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The first total synthesis of kwakhurin, a characteristic component of a rejuvenating plant, "kwao keur": toward an efficient synthetic route to phytoestrogenic isoflavones

Fumihiro Ito,[a] Misako Iwasaki,[a] Toshiko Watanabe,*[a] Tsutomu Ishikawa*[a] and Yoshihiro Higuchi[b]

[a] *Graduate School of Pharmaceutical Sciences, Chiba University, 1-33 Yayoi, Inage, Chiba, 263-8522, Japan. E-mail: toshiw@p.chiba-u.ac.jp*

[b] *Central Research Laboratory, Shiratori Pharmaceutical Co. Ltd., 6-11-24 Tsudanuma, Narashino, Chiba, 275-0016, Japan*

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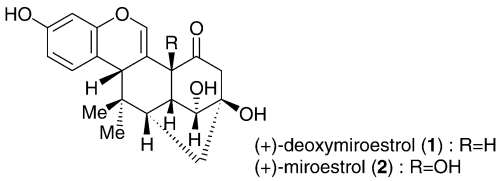
A convergent synthesis of kwakhurin (**5**), a characteristic estrogen-like isoflavone of *Pueraria mirifica* (Leguminosae), is described. Isoflavone skeleton **31** was constructed by Suzuki–Miyaura coupling of 3-bromochromone **26** (AC-ring) and arylboronic acid **30** (B-ring) in the presence of TBAB as an additive. Microwave-assisted coupling was also examined, but did not improve the yield. Baeyer–Villiger oxidation, followed by propargylation and reduction afforded 1,1-dimethylallyl ether **37**. 6′-Prenylisoflavone **34** was obtained in high yield by Claisen rearrangement of **37** in *N*,*N*-diethylaniline. On the other hand, 1,3-rearrangement of prenyl ether **33** with clay gave **34** in poor yield. Successive methylation of **34** and deprotection yielded the target kwakhurin (**5**) in 12% overall yield from 2,4-dihydroxybenzaldehyde (**23**).

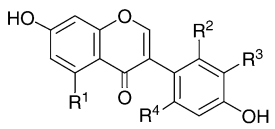
Introduction

A medicinal plant "kwao keur" has been locally considered to be a rejuvenating drug in Thailand and Burma and at present is commercially available in some countries including Japan. Therefore, the relationship between the chemical constituents (*e.g.* **1**–**5**, Fig. 1) and estrogenic activity has been widely studied.[1,2] The source of "kwao keur" is the tuberous root of *Pueraria mirifica* (Leguminosae); however, the quality of the commercial product is occasionally in doubt, because the aerial parts are very similar to those of other vine legume species. Therefore, it is necessary to determine whether the commercial "kwao keur" is genuine or not. We have focused on kwakhurin[3] (**5**) as an index of quality standard because **5** is not only a characteristic component of *P. mirifica* showing estrogenic activity[2b] but also an isolated peak with a long retention time due to **5** is observed in HPLC.[4]

As the amount of kwakhurin (**5**) as a natural source is not enough to examine the quality of "kwao keur", we planned to artificially obtain **5** and, in the previous paper,[5] reported a stepwise approach to **5** *via* deoxybenzoin **8** as outlined in Scheme 1. However, the final deprotection of the isopropyl (IP) groups in **6** was unsuccessful. In this paper we report the first total synthesis of kwakhurin (**5**) by a convergent route using a methoxyethoxymethyl (MEM) group for phenol protection in addition to further trials of the deoxybenzoin route.



(+)-deoxymiroestrol (**1**) : R=H
(+)-miroestrol (**2**) : R=OH



	R^1	R^2	R^3	R^4
daizein (**3**)	H	H	H	H
genistein (**4**)	OH	H	H	H
kwakhurin (**5**)	H	3,3-dimethylallyl	OMe	OH

Fig. 1 Selected chemical constituents of *Pueraria mirifica*.

Results and discussion

We first examined the deoxybenzoin route by changing the protecting group from the IP group to a triisopropylsilyl (TIPS) group (Scheme 2). After benzoylation of triisopropoxyphenol[5] **11**, replacement of the IP group in **12** with TIPS afforded tri-TIPS isoflavone **14**. Trials of the debenzoylation of **14** with either a base (KOH, NaOMe, or K_2CO_3) or a hydride reagent ($NaBH_4$, $LiAlH_4$, or NaH) yielded phenol **15**; however, a partially TIPS-deprotected compound **16** was always formed as a co-product. Therefore, we decided to change the synthetic strategy.

Two other possible pathways would be available from the literature:[6] 1) the oxidative rearrangement of chalcones and flavanones and 2) the arylation of a pre-formed chromanone ring. The latter coupling pathway was adopted because of its potential application to various types of isoflavones and an easily removable methoxyethoxymethyl (MEM) group was chosen for phenol protection. The retrosynthesis is shown in Scheme 3. 6′-Prenylisoflavones, which are obtained from aldehyde **19** *via* Baeyer–Villiger oxidation, can be afforded by 1,3- or 3,3-rearrangement of *O*-allyl ethers **17**. The isoflavone skeleton **19** is constructed by palladium catalyzed cross-coupling from chromone ring **20** (AC-ring) and arylboronic acid **21** (B-ring).

The chromone **26** and the arylboronic acid **30** were prepared from 2,4-dihydroxyacetophenone (**22**) and 2,4-dihydroxybenzaldehyde (**23**), respectively, as shown in Scheme 4. After selective alkylation of **22** with MEMCl, the resulting mono-MEM ketone[7] **24** was then converted into enaminoketone **25** with DMF–dimethylacetal (DMF–DMA) in good yield. Treatment of **25** with bromine in $CHCl_3$[8] afforded 3-bromochromone **26** in 60–70% yield. It was found that an easily handled *N*-bromosuccinimide (NBS)–SiO_2 system[9] was also effective. On the other hand, B-ring unit **30** was prepared from **23** by

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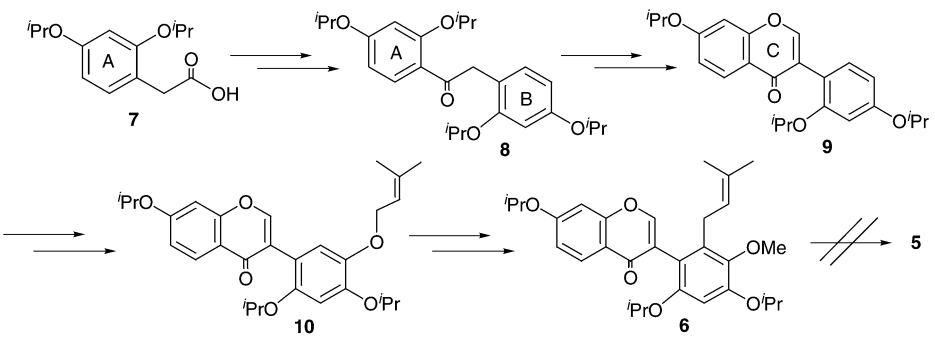
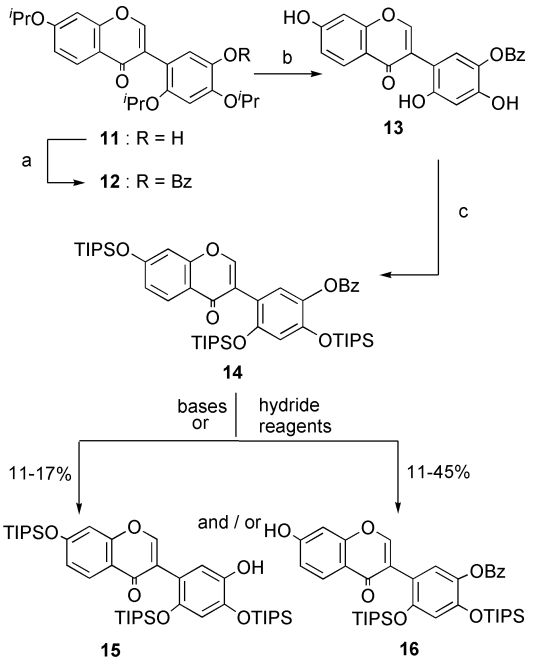
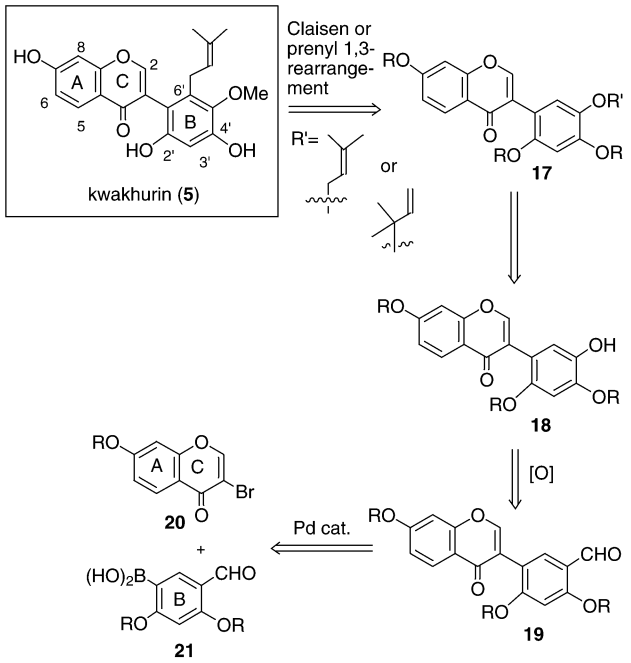


