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KWAKHURIN, A UNIQUE ISOFLAVONE WITH REJUVENATING ACTIVITY FROM "KWAO KEUR": FURTHER CHARACTERIZATION BY 2D-NMR SPECTROMETRY AND SYNTHESIS OF TRIISOPROPYLKWAKHURIN

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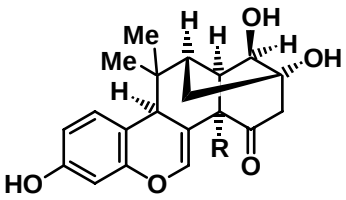
Abstract - Kwakhurin (**5**), a characteristic isoflavone component of *Pueraria mirifica* which has been used in folk medicine as "kwao keur" for rejuvenating purpose, was structurally approached by 2D-NMR experiments. Furthermore, the synthesis of kwakhurin (**5**) was attempted starting from the methyl ketone (**12**). Thus, deoxybenzoin derivative (**22**) was prepared by Friedel-Crafts acylation after protection of the phenolic function with a triisopropyl group. Modification of the substituents, *O*-prenylation, prenyl 1,3-rearrangement, and *O*-methylation afforded kwakhurin triisopropyl ether (**38**).

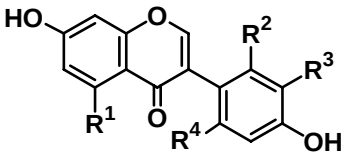
INTRODUCTION

A medicinal plant "kwao keur" (known by other Thai native names: kwao krua, kwao khua, and kwao kreu) 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 relation between the chemical constituents (Figure 1) and estrogenic activity has been widely studied.[1] Recently, we[2] reported that the actual estrogenic component of "kwao keur" might be a new (+)-deoxymiroestrol (**1**), but not the known

(+)-miroestrol (**2**) because of spontaneous conversion of **1** into **2** in methanol solution. On the other hand, kwakhurin (**5**) was at first isolated from the extract of "kwao keur" as compound PM-7 by Tahara, Ingham and co-workers in 1986,[3a] and then named kwakhurin after structural elucidation.[3b] We also isolated kwakhurin (**5**) as a minor component in the bioassay-guided isolation of phytoestrogens from the same plant and it was found that it showed moderate activity, nearly equal to that of daizein (**3**), but less than that of genistein (**4**).[4]



(+)-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

Figure 1. Selected Chemical Constituents of *Pueraria mirifica*.

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 of *P. mirifica* 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 focused on kwakhurin (**5**) as an index of quality standard because of one characteristic component of *P. mirifica*. In this paper we present the precise structural assignment of kwakhurin (**5**) using 2D-NMR spectral experiments and synthetic approaches to kwakhurin (**5**).

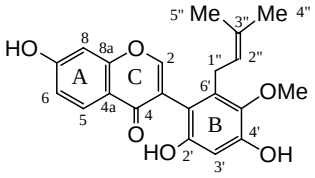
RESULTS AND DISCUSSION

The spectral data of HMQC and HMBC experiments of kwakhurin (**5**) are summarized in Table 1, resulting in reasonable confirmation of the assignment of each signal reported previously.[3b]

The synthesis of isoflavones can be divided into three main synthetic pathways:[5] 1) the formylation of deoxybenzoins, 2) the oxidative rearrangement of chalcones and flavanones, and 3) the arylation of a preformed chromanone ring. We decided to adopt pathway 1, because the deoxybenzoin derivative (**9**) could be easily obtained by acylation of the phenolic compound with arylacetyl halide (Scheme 1).

Retrosynthetically, the 6'-prenyl group in the B-ring of **5** is envisaged to arise *via* prenyl 1,3-rearrangement of **6**. This intermediate originates from phenol (**7**), which is available by oxidative conversion of a halogen or an acyl substituent in the B-ring of isoflavone (**8**).

