent than the well-known α-glucosidase inhibitor, 1-deoxynojirimycin (dNM, IC_{50} = 250 μM) (Table 1).

Table 1. α-Glucosidase-inhibitory activity of typical LXR ligands

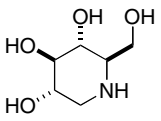
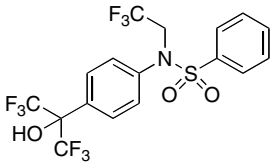
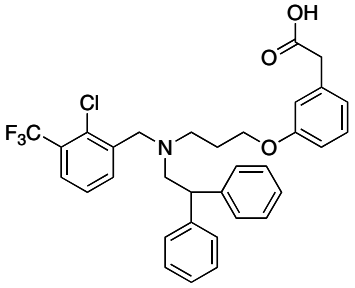
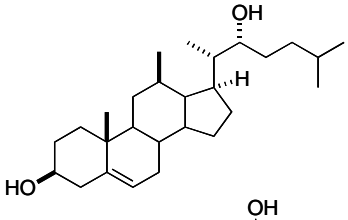
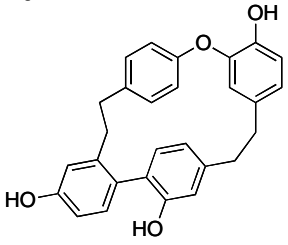
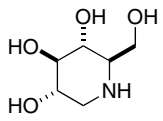
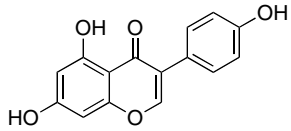
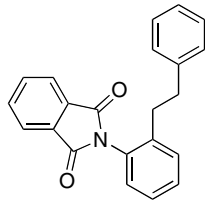
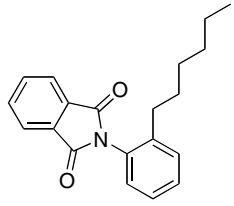
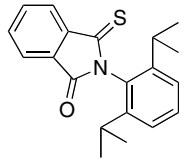
		IC_{50} (μM)
	1-Deoxynojirimycin (dNM)	250
	T0901317	100
	GW3965	4.8
	HC	100
	Riccardin C	9.9

Table 2. LXR-antagonistic activities of typical α-glucosidase inhibitors

		IC_{50} (μM)		α-Glucosidase
		LXRα	LXRβ	IC_{50} (μM)
	dNM	>100	>100	250
	Genistein	31	22	100
	PP2P	9.8	44	16.2
	PP60	13	65	24.7
	PPS-33	3.1	18	8.0

Next, we investigated the LXR-modulating activities of typical α-glucosidase inhibitors, 1-deoxynojirimycin (dNM),[11] genistein,[12] and our α-glucosidase inhibitors derived from thalidomide (PP2P, PP60, and PPS-33; see Table 2) using a reporter gene assay method with CMX-GAL4N-hLXR as the recombinant receptor gene, TK-MH100x4-LUC as the reporter gene, and the CMX β-galactosidase gene for normalization of errors made by the transfection efficiency and the toxicity of compounds, as previously reported.[13–15] Although none of the inhibitors examined showed any agonistic activity (data not shown), all the inhibitors except for dNM showed moderate LXR-antagonistic activity toward both LXR α and LXRβ, with IC_{50} values of 3.1–65 μM. Among the compounds examined, PPS-33 showed the most potent antagonistic activity. The PP compounds seem to be LXRα-selective, while genistein is non-selective or weakly LXRβ-selective (Table 2). Considering the α-glucosidase inhibition exhibited by typical LXR ligands, these results support the idea that there is some relationship between LXR modulation and α-glucosidase inhibition, which might be attributed to common structural features of molecular recognition by LXRs and α-glucosidase.

To confirm whether LXR ligands with α-glucosidase-inhibitory activity are recognized by the enzyme as pseudo-substrates (competitive binding to the substrate-binding pocket), we investigated the mode of α-glucosidase inhibition of the compounds by means of Lineweaver-Burk plot analysis (Fig. 2). We confirmed that dNM showed competitive inhibition, as previously reported. However, all the LXR ligands examined exhibited non-competitive inhibition, indicating that these LXR ligands inhibit α-glucosidase by binding to a site different from the substrate (sugar) binding pocket. Based on these results, we anticipated that LXR-regulatory activity and α-glucosidase-inhibitory activity elicited by the above-mentioned dually active compounds could be separated by appropriate structural development. To test this idea, we planned to synthesize derivatives of riccardin C and investigate their LXR-modulating and the α-glucosidase-inhibitory activities. Riccardin C was chosen because it has a relatively simple structure with only three phenolic hydroxyl groups, one ether linkage and four benzene rings.

From the structure–activity relationships (SAR) of genistein-related flavonoids as non-competitive α-gluco-

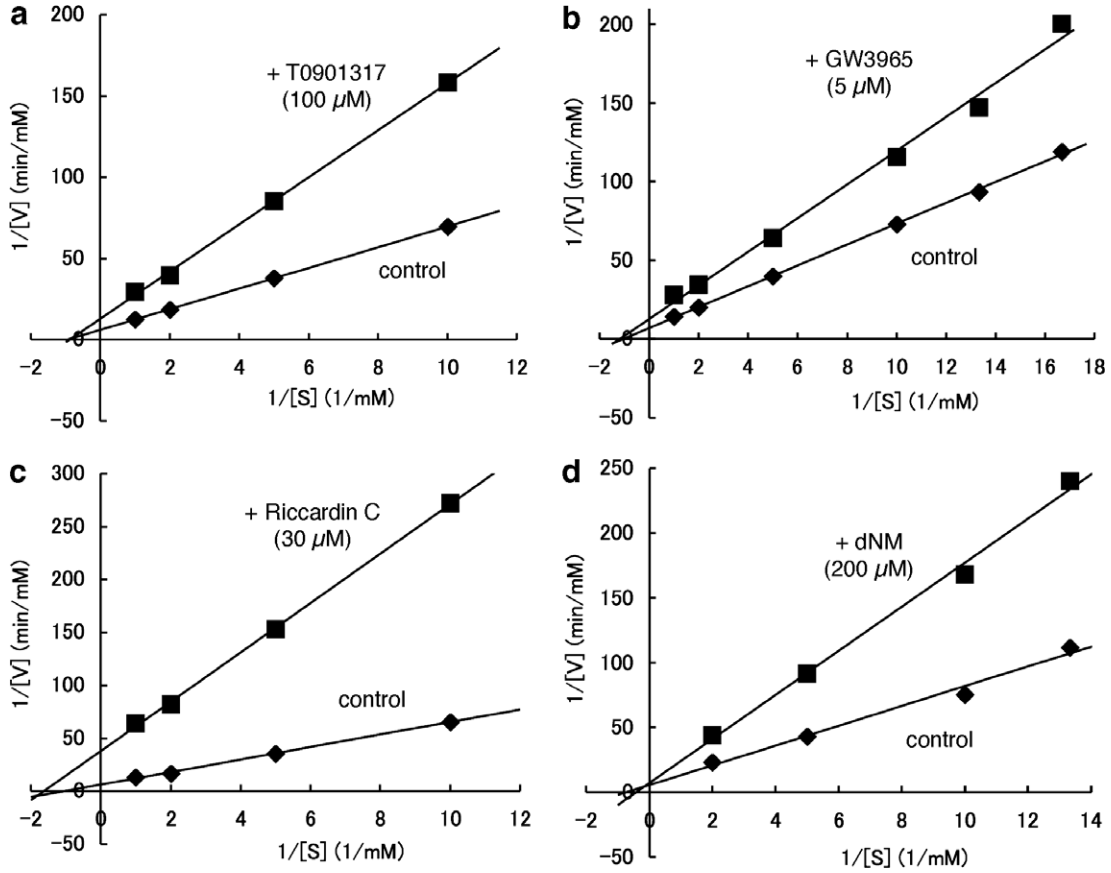
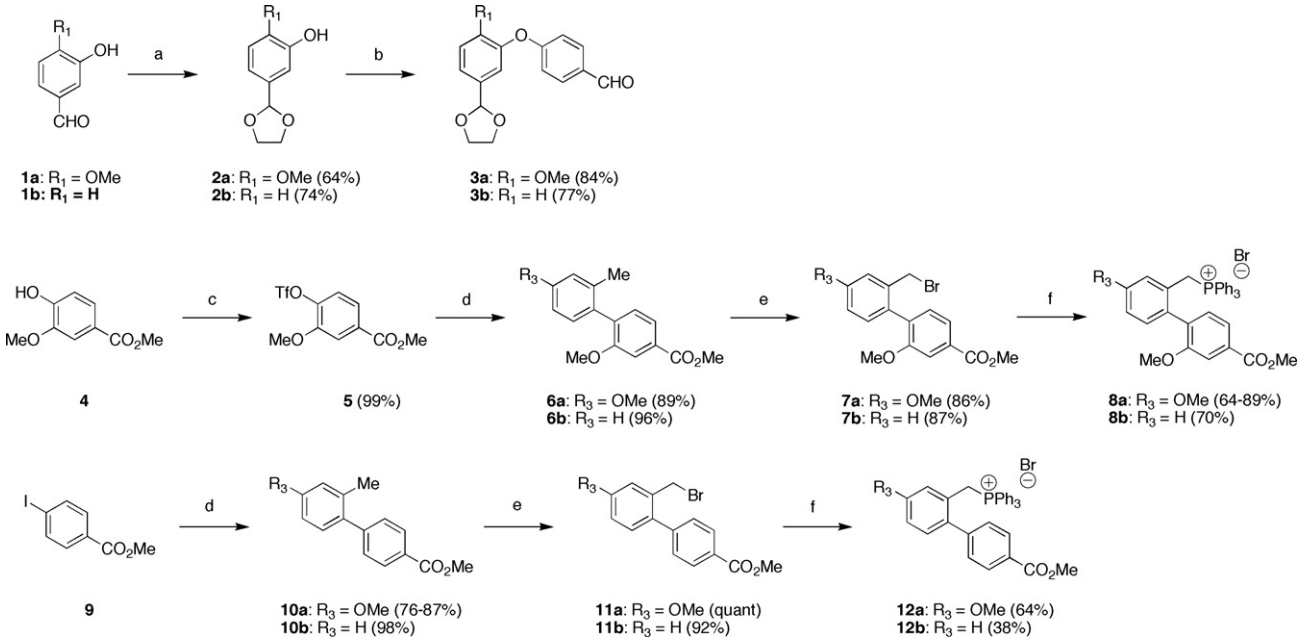


Figure 2. Lineweaver-Burk plot analysis of the inhibition of α-glucosidase by (a) T0901317, (b) GW3965, (c) riccardin C, and (d) dNM.