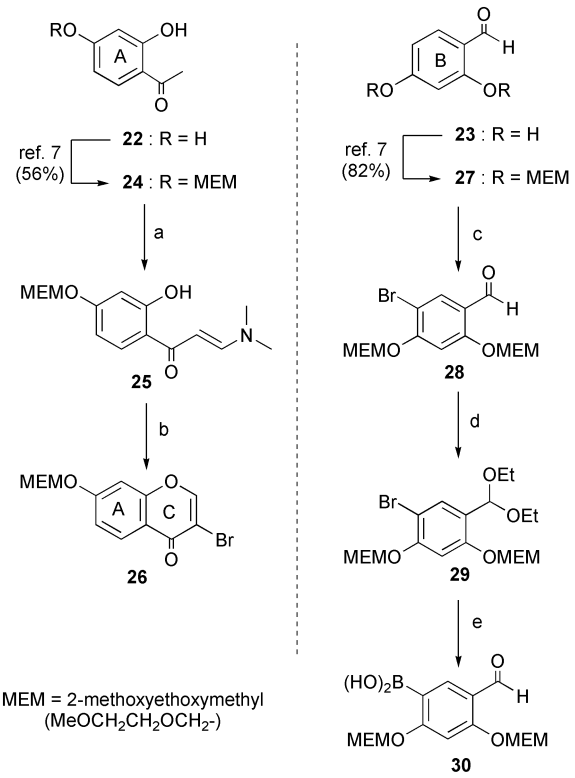
Scheme 1



Scheme 2 *Reagents and conditions*: a, BzCl, Et_3N, CH_2Cl_2, −20 °C, 5 h, 100%; b, BCl_3, CH_2Cl_2, −50 °C, 9 h, 80%; c, TIPSCl, imidazole, DMF, rt, 2 h, 64%.



Scheme 3 Retrosynthetic analysis of kwakhurin (**5**) by a convergent route.



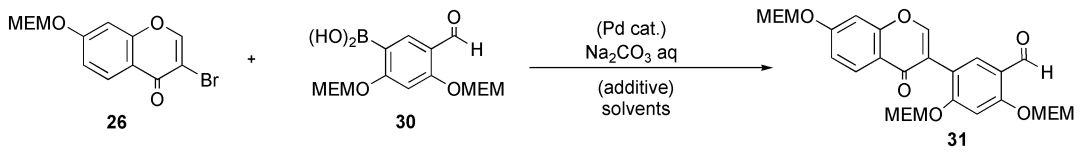
Scheme 4 *Reagents and conditions*: a, DMF–DMA, 90 °C, 2 h, 92%; b, NBS, SiO_2, $CHCl_3$, 0 °C, 0.5 h, 64%; c, NBS, SiO_2, $CHCl_3$, 30 °C, 20 h, 73%; d, NH_4Cl, $HC(OEt)_3$, EtOH, 90 °C, 2 h, 100%; e, i) *n*-*B*uLi, $B(OiPr)_3$, THF, −78 °C to rt, 1 h, ii) 1% HCl aq., 0 °C, 20 min, 74%.

successive reaction of bromination with NBS–SiO_2, after MEM protection of phenolic functions, ketalization with $HC(OEt)_3$, and metallation with *n*-BuLi and $B(OiPr)_3$.

Next, Suzuki–Miyaura cross-coupling of chromone **26** with arylboronic acid **30** was examined for the construction of the isoflavone skeleton (Table 1). Although application of microwave[10] (MW)-assisted metal-free coupling reaction according to the Leadbeater and Marco[11] conditions failed (entry 1), in the presence of a palladium catalyst the MW-assisted reaction was completed in only 6 min to afford the desired isoflavone **31** in moderate yield (entry 2). In contrast, under conventional conditions better results were obtained even though a longer reaction time was needed. The presence of tetrabutylammonium bromide (TBAB) as an additive[12] led to a satisfactory yield (entry 4). Thus, in this coupling reaction, MW irradiation strongly accelerated the reaction rate, but was not necessarily effective.

The formyl group of **31** was then converted to a phenolic function by Baeyer–Villiger oxidation followed by alkaline hydrolysis. In the previous paper[5] we used prenyl 1,3-migration of 5′-(3,3-dimethylallyloxy)isoflavone with montmorillonite clay for the introduction of a C_5-unit. Thus, we investigated the

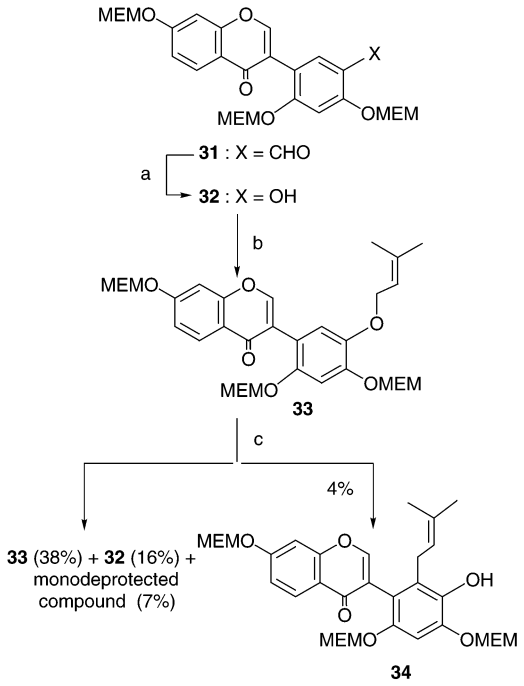
Table 1 Preparation of isoflavone **31** by Suzuki–Miyaura coupling



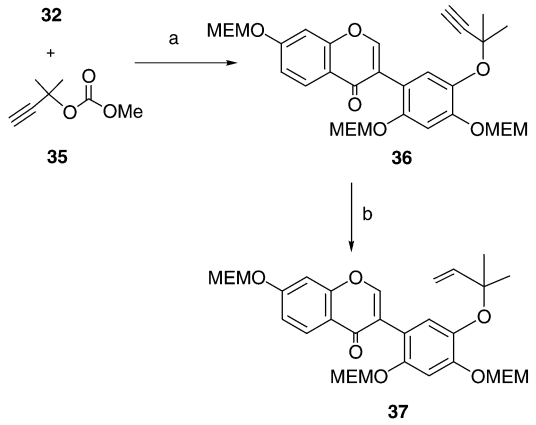
Entry	Catalyst	Solvents	Additive	Conditions: Microwave	Conditions: Conventional	Yield of **31** (%)
1	None	H_2O	TBAB	100 W, 130 °C, 2 min	—	Complex mixture
2	$Pd(PPh_3)_4$	H_2O–DME–EtOH (2 : 4 : 1)	None	55 W, 90 °C, 6 min	—	51
3	$Pd(PPh_3)_4$	Benzene	None	—	80 °C, 6 h	63
4	$Pd(PPh_3)_4$	Benzene	TBAB	—	80 °C, 3 h	89

TBAB = tetrabutylammonium bromide.

migration of a prenyl ether **33** derived from **32**. Treatment with montmorillonite KSF[5,13] in benzene gave poor yield (4%) of the desired prenylated isoflavone **34**. Further trials using montmorillonite K10[14] or Florisil[15] showed no improvement in the yield of **34**, presumably because of lability of the MEM group in **33** under these conditions (Scheme 5).

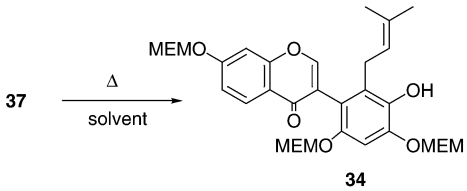


Scheme 5 *Reagents and conditions*: a, i) *m*CPBA, $NaHCO_3$, CH_2Cl_2, −10 °C, 25 min, ii) KOH, MeOH, rt, 30 min, 80%; b, prenyl bromide, K_2CO_3, acetone, rt, 22 h, 78%; c, montmorillonite K10, CH_2Cl_2, 0 °C, 2 d then rt, 2 d.