Table 1. ^{1}H- and ^{13}C-NMR Spectral Data of Kwakhurin (**5**) (δ ppm).*

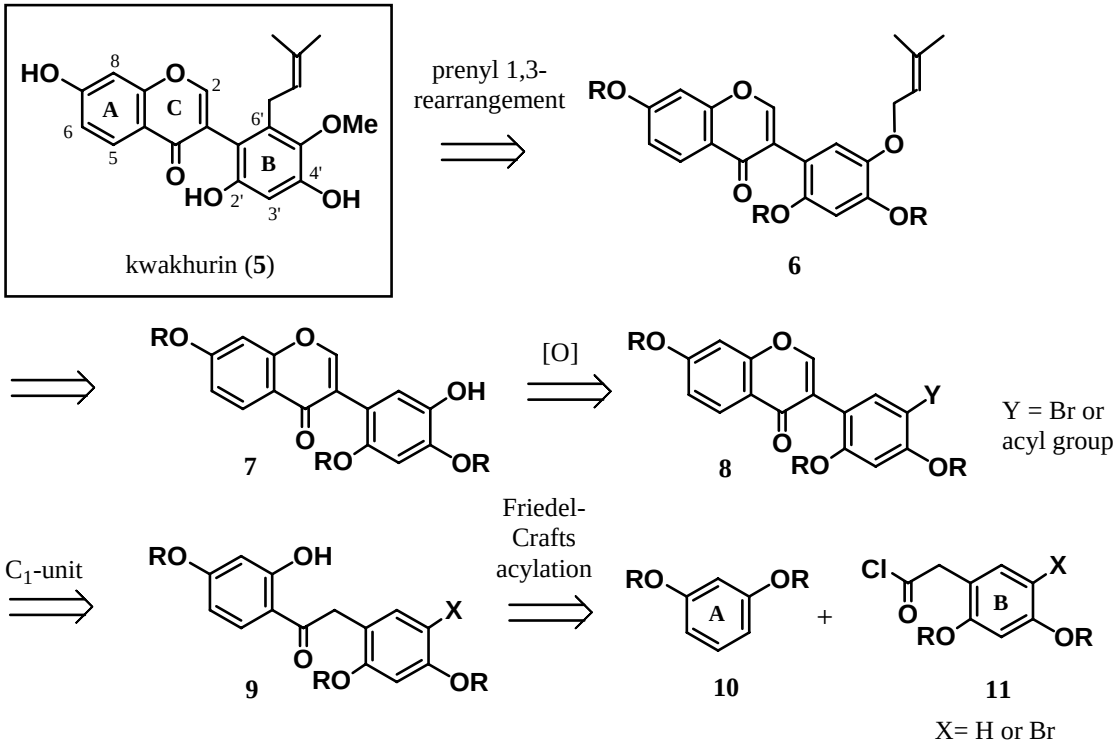


kwakhurin (**5**)

C#	δ_C (150 MHz, CD_3OD) (reported: 60 MHz, acetone-d_6)[3b]	δ_H (600 MHz, CD_3OD) [reported: 500 MHz, acetone-d_6][3b]
2	155.3 (155.5)	7.74 (s) [7.84 (s)]
3	120.6 (121.4)	—
4	177.8 (176.6)	—
4a	117.3 (118.7)	—
5	127.7 (128.3)	8.02 (d, *J*=8.5) [8.02 (d, *J*=8.5)]
6	115.3 (115.4)	6.91 (dd, *J*=8.5, 2.2) [6.98 (dd, *J*=8.5, 2.4)]
7	162.7 (163.0)	—
8	102.5 (102.4)	6.84 (d, *J*=2.2) [6.91 (d, *J*=2.4)]
8a	158.5 (159.0)	—
1'	111.4 (**)	—
2'	152.4 (**)	—
3'	102.3 (103.1)	6.39 (s) [6.39 (s)]
4'	150.3 (**)	—
5'	139.6 (**)	—
6'	135.7 (**)	—
1"	26.9 (27.5)	3.11 (dd, *J*=14.7, 7.0) [3.09 (dd, *J*=14.7, 7.3)] 3.30 (dd, *J*=14.7, 7.0) [3.31 (dd, *J*=14.7, 6.1)]
2"	123.5 (124.8)	4.97 (br t, *J*=6.9) [5.01 (br t, *J*=6.7)]
3"	131.3 (130.8)	—
4"	25.4 (25.6)	1.51 (s) [1.49 (br s)]
5"	17.5 (17.6)	1.38 (s) [1.39 (br s)]
OMe	61.2 (61.1)	3.75 (s) [3.71 (s)]