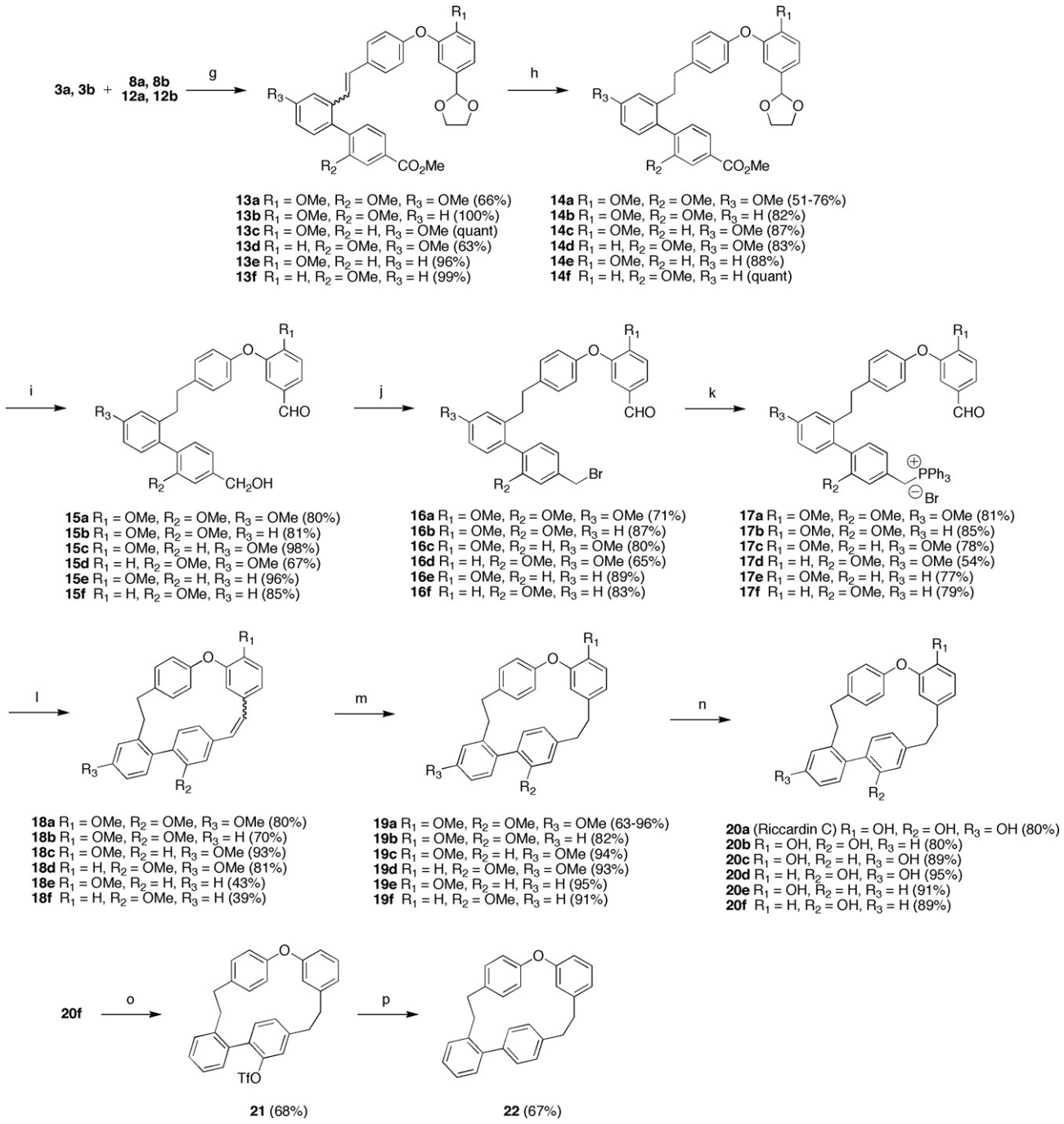
sidase inhibitors, the phenolic hydroxyl groups of riccardin C were expected to be important for the α-glucosidase-inhibitory activity.[16] Therefore, we expected that the modification of hydroxyl groups in riccardin C would reduce the α-glucosidase-inhibitory activity. On this basis, we planned to synthesize methylated or deoxy derivatives of riccardin C. Riccardin C and its derivatives were synthesized by coupling of the diphenyl ether



Scheme 1. Synthesis of the diphenyl ether aldehyde **3** and biphenyl phosphonium salts **8** and **12**. Reagents and conditions: (a) ethylene glycol, PPTS, benzene, reflux; (b) 4-fluorobenzaldehyde, K_2CO_3, DMF, 120 °C; (c) Tf_2O, pyridine CH_2Cl_2, 0 °C; (d) 4-substituted 2-methylphenyl boronic acid, $Pd(PPh_3)_4$, K_3PO_4, DMF, 100 °C; (e) NBS, AIBN, CCl_4, reflux; (f) PPh_3, CH_3CN, reflux.

aldehyde **3** with the biphenyl phosphonium salt **8** or **12**, according to the reported method.[17] All the synthetic block units were synthesized as illustrated in Scheme 1. The starting material **1** was protected as an acetal, and the resulting **2** was allowed to react with 4-fluorobenzaldehyde in the presence of K_2CO_3 to afford the diphenyl ether aldehyde **3**. The biphenyl phosphonium salt **8** was obtained by the Suzuki coupling of triflate **5** derived from **4** with phenylboronic acid, followed by NBS bromination and reaction with triphenylphosphane. The biphenyl phosphonium salt **12** was similarly synthesized, except that the Suzuki coupling was performed by using iodide **9** instead of triflate **5**.

Finally, the diphenyl ether aldehyde **3** and biphenyl phosphonium salt **8** or **12** were combined to obtain riccardin C derivatives as shown in Scheme 2. Stilbene **13**, which was obtained by the Wittig reaction of diphenyl ester aldehyde with biphenyl phosphonium salt in the presence of K_2CO_3 and 18-crown-6, was subjected to stepwise conversion of functional groups, hydrogenation of the olefin, reduction of the ester, deprotection



Scheme 2. Synthesis of riccardin C and its derivatives. Reagents and conditions: (g) K_2CO_3, 18-crown-6, CH_2Cl_2, reflux; (h) H_2, 10% Pd/C, Et_3N, AcOEt, rt; (i) 1—$LiAlH_4$, Et_2O, 0 °C; 2—H^+, H_2O, rt; (j) CBr_4, PPh_3, CH_2Cl_2, 0 °C; (k) PPh_3, toluene, 110 °C; (l) NaOMe, CH_2Cl_2, rt; (m) H_2 10% Pd/C, AcOEt, rt; (n) BBr_3, CH_2Cl_2, 0 °C; (o) Tf_2O, pyridine, CH_2Cl_2, 0 °C; (p) H_2, 10% Pd/C, Et_2NH_2, EtOH, rt.

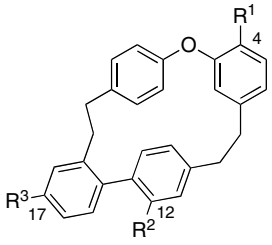
of the acetal, bromination of the alcohol, and reaction with triphenylphosphine to afford compound **17** as a phosphonium salt bearing an aldehyde group. Then, the bifunctional phosphonium salt **17** was cyclized via an intramolecular Wittig reaction, followed by hydrogenation to afford the methylated riccardin C analogs **19a**–**f**. Finally, demethylation using BBr_3 gave riccardin C and its analogs **20a**–**f**. The deoxy derivative **22** was obtained by the Pd-catalyzed reduction of triflate **21** prepared from **20f**.

The LXR-modulating and α-glucosidase-inhibitory activities of the prepared riccardin C and its derivatives were investigated (Table 3). Though riccardin C was reported to be an agonist for LXRα and an antagonist for LXRβ,[8] we found no agonistic activity of the compounds toward LXRs under our experimental conditions. We cannot explain this discrepancy at this stage, but it might be due to the difference of cells used in the reported assay system (African green monkey kidney, CV-1 cells) and in ours (human embryonic kidney cells, HEK293 cells), at least in part. As far as we determined in our assay systems, riccardin C exhibited moderate LXR-antagonistic activity toward both LXRs α and β with the IC_{50} values of 4.9 and 6.6 μM, respectively.

As mentioned above, riccardin C possesses potent α-glucosdidase-inhibitory activity with the IC_{50} value of 9.9 μM, and moderate LXR-antagonistic activity toward both LXRs α and β with the IC_{50} values of 4.9 and 6.6 μM, respectively, under our experimental conditions. Because these three IC_{50} values of riccardin C are in a similar range (4.9–9.9 μM), the compound could be said to be a non-selective dual inhibitor of LXRs and α-glucosidase. As expected, methylation of the hydroxyl groups of riccardin C remarkably reduced the α-glucosidase-inhibitory activity, as seen with compounds **19a**–**f**, which have IC_{50} values higher than 30 μM. But, surprisingly, removal of one hydroxyl group from riccardin C, that is, compounds **20b**–**d**, resulted in more potent α-glucosidase-inhibitory activity (IC_{50} values of 4.9–8.6 μM) than that of riccardin C, regardless of the position of the removed hydroxyl group. In contrast, removal of two or three (all) hydroxyl groups from riccardin C, that is, compounds **20e**, **20f**, and **22**, resulted in a slight decrease of the α-glucosidase-inhibitory activity (IC_{50} values are 15–19 μM). It is difficult to interpret these SAR findings at this stage.

Concerning LXR-modulating activity, none of the riccardin C derivatives examined exhibited agonistic activity (data not shown, vide supra) under our experimental conditions. However, all of the compounds showed LXR-antagonistic activity, though the potency and LXR subtype selectivity are diverse (Table 3). All of the methylated and dehydroxylated derivatives of riccardin C prepared were less potent LXRβ antagonists. In particular, compound **22** showed no LXRβ-antagonistic activity in the concentration range examined. This compound (**22**) possesses potent LXRα-antagonistic activity with the IC_{50} value of 7.1 μM, that is, it is a LXRα-selective antagonist, though it also possesses moderate α-glucosidase-inhibitory activity. Concerning LXRα-antagonistic activity, some derivatives (compounds **19a**–**c**, **19f**, **22c**, and **20f**) showed more potent activity than riccardin C, while others (compounds **19d**, **19e**, **20b**, **20d**, **20e**, and **22**) showed less potent activity than

Table 3. LXR-antagonistic and α-glucosidase-inhibitory activities of riccardin C derivatives



	R^1	R^2	R^3	IC_{50} (μM)		α-Glucosidase
				LXRα	LXRβ	IC_{50} (μM)
Riccardin C (**20a**)	–OH	–OH	–OH	4.9	6.6	9.9
19a	–OMe	–OMe	–OMe	2.0	14	49
19b	–OMe	–OMe	–H	2.2	12	42
19c	–OMe	–H	–OMe	3.6	26	40
19d	–H	–OMe	–OMe	25	46	>30[a]
19e	–OMe	–H	–H	7.6	41	>100
19f	–H	–OMe	–H	2.5	11	67
20b	–OH	–OH	–H	6.6	13	8.6
20c	–OH	–H	–OH	4.4	7.6	4.9
20d	–H	–OH	–OH	8.4	10	5.1
20e	–OH	–H	–H	5.7	14	15
20f	–H	–OH	–H	3.2	7.3	19
22	–H	–H	–H	7.1	77	18

[a] Precipitation was observed at the higher concentration than 30 μM.

riccardin C. The effects of methylation and removal of the hydroxyl group(s) of riccardin C on the LXRs-antagonistic activities seem to be larger for LXRβ than for LXRα. The selectivity of the methylated derivatives **19a–f** for LXRα may indicate that the reduction of LXRβ-antagonistic activity coincides with the decrease of α-glucosidase-inhibitory activity. Finally, we obtained compounds **19e** and **19f** as a novel LXR antagonists lacking α-glucosidase-inhibitory activity, and compound **22** as a LXRα-selective antagonist.