Scheme 6 *Reagents and conditions*: a, $CuCl_2$, DBU, CH_3CN, 0 °C, 6.5 h, 70%; b, H_2, Lindlar's cat., quinoline, EtOH, rt, 40 min, 88%.

Table 2 Solvent effect on Claisen rearrangement of **37**



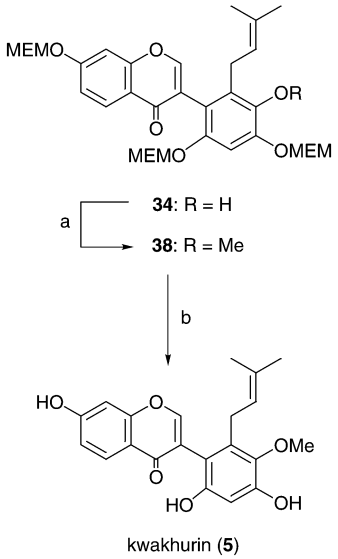
Entry	Solvents	Conditions: Temp.	Conditions: Time/h	Yield of **34** (%)
1	Benzene	Reflux	2	0
2	Toluene	Reflux	4	50
3	Xylene	Reflux	4	56
4	$PhNEt_2$	180 °C	4	89

Therefore, we changed the migration mode to thermal rearrangement of 1,1-dimethylallyl ether. Alkylation of phenol **32** with propargyl carbonate **35** in the presence of a copper catalyst[16] yielded ether **36** followed by hydrogenation to afford 1,1-dimethylallyl ether **37** in high yield (Scheme 6).

As shown in Table 2, the Claisen rearrangement of **37** afforded a prenyl isoflavone **34** in good yield when *N*,*N*-diethylaniline was used as a solvent (entry 4).

Although conventional methylation (dimethyl sulfate–K_2CO_3–DMF) of phenol **34** gave **38** in moderate yield (64%), methylation of **34** using a phase transfer catalyst (PTC) yielded **38** in more satisfactory yield (89%). The final stage was achieved by deprotection of **38** with 10% aqueous solution of HCl in MeOH to afford the target kwakhurin (**5**) in 81% yield, the physical and spectral data of which, including the HPLC peak, were identical with those of the natural product (Scheme 7). Full assignments for the hydroxy groups in synthetic **5** were determined by HMBC experiments (Fig. 2).

In summary, we have achieved the total synthesis of kwakhurin (**5**) *via* a convergent pathway in 10 steps from **22** and 11 steps from **23** in 10% and 12% overall yields, respectively. A structurally related mirificoumestan[17] (**39**) was also isolated from *P. mirifica* along with kwakhurin (**5**). The hydrogenative cyclization followed by oxidation of the isoflavone skeleton to coumestan has been reported.[18] It is suggested that our synthetic method could be applied to the synthesis of **39** after modification of the reaction conditions (Scheme 8). Thus, this synthetic method could provide an efficient route to isoflavones



Scheme 7 *Reagents and conditions*: a, Me_2SO_4, $PhCH_2Bu_3NCl$, 2% NaOH aq., benzene, rt, 30 min, 89%; b, 10% HCl, MeOH, 70 °C, 1 h, 81%.

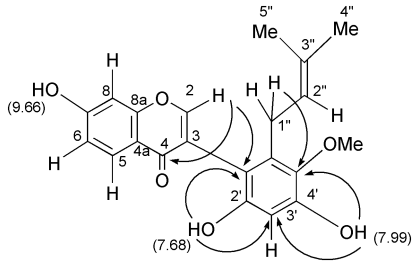
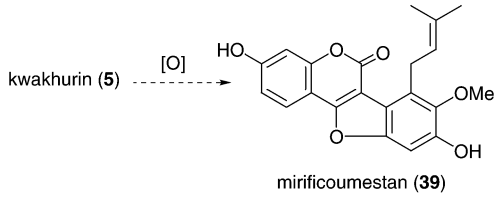


Fig. 2 Selected HMBC correlation and assignments for 7-, 2′-, and 4′-hydroxy groups of kwakhurin (**5**). Chemical shift values (δ, ppm) of each hydroxy group are given in parentheses.



Scheme 8

and coumestans to examine the structure–activity relationship of their estrogenic activity.

Experimental

General

All melting points were measured on a melting-point hot stage MP-3S (Yanaco) and are uncorrected. Infrared spectra were recorded on a JASCO FT/IR-300E spectrometer. ^{1}H- and ^{13}C-NMR spectra were recorded in chloroform-*d* ($CDCl_3$) unless otherwise stated, on JEOL JNM GSX-400A, GSX-500A, and ECP-400 spectrometers with tetramethylsilane (TMS) as internal reference. Low-resolution mass spectra were recorded on a JEOL JMS-GCmate with electron impact (EI) ionisation, and JEOL JMS-AX-500 and JMS-HX 110A fast atom bombardment (FAB) ionisation. High-resolution mass spectra were recorded on JEOL JMS-HX 110A (FAB) spectrometer. For column chromatography, silica gel [FL-100D; particle size: 100 μm (Fuji Silysia) or silica gel 60; particle size 63–230 μm (Kanto Kagaku)] was used unless otherwise stated. For thin-layer chromatography (TLC), pre-coated silica gel 60 F_{254} (Merck) was used. Microwave-assisted reaction was carried out in a CEM Discover instrument.

5′-Benzoyloxy-7,2′,4′-triisopropoxyisoflavone (12)

To a solution of 5′-hydroxyisoflavone[5] **11** (2.19 g, 5.30 mmol) in CH_2Cl_2 (22 mL) were added Et_3N (0.74 mL, 5.31 mmol) and benzoyl chloride (0.65 mL, 5.60 mmol) under ice–salt cooling and the whole mixture was stirred at −20 °C for 5 h. The reaction mixture was diluted with $CHCl_3$ (100 mL) followed by successive washing with H_2O (30 mL), saturated aqueous solution of $NaHCO_3$ (30 mL), H_2O (30 mL), 1 M aqueous solution of HCl (30 mL) and brine (30 mL), then dried over $MgSO_4$ and evaporated to dryness *in vacuo* to afford a yellow oil (3.15 g). The crude product was purified by column chromatography using hexane–AcOEt (20 : 1 to 3 : 1) as eluent to give **12** as a colourless oil (2.74 g, 100%) (Found: C, 72.2; H, 6.3. $C_{31}H_{32}O_7$ requires C, 72.1; H, 6.2%); ν_{max} (neat)/cm^{-1} 1655 and 1637 (C=O); δ_H (400 MHz) 1.27 [6 H, d, *J* 6.0, $CH(CH_3)_2$], 1.28 [6 H, d, *J* 6.0, $CH(CH_3)_2$], 1.41 [6 H, d, *J* 6.0, $CH(CH_3)_2$], 4.41 [1 H, sep, *J* 6.0, $OCH(CH_3)_2$], 4.49 [1 H, sep, *J* 6.0, $OCH(CH_3)_2$], 4.67 [1 H, sep, *J* 6.0, $OCH(CH_3)_2$], 6.66 (1 H, s, 3′-H), 6.84 (1 H, d, *J* 2.2, 8-H), 6.94 (1 H, dd, *J* 9.0 and 2.2, 6-H), 7.27 (1 H, s, 6′-H), 7.49 (2 H, dd, *J* 7.9 and 7.9, benzoyl-3,5-H), 7.61 (1 H, dd, *J* 7.9 and 7.9, benzoyl-4-H), 8.02 (1 H, s, 2-H), 8.17 (1 H, d, *J* 9.0, 5-H) and 8.19–8.21 (2 H, m, benzoyl-2,6-H); *m*/*z*: (EI) 516 (M^+, 34%), 474 (12), 432 (7), 369 (10), 327 (31), 285 (13) and 105 (100).