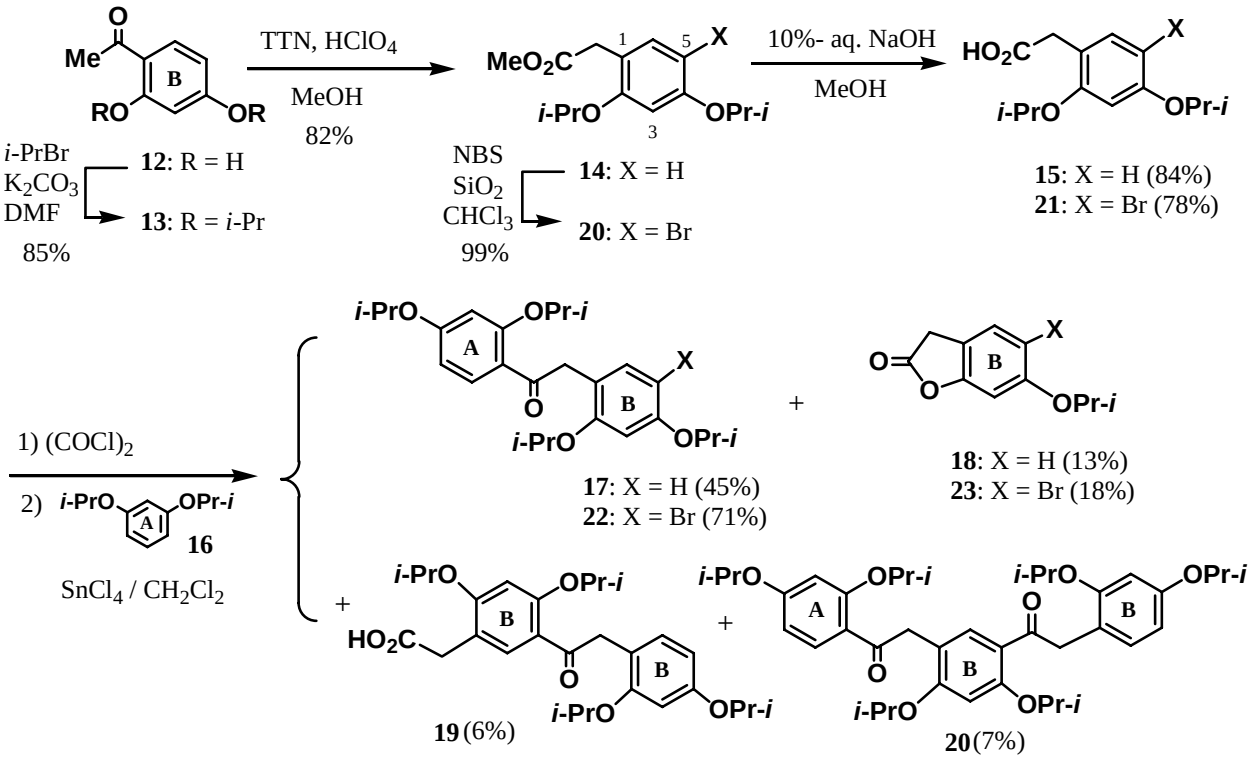
*All assignments are based on 2D-NMR (HMQC and HMBC) spectral experiments. Peak multiplicities in ^{1}H-NMR spctrum are quoted in Hz.
**Five carbons (δ 111.5, 136.3, 140.1, 151.4 and 153.3 ppm) of B-ring were not assigned in reference 3b.