In conclusion, the results obtained here support our working hypothesis that the separation of LXR-modulating activity and α-glucosidase-inhibitory activity by the structural development of LXR ligands showing non-competitive α-glucosidase inhibition is feasible. We intend to apply this strategy to develop other LXR-selective ligands lacking α-glucosidase-inhibitory activity.

3. Experimental

3.1. Biology

3.1.1. α-Glucosidase inhibition assay. The α-glucosidase-inhibitory activity of test compounds was determined as described previously. α-Glucosidase (*Saccharomyces* sp., Wako) 0.2 mU/ml in 10 mM phosphate buffer (pH 7.0) was treated with DMSO solution of various compounds (final DMSO concentration 1% v/v) in a 96-well plate (final volume 90 μl). After 10 min incubation at 37 °C, 10 μl pNPG solution (final concentration 0.2 mM) was added. The mixture was incubated at 37 °C for 15 min, then basified by adding 100 μl of 0.5 M Na_2CO_3 solution. The amount of released *p*-nitrophenol was measured based on the absorbance at 405 nm.

3.1.2. Reporter gene assay. Human embryonic kidney (HEK) 293 cells were cultured in D-MEM medium containing 5% fetal bovine serum at 37 °C in a humidified atmosphere of 5% CO_2 in air. Transfections were performed by the calcium phosphate coprecipitation method. Test compounds with or without 100 nM T0901317 were added 8 h after the transfection. After overnight incubation, luciferase and β-galactosidase activities were assayed using a luminometer and microplate reader.

4. Chemistry

4.1. General

Melting points were determined by using a Yanagimoto hot-stage melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a JEOL JNM-GX500 (500 MHz) spectrometer. Chemical shifts are expressed in parts per million relative to tetramethylsilane. Mass spectra were recorded on a JEOL JMS-DX303 spectrometer.

4.1.1. 5-(1,3-Dioxolan-2-yl)-2-methoxyphenol (2a). A mixture of 3-hydroxy-4-methoxybenzaldehyde (3.36 g, 22.1 mmol), pyridinium *p*-toluenesulfonate (228 mg, 0.910 mmol), ethylene glycol (4.0 mL, 72 mmol), and 80 mL of dehydrated benzene was refluxed for 3.5 h. The reaction mixture was washed with sat. $NaHCO_3$ aq, water and brine, dried over anhydrous magnesium sulfate, and concentrated. The residue was purified by Chromatorex® silica gel column chromatography (eluent; *n*-hexane/ethyl acetate = 1:1, v/v) to afford 2.79 g (64%) of the title compound as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.06 (d, J = 2.1 Hz, 1H), 6.98 (dd, J = 8.1, 2.1 Hz, 1H), 6.84 (d, J = 8.1 Hz, 1H), 5.73 (s, 1H), 4.13–3.99 (m, 4H), 3.89 (s, 3H); MS (FAB) 197 $(M+H)^+$.

4.1.2. 3-(1,3-Dioxolan-2-yl)phenol (2b). This compound was prepared from 3-hydroxybenzaldehyde by means of a procedure similar to that used for **2a**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25 (dd, J = 8.1, 7.7 Hz, 1H), 7.05 (d, J = 7.7 Hz, 1H), 6.97–6.94 (m, 1H), 6.83 (dd, J = 8.1, 2.6 Hz, 1H), 5.78 (s, 1H), 4.91 (s, 1H), 4.15–4.00 (m, 4H); MS (FAB) 167 $(M+H)^+$.

4.1.3. 4-(5-(1,3-Dioxolan-2-yl)-2-methoxyphenoxy)benzaldehyde (3a). To a solution of **2a** (7.80 g, 39.8 mmol) and 140 mL of dehydrated DMF were added 4-fluorobenzaldehyde (4.20 mL, 39.8 mmol) and potassium carbonate (5.78 g, 41.8 mmol). The mixture was stirred for 14 h at 150 °C. The mixture was evaporated, and the residue was purified by alumina column chromatography (eluent; *n*-hexane/ethyl acetate = 3:1, v/v) to afford 10.1 g (84%) of the title compound as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.90 (s, 1H), 7.81 (d, J = 8.7 Hz, 2H), 7.35 (dd, J = 8.5, 2.1 Hz, 1H), 7.24 (d, J = 2.1 Hz, 1H), 7.03 (d, J = 8.5 Hz, 1H), 6.98 (d, J = 8.7 Hz, 2H), 5.75 (s, 1H), 4.13–4.00 (m, 4H), 3.80 (s, 3H); MS (FAB) 301 $(M+H)^+$.

4.1.4. 4-{3-(1,3-Dioxolan-2-yl)phenoxy}benzaldehyde (3b). This compound was prepared from **2b** by means of a procedure similar to that used for **3a**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.93 (s, 1H), 7.85 (d, J = 8.5 Hz, 2H), 7.43 (dd, J = 8.1, 7.7 Hz, 1H), 7.34 (d, J = 7.7 Hz, 1H), 7.23–7.21 (m, 1H), 7.10–7.08 (m, 1H), 7.07 (d, J = 8.5 Hz, 2H), 5.81 (s, 1H), 4.14–4.02 (m, 4H); MS (FAB) 271 $(M+H)^+$.

4.1.5. Methyl 3-methoxy-4-[(trifluoromethylsulfonyl)oxy]benzoate (5). To a solution of methyl 4-hydroxy-3-methoxybenzoate (3.00 g, 16.5 mmol, **4**), 6 mL of pyridine, and 55 mL of dichloromethane was added dropwise trifluoromethanesulfonic anhydride (3.0 mL, 18 mmol) at 0 °C. The mixture was stirred for 4 h at 0 °C. The mixture was poured into ice water. The organic layer was washed with sat. $NaHCO_3$ aq, water and brine, dried over anhydrous magnesium sulfate, and concentrated. The residue was purified by silica gel column chromatography (eluent; *n*-hexane/ethyl acetate = 5:1, v/v) to afford 5.13 g (99%) of the title compound as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.72 (d, J = 1.7 Hz, 1H), 7.68 (dd, J = 8.6, 1.7 Hz, 1H), 7.28 (d, J = 8.6 Hz, 1H), 3.98 (s, 3H), 3.94 (s, 3H); MS (FAB) 315 $(M+H)^+$.

4.1.6. Methyl 3-methoxy-4-(4-methoxy-2-methylphenyl) benzoate (6a). A mixture of **5** (4.16 g, 13.2 mmol), 4-methoxy-2-methylphenylboronic acid (2.41 g, 13.7 mmol), tetrakis(triphenylphosphine)palladium(0) (363 mg, 0.314 mmol), potassium phosphate tribasic (4.20 g, 19.8 mmol), and 50 mL of dehydrated DMF was stirred for 1.5 h at 100 °C under an argon atmosphere. The mixture was filtered and washed with diethyl ether. The organic layer was washed with water and brine, dried over anhydrous magnesium sulfate, and concentrated. The residue was purified by silica gel column chromatography (eluent; *n*-hexane/ethyl acetate = 20:1, v/v) to afford 3.37 g (89%) of the title compound as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70 (dd, J = 9.9, 1.5 Hz, 1H), 7.61 (d, J = 1.5 Hz, 1H), 7.19 (d, J = 9.9 Hz, 1H), 7.08 (d, J = 8.1 Hz, 1H), 6.82–6.78 (m, 2H), 3.94 (s, 3H), 3.83 (s, 6H), 2.10 (s, 3H); MS (FAB) 286 $(M+H)^+$.

4.1.7. Methyl 3-methoxy-4-(2-methylphenyl)benzoate (6b). This compound was prepared from **5** and 2-methylphenylboronic acid by means of a procedure similar to that used for **6a**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70 (dd, J = 7.7, 1.3 Hz, 1H), 7.63 (d, J = 1.3 Hz, 1H), 7.29–7.24 (m, 3H), 7.21 (d, J = 7.7 Hz, 1H), 7.16 (d, J = 7.3 Hz, 1H), 3.95 (s, 3H), 3.83 (s, 3H), 2.12 (s, 3H); MS (FAB) 256 $(M+H)^+$.

4.1.8. 5-Methoxy-2-[2-methoxy-4-(methoxycarbonyl) phenyl]benzyl bromide (7a). To a solution of **6a** (480 mg, 1.68 mmol) and 10 mL of carbon tetrachloride were added *N*-bromosuccinimide (323 mg, 1.81 mmol) and 2,2′-azobis(isobutyronitrile) (42.0 mg, 0.256 mmol). The mixture was stirred for 48 h at 95 °C. The mixture was filtered and concentrated. The residue was purified by silica gel column chromatography (eluent; *n*-hexane/ethyl acetate = 5:1, v/v) to afford 423 mg (69%) of the title compound as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.72 (dd, J = 7.7, 1.5 Hz, 1H), 7.63 (d, J = 1.5 Hz, 1H), 7.31 (d, J = 7.7 Hz, 1H), 7.11 (d, J = 8.6 Hz, 1H), 7.07 (d, J = 2.6 Hz, 1H), 6.91 (dd, J = 8.6, 2.6 Hz, 1H), 4.36–4.24 (m, 2H), 3.95 (s, 3H), 3.86 (s, 3H), 3.82 (s, 3H); MS (FAB) 364, 366 (M^+).

4.1.9. 2-{2-Methoxy-4-(methoxycarbonyl)phenyl}benzyl bromide (7b). This compound was prepared from **6b** by means of a procedure similar to that used for **7a**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.74 (dd, J = 7.7, 1.3 Hz, 1H), 7.65 (d, J = 1.3 Hz, 1H), 7.54 (dd, J = 7.7, 1.7 Hz, 1H), 7.39–7.36 (m, 2H), 7.33 (d, J = 7.7 Hz, 1H), 7.18 (dd, J = 7.7, 1.7 Hz, 1H), 4.40–4.27 (m, 2H), 3.96 (s, 3H), 3.82 (s, 3H); MS (FAB) 335 (M^+).

4.1.10. {5-Methoxy-2-[2-methoxy-4-(methoxycarbonyl) phenyl]benzyl}triphenylphosphonium bromide (8a). A mixture of **7a** (423 mg, 1.16 mmol), triphenylphosphine (866 mg, 3.30 mmol) and 10 mL of acetonitrile was refluxed for 3.5 h. The reaction mixture was concentrated and mixed with 50 mL of toluene. The whole was filtered to afford 648 mg (89%) of the title compound as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.75–7.36 (m, 17H), 6.96 (d, J = 8.6 Hz, 1H), 6.87–6.84 (m, 2H), 6.36 (d, J = 7.7 Hz, 1H), 5.62 and 4.68 (t, J (^{31}P–^{1}H)= 15 Hz, each 1H), 3.97 (s, 3H), 3.75 (s, 3H), 3.55 (s, 3H); MS (FAB) 627 (M^+).