5′-Benzoyloxy-7,2′,4′-trihydroxyisoflavone (13)

To a solution of triisopropoxyisoflavone **12** (0.659 g, 1.28 mmol) in CH_2Cl_2 (3.3 mL) was added a solution of 0.3 M BCl_3 in CH_2Cl_2 (42.5 mL, 12.8 mmol; prepared from commercial 1 M solution) at −78 °C. The whole mixture was stirred at −50 °C for 9 h under an argon atmosphere and poured into H_2O (170 mL). The resulting precipitates were collected by filtration, washed with H_2O and $CHCl_3$, and dried to afford a pale yellow solid (0.544 g). The crude solid was purified by column chromatography using $CHCl_3$–MeOH (30 : 1) as eluent to give **13** as a pale yellow powder (0.398 g, 80%), mp 152–154 °C. ν_{max} (Nujol)/cm^{-1} 3313 (OH), 1718 and 1655 (C=O); δ_H (400 MHz; $CDCl_3$ + 1 drop of CD_3OD) 6.68 (1 H, s, 3′-H), 6.88 (1 H, d, *J* 2.2, 8-H), 6.98 (1 H, s, 6′-H), 6.99 (1 H, dd, *J* 9.0 and 2.2, 6-H), 7.51 (2 H, dd, *J* 8.4 and 8.4, benzoyl-3,5-H), 7.64 (1 H, dd, *J* 8.4 and 8.4, benzoyl-4-H), 8.09 (1 H, s, 2-H), 8.18 (1 H, d, *J* 9.0, 5-H) and 8.23 (2 H, d, *J* 8.4, benzoyl-2,6-H); *m*/*z*: (FAB) 391 (MH^+), 390 (M^+) and 105; found (FAB): 391.0804 (MH^+). $C_{22}H_{15}O_7$ requires 391.0818.

5′-Benzoyloxy-7,2′,4′-tris(triisopropylsilyloxy)isoflavone (14)

To a solution of trihydroxyisoflavone **13** (0.398 g, 1.02 mmol) and imidazole (0.487 g, 7.14 mmol) in DMF (1 mL) was added TIPSCl (0.74 mL, 3.35 mmol). The whole mixture was stirred at room temperature for 2 h under an argon atmosphere, diluted with H_2O (10 mL), and extracted with AcOEt (3 × 10 mL). The organic layer was washed with H_2O (2 × 10 mL) and brine (10 mL), dried over $MgSO_4$, and evaporated to dryness *in vacuo* to afford a pale yellow oil (1.27 g). The crude product was purified by column chromatography using benzene as eluent to give **14** as pale yellow prisms (0.559 g, 64%), mp 150–155 °C. ν_{max} (Nujol)/cm^{-1} 1718 (C=O) and 1655 (C=O); δ_H (400 MHz) 1.00 [18 H, d, *J* 7.5, 3 × $CH(CH_3)_2$], 1.02 [18 H, d, *J* 7.5, 3 × $CH(CH_3)_2$], 1.13 [18 H, d, *J* 7.5, 3 × $CH(CH_3)_2$], 1.08–1.25 [6 H, sep, *J* 7.5, 6 × $SiCH(CH_3)_2$], 1.32 [3 H, sep, *J* 7.5, 3 × $SiCH(CH_3)_2$], 6.55 (1 H, s, 5′-H), 6.88 (1 H, d, *J* 2.2, 8-H), 6.92 (1 H, dd, *J* 8.8 and 2.2, 6-H), 7.20 (1 H, s, 3′-H), 7.49 (2 H, dd, *J* 7.5 and 7.5, benzoyl-3,5-H), 7.59 (1 H, dd, *J* 7.5 and 7.5, benzoyl-4-H), 7.98 (1 H, s, 2-H), 8.13 (1 H, d, *J* 8.8, 5-H) and 8.18 (2 H, d, *J* 7.5, benzoyl-2,6-H); *m*/*z*: (FAB) 859 (MH^+), 815, 667, 581, 495 and 105.

Trials of debenzoylation of 14: 5′-hydroxy-7,2′,4′-tris-(triisopropylsilyloxy)isoflavone (15) and 5′-benzoyloxy-7-hydroxy-2′,4′-bis(triisopropylsilyloxy)isoflavone (16)

A mixture of tris-TIPS isoflavone **14** (20 mg, 0.024 mmol), NaH (4 mg, 0.17 mmol) and THF (0.2 mL) was stirred at 20 °C for 2.5 days under an argon atmosphere. The reaction mixture was poured into H_2O (10 mL) and acidified with 10% aqueous solution of HCl (1.5 mL) followed by extraction with $CHCl_3$ (3 × 10 mL). The organic layer was washed with H_2O (10 mL) and brine (10 mL), dried over $MgSO_4$, and evaporated to dryness *in vacuo* to afford a yellow oil (25 mg). The crude product was purified by preparative TLC (hexane–AcOEt = 3 : 1) to give two compounds; **15** (R_f; 0.58) as a colourless amorphous powder (3 mg, 17%) and **16** (R_f; 0.25) as a colourless amorphous powder (2 mg, 11%).

15: δ_H (400 MHz, $CDCl_3$ + 1 drop of CD_3OD) 0.95 [18 H, d, *J* 7.4, 3 × CH(CH_3)$_2$], 1.10 [18 H, d, *J* 7.7, 3 × CH(CH_3)$_2$], 1.13 [18 H, d, *J* 7.5, 3 × CH(CH_3)$_2$], 1.20–1.34 [9 H, m, 9 × SiC*H*(CH$_3$)$_2$], 6.45 (1 H, s, 3′-H), 6.81 (1 H, d, *J* 1.5, 8-H), 6.86 (1 H, s, 6′-H), 6.89 (1 H, dd, *J* 8.8 and 1.5, 6-H), 7.89 (1 H, s, 2-H) and 8.09 (1 H, d, *J* 8.8, 5-H); *m*/*z*: (EI) 754 (M^+, 73%), 711 (100), 511 (58) and 425 (15).

16: δ_H (400 MHz) 0.98 [18 H, d, *J* 7.3, 3 × CH(CH_3)$_2$], 1.01 [18 H, d, *J* 7.3, 3 × CH(CH_3)$_2$], 1.08–1.23 [6 H, m, 6 × SiC*H*(CH$_3$)$_2$], 6.55 (1 H, s, 3′-H), 6.78 (1 H, d, *J* 2.2, 8-H), 6.88 (1 H, dd, *J* 8.8 and 2.2, 6-H), 7.25 (1 H, s, 6′-H), 7.48 (2 H, dd, *J* 7.6 and 7.6, benzoyl-3,5-H), 7.61 (1 H, dd, *J* 7.6 and 7.6, benzoyl-4-H), 7.81 (1 H, s, 2-H), 8.10 (1 H, d, *J* 8.6, 5-H) and 8.19 (2 H, d, *J* 7.6, benzoyl-2,6-H); *m*/*z*: (FAB) 704 (MH^+), 660, 600 and 511.

1-[2-Hydroxy-4-(2-methoxyethoxymethoxy)phenyl]-3-dimethylaminopropen-1-one (25)

A mixture of ketone **24** (0.801 g, 3.33 mmol; prepared from **22** by reported alkylation[7] in 56% yield) and DMF–DMA (0.66 mL, 5.00 mmol) was stirred at 90 °C for 2 h. After removal of the MeOH formed *in vacuo*, the residue was extracted with AcOEt (10 mL). The organic layer was washed with H_2O (3 × 2 mL) and the aqueous layer was extracted again with AcOEt (3 × 10 mL). The combined organic solution was washed with brine (10 mL), dried over $MgSO_4$, and evaporated to dryness *in vacuo* to give a brown oil (0.972 g). The crude product was purified with column chromatography using hexane–AcOEt (1 : 2) as eluent to afford **25** (0.904 g, 92%) as yellow prisms, mp 80–81 °C, which were recrystallised from Et_2O–hexane. (Found: C, 61.0; H, 7.1; N, 4.7. $C_{15}H_{21}NO_5$ requires C, 61.0; H, 7.2; N, 4.7%); ν_{max} (Nujol)/cm^{-1} 2923 (OH) and 1627 (C=O); δ_H (400 MHz) 2.96 and 3.18 (each 3 H, br s, NMe_2), 3.38 (3 H, s, OMe), 3.55–3.57 (2 H, m, OCH$_2$C*H*$_2$OMe), 3.80–3.83 (2 H, m, OC*H*$_2$CH$_2$OMe), 5.28 (2 H, s, OCH_2O), 5.69 (1 H, d, *J* 12.2, 2-H), 6.50 (1 H, dd, *J* 8.8 and 2.5, C5′-H), 6.58 (1 H, d, *J* 2.5, 3′-H), 7.62 (1 H, d, *J* 8.8, 6′-H), 7.85 (1 H, d, *J* 12.2, 3-H) and 14.3 (1 H, s, OH); δ_C (100 MHz) 37.2 and 45.2 (NMe_2), 58.9 (OMe), 67.8 (OCH$_2$CH$_2$OMe), 71.4 (OCH$_2$*C*H$_2$OMe), 89.6 (C-3′), 92.9 (OCH_2O), 103.9 (C-2), 106.8 (C-5′), 114.8 (C-1′), 129.6 (C-6′), 154.1 (C-3), 161.6 (C-2′), 165.0 (C-4′) and 190.4 (C-1); *m*/*z*: (EI) 295 (M^+, 47%,), 251 (73), 190 (7.6) and 89 (41).