The isoflavone skeleton (**8**) is constructed by formylation of 2-hydroxyphenyl phenymethyl ketone (**9**), which is prepared from a protected resorcinol (**10**) by Friedel-Crafts acylation with arylacetyl chloride (**11**). An isopropyl group was chosen for phenol protection[6] of 2,4-dihydroxyacetophenone (**12**). Thus, phenylacetic acid (**15**) was prepared in good yield by oxidative rearrangement of **13** with thallium trinitrate (TTN) and perchloric acid in methanol[7] followed by alkaline hydrolysis. Friedel-Crafts acylation of diisopropylresorcinol (**16**) with **15** after conversion to acid chloride in the presence of tin chloride ($SnCl_4$) afforded four products including the desired phenyl phenylmethyl ketone (**17**) (45%).



Scheme 1. Retrosynthetic Analysis of Kwakhurin (**5**).

The ^{1}H-NMR spectra of the side products showed that they were the γ-lactone (**18**) (13%), the self-coupling product (**19**) (6%), and the over-coupling product (**20**) (7%), respectively. To avoid the formation of these self-acylation products, the reactive C-5 position of the starting (**15**) was blocked by a



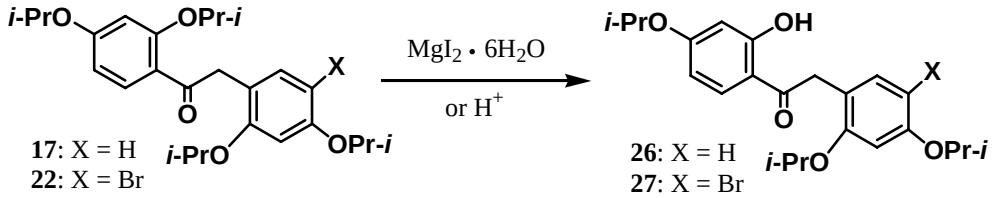
Scheme 2

bromo group, which may be available as an oxygen synthon. Bromination of ester (**14**) with NBS-SiO_2[8] followed by hydrolysis yielded 5-bromophenylacetic acid (**21**). Friedel-Crafts acylation of **16** with acyl chloride from **21** smoothly proceeded to give deoxybenzoin (**22**) in 71% yield; however, concomitant formation of γ-lactone (**23**) was inevitable even in low yield (18%) (Scheme 2).

Next, selective deprotection of tetraisopropoxy derivatives (**17**) and (**22**) was tried (Table 2). Previously, we reported the successful use of magnesium iodide (MgI_2) as a reagent for selective demethylation of an aryl methoxy group in the *ortho* position to the acyl group.[9] Thus, treatment of deoxybenzoin (**17**) with MgI_2 proceeded smoothly to give phenol (**26**) in good yield (entries 1 and 2), but a complex mixture was formed in the case of the bromo derivative (**22**) (entry 3).

We have found that protic acids in AcOH act as efficient deisopropylating agents.[10] The use of concentrated HCl led to desired deprotection in moderate yield (entry 4). On the other hand, higher yield (71%) was observed when concentrated H_2SO_4 was used (entry 5).

Table 2. Selective Deisopropylation of Deoxybenzoin Derivatives (**17** and **22**).