4.1.11. [2-{2-Methoxy-4-(methoxycarbonyl)phenyl}benzyl] triphenylphosphonium bromide (8b). This compound was prepared from **7b** by means of a procedure similar to that used for **8a**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.76–7.73 (m, 3H), 7.57–7.51 (m, 7H), 7.40–7.19 (m, 10H), 7.07 (d, J = 7.7 Hz, 1H), 6.24 (d, J = 7.7 Hz, 1H), 5.65 and 4.60 (t, J (^{31}P–^{1}H) = 15 Hz, each 1H), 3.98 (s, 3H), 3.79 (s, 3H); MS (FAB) 517 $(M-Br)^+$.

4.1.12. Methyl 4-(4-methoxy-2-methylphenyl)benzoate (10a). This compound was prepared from methyl 4-iodobenzoate (**9**) and 4-methoxy-2-methylphenylboronic acid by means of a procedure similar to that used for **6a**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.07 (d, J = 8.3 Hz, 2H), 7.37 (d, J = 8.3 Hz, 2H), 7.10 (d, J = 8.5 Hz, 1H), 6.83–6.80 (m, 2H), 3.94 (s, 3H), 3.84 (s, 3H), 2.26 (s, 3H); MS (FAB) 256 (M^+).

4.1.13. Methyl 4-(2-methylphenyl)benzoate (10b). This compound was prepared from methyl 4-iodobenzoate (**9**) and 2-methylphenylboronic acid by means of a procedure similar to that used for **6a**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.09 (d, J = 8.6 Hz, 2H), 7.40 (d, J = 8.6 Hz, 2H), 7.30–7.22 (m, 4H), 3.95 (s, 3H), 2.27 (s, 3H); MS (FAB) 227 $(M+H)^+$.

4.1.14. 5-Methoxy-2-{4-(methoxycarbonyl)phenyl}benzyl bromide (11a). This compound was prepared from **10a** by means of a procedure similar to that used for **7a**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.11 (d, J = 8.1 Hz, 2H), 7.50 (d, J = 8.1 Hz, 2H), 7.18 (d, J = 8.6 Hz, 1H), 7.06 (d, J = 2.8 Hz, 1H), 6.92 (dd, J = 8.6, 2.8 Hz, 1H), 4.40 (s, 2H), 3.95 (s, 3H), 3.87 (s, 3H); MS (FAB) 335 $(M+H)^+$.

4.1.15. 2-{4-(Methoxycarbonyl)phenyl}benzyl bromide (11b). This compound was prepared from **10b** by means of a procedure similar to that used for **7a**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.11 (d, J = 8.6 Hz, 2H), 7.51 (d, J = 8.6 Hz, 2H), 7.40–7.34 (m, 2H), 7.26–7.22 (m, 2H), 4.40 (s, 2H), 3.94 (s, 3H); MS (FAB) 305 $(M+H)^+$.

4.1.16. [5-Methoxy-2-{4-(methoxycarbonyl)phenyl}benzyl] triphenylphosphonium bromide (12a). This compound was prepared from **11a** by means of a procedure similar to that used for **8a**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.86 (d, J = 8.5 Hz, 2H), 7.77–7.73 (m, 3H), 7.58–7.54 (m, 7H), 7.43 (d, J = 8.6 Hz, 2H), 7.41 (d, J = 8.1 Hz, 2H), 7.04–7.00 (m, 3H), 6.89–6.87 (m, 1H), 6.79 (d, J = 8.1 Hz, 2H), 5.49 (d, J (^{31}P–^{1}H) = 15 Hz, 2H), 3.95 (s, 3H), 3.55 (s, 3H); MS (FAB) 517 $(M-Br)^+$.

4.1.17. [2-{4-(Methoxycarbonyl)phenyl}benzyl]triphenylphosphonium bromide (12b). This compound was prepared from **11b** by means of a procedure similar to that used for **8a**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.86 (d, J = 8.1 Hz, 2H), 7.73 (dd, J = 7.7, 6.0 Hz, 2H), 7.55–7.46 (m, 8H), 7.39–7.30 (m, 8H), 7.06 (d, J (^{31}P–^{1}H) = 7.3 Hz, 1H), 6.75 (d, J = 8.1 Hz, 2H), 5.57 (d, J = 15 Hz, 2H), 3.94 (s, 3H); MS (FAB) 487 $(M-Br)^+$.

4.1.18. Methyl 4-{2-[(*E*/*Z*)-2-{4-[5-(1,3-dioxolan-2-yl)-2-methoxyphenoxy]phenyl}-1-ethenyl]-4-methoxyphenyl}-3-methoxybenzoate (13a). A mixture of **3a** (348 mg, 1.16 mmol), **8a** (753 mg, 1.20 mmol), potassium carbon-

ate (175 mg, 1.26 mmol), 18-crown-6 (55.2 mg, 0.209 mmol), and 15 mL of dehydrated dichloromethane was refluxed for 42 h. The mixture was filtered and concentrated. The residue was purified by Chromatorex® column chromatography (eluent; *n*-hexane/ethyl acetate = 2:1, v/v) to afford 402 mg (61%) of the title compound as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.71–6.19 (m, 15H), 5.71 and 5.70 (s, 1H), 4.09–3.96 (m, 4H), 3.95 (s, 3H), 3.89 (s, 3H), 3.82 (s, 3H), 3.79 (s, 3H); MS (FAB) 568 (M^+).

4.1.19. Methyl 4-{2-[(*E*/*Z*)-2-{4-[5-(1,3-dioxolan-2-yl)-2-methoxyphenoxy]phenyl}-1-ethenyl]phenyl}-3-methoxybenzoate (13b). This compound was prepared from **3a** and **8b** by means of a procedure similar to that used for **13a**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.77–7.37 (m, 7H), 7.32–7.17 (m, 2H), 7.12–7.10 (m, 1H), 7.00 (d, J = 4.3 Hz, 1H), 6.97 (d, J = 3.4 Hz, 1H), 6.84 (d, J = 9.0 Hz, 1H), 6.75 (s, 1H), 6.73 (d, J = 9.0 Hz, 1H), 6.33–6.19 (m, 1H), 5.72 and 5.70 (s, 1H), 4.09–3.99 (m, 4H), 3.96 and 3.94 (s, 3H), 3.84 and 3.83 (s, 3H), 3.79 and 3.73 (s, 3H); MS (FAB) 538 (M^+).

4.1.20. Methyl 4-{2-[(*E*/*Z*)-2-{4-[5-(1,3-dioxolan-2-yl)-2-methoxyphenoxy]phenyl}-1-ethenyl]-4-methoxyphenyl} benzoate (13c). This compound was prepared from **3a** and **12a** by means of a procedure similar to that used for **13a**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.08 (d, J = 8.6 Hz, 1H), 8.00 (d, J = 8.1 Hz, 1H), 7.68 (d, J = 6.8 Hz, 1H), 7.66 (d, J = 6.8 Hz, 1H), 7.57–7.53 (m, 1H), 7.48–7.42 (m, 3H), 7.30–7.23 (m, 2H), 7.14–7.12 (m, 1H), 7.00–6.87 (m, 3H), 6.78 (d, J = 8.6 Hz, 1H), 6.48–6.32 (m, 1H), 5.71 (s, 1H), 4.10–3.97 (m, 4H), 3.95–3.67 (s not resolved, 9H); MS (FAB) 538 (M^+).

4.1.21. Methyl 4-{2-[(*E*/*Z*)-2-{4-[5-(1,3-dioxolan-2-yl) phenoxy]phenyl}-1-ethenyl]-4-methoxyphenyl}-3-methoxybenzoate (13d). This compound was prepared from **3b** and **8a** by means of a procedure similar to that used for **13a**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69 (dd, J = 7.7 Hz, 1H), 7.63 (s, 1H), 7.60 (d, J = 7.7 Hz, 1H), 7.55 (dd, J = 6.0 Hz, 1H), 7.43 (d, J = 2.6 Hz, 1H), 7.39–7.33 (m, 1H), 7.25–7.11 (m, 5H), 6.98–6.96 (m, 2H), 6.89 (d, J = 8.5 Hz, 1H), 6.85–6.80 (m, 1H), 6.74–6.66 (m, 1H), 5.79–5.75 (m, 1H), 4.13–3.92 (m, 4H), 4.00–3.63 (s, not resolved, 9H); MS (FAB) 538 (M^+).

4.1.22. Methyl 4-{2-[(*E*/*Z*)-2-{4-[5-(1,3-dioxolan-2-yl)-2-methoxyphenoxy]phenyl}-1-ethenyl]-4-methoxyphenyl}-3-methoxybenzoate (13e). This compound was prepared from **3a** and **12b** by means of a procedure similar to that used for **13a**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.10 (d, J = 8.6 Hz, 1H), 8.02 (d, J = 8.1 Hz, 1H), 7.75 (d, J = 7.7 Hz, 1H), 7.48–7.45 (m, 3H), 7.40–7.21 (m, 4H), 7.13 (dd, J = 6.4, 2.1 Hz, 1H), 7.10 (d, J = 9.0 Hz, 2H), 6.99 (dd, J = 8.1, 3.4 Hz, 2H), 6.87 (d, J = 8.6 Hz, 1H), 6.75 (d, J = 9.0 Hz, 1H), 5.72 and 5.71 (s, 1H), 4.13–3.97 (m, 4H), 3.95 and 3.93 (s, 3H), 3.84 and 3.83 (s, 3H); MS (FAB) 509 ($M+H)^+$.

4.1.23. Methyl 4-{2-[(*E*/*Z*)-2-{4-[3-(1,3-dioxolan-2-yl) phenoxy]phenyl}-1-ethenyl]phenyl}-3-ethoxybenzoate (13f). This compound was prepared from **3b** and **8b** by means of a procedure similar to that used for **13a**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.75 (d, J = 8.1 Hz, 1H), 7.71 (dd, J = 7.7, 1.7 Hz, 1H), 7.66 (d, J = 1.7 Hz, 1H), 7.44–7.38 (m, 1H), 7.31–7.11 (m, 5H), 7.00–6.97 (m, 3H), 6.89 (d, J = 9.0 Hz, 2H), 6.78 (d, J = 9.0 Hz, 1H), 6.74 (d, J = 16 Hz, 2H), 5.77 and 5.75 (s, 1H), 4.11–4.00 (m, 4H), 3.98 and 3.94 (s, 3H), 3.78 and 3.72 (s, 3H); MS (FAB) 508 (M^+).