3-Bromo-7-(2-methoxyethoxymethoxy)chromone (26)

To a solution of **25** (0.630 g, 2.13 mmol) in $CHCl_3$ (10 mL) were added silica gel (Fuji Silysia, Microbead 3A, 2.10 g) and NBS (0.401 g, 2.25 mmol). The whole mixture was vigorously stirred at 0 °C for 30 min. The insoluble material was filtered off and filtrate was washed with 10% aqueous solution of $Na_2S_2O_3$ (3 × 10 mL) and brine (10 mL), dried over $MgSO_4$, and evaporated to dryness *in vacuo*. The crude product was purified by column chromatography using hexane–AcOEt (17 : 10) as eluent to give **26** (0.446 g, 64%) as colourless prisms, mp 75–76 °C, which were recrystallised from Et_2O–hexane. ν_{max} (Nujol)/cm^{-1} 1637 (C=O); δ_H (400 MHz) 3.37 (3 H, s, OMe), 3.55–3.57 (2 H, m, OCH$_2$C*H*$_2$OMe), 3.83–3.86 (2 H, m, OC*H*$_2$CH$_2$OMe), 5.37 (2 H, s, OCH_2O), 7.12 (1 H, dd, *J* 9.5 and 2.2, 6-H), 7.12 (1 H, d, *J* 2.2, 8-H), 8.16 (1 H, s, 2-H) and 8.18 (1H, d, *J* 9.5, 5-H); δ_C (100 MHz) 59.0 (OMe), 68.2 (OCH$_2$CH$_2$OMe), 71.4 (OCH$_2$*C*H$_2$OMe), 93.4 (OCH_2O), 103.1 (C-8), 110.7 (C-3), 116.2 (C-6), 117.7 (C-4a), 127.8 (C-5), 153.4 (C-2), 157.5 (C-8a), 161.8 (C-7) and 171.6 (C-4); *m*/*z*: (FAB) 331 (MH^+ + 2) and 329 (MH^+); Found (FAB) 329.0016. $C_{13}H_{14}BrO_5$ requires 329.0025.

5-Bromo-2,4-bis(2-methoxyethoxymethoxy)benzaldehyde (28)

To a solution of aldehyde **27** (0.520 g, 1.66 mmol; prepared from **23** by reported alkylation[7] in 82% yield) in $CHCl_3$ (16 mL) were added silica gel (Fuji Silysia, Microbead 3A, 1.79 g) and NBS (0.329 g, 1.85 mmol). The whole mixture was stirred at room temperature for 20 h in the dark. The insoluble material was filtered off and the filtrate was washed with 10% aqueous solution of $Na_2S_2O_3$ (3 × 10 mL) and brine (10 mL), dried over $MgSO_4$, and evaporated to dryness *in vacuo*. The crude product was purified by column chromatography using hexane–AcOEt (17 : 10) as eluent to give **28** (0.474 g, 73%) as colourless prisms, mp 56–57 °C, which were recrystallised from Et_2O–hexane. (Found: C, 45.6; H, 5.3. $C_{15}H_{21}BrO_7$ requires C, 45.8; H, 5.4%); ν_{max} (Nujol)/cm^{-1} 1665 (C=O); δ_H (400 MHz) 3.37 (6 H, s, 2 × OMe), 3.55–3.58 (4 H, m, 2 × OCH$_2$C*H*$_2$OMe), 3.85–3.88 (4 H, m, 2 × OC*H*$_2$CH$_2$OMe), 5.38 and 5.40 (each 2 H, s, OCH_2O), 7.06 (1 H, s, 3-H), 8.02 (1 H, s, 6-H) and 10.28 (1H, s, CHO); δ_C (100 MHz) 58.97 and 59.00 (OMe), 68.37 and 68.42 (OCH$_2$CH$_2$OMe), 71.36 and 71.43 (OCH$_2$*C*H$_2$OMe), 93.9 and 94.0 (OCH_2O), 102.5 (C-3), 105.8 (C-5), 121.0 (C-1), 132.7 (C-6), 159.2 (C-2), 160.3 (C-4) and 187.2 (C=O); *m*/*z*: (FAB) 395 (MH^+ + 2) and 393 (MH^+).

5′-Formyl-7,2′,4′-tris(2-methoxyethoxymethoxy)isoflavone (31)

i) Ketalization: 5-bromo-2,4-bis(2-methoxyethoxymethoxy)-benzaldehyde diethylacetal (29). To a solution of aldehyde **28** (1.43 g, 3.64 mmol) and NH_4Cl (37 mg, 0.69 mmol; freshly prepared by sublimation) in dry EtOH (10 mL) was added $HC(OEt)_3$ (1.8 mL, 11.0 mmol) under an argon atmosphere and the whole mixture was stirred at 90 °C for 2 h. The reaction mixture was diluted with Et_2O (200 mL) and washed with H_2O (50 mL) and brine (50 mL), dried over K_2CO_3, and evaporated to dryness *in vacuo*. Removal of the excess reagent by distillation (100 °C/1 mmHg) gave **29** (1.69 g, 100%) as a yellow oil. ν_{max} (neat)/cm^{-1} no characteristic absorption; δ_H (400 MHz) 1.22 (6 H, t, *J* 7.2, 2 × CH_3CH$_2$O), 3.38 (6 H, s, 2 × OMe), 3.49–3.63 (8 H, m, 2 × OCH$_2$C*H*$_2$OMe and 2 × CH$_3$C*H*$_2$O), 3.80–3.83 and 3.86–3.88 (each 2 H, m, OC*H*$_2$CH$_2$OMe), 5.27 and 5.31 (each 2 H, s, OCH_2O), 5.68 [1 H, s, ArC*H*(OEt)$_2$], 7.00 (1 H, s, 3-H) and 7.71 (1H, s, 6-H); δ_C (100 MHz) 15.2 (CH$_2$*C*H$_3$), 58.9 and 59.0 (OMe), 61.6 (OCH$_2$CH$_3$), 67.8 and 68.0 (OCH$_2$CH$_2$OMe), 71.4 and 71.5 (OCH$_2$*C*H$_2$OMe), 93.7 and 94.3 (OCH_2O), 96.5 (Ar*C*H), 104.0 (C-3), 104.9 (C-5), 123.6 (C-1), 131.4 (C-6), 154.2 (C-2) and 154.7 (C-4); *m*/*z*: (FAB) 468 (M^++2) and 466 (M^+); Found (FAB) 466.1209. $C_{19}H_{31}BrO_8$ requires 466.1202. This compound was used for the next reaction without further purification.

ii) Preparation of arylboronic acid: 5-borono-2,4-bis(2-methoxyethoxymethoxy)benzaldehyde (30). To a solution of acetal **29** (0.205 g, 0.438 mmol) in THF (2 mL) was added *n*-BuLi (1.26 M solution in hexane, 0.52 mL, 0.655 mmol) at −78 °C for 10 min under an argon atmosphere. After stirring for 1 h, B(O^{i}Pr)$_3$ (0.2 mL, 0.867 mmol) was added and the whole mixture was stirred for 20 min and allowed to stand at room temperature for 1 h. The reaction mixture was poured into H_2O (4 mL), acidified with 1% aqueous solution of HCl, and the whole mixture was stirred for 20 min followed by dilution with H_2O (10 mL). The mixture was extracted with AcOEt

(4 × 50 mL). The organic layer was washed with brine (40 mL), dried over $MgSO_4$, and evaporated to dryness *in vacuo* under 20 °C to give a yellow oil (0.210 g). The crude oil was solidified and washed with Et_2O–hexane to afford arylboronic acid **30** (0.116 g, 74%) as a labile colourless powder. ν_{max} (Nujol)/cm^{-1} 3282 (OH) and 1670 (C=O); δ_H (400 MHz) 3.37 (6 H, s, 2 × OMe), 3.56–3.58 (4 H, m, 2 × OCH_2CH_2OMe), 3.85–3.88 (4 H, m, 2 × OCH_2CH_2OMe), 5.42 and 5.44 (each 2 H, s, OCH_2O), 5.53 (2 H, s, 2 × OH), 6.95 (1 H, s, 3-H), 8.36 (1 H, s, 6-H) and 10.33 (1H, s, CHO); δ_C (100 MHz) 58.97 and 59.01 (OMe), 68.3 and 68.8 (OCH_2CH_2OMe), 71.4 and 71.6 (OCH_2CH_2OMe), 93.55 and 93.63 (OCH_2O), 99.8 (C-3), 120.2 (C-1 and C-5), 138.6 (C-6), 163.2 (C-2), 167.8 (C-4) and 188.4 (C=O). This compound was used for the coupling reaction without further purification.