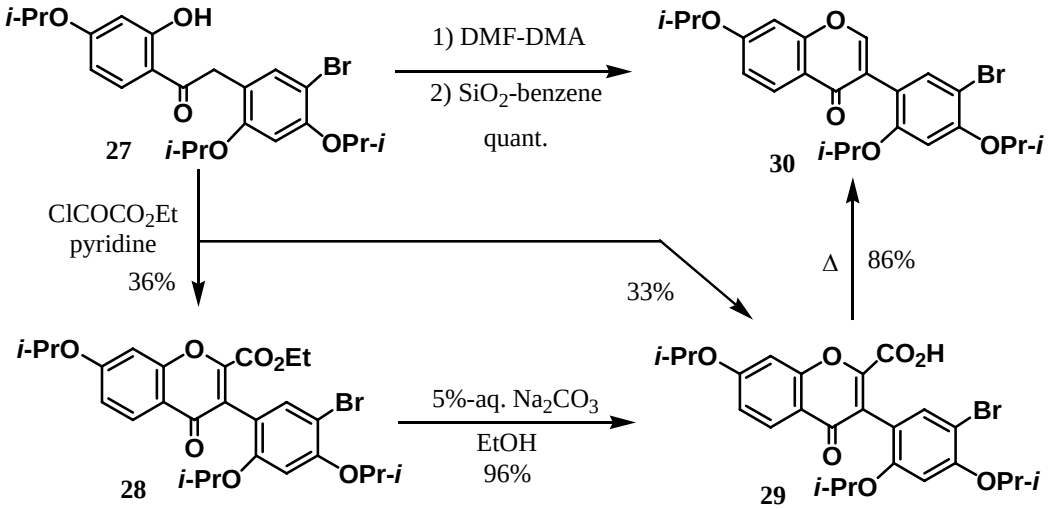
17: X = H
22: X = Br

26: X = H
27: X = Br

entry	X =	Reagent	Solvent	Condition		Yield (%)	
				Temp.	Time (h)	**26**	**27**
1	H	$MgI_2 \cdot 6H_2O$	benzene	reflux	70	70	—
2	H	$MgI_2 \cdot 6H_2O$	toluene	reflux	20	72	—
3	Br	$MgI_2 \cdot 6H_2O$	toluene	reflux	5	a complex mixture	
4	Br	conc. HCl	AcOH	60 °C	22	—	46
5	Br	conc. H_2SO_4	AcOH	50 °C	4	—	71

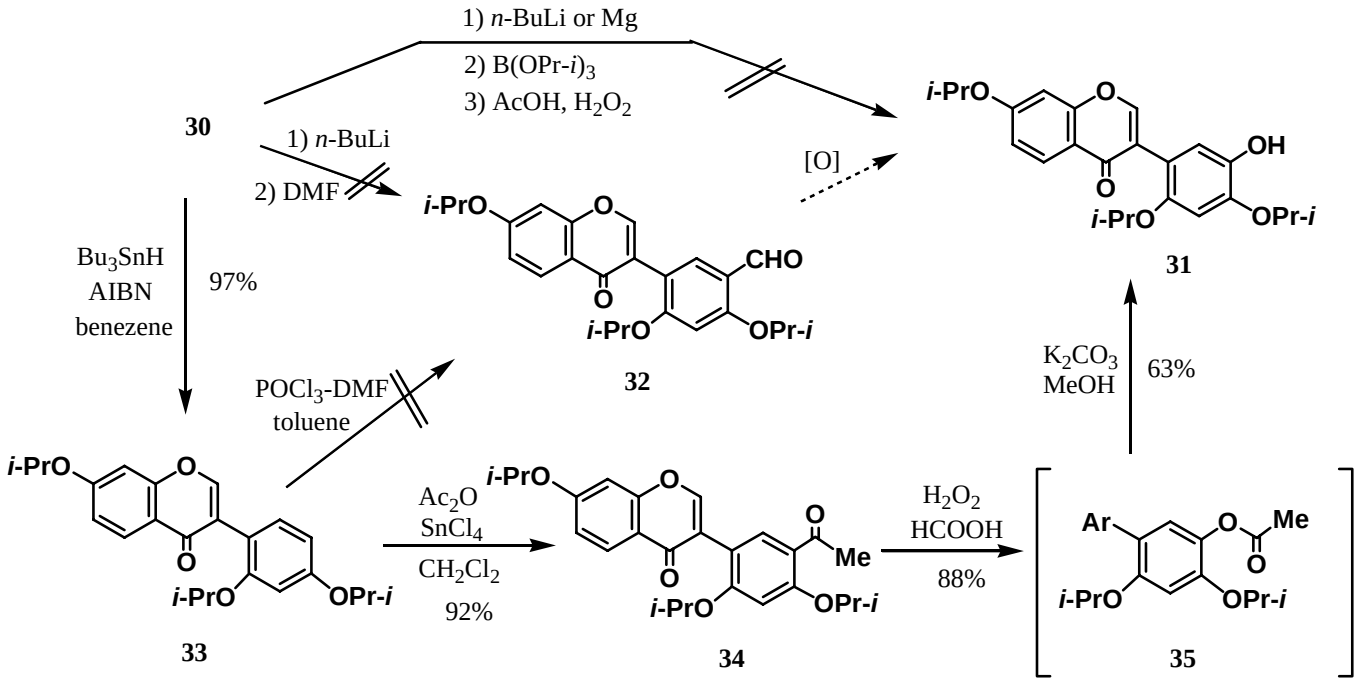
For C-ring construction of an isoflavone skeleton, treatment of **27** with ethyl oxalyl chloride in pyridine[11] provided a mixture of an expected ester (**28**) and a hydrolyzed product (**29**) in nearly equal amount, and the former was completely converted to the latter by alkaline hydrolysis. Thermal decarboxylation of (**29**) afforded isoflavone (**30**), in which C-2 proton was newly born at δ 7.91 ppm in the ^{1}H-NMR spectrum. The isoflavone (**30**) was also obtained by formylation with *N*,*N*-dimethylformamide dimethylacetal (DMF-DMA)[12] followed by cyclization with silica gel. The yield was quantitative; however, the use of