4.1.24. Methyl 4-(2-{4-[5-(1,3-dioxolan-2-yl)-2-methoxyphenoxy]phenethyl}-4-methoxyphenyl)-3-methoxybenzoate (14a). Compound **13a** (2.40 g, 4.22 mmol) was hydrogenated with 10% Pd/C (214 mg) in 10 mL of triethylamine and 80 mL of dehydrated ethyl acetate, affording 1.57 g (65%) of the title compound. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68 (dd, J = 7.7, 1.3 Hz, 1H), 7.62 (d, J = 1.3 Hz, 1H), 7.23 (dd, J = 8.1, 1.9 Hz, 1H), 7.14 (d, J = 7.7 Hz, 1H), 7.06 (s, 1H), 7.04 (d, J = 1.9 Hz, 1H), 6.98 (d, J = 8.1 Hz, 1H), 6.84–6.76 (m, 6H), 5.68 (s, 1H), 4.07–3.96 (m, 4H), 3.95 (s, 3H), 3.83 (s, 3H), 3.82 (s, 3H), 3.81 (s, 3H), 2.64 (br s, 4H); MS (FAB) 571 $(M+H)^+$.

4.1.25. Methyl 4-(2-{4-[5-(1,3-dioxolan-2-yl)-2-methoxyphenoxy]phenethyl}phenyl)-3-methoxybenzoate (14b). This compound was prepared from **13b** by means of a procedure similar to that used for **14a**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70 (dd, J = 7.7, 1.5 Hz, 1H), 7.63 (d, J = 1.5 Hz, 1H), 7.32–7.21 (m, 4H), 7.15 (d, J = 7.7 Hz, 1H), 7.04 (d, J = 2.1 Hz, 1H), 6.98 (d, J = 8.1 Hz, 1H), 6.86–6.76 (m, 5H), 5.69 (s, 1H), 4.07–3.98 (m, 4H), 3.95 (s, 3H), 3.84 (s, 3H), 3.81 (s, 3H), 2.76–2.62 (m, 4H); MS (FAB) 541 $(M+H)^+$.

4.1.26. Methyl 4-(2-{4-[5-(1,3-dioxolan-2-yl)-2-methoxyphenoxy]phenethyl}-4-methoxyphenyl)benzoate (14c). This compound was prepared from **13c** by means of a procedure similar to that used for **14a**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.05 (d, J = 8.6 Hz, 2H), 7.31 (d, J = 8.1 Hz, 2H), 7.23 (dd, J = 8.1, 1.7 Hz, 1H), 7.12 (d, J = 8.6 Hz, 2H), 7.04 (d, J = 2.1 Hz, 1H), 6.98 (d, J = 8.1 Hz, 2H), 6.86–6.77 (m, 4H), 5.69 (s, 1H), 4.07–3.95 (m, 4H), 3.94 (s, 3H), 3.86 (s, 3H), 2.83–2.68 (m, 4H); MS (FAB) 541 $(M+H)^+$.

4.1.27. Methyl 4-(2-{4-[3-(1,3-dioxolan-2-yl)phenoxy] phenethyl}-4-methoxyphenyl)-3-methoxybenzoate (14d). This compound was prepared from **13d** by means of a procedure similar to that used for **14a**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69 (dd, J = 7.7, 1.3 Hz, 1H), 7.63 (d, J = 1.3 Hz, 1H), 7.33–7.29 (m, 1H), 7.18 (d, J = 7.7 Hz, 1H), 7.16 (d, J = 7.7 Hz, 1H), 7.09–7.05 (m, 2H), 7.93 (dd, J = 8.5, 1.3 Hz, 1H), 6.88–6.81 (m, 6H), 5.77 and 5.76 (s, 1H), 4.13–4.00 (m, 4H), 3.95 (s, 3H), 3.83 (s, 3H), 3.82 (s, 3H), 2.66–2.05 (m, 4H); MS (FAB) 541 $(M+H)^+$.

4.1.28. Methyl 4-(2-{4-[5-(1,3-dioxolan-2-yl)-2-methoxyphenoxy]phenethyl}phenyl)benzoate (14e). This compound was prepared from **13e** by means of a procedure similar to that used for **14a**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.08 (d, J = 8.6 Hz, 2H), 7.33 (d, J = 8.1 Hz, 2H), 7.32 (dd, J = 6.8, 2.6 Hz, 1H), 7.29

(dd, J = 7.7, 3.4 Hz, 1H), 7.25 (d, J = 2.1 Hz, 1H), 7.23 (dd, J = 8.1, 2.1 Hz, 1H), 7.18 (d, J = 7.3 Hz, 1H), 7.05 (d, J = 2.1 Hz, 1H), 6.98 (d, J = 8.6 Hz, 2H), 6.84–6.77 (m, 3H), 5.69 (s, 1H), 4.08–3.96 (m, 4H), 3.95 (s, 3H), 3.84 (s, 3H), 2.86–2.66 (m, 4H); MS (FAB) 511 $(M+H)^+$.

4.1.29. Methyl 4-(2-{4-[3-(1,3-dioxolan-2-yl)phenoxy] phenethyl}phenyl)-3-methoxybenzoate (14f). This compound was prepared from **13f** by means of a procedure similar to that used for **14a**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70 (dd, J = 7.7, 1.3 Hz, 2H), 7.64 (s, 2H), 7.33–7.14 (m, 5H), 6.94 (d, J = 8.1 Hz, 2H), 6.87–6.82 (m, 4H), 5.77 (s, 1H), 4.13–4.00 (m, 4H), 3.96 (s, 3H), 3.82 (s, 3H), 2.76–2.67 (m, 4H); MS (FAB) 511 $(M+H)^+$.

4.1.30. 4-Methoxy-3-[4-(5-methoxy-2-{(2-methoxy-4-hydroxymethyl)phenyl}phenethyl)phenoxy]benzaldehyde (15a). To a suspension of lithium aluminum hydride (155 mg, 4.10 mmol) and dehydrated 30 mL of diethyl ether was added dropwise **14a** (1.57 g, 2.75 mmol) in 30 mL of dehydrated diethyl ether at 0 °C under an argon atmosphere. The mixture was stirred for 17.5 h at room temperature. The mixture was poured into sat. NH_4Cl aq, filtered and washed with diethyl ether. The organic layer was washed with brine, dried over anhydrous magnesium sulfate, and concentrated. The residue was purified by silica gel column chromatography (eluent; *n*-hexane/ethyl acetate = 1:1, v/v) to afford 1.10 g (80%) of the title compound as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.79 (s, 1H), 7.62 (dd, J = 8.6, 1.9 Hz, 1H), 7.35 (d, J = 1.9 Hz, 1H), 7.09 (d, J = 8.6 Hz, 1H), 7.08 (d, J = 7.7 Hz, 1H), 7.01 (s, 1H), 6.98 (d, J = 7.7 Hz, 1H), 6.90 (d, J = 8.5 Hz, 1H), 6.83–6.78 (m, 6H), 4.75 (s, 2H), 3.96 (s, 3H), 3.82 (s, 3H), 3.78 (s, 3H), 2.70 (br s, 4H); MS (FAB) 498 (M^+).

4.1.31. 4-Methoxy-3-[4-(2-{(2-methoxy-4-hydroxymethyl) phenyl}phenethyl)phenoxy]benzaldehyde (15b). This compound was prepared from **14b** by means of a procedure similar to that used for **15a**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.79 (s, 1H), 7.61 (dd, J = 8.6, 2.1 Hz, 1H), 7.35 (d, J = 2.1 Hz, 1H), 7.32–7.23 (m, 3H), 7.16 (d, J = 7.3 Hz, 1H), 7.10 (d, J = 4.3 Hz, 2H), 7.08 (d, J = 5.6 Hz, 2H), 6.90 (d, J = 8.6 Hz, 2H), 6.82 (d, J = 8.6 Hz, 2H), 4.76 (s, 2H), 3.96 (s, 3H), 3.77 (s, 3H), 2.78–2.67 (m, 4H); MS (FAB) 468 (M^+).

4.1.32. 4-Methoxy-3-[4-(5-methoxy-2-{(4-hydroxymethyl) phenyl}phenethyl)phenoxy]benzaldehyde (15c). This compound was prepared from **14c** by means of a procedure similar to that used for **15a**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.79 (s, 1H), 7.62 (dd, J = 8.2, 1.7 Hz, 1H), 7.40 (d, J = 8.1 Hz, 2H), 7.36 (d, J = 2.1 Hz, 1H), 7.24 (m, 2H), 7.14 (d, J = 8.6 Hz, 1H), 7.09 (d, J = 8.6 Hz, 1H), 6.93 (d, J = 8.6 Hz, 2H), 6.85–6.80 (m, 4H), 4.75 (s, 2H), 3.96 (s, 3H), 3.84 (s, 3H), 2.88–2.72 (m, 4H); MS (FAB) 468 (M^+).

4.1.33. 3-[4-(5-Methoxy-2-{(2-methoxy-4-hydroxymethyl) phenyl}phenethyl)phenoxy]benzaldehyde (15d). This compound was prepared from **14d** by means of a procedure similar to that used for **15a**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.94 (s, 1H), 7.56 (dd, J = 7.7 Hz, 1H), 7.47 (dd, J = 8.1, 7.7 Hz, 1H), 7.40–7.38 (m, 1H), 7.26 (m, 1H), 7.09 (d, J = 7.7 Hz, 2H), 7.01 (s, 1H), 6.98 (d, J = 7.7 Hz, 1H), 6.94 (d, J = 8.1 Hz, 2H), 6.87 (d, J = 8.6 Hz, 2H), 6.82–6.80 (m, 2H), 4.76 (s, 2H), 3.83 (s, 3H), 3.78 (s, 3H), 2.72 (br s, 4H); MS (FAB) 468 (M^+).

4.1.34. 4-Methoxy-3-[4-(2-{(4-hydroxymethyl)phenyl} phenethyl)phenoxy]benzaldehyde (15e). This compound was prepared from **14e** by means of a procedure similar to that used for **15a**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.79 (s, 1H), 7.62 (dd, J = 8.6, 1.7 Hz, 1H), 7.42 (d, J = 7.7 Hz, 2H), 7.36 (d, J = 1.7 Hz, 1H), 7.31–7.20 (m, 6H), 7.09 (d, J = 8.1 Hz, 1H), 6.91 (d, J = 8.1 Hz, 2H), 6.83 (d, J = 8.5 Hz, 2H), 4.76 (s, 2H), 3.96 (s, 3H), 2.90–2.87 (m, 2H), 2.74–2.71 (m, 2H); MS (FAB) 438 (M^+).

4.1.35. 3-[4-(2-{(2-Methoxy-4-hydroxymethyl)phenyl} phenethyl)phenoxy]benzaldehyde (15f). This compound was prepared from **14f** by means of a procedure similar to that used for **15a**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.94 (s, 1H), 7.58–7.55 (m, 1H), 7.47 (dd, J = 7.7 Hz, 1H), 7.39 (m, 1H), 7.33–7.24 (m, 4H), 7.17 (d, J = 7.7 Hz, 1H), 7.11 (d, J = 7.3 Hz, 1H), 7.03 (s, 1H), 6.99 (d, J = 9.0 Hz, 1H), 6.94 (d, J = 8.6 Hz, 2H), 6.87 (d, J = 8.6 Hz, 2H), 4.78 and 4.76 (s, 2H), 3.78 (s, 3H), 2.80–2.71 (m, 4H); MS (FAB) 438 (M^+).