iii) Suzuki–Miyaura coupling (conventional method). To a solution of chromone **26** (0.516 g, 1.57 mmol), arylboronic acid **30** (0.616 g, 1.72 mmol), $Pd(PPh_3)_4$ (56 mg, 48 μmol), and TBAB (0.103 g, 0.318 mmol) in dry benzene (3 mL) was added 2 M aqueous solution of Na_2CO_3 (1.6 mL). The whole mixture was heated at 80 °C for 3 h under an argon atmosphere. The reaction mixture was diluted with AcOEt (100 mL) and washed with H_2O (2 × 30 mL) and brine (30 mL), dried over K_2CO_3 and evaporated to dryness *in vacuo* to afford a red oil (1.12 g). The crude product was purified by column chromatography [silica gel 60N (spherical neutral, 63–210 μm); Kanto Kagaku] using hexane–AcOEt (1 : 14) as eluent to give isoflavone **31** (0.785 g, 89%) as colourless prisms, mp 50–51 °C, which were recrystallised from Et_2O–benzene. (Found: C, 59.6; H, 6.1. $C_{28}H_{34}O_{12}$ requires C, 59.8; H, 6.1%); ν_{max} (Nujol)/cm^{-1} 1678 and 1620 (C=O); δ_H (400 MHz) 3.35, 3.39 and 3.40 (each 3 H, s, OMe), 3.52–3.60 (6 H, m, 3 × OCH_2CH_2OMe), 3.77–3.90 (6 H, m, 3 × OCH_2CH_2OMe), 5.29, 5.38 and 5.43 (each 2 H, s, OCH_2O), 7.09 (1 H, dd, *J* 8.8 and 2.3, 6-H), 7.09 (1 H, s, 3′-H), 7.13 (1 H, d, *J* 2.3, 8-H), 7.76 (1 H, s, 6′-H), 7.85 (1 H, s, 2-H), 8.17 (1 H, d, *J* 8.8, 5-H) and 10.36 (1H, s, CHO); δ_C (100 MHz) 58.9, 59.01 and 59.03 (OMe), 68.09, 68.12 and 68.3 (OCH_2CH_2OMe), 71.41, 71.44 and 71.5 (OCH_2CH_2OMe), 93.3, 93.5 and 93.8 (OCH_2O), 101.2 (C-3′), 103.2 (C-8), 115.4 (C-6), 116.3 (C-1′), 118.9 (C-5′), 119.7 (C-4a), 122.3 (C-3), 127.7 (C-6′), 131.4 (C-5), 153.4 (C-2), 157.8 (C-8a), 161.4 (C-4′), 161.6 (C-2′), 161.7 (C-7), 175.1 (C-4) and 188.1 (C=O); *m*/*z*: (FAB) 563 (MH^+).

iv) Suzuki–Miyaura coupling (microwave-assisted method). A mixture of chromone **26** (0.101 g, 0.308 mmol), aryl boronic acid **30** (0.123 g, 0.342 mmol), $Pd(PPh_3)_4$ (11 mg, 9.3 μmol), and Na_2CO_3 (66 mg, 0.621 mmol) in the mixture of H_2O (0.6 mL), EtOH (0.3 mL), and DME (1.2 mL) was stirred in a microwave instrument (55 W) at 90 °C for 6 min. The same work-up and purification as above gave isoflavone **31** (0.088 g, 51%) as colourless prisms.

5′-Hydroxy-7,2′,4′-tris(2-methoxyethoxymethoxy)isoflavone (32)

To a suspension of 5′-formylisoflavone **31** (0.301 g, 0.535 mmol) and $NaHCO_3$ (0.135 g, 1.60 mmol) in CH_2Cl_2 (3 mL) was added *m*CPBA (65%, 0.170 g, 0.641 mmol) and the whole mixture was vigorously stirred at −10 °C for 25 min. After removal of the solvent *in vacuo*, the residue was dissolved in AcOEt (100 mL). The organic solution was washed with saturated aqueous solution of $NaHCO_3$ (20 mL) and brine (20 mL), dried over $MgSO_4$ and evaporated to dryness *in vacuo* to afford formate (0.429 g) as a brown oil.

The formate was dissolved in MeOH (4 mL), basified (pH 9–10) with 10% methanolic solution of KOH and the whole mixture was stirred at room temperature for 30 min. After evaporation of the solvent *in vacuo*, the residue was dissolved in H_2O (10 mL) and acidified with 10% aqueous solution of HCl followed by dilution with H_2O (10 mL) and extracted with AcOEt (4 × 50 mL). The organic layer was washed with brine (20 mL), dried over $MgSO_4$ and evaporated to dryness *in vacuo* to give a brown oil (0.372 g). The crude product was purified by column chromatography using AcOEt as eluent to afford phenol **32** (0.236 g, 80%) as a brown oil. ν_{max} (Nujol)/cm^{-1} 3396 (OH) and 1637 (C=O); δ_H (400 MHz) 3.35, 3.39 and 3.42 (each 3 H, s, OMe), 3.51–3.63 (6 H, m, 3 × OCH_2CH_2OMe), 3.73–3.91 (6 H, m, 3 × OCH_2CH_2OMe), 5.12, 5.28 and 5.37 (each 2 H, s, OCH_2O), 6.27 (1 H, s, OH), 6.88 (1 H, s, 3′-H), 7.05 (1H, s, 6′-H), 7.08 (1 H, dd, *J* 8.8 and 2.4, 6-H), 7.11 (1 H, d, *J* 2.4, 8-H), 7.86 (1 H, s, 2-H) and 8.19 (1 H, d, *J* 8.8, 5-H); δ_C (100 MHz) 58.95, 59.02 and 59.08 (OMe), 67.6, 68.1 and 68.9 (OCH_2CH_2OMe), 71.50, 71.58 and 71.64 (OCH_2CH_2OMe), 93.4, 95.2 and 96.3 (OCH_2O), 103.2 (C-3′), 106.7 (C-8), 115.3 (C-6), 117.2 (C-1′), 118.1 (C-6′), 119.2 (C-4a), 122.6 (C-3), 127.8 (C-5), 142.2 (C-5′), 145.2 (C-4′), 149.0 (C-2′), 153.7 (C-2), 157.7 (C-8a), 161.3 (C-7) and 175.4 (C-4); *m*/*z*: (FAB) 551 (MH^+); Found (FAB) 551.2109. $C_{27}H_{35}O_{12}$ requires 551.2129.

7,2′,4′-Tris(2-methoxyethoxymethoxy)-5′-(3,3-dimethylallyloxy)isoflavone (33)

A mixture of 5′-hydroxyisoflavone **32** (110 mg, 0.201 mmol), dry K_2CO_3 (72 mg, 0.522 mmol; dried at 100 °C for 12 h prior to use), and prenyl bromide (0.07 mL, 0.583 mmol) in dry acetone (1 mL) was stirred at room temperature for 22 h under an argon atmosphere. The reaction mixture was poured into H_2O (10 mL) and extracted with Et_2O (3 × 20 mL). The organic layer was washed with 2% aqueous solution of NaOH (10 mL) and brine (10 mL), dried over K_2CO_3, and evaporated to dryness *in vacuo* to give a yellow solid (129 mg). The crude product was purified by column chromatography using hexane–AcOEt (1 : 9) as eluent to afford prenyl ether **33** (96 mg, 78%) as colourless fine needles, mp 61–62 °C, which were recrystallised from Et_2O. (Found: C, 61.9; H, 6.75. $C_{32}H_{42}O_{12}$ requires C, 62.1; H, 6.8%); ν_{max} (Nujol)/cm^{-1} 1641 (C=O); δ_H (400 MHz) 1.70 and 1.76 [each 3 H, s, $=C(CH_3)_2$], 3.34 (3 H, s, OMe), 3.39 (6 H, s, 2 × OMe), 3.49–3.59 (6 H, m, 3 × OCH_2CH_2OMe), 3.72–3.90 (6 H, m, 3 × OCH_2CH_2OMe), 4.52 (2 H, d, *J* 6.7, 1″-H_2), 5.14, 5.32 and 5.38 (each 2 H, s, OCH_2O), 5.48-5.52 (1 H, m, 2″-H), 6.92 (1 H, s, 3′-H), 7.08 (1 H, dd, *J* 8.8 and 2.2, 6-H), 7.12 (1 H, d, *J* 2.2, 8-H), 7.14 (1H, s, 6′-H), 7.93 (1 H, s, 2-H) and 8.20 (1 H, d, *J* 8.8, 5-H); δ_C (100 MHz) 18.2 (C-4″), 25.8 (C-5″), 58.97, 59.03 and 59.09 (OMe), 66.6 (C-1″), 67.75, 67.83 and 68.16 (OCH_2CH_2OMe), 71.50, 71.56 and 71.58 (OCH_2CH_2OMe), 93.4, 94.8 and 95.1 (OCH_2O), 103.2 (C-3′), 107.5 (C-8), 115.4 (C-6), 115.6 (C-1′), 117.4 (C-6′), 119.3 (C-4a), 120.0 (C-2″), 122.1 (C-3), 127.8 (C-5), 137.7 (C-3″), 144.3 (C-5′), 147.7 (C-4′), 149.6 (C-2′), 154.2 (C-2), 157.7 (C-8a), 161.3 (C-7) and 175.5 (C-4); *m*/*z*: (EI) 618 (M^+, 11%), 550 (36), 475 (11), 386 (41) and 89 (100).