DMF- $POCl_3$[13] in place of DMF-DMA resulted in the formation of a complex mixture (Scheme 3).



Scheme 3

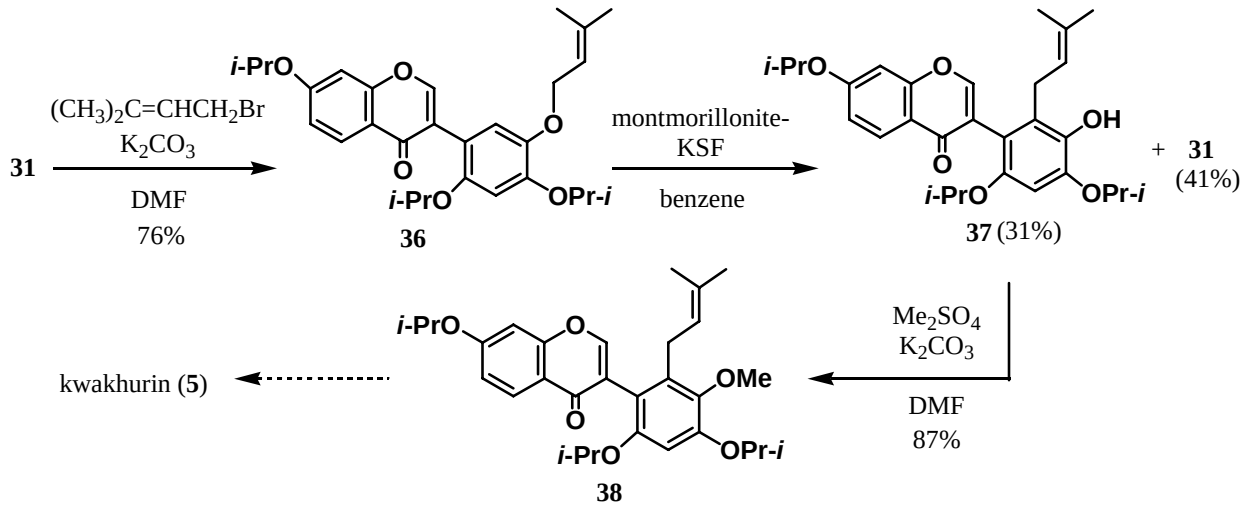
Since all trials for conversion of the bromo substituent of **30** to a phenolic function in isoflavone (**31**) *via* metallation, boration or formylation failed, the bromo group was reductively removed with tributyltin hydride to afford **33** in 97% yield. Although Vilsmeier formylation of **33** was unsuccessful, introduction of an acetyl group under the conditions of Friedel-Crafts acylation with acetic anhydride in the presence of $SnCl_4$ smoothly proceeded to give acetyl compound (**34**). Baeyer-Viliger oxidation of **34** followed by hydrolysis yielded the desired phenolic compound (**31**) (Scheme 4).