4.1.36. 4-Methoxy-3-[4-(5-methoxy-2-{(2-methoxy-4-bromomethyl)phenyl}phenethyl)phenoxy]benzaldehyde (16a). A mixture of **15a** (1.10 g, 2.21 mmol), carbon tetrabromide (811 mg, 2.46 mmol), triphenylphosphine (609 mg, 2.32 mmol) and 20 mL of dehydrated dichloromethane was stirred for 16 h at 0 °C under an argon atmosphere. The mixture was poured into water and the dichloromethane layer was separated. The organic layer was washed with brine, dried over anhydrous magnesium sulfate, and concentrated. The residue was purified by silica gel column chromatography (eluent; *n*-hexane/ethyl acetate = 2:1, v/v) to afford 876 mg (71%) of the title compound as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.80 (s, 1H), 7.62 (dd, J = 8.1, 1.7 Hz, 1H), 7.36 (d, J = 1.7 Hz, 1H), 7.09–7.02 (m, 4H), 6.99 (s, 1H), 6.88–6.78 (m, 6H), 4.56 (s, 2H), 3.95 (s, 3H), 3.82 (s, 3H), 3.77 (s, 3H), 2.66 (br s, 4H); MS (FAB) 560 (M^+).

4.1.37. 4-Methoxy-3-[4-(2-{(2-methoxy-4-bromomethyl) phenyl}phenethyl)phenoxy]benzaldehyde (16b). This compound was prepared from **15b** by means of a procedure similar to that used for **16a**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.80 (s, 1H), 7.62 (dd, J = 8.1, 1.7 Hz, 1H), 7.35 (d, J = 2.1 Hz, 1H), 7.31–7.24 (m, 5H), 7.16 (d, J = 7.7 Hz, 1H), 7.09–7.00 (m, 3H), 6.86–6.81 (m, 3H), 4.65 and 4.57 (s, 2H), 3.95 (s, 3H), 3.77 (s, 3H), 2.77–2.62 (m, 4H); MS (FAB) 530 (M^+).

4.1.38. 4-Methoxy-3-[4-(5-methoxy-2-{(4-bromomethyl) phenyl}phenethyl)phenoxy]benzaldehyde (16c). This compound was prepared from **15c** by means of a procedure similar to that used for **16a**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.80 (s, 1H), 7.62 (dd, J = 8.5, 2.1 Hz, 1H),

7.42 (d, J = 8.1 Hz, 2H), 7.36 (d, J = 1.7 Hz, 1H), 7.23 (d, J = 7.7 Hz, 2H), 7.13 (d, J = 8.6 Hz, 1H), 7.09 (d, J = 8.1 Hz, 1H), 6.89–6.80 (m, 6H), 4.65 and 4.56 (s, 2H), 3.95 (s, 3H), 3.84 (s, 3H), 2.89–2.67 (m, 4H); MS (FAB) 530 (M^+).

4.1.39. 3-[4-(5-Methoxy-2-{(2-methoxy-4-bromomethyl) phenyl}phenethyl)phenoxy]benzaldehyde (16d). This compound was prepared from **15d** by means of a procedure similar to that used for **16a**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.92 (s, 1H), 7.54 (d, J = 7.7 Hz, 1H), 7.45 (dd, J = 8.1, 7.7 Hz, 1H), 7.40–7.39 (m, 1H), 7.07 (dd, J = 7.7 Hz, 1H), 7.03–6.98 (m, 3H), 6.91–6.79 (m, 7H), 4.63 and 4.54 (s, 2H), 3.81 (s, 3H), 3.76 (s, 3H), 2.66 (br s, 4H); MS (FAB) 530 (M^+).

4.1.40. 4-Methoxy-3-[4-(2-{(4-bromomethyl)phenyl}phenethyl)phenoxy]benzaldehyde (16e). This compound was prepared from **15e** by means of a procedure similar to that used for **16a**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.80 (s, 1H), 7.62 (dd, J = 8.1, 2.1 Hz, 1H), 7.44 (d, J = 8.1 Hz, 2H), 7.36 (d, J = 1.7 Hz, 1H), 7.32–7.24 (m, 5H), 7.20 (d, J = 7.3 Hz, 1H), 7.09 (d, J = 8.1 Hz, 1H), 6.88–6.82 (m, 4H), 4.66 and 4.57 (s, 2H), 3.95 (s, 3H), 2.89–2.86 (m, 2H), 2.70–2.67 (m, 2H); MS (FAB) 500 (M^+).

4.1.41. 3-[4-(2-{(2-Methoxy-4-bromomethyl)phenyl}phenethyl)phenoxy]benzaldehyde (16f). This compound was prepared from **15f** by means of a procedure similar to that used for **16a**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.94 (s, 1H), 7.56 (d, J = 7.7 Hz, 1H), 7.47 (dd, J = 8.1, 7.7 Hz, 1H), 7.39 (s, 1H), 7.31–7.23 (m, 3H), 7.17 (d, J = 7.7 Hz, 1H), 7.09 (d, J = 7.3 Hz, 1H), 7.06–7.01 (m, 2H), 6.88 (d, J = 4.7 Hz, 2H), 6.90–6.85 (m, 3H), 4.66 and 4.57 (s, 2H), 3.78 (s, 3H), 2.78–2.64 (m, 4H); MS (FAB) 500 (M^+).

4.1.42. 4-Methoxy-3-[4-(5-methoxy-2-{2-methoxy-4-[(1,1,1-triphenylphosphino)methyl]phenyl}phenethyl)phenoxy] benzaldehyde bromide (17a). A mixture of **16a** (876 mg, 1.56 mmol), triphenylphosphine (540 mg, 2.06 mmol), and 15 mL of toluene was stirred for 19 h at 110 °C. The mixture was filtered to afford 1.05 g (81%) of the title compound as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.77 (s, 1H), 7.77–7.73 (m, 9H), 7.63–7.57 (m, 7H), 7.32 (d, J = 1.7 Hz, 1H), 7.10 (d, J = 8.6 Hz, 1H), 6.99 (d, J = 8.1 Hz, 1H), 6.92–6.90 (m, 3H), 6.84–6.76 (m, 5H), 6.58 (d, J = 8.1 Hz, 1H), 5.42–5.37 (m, 2H), 3.95 (s, 3H), 3.81 (s, 3H), 3.43 (s, 3H), 2.69 (br s, 4H); MS (FAB) 743 (M^+).

4.1.43. 4-Methoxy-3-[4-(2-{2-methoxy-4-[(1,1,1-triphenylphosphino)methyl]phenyl}phenethyl)phenoxy]benzaldehyde bromide (17b). This compound was prepared from **16b** by means of a procedure similar to that used for **17a**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.76 (s, 1H), 7.79–7.73 (m, 10H), 7.63–7.57 (m, 7H), 7.32 (d, J = 1.7 Hz, 1H), 7.29–7.21 (m, 2H), 7.10 (d, J = 8.1 Hz, 1H), 7.06 (d, J = 7.3 Hz, 1H), 6.97 (s, 1H), 6.90 (d, J = 8.6 Hz, 2H), 6.84 (d, J = 7.3 Hz, 1H), 6.80 (d, J = 8.1 Hz, 2H), 6.60 (d, J = 7.7 Hz, 1H), 5.48–5.40 (m, 2H), 3.95 (s, 3H), 3.44 (s, 3H), 2.70 (br m, 4H); MS (FAB) 713 $(M-Br)^+$.

4.1.44. 4-Methoxy-3-[4-(5-methoxy-2-{4-[(1,1,1-triphenylphosphino)methyl]phenyl}phenethyl)phenoxy]benzaldehyde bromide (17c). This compound was prepared from **16c** by means of a procedure similar to that used for **17a**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.78 (s, 1H), 7.78–7.72 (m, 9H), 7.63 (dd, J = 8.1, 1.7 Hz, 1H), 7.60–7.56 (m, 6H), 7.34 (d, J = 1.7 Hz, 1H), 7.11 (d, J = 8.1 Hz, 3H), 7.03 (d, J = 7.7 Hz, 3H), 6.90 (d, J = 8.6 Hz, 2H), 6.81–6.77 (m, 4H), 5.48 (d, J (^{31}P–^{1}H) = 14 Hz, 2H), 3.95 (s, 3H), 3.82 (s, 3H), 2.80–2.67 (br m, 4H); MS (FAB) 713 $(M-Br)^+$.

4.1.45. 3-[4-(5-Methoxy-2-{2-methoxy-4-[(1,1,1-triphenylphosphino)methyl]phenyl}phenethyl)phenoxy]benzaldehyde bromide (17d). This compound was prepared from **16d** by means of a procedure similar to that used for **17a**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.92 (s, 1H), 7.80–7.73 (m, 10H), 7.61–7.56 (m, 7H), 7.48 (d, J = 7.7 Hz, 1H), 7.46 (d, J = 2.1 Hz, 1H), 7.03 (m, 1H), 6.99 (d, J = 8.1 Hz, 1H), 7.02 (s, 1H), 6.99 (d, J = 8.6 Hz, 1H), 6.94 (d, J = 8.6 Hz, 1H), 6.86–6.77 (m, 4H), 6.60–6.57 (m, 1H), 5.49–5.43 (m, 2H), 3.81 (s, 3H), 3.45 (s, 3H), 2.70 (br s, 4H); MS (FAB) 713 $(M-Br)^+$.

4.1.46. 4-Methoxy-3-[4-(2-{4-[(1,1,1-triphenylphosphino)methyl]phenyl}phenethyl)phenoxy]benzaldehyde bromide (17e). This compound was prepared from **16e** by means of a procedure similar to that used for **17a**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.76 (s, 1H), 7.78–7.70 (m, 10H), 7.62–7.57 (m, 8H), 7.32 (d, J = 2.1 Hz, 1H), 7.30–7.22 (m, 2H), 7.15–7.03 (m, 5H), 6.87 (d, J = 8.6 Hz, 2H), 6.78 (d, J = 8.6 Hz, 2H), 5.50 (d, J (^{31}P–^{1}H) = 14 Hz, 2H), 3.93 (s, 3H), 2.83–2.77 (m, 2H), 2.72–2.70 (m, 2H); MS (FAB) 683 $(M-Br)^+$.

4.1.47. 3-[4-(2-{2-Methoxy-4-[(1,1,1-triphenylphosphino)methyl]phenyl}phenethyl)phenoxy]benzaldehyde bromide (17f). This compound was prepared from **16f** by means of a procedure similar to that used for **17a**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.90 (s, 1H), 7.78–7.71 (m, 10H), 7.62–7.55 (m, 8H), 7.46 (dd, J = 8.1, 7.7 Hz, 1H), 7.38–7.36 (m, 1H), 7.05–7.03 (m, 3H), 6.91 (d, J = 8.5 Hz, 2H), 6.84–6.82 (m, 4H), 6.61–6.58 (m, 1H), 5.50–5.46 (m, 2H), 3.44 (s, 3H), 2.76–2.63 (m, 4H); MS (FAB) 683 (M^+).