1,3-Rearrangement of 5′-prenyloxyisoflavone 33: 5′-hydroxy-7,2′,4′-tris(2-methoxyethoxymethoxy)-6′-(3,3-dimethylallyl)isoflavone (34)

A mixture of prenyl ether **33** (52 mg, 0.084 mmol) and montmorillonite K10 (53 mg) in CH_2Cl_2 (1 mL) was stirred at 0 °C for 2 days under an argon atmosphere. The clay was filtered off and the filtrate was evaporated to dryness *in vacuo* to afford a brown oil (50 mg). The crude product was purified by preparative TLC (hexane–AcOEt = 2 : 1) to give **34** (2 mg, 4%) as a colourless oil along with the starting compound **33** (20 mg, 38%), phenol **32** (8 mg, 16%) and an unidentified monodeprotected compound (3 mg, 7%). The desired compound **34** was identical to the sample obtained from **37** described later.

7,2′,4′-Tris(2-methoxyethoxymethoxy)-5′-(1,1-dimethylpropargyloxy)isoflavone (36)

To an ice-cooled mixture of 5′-hydroxyisoflavone **32** (0.215 g, 0.391 mmol) and $CuCl_2$ (1.9 mg, 0.014 mmol) in dry CH_3CN (7 mL) was added DBU (0.08 mL, 0.535 mmol). After 15 min

carbonate **35** (84.2 mg, 0.592 mmol; freshly prepared by reported procedure[16]) was added and the whole mixture was stirred at room temperature for 6.5 h under an argon atmosphere. The reaction mixture was poured into H_2O (20 mL) and extracted with Et_2O (3 × 40 mL). The organic layer was washed with 10% aqueous solution of $CuSO_4$ (30 mL) and brine (30 mL), dried over K_2CO_3, and evaporated to dryness *in vacuo* to afford a brown oil (0.241 g). The crude product was purified by column chromatography using hexane–AcOEt (1 : 12) as eluent to give **36** (0.168 g, 70%) as a yellow oil. ν_{max} (neat)/cm^{-1} 3256, 2110 (terminal alkyne) and 1648 (C=O); δ_H (400 MHz) 1.65 [6 H, s, C(CH$_3$)$_2$], 2.50 (1 H, s, 1″-H), 3.34, 3.39 and 3.40 (each 3 H, s, OMe), 3.51–3.60 (6 H, m, 3 × OCH$_2$C*H*$_2$OMe), 3.74–3.89 (6 H, m, 3 × OCH$_2$C*H*$_2$OMe), 5.18, 5.27 and 5.38 (each 2 H, s, OCH$_2$O), 7.08 (1 H, dd, *J* 8.8 and 2.4, 6-H), 7.10 (1 H, s, 3′-H), 7.12 (1 H, d, *J* 2.4, 8-H), 7.36 (1H, s, 6′-H), 7.89 (1 H, s, 2-H) and 8.19 (1 H, d, *J* 8.8, 5-H); δ_C (100 MHz) 29.3 (CMe), 58.88, 58.96 and 58.99 (OMe), 67.7, 67.8 and 68.1 (O*C*H$_2$CH$_2$OMe), 71.41, 71.49 and 71.53 (OCH$_2$*C*H$_2$OMe), 73.4 (C-1″), 74.3 (C-3″), 86.3 (C-2″), 93.3 (OCH$_2$O), 94.6 (OCH$_2$O), 94.9 (OCH$_2$O), 103.1 (C-3′), 105.9 (C-8), 115.2 (C-6), 115.4 (C-1′), 119.2 (C-4a), 122.2 (C-3), 126.8 (C-6′), 127.7 (C-5), 139.8 (C-5′), 151.3 (C-4′), 151.9 (C-2′), 153.9 (C-2), 157.6 (C-8a), 161.2 (C-7) and 175.2 (C-4); *m*/*z*: (FAB) 617 (MH$^+$); Found (FAB) 617.2600. $C_{32}H_{41}O_{12}$ requires 617.2598.

7,2′,4′-Tris(2-methoxyethoxymethoxy)-5′-(1,1-dimethylallyloxy)isoflavone (37)

A mixture of ether **36** (0.180 g, 0.292 mmol) and quinoline (0.02 mL) in EtOH (2 mL) was hydrogenated over Lindlar's catalyst (18 mg) at room temperature for 40 min under ambient pressure. The reaction mixture was filtered through a Celite pad. After removal of the solvent a crude product (0.194 g) was purified by chromatography using hexane–acetone (3 : 1) as eluent to afford **37** (0.160 g, 88%) as a yellow oil. ν_{max} (neat)/cm^{-1} 1648 (C=O); δ_H (400 MHz) 1.44 (6 H, s, 2 × CCH$_3$), 3.34, 3.39 and 3.40 (each 3 H, s, OMe), 3.50–3.60 (6 H, m, 3 × OCH$_2$C*H*$_2$OMe), 3.73–3.89 (6 H, m, 3 × OCH$_2$C*H*$_2$OMe), 5.07 (1 H, dd, *J* 10.8 and 1.1, 1″-Ha), 5.15 (1 H, dd, *J* 17.4 and 1.1, 1″-Hb), 5.16, 5.28 and 5.37 (each 2 H, s, OCH$_2$O), 6.15 (1 H, dd, *J* 17.4 and 10.8, 2″-H), 7.02 (1 H, s, 3′-H), 7.07 (1 H, dd, *J* 8.8 and 2.4, 6-H), 7.07 (1H, s, 6′-H), 7.11 (1 H, d, *J* 2.4, 8-H), 7.87 (1 H, s, 2-H) and 8.19 (1 H, d, *J* 8.8, 5-H); δ_C (100 MHz) 26.5 (CMe), 58.93, 59.00 and 59.05 (OMe), 67.7, 67.9 and 68.1 (O*C*H$_2$CH$_2$OMe), 71.45, 71.54 and 71.58 (OCH$_2$*C*H$_2$OMe), 80.9 (C-3″), 93.3, 94.7 and 95.0 (OCH$_2$O), 103.1 (C-3′), 106.8 (C-8), 113.3 (C-1″), 115.2 (C-6), 115.3 (C-1′), 119.2 (C-4a), 122.0 (C-3), 127.2 (C-6′), 127.8 (C-5), 140.1 (C-5′), 144.0 (C-2″), 151.4 (C-4′), 151.4 (C-2′), 154.0 (C-2), 157.6 (C-8a), 161.2 (C-7) and 175.3 (C-4); *m*/*z*: (FAB) 619 (MH$^+$); Found (FAB) 619.2726. $C_{32}H_{43}O_{12}$ requires 619.2755.

Claisen rearrangement of 1,1-dimethylallyloxyisoflavone 37: 5′-hydroxy-7,2′,4′-tris(2-methoxyethoxymethoxy)-6′-(3,3-dimethylallyl)isoflavone (34)