Scheme 4

After prenylation of phenol (**31**) with prenyl bromide and potassium carbonate, a prenyl 1,3-rearrangement was examined. The reaction of prenyl ether (**36**) with montmorillonite-KSF clay[14] in benzene yielded the desired ether (**37**) in 31% yield along with phenol (**31**) (41%). In other solvent systems such as THF and CH_2Cl_2, or under sonication conditions no improvement of the reaction was observed. Conventional methylation of **37** afforded triisopropylkwakhurin (**38**) (Scheme 5).

In the ^{1}H-NMR spectrum this compound showed very similar signal patterns to those of kwakhurin triethyl ether prepared from natural kwakhurin (**5**) by Tahara *et al*.[3b] We attempted deprotection of the triisopropyl group in **38** under various conditions, but unfortunately no production of kwakhurin (**5**) was observed.[15] Further efforts are underway to complete the synthesis of kwakhurin (**5**) itself.



Scheme 5

CONCLUSION

The structure of kwakhurin (**5**) was further confirmed by the inspection of the 2D-NMR spectra. Triisopropylkwakhurin (**38**) was synthesized from **12** in 3.4% overall yield. Although successful results were not obtained in the final deprotection step, this method could provide a synthetic route to biologically active isoflavones from easily prepared deoxybenzoin compounds.

EXPERIMENTAL

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 spectrophotometer. ^{1}H- and ^{13}C-NMR spectra were recorded in $CDCl_3$ unless otherwise stated, on JEOL JNM GSX-400A, GSX-500A, ECP-400 and ECP-600 spectrometers with tetramethylsilane (TMS) as internal reference. MS spectra were recorded on

a JEOL JMS-AM20 (EI), and JEOL JMS-AX-500 and JMS-HX 10A (FAB). For column chromatography, silica gel (particle size: 100 μm) (FL-100D, Fuji Silysia) was used unless otherwise stated.

Isolation and Structural Determination of Kwakhurin (5)

Isolation of kwakhurin (**5**) from *Pueraria mirifica* was described in the previous report.[4] The precise structural assignment of **5** was obtained from 2D-NMR (HMQC and HMBC) spectral experiments (Table 1).

2,4-Diisopropoxyacetophenone (13). To a mixture of 2,4-dihydroxyacetophenone (**12**) (15.0 g, 99 mmol) and K_2CO_3 (109 g, 789 mmol) was added a solution of isopropyl bromide (32 mL, 341 mmol) in DMF (150 mL). The whole mixture was sirred at 55 ^oC for 3.3 h under argon atmosphere, poured into water (750 mL), and extracted with AcOEt (400 mL + 200 mL x 2). The organic layer was washed with water (250 mL x 3) and brine (250 mL), dried over $MgSO_4$, and evaporated to dryness *in vacuo* to afford a yellow oil (28.4 g), which was purified by distillation (bp 142-146 ^oC/9 mmHg) to give **13** as a colorless oil (19.9 g, 85%). IR ν_{max} cm^{-1} (neat): 1664 (C=O). ^{1}H-NMR (400 MHz) δ : 1.35 [6H, d, *J*=6.0 Hz, CH(