4.1.48. Trimethyl ether of (*E*/*Z*)-dehydroriccardin C (18a). To a suspension of sodium methoxide (15.5 mg, 0.287 mmol) and 100 mL of dehydrated dichloromethane was added dropwise a solution of **17a** (98.0 mg, 0.119 mmol) in 100 mL of dehydrated dichloromethane. The mixture was refluxed for 30 h, filtered, and concentrated. The residue was purified by silica gel column chromatography (eluent; *n*-hexane/ethyl acetate = 3:1, v/v) to afford 44.3 mg (80%) of the title compound as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 (d, J = 8.1 Hz, 1H), 7.07 (d, J = 8.6 Hz, 1H), 7.02–6.61 (m, 10H), 6.36 (d, J = 3.9 Hz, 1H), 6.17 (d, J = 6.2 Hz, 1H), 5.04 (s, 1H), 3.98 and 3.95 (s, 3H), 3.88 and 3.87 (s, 3H), 3.71 and 3.66 (s, 3H), 3.16–2.57 (m, 4H); MS (FAB) 464 (M^+).

4.1.49. 17-Dehydroxy-4,12-dimethyl ether of (*E*/*Z*)-dehydroriccardin C (18b). This compound was prepared from **17b** by means of a procedure similar to that used for **18a**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46–7.24 (m, 4H), 7.14 (dd, J = 7.7, 1.3 Hz, 1H), 7.04–6.74 (m, 5H), 6.63 (d, J = 1.3 Hz, 2H), 6.37 (d, J = 2.1 Hz, 2H), 6.18 (d, J = 16 Hz, 1H), 5.05 (d, J = 1.7 Hz, 1H), 3.98 and 3.96 (s, 3H), 3.71 and 3.66 (s, 3H), 3.17–2.58 (m, 4H); MS (FAB) 434 (M^+).

4.1.50. 12-Dehydroxy-4,17-dimethyl ether of (*E*/*Z*)-dehydroriccardin C (18c). This compound was prepared from **17c** by means of a procedure similar to that used for **18a**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.12–6.82 (m, 14H), 6.37 (d, J = 13 Hz, 1H), 5.28–5.23 (m, 1H), 3.98 and 3.95 (s, 3H), 3.90 and 3.89 (s, 3H), 3.13–2.83 (m, 4H); MS (FAB) 434 (M^+).

4.1.51. 4-Dehydroxy-12,17-dimethyl ether of (*E*/*Z*)-dehydroriccardin C (18d). This compound was prepared from **17d** by means of a procedure similar to that used for **18a**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.08–6.39 (m, 16H), 3.88 and 3.87 (s, 3H), 3.71 and 3.65 (s, 3H), 2.86–2.68 (m, 4H); MS (FAB) 434 (M^+).

4.1.52. 12,17-Dehydroxy-4-methyl ether of (*E*/*Z*)-dehydroriccardin C (18e). This compound was prepared from **17e** by means of a procedure similar to that used for **18a**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45 (dd, J = 7.3, 1.3 Hz, 1H), 7.40–7.37 (m, 1H), 7.29–7.23 (m, 2H), 7.18 (dd, J = 7.7, 1.3 Hz, 1H), 7.13 (d, J = 8.1 Hz, 2H), 6.97 (d, J = 8.1 Hz, 2H), 6.89–6.83 (m, 2H), 6.75–6.72 (m, 2H), 6.66 (d, J = 8.1 Hz, 2H), 6.42–6.35 (m, 2H), 3.98 and 3.95 (s, 3H), 3.18–3.16 (m, 2H), 2.84–2.82 (m, 2H); MS (FAB) 404 (M^+).

4.1.53. 4,17-Dehydroxy-12-methyl ether of (*E*/*Z*)-dehydroriccardin C (18f). This compound was prepared from **17f** by means of a procedure similar to that used for **18a**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43 (d, J = 6.4 Hz, 1H), 7.40–7.36 (m, 1H), 7.30–7.23 (m, 4H), 7.13 (dd, J = 7.7, 0.85 Hz, 1H), 6.98 (dd, J = 6.4, 2.1 Hz, 1H), 6.87 (d, J = 7.7 Hz, 1H), 6.84 (d, J = 7.7 Hz, 1H), 6.76–6.70 (m, 3H), 6.62 (s, 2H), 6.49–6.40 (m, 2H), 3.65 (s, 3H), 3.17–3.13 (m, 1H), 2.96–2.92 (m, 1H), 2.81–2.76 (m, 1H), 2.72–2.68 (m, 1H); MS (FAB) 404 (M^+).

4.1.54. Trimethyl ether of riccardin C (19a). Compound **18a** (44.3 mg, 0.0954 mmol) was hydrogenated with 10% Pd/C (5.0 mg) in 3 mL of ethyl acetate, affording 28.0 mg (63%) of the title compound. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.06 (d, J = 8.1 Hz, 1H), 6.96 (d, J = 3.0 Hz, 1H), 6.88 (d, J = 8.1 Hz, 2H), 6.84–6.69 (m, 6H), 6.44 (d, J = 1.3 Hz, 1H), 6.24 (dd, J = 7.7, 1.7 Hz, 1H), 5.37 (d, J = 1.7 Hz, 1H), 3.95 (s, 3H), 3.88 (s, 3H), 3.68 (s, 3H), 3.12–2.63 (m, 8H). HRMS (FAB) calcd for $C_{31}H_{30}O_4$ 466.2144; found: 466.2119 $(M)^+$.

4.1.55. 17-Dehydroxy-4,12-dimethyl ether of riccardin C (19b). This compound was prepared from **18b** by means of a procedure similar to that used for **19a**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45–7.42 (m, 1H), 7.39–7.35 (m, 1H), 7.25–7.23 (m, 1H), 7.12 (d, J = 7.7 Hz, 1H), 6.89 (d, J = 8.1 Hz, 2H), 6.85 (d, J = 7.3 Hz, 1H), 6.79 (dd, J = 8.1, 2.1 Hz, 1H), 6.79–6.64 (m, 3H), 6.46 (s, 1H), 6.26 (dd, J = 7.7, 1.3 Hz, 1H), 5.38 (d, J = 2.1 Hz, 1H), 3.95 (s, 3H), 3.68 (s, 3H), 3.13–2.62 (m, 8H). HRMS (FAB) calcd for $C_{30}H_{28}O_3$ 436.2038; found: 436.2067 $(M)^+$.

4.1.56. 12-Dehydroxy-4,17-dimethyl ether of riccardin C (19c). This compound was prepared from **18c** by means of a procedure similar to that used for **19a**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.10 (d, J = 8.6 Hz, 1H), 7.01 (d, J = 8.1 Hz, 2H), 6.98 (d, J = 2.6 Hz, 1H), 6.88 (d, J = 8.5 Hz, 1H), 6.84 (dd, J = 8.6, 2.6 Hz, 1H), 6.78 (dd, J = 8.5, 2.1 Hz, 1H), 6.75 (d, J = 8.1 Hz, 2H), 6.73–6.71 (m, 4H), 5.31 (d, J = 1.7 Hz, 1H), 3.94 (s, 3H), 3.89 (s, 3H), 3.11–2.88 (m, 4H). HRMS (FAB) calcd for $C_{30}H_{28}O_3$ 436.2038; found: 436.2005 $(M)^+$.

4.1.57. 4-Dehydroxy-12,17-dimethyl ether of riccardin C (19d). This compound was prepared from **18d** by means of a procedure similar to that used for **19a**. Mp 197 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29–7.23 (m, 3H), 7.05 (d, J = 8.1 Hz, 1H), 6.98 (d, J = 2.6 Hz, 1H), 6.96 (d, J = 2.6 Hz, 1H), 6.84 (d, J = 7.3 Hz, 1H), 6.81 (d, J = 7.7 Hz, 2H), 6.68 (m, 2H), 6.42–6.40 (m, 1H), 6.23–6.19 (m, 1H), 5.37–5.34 (m, 1H), 3.88 (s, 3H), 3.66 (s, 3H), 2.87–2.65 (m, 8H). HRMS (FAB) calcd for $C_{30}H_{28}O_3$ 436.2038; found: 436.2080 $(M)^+$.

4.1.58. 12,17-Dehydroxy-4-methyl ether of riccardin C (19e). This compound was prepared from **18e** by means of a procedure similar to that used for **19a**. Mp 130–131 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44 (dd, J = 7.3, 1.0 Hz, 1H), 7.40–7.36 (m, 1H), 7.14 (d, J = 8.1 Hz, 1H), 7.02 (d, J = 8.1 Hz, 2H), 6.86 (d, J = 8.2 Hz, 1H), 6.77–6.69 (m, 8H), 5.33–5.30 (m, 1H), 3.92 (s, 3H), 3.13–3.10 (m, 2H), 2.88–2.87 (m, 2H), 2.71 (s, 4H); MS (FAB) 406 (M^+). Anal. Calcd for $C_{29}H_{26}O_2$ C, 85.68; H, 6.45. Found: C, 85.77; H, 6.64.

4.1.59. 4,17-Dehydroxy-12-methyl ether of riccardin C (19f). This compound was prepared from **18f** by means of a procedure similar to that used for **19a**. Mp 125 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43 (d, J = 7.7 Hz, 1H), 7.40–7.35 (m, 1H), 7.28–7.22 (m, 1H), 7.12 (d, J = 7.7 Hz, 1H), 6.98 (dd, J = 8.1, 2.6 Hz, 1H), 6.85 (d, J = 7.7 Hz, 1H), 6.84 (d, J = 7.7 Hz, 2H), 6.88–6.68 (m, 4H), 6.43 (s, 1H), 6.23 (d, J = 7.7 Hz, 1H), 5.38–5.36 (m, 1H), 3.66 (s, 3H), 3.14–2.67 (m, 8H); MS (FAB) 406 (M^+). Anal. Calcd for $C_{29}H_{26}O_2$ C, 85.68; H, 6.45. Found: C, 85.87; H, 6.67.

4.1.60. Riccardin C (20a). To a solution of **19a** (15.2 mg, 0.0326 mmol) and 65 mL of dehydrated dichloromethane was added dropwise 330 mL of boron tribromide (1.0 M solution in dichloromethane) at 0 °C under an argon atmosphere. The mixture was stirred for 5 h, then poured into ice water. The organic layer was washed with water and brine, dried over anhydrous magnesium sulfate, and concentrated. The residue was purified by silica gel column chromatography (eluent; *n*-hexane/

ethyl acetate = 2:1, v/v) to afford 11.1 mg (80%) of the title compound as colorless crystals. Mp 205–206 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.04 (d, J = 8.1 Hz, 1H), 6.97 (d, J = 2.6 Hz, 1H), 6.92 (d, J = 8.1 Hz, 1H), 6.81 (d, J = 2.6 Hz, 1H), 6.79–6.73 (m, 6H), 6.39 (d, J = 1.7 Hz, 1H), 6.23 (dd, J = 7.7, 1.7 Hz, 1H), 5.35 (d, J = 2.1 Hz, 1H), 3.05–2.89 (m, 4H), 2.72–2.63 (m, 4H). HRMS (FAB) calcd for $C_{28}H_{24}O_4$ 424.1675; found: 424.1697 $(M)^+$.