A solution of 1,1-dimethylally ether **37** (0.268 g, 0.433 mmol) in PhNEt$_2$ (2.5 mL) was heated at 180 °C for 30 min under an argon atmosphere. The reaction mixture was diluted with AcOEt (50 mL), washed with 5% aqueous solution of HCl (8 × 2 mL) and brine (8 mL), dried over $MgSO_4$, and evaporated to dryness *in vacuo* to afford a yellow oil (0.286 g). The crude product was purified by chromatography using hexane–acetone (3 : 2) as eluent to afford **34** (0.239 g, 89%) as a yellow oil. ν_{max} (neat)/cm^{-1} 3373 (OH) and 1647 (C=O); δ_H (400 MHz) 1.44 (3 H, s, 5″-H$_3$), 1.58 (3 H, s, 4″-H$_3$), 3.08 (1 H, dd, *J* 14.5 and 7.7, 1″-Ha), 3.33, 3.39 and 3.42 (each 3 H, s, OMe), 3.33–3.42 (1 H, m, 1″-Hb), 3.47–3.62 (6 H, m, 3 × OCH$_2$C*H*$_2$OMe), 3.65–3.90 (6 H, m, 3 × OCH$_2$C*H*$_2$OMe), 5.01 (1 H, d, *J* 6.8, OCH$_2$O), 5.08 (1 H, br t, *J* 7.7, 2″-H), 5.09 (1 H, d, *J* 6.8, OCH$_2$O), 5.28 and 5.31 (each 1 H, d, *J* 6.8, OCH$_2$O), 5.38 (2 H, s, OCH$_2$O), 6.04 (1 H, s, OH), 6.93 (1 H, s, 3′-H), 7.08 (1 H, dd, *J* 8.8 and 2.2, 6-H), 7.12 (1 H, d, *J* 2.2, 8-H), 7.66 (1 H, s, 2-H) and 8.18 (1 H, d, *J* 8.8, 5-H); δ_C (100 MHz) 17.6 (C-5″), 25.5 (C-4″), 26.9 (C-1″), 58.90 (OMe), 59.00, 59.04 and 67.4, 68.1 and 68.6 (O*C*H$_2$CH$_2$OMe), 71.46, 71.51 and 71.60 (OCH$_2$*C*H$_2$OMe), 93.4, 94.8 and 95.7 (OCH$_2$O), 103.09 (C-3′), 103.11 (C-8), 115.2 (C-6), 116.5 (C-1′), 119.1 (C-4a), 121.2 (C-3), 122.7 (C-2″), 127.8 (C-5), 128.7 (C-6′), 131.2 (C-3″), 140.2 (C-5′), 144.7 (C-4′), 149.0 (C-2′), 153.9 (C-2), 157.8 (C-8a), 161.3 (C-7) and 175.9 (C-4); *m*/*z*: (FAB) 619 (MH$^+$); found (FAB) 619.2747. $C_{32}H_{43}O_{12}$ requires 619.2755.

5′-Methoxy-7,2′,4′-tris(2-methoxyethoxymethoxy)-6′-(3,3-dimethylallyl)isoflavone (38)

To a solution of 6′-prenylisoflavone **34** (76 mg, 0.123 mmol) and benzyltributylammonium chloride (36 mg, 0.115 mmol) in benzene (4 mL) were added 2% aqueous solution of NaOH (2 mL) and Me_2SO_4 (0.05 mL, 0.528 mmol). The whole mixture was stirred at room temperature for 2.5 h under an argon atmosphere. The excess reagent was quenched with 5% aqueous solution of NH_3 (6 mL) with stirring for 30 min followed by extraction with AcOEt (2 × 20 mL). The organic layer was washed with 5% aqueous solution of NH_3 (10 mL), H_2O (2 × 10 mL), and brine (10 mL), dried over K_2CO_3, and evaporated to dryness *in vacuo* to afford a brown oil (72 mg, 92%). The crude product was purified with column chromatography using hexane–acetone (2 : 1) as eluent to give **38** (70 mg, 89%) as a yellow oil. ν_{max} (neat)/cm^{-1} 1648 (C=O); δ_H (400 MHz) 1.42 (3 H, s, 5″-H$_3$), 1.55 (3 H, s, 4″-H$_3$), 3.10 (1 H, dd, *J* 14.5 and 7.3, 1″-Ha), 3.33, 3.39 and 3.40 (each 3 H, s, CH$_2$O*Me*), 3.33–3.42 (1 H, m, 1″-Hb), 3.47–3.61 (6 H, m, 3 × OCH$_2$C*H*$_2$OMe), 3.66–3.90 (6 H, m, 3 × OCH$_2$C*H*$_2$OMe), 3.79 (3 H, s, 5′-OMe), 5.00 (1 H, dd, *J* 7.3 and 6.2, 2″-H), 5.06 and 5.13 (each 1 H, d, *J* 6.8, OCH$_2$O), 5.33 and 5.38 (each 2 H, s, OCH$_2$O), 6.97 (1 H, s, 3′-H), 7.08 (1 H, dd, *J* 8.8 and 2.2, 6-H), 7.12 (1 H, d, *J* 2.2, 8-H), 7.65 (1 H, s, 2-H) and 8.18 (1 H, d, *J* 8.8, 5-H); δ_C (100 MHz) 17.6 (C-5″), 25.5 (C-4″), 27.2 (C-1″), 58.94, 59.06 and 59.08 (OMe), 60.9 (ArO*Me*), 67.6, 67.9 and 68.2 (O*C*H$_2$CH$_2$OMe), 71.51, 71.54 and 71.59 (OCH$_2$*C*H$_2$OMe), 93.41, 94.29 and 94.34 (OCH$_2$O), 102.9 (C-3′), 103.1 (C-8), 115.2 (C-6), 115.7 (C-1′), 119.2 (C-4a), 121.2 (C-3), 123.4 (C-2″), 127.8 (C-5), 131.0 (C-6′), 136.4 (C-3″), 143.0 (C-5′), 150.9 (C-4′), 152.2 (C-2′), 154.0 (C-2), 157.8 (C-8a), 161.3 (C-7) and 176.0 (C-4); *m*/*z*: (FAB) 633 (MH$^+$); found (FAB) 633.2898. $C_{33}H_{45}O_{12}$ requires 633.2921.

Kwakhurin (5)

To a solution of tris-MEM-kwakhurin **38** (105 mg, 0.166 mmol) in MeOH (10 mL) was added 10% aqueous solution of HCl (2 mL). The whole mixture was stirred at 70 °C for 1 h under an argon atmosphere, diluted with H_2O (30 mL) and extracted with AcOEt (3 × 50 mL). The organic layer was washed with H_2O (30 mL) and brine (30 mL), dried over $MgSO_4$, and evaporated to dryness *in vacuo* to afford a brown amorphous solid (61 mg, 99%) which was washed with $CHCl_3$ to give kwakhurin (**5**) (50 mg, 81%) as a labile colourless powdered solid, mp 210–212 °C (lit.,[3b] no data, lit.,[19] 209–212 °C). (Found: C, 66.9; H, 5.5. 1/10 $CHCl_3 \cdot C_{21}H_{20}O_6$ requires C, 66.6; H, 5.5%); ν_{max} (KBr)/cm^{-1} 3372 (OH) and 1625 (C=O); δ_H (400 MHz; acetone-d_6) 1.42 (3 H, s, 5″-H$_3$), 1.53 (3 H, s, 4″-H$_3$), 3.12 (1 H, dd, *J* 14.6 and 7.1, 1″-Ha), 3.35 (1 H, dd, *J* 14.6 and 6.7, 1″-Hb), 3.74 (3 H, s, OMe), 5.04 (1 H, ddq, *J* 7.1, 6.7 and 1.2, 2″-H), 6.43 (1 H, s, 3′-H), 6.95 (1 H, d, *J* 2.2, 8-H), 7.02 (1 H, dd, *J* 8.8 and 2.2, 6-H), 7.89 (1 H, s, 2-H), 7.68 (1 H, br s, 2′-OH), 7.99 (1 H, br s, 4′-OH), 8.06 (1 H, d, *J* 8.8, 5-H) and 9.66 (1 H, br s, 7-OH); δ_C (100 MHz; acetone-d_6) 17.2 (C-5″), 25.3 (C-4″), 27.2 (C-1″), 60.7 (OMe), 102.2 (C-3′), 102.8 (C-8), 111.1 (C-1′), 115.1 (C-6), 118.3 (C-4a), 121.1 (C-3), 124.5 (C-2″), 127.9 (C-5), 130.5 (C-3″), 136.0 (C-6′), 139.8 (C-5′), 151.1 (C-4′), 153.0 (C-2′), 155.5 (C-2), 158.7 (C-8a),

162.7 (C-7) and 176.3 (C-4); *m/z*: (FAB) 391 (M^++Na) and 369 (MH^+); Found (FAB) 369.1331. $C_{21}H_{21}O_6$ requires 369.1338.

This compound was completely identical with the natural product[3b] in all spectral data. Precise assignments in ^{1}H- and ^{13}C-NMR were obtained from 2D-NMR experiments (HMQC and HMBC).

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4 Retention time 45.3 min for kwakhurin (**5**) using the following conditions: column, YMC-Pack ODS-AM-303 (4.6 mm I.D. × 250 mm L); mobile phase, CH_3CN–H_2O–CH_3CO_2H (linear gradient 150 : 850 : 1 to 350 : 650 : 1); flow rate, 1.0 mL min^{-1}; detection, 254 nm; injection volume, 20 μL; column temperature, 35 °C. [S. Shimokawa, T. Kumamoto, T. Ishikawa, M. Takashi and Y. Higuchi, unpublished result; under these conditions retention time for daizein (**3**): 27.3 min and for genistein (**4**): 38.7 min].

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