4.1.61. 17-Dehydroxyriccardin C (20b). This compound was prepared from **19b** by means of a procedure similar to that used for **20a**. Mp 130–131 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52 (d, J = 6.8 Hz, 1H), 7.47–7.43 (m, 1H), 7.34–7.30 (m, 1H), 7.17 (d, J = 6.8 Hz, 1H), 6.92 (d, J = 7.7 Hz, 1H), 6.82 (d, J = 7.7 Hz, 2H), 6.75–6.73 (m, 3H), 6.40 (d, J = 1.3 Hz, 1H), 6.26 (dd, J = 7.7, 1.3 Hz, 1H), 5.59 (s, 1H), 5.36 (d, J = 1.7 Hz, 1H), 5.30 (s, 1H), 4.79 (s, 1H), 3.14–2.64 (m, 8H). HRMS (FAB) calcd for $C_{28}H_{24}O_3$ 408.1725; found: 408.1680 $(M)^+$.

4.1.62. 12-Dehydroxyriccardin C (20c). This compound was prepared from **19c** by means of a procedure similar to that used for **20a**. Mp 200–201 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.04 (d, J = 8.1 Hz, 1H), 6.97 (d, J = 8.1 Hz, 2H), 6.93–6.91 (m, 2H), 6.77–6.74 (m, 4H), 6.72–6.68 (m, 4H), 5.57 (s, 1H), 5.24 (d, J = 1.7 Hz, 1H), 3.08–2.88 (m, 8H); MS (FAB) 408 (M^+). Anal. Calcd for $C_{28}H_{24}O_3$ C, 82.33; H, 5.92. Found: C, 82.23; H, 6.12.

4.1.63. 4-Dehydroxyriccardin C (20d). This compound was prepared from **19d** by means of a procedure similar to that used for **20a**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25 (dd, J = 8.1, 7.7 Hz, 1H), 7.05 (d, J = 8.1 Hz, 1H), 6.98 (d, J = 2.6 Hz, 1H), 6.97 (d, J = 2.6 Hz, 2H), 6.83 (d, J = 7.7 Hz, 2H), 6.79 (d, J = 7.7 Hz, 2H), 6.74 (br s, 1H), 6.41 (d, J = 1.7 Hz, 1H), 6.25 (dd, J = 7.7, 1.7 Hz, 2H), 5.41–5.40 (m, 1H), 4.98 (s, 1H), 4.78 (s, 1H), 3.05–2.65 (m, 8H). HRMS (FAB) calcd for $C_{28}H_{24}O_3$ 408.1725; found: 408.1707 $(M)^+$.

4.1.64. 12,17-Dehydroxyriccardin C (20e). This compound was prepared from **19e** by means of a procedure similar to that used for **20a**. Mp 126 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46 (dd, J = 7.7, 1.3 Hz, 1H), 7.41–7.37 (m, 1H), 7.29–7.25 (m, 2H), 7.15 (dd, J = 7.7, 0.86 Hz, 1H), 7.02 (d, J = 8.1 Hz, 2H), 6.92 (d, J = 8.1 Hz, 1H), 6.76–6.69 (m, 7H), 5.56 (s, 1H), 5.26 (d, J = 1.7 Hz, 1H), 3.14–3.12 (m, 2H), 2.92–2.90 (m, 2H), 2.72 (s, 4H). HRMS (FAB) calcd for $C_{28}H_{24}O_2$ 392.1776; found: 392.1770 $(M)^+$.

4.1.65. 4,17-Dehydroxyriccardin C (20f). This compound was prepared from **19f** by means of a procedure similar to that used for **20a**. Mp 130 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.49 (dd, J = 7.7, 1.3 Hz, 1H), 7.45–7.40 (m, 1H), 7.32–7.28 (m, 1H), 7.24 (dd, J = 8.6, 7.3 Hz, 1H), 7.15 (dd, J = 7.7, 1.3 Hz, 1H), 6.96 (dd, J = 7.7, 2.7 Hz, 1H), 6.82 (d, J = 7.7 Hz, 2H), 6.85–6.71 (m, 5H), 6.41 (d, J = 1.3 Hz, 1H), 6.26 (dd, J = 7.7, 1.7 Hz, 1H), 5.41–5.39 (m, 1H), 4.77 (s, 1H), 3.10–2.65 (m, 8H). HRMS (FAB) calcd for $C_{28}H_{24}O_2$ 392.1776; found: 392.1747 $(M)^+$.

4.1.66. 4,17-Dehydroxy-12-[(trifluoromethylsulfonyl) oxy]riccardin C (21). This compound was prepared from **20f** by means of a procedure similar to that used for **5**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46 (d, J = 3.9 Hz, 2H), 7.29 (dd, J = 8.6, 8.1 Hz, 1H), 7.29 (dd, J = 8.1, 7.7 Hz, 1H), 7.10 (d, J = 7.7 Hz, 1H), 7.00 (d, J = 8.1 Hz, 1H), 6.99 (d, J = 7.7 Hz, 1H), 6.95 (d, J = 1.3 Hz, 1H), 6.95 (d, J = 5.6 Hz, 1H), 6.86 (d, J = 7.3 Hz, 1H), 6.84 (d, J = 8.1 Hz, 1H), 6.64 (d, J = 8.1 Hz, 1H), 6.54 (d, J = 7.7 Hz, 1H), 6.45 (dd, J = 7.7, 1.3 Hz, 1H), 5.32–5.30 (m, 1H), 3.23–3.20 (m, 1H), 3.08–3.00 (m, 3H), 2.84–2.77 (m, 1H), 2.61–2.44 (m, 3H); MS (FAB) 524 (M^+).

4.1.67. 4,12,17-Dehydroxyriccardin C (22). 21 (7.6 mg, 0.015 mmol) was hydrogenated with 10% Pd/C (3.0 mg) in 7.5 mL of diethylamine and 550 mL of ethanol affording 4.1 mg (75%) of the title compound. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46 (dd, J = 7.7, 1.3 Hz, 1H), 7.40–7.36 (m, 1H), 7.28–7.24 (m, 2H), 7.16 (dd, J = 7.7, 1.3 Hz, 1H), 7.03 (d, J = 8.1 Hz, 2H), 6.96 (dd, J = 8.1, 2.6 Hz, 1H), 6.85 (d, J = 7.3 Hz, 1H), 6.74 (d, J = 7.7 Hz, 2H), 6.70 (q, J = 8.5 Hz, 4H), 5.32–5.30 (m, 1H), 3.16–3.11 (m, 2H), 2.91–2.87 (m, 2H), 2.80–2.75 (m, 4H). HRMS (FAB) calcd for $C_{28}H_{24}O$ 376.1827; found: 376.1790 $(M)^+$.

Acknowledgments

The work described in this paper was partially supported by Grants-in-Aid for Scientific Research from The Ministry of Education, Culture, Sports, Science and Technology, Japan, and the Japan Society for the Promotion of Science.

References and notes

1. Janowski, B. A.; Willy, P. J.; Devi, T. R.; Falck, J. R.; Mangelsdorf, D. J. *Nature* **1996**, *383*, 728–731.
2. Lehman, J. M.; Kliewer, S. A.; Moore, L. B.; Smith-Oliver, T. A.; Oliver, B. B.; Su, J.-L.; Sundseth, S. S.; Winegar, D. A.; Blanchard, D. E.; Spencer, T. A.; Wilson, T. M. *J. Biol. Chem.* **1997**, *272*, 3137–3140.
3. Peet, D. J.; Turley, S. D.; Ma, W.; Janowski, B. A.; Lobaccaro, J.-M. A.; Hammer, R. E.; Mangelsdorf, D. J. *Cell* **1998**, *93*, 693–704.
4. Schultz, J. R.; Tu, H.; Luk, A.; Repa, J. J.; Medina, J. C.; Li, L.; Schwendner, S.; Wang, S.; Thoolen, M.; Mangelsdorf, D. J.; Lustig, K. D.; Shan, B. *Genes Dev.* **2000**, *14*, 2831–2838.
5. Delvecchio, C. J.; Bilan, P.; Radford, K.; Stephen, J.; Trigatti, B. L.; Cox, G.; Parameswaran, K.; Capone, J. P. *Mol. Endocrinol.* **2007**, *21*, 1324–1334.
6. Mitro, N.; Mak, P. A.; Vagas, L.; Godio, C.; Hampton, E.; Molteni, V.; Kreusch, A.; Saez, E. *Nature* **2007**, *445*, 219–223.
7. Collins, J. L.; Fivush, A. M.; Watson, M. A.; Galardi, C. M.; Lewis, M. C.; Moore, L. B.; Parks, D. J.; Wilson, J. G.; Tippin, T. K.; Binz, J. G.; Plunket, K. D.; Morgan, D.

G.; Beaudet, E. J.; Whitney, K. D.; Kliewer, S. A.; Wilson, T. M. *J. Med. Chem.* **2002**, *45*, 1963–1966.
8. Tamehiro, N.; Sato, Y.; Suzuki, T.; Hashimoto, T.; Asakawa, Y.; Yokoyama, S.; Kawanishi, T.; Ohno, Y.; Inoue, K.; Nagao, T.; Nishimaki-Mogami, T. *FEBS Lett.* **2005**, *579*, 5299–5304.
9. Noguchi-Yachide, T.; Aoyama, A.; Makishima, M.; Miyachi, H.; Hashimoto, Y. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 3957–3961.
10. Noguchi-Yachide, T.; Miyachi, H.; Aoyama, A.; Makishima, M.; Aoyama, H.; Hashimoto, Y. *Chem. Pharm. Bull.* **2007**, *55*, 1750–1754.
11. Asano, N.; Oseki, K.; Kaneko, E.; Matsui, K. *Carbohydr. Res.* **1994**, *258*, 255–266.
12. Lee, D.-S.; Lee, S.-H. *FEBS Lett.* **2001**, *501*, 84–86.
13. Makishima, M.; Okamoto, A. Y.; Repa, J. J.; Tu, H.; Learned, R. M.; Luk, A.; Hull, M. V.; Lustig, K. D.; Mangelsdorf, D. J.; Shan, B. *Science* **1999**, *284*, 1362–1365.
14. Makishima, M.; Lu, T. T.; Xie, W.; Whitfield, G. K.; Domoto, H.; Evans, R. M.; Haussler, M. R.; Mangelsdorf, D. J. *Science* **2002**, *296*, 1313–1316.
15. Kasuga, J.; Makishima, M.; Hashimoto, Y.; Miyachi, H. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 554–558.
16. Gao, H.; Nishioka, T.; Kawabata, J.; Kasai, T. *Biosci. Biotechnol. Biochem.* **2004**, *68*, 369–375.
17. Eicher, T.; Fey, S.; Puhl, W.; Büchel, E.; Speicher, A. *Eur. J. Org. Chem.* **1998**, 877–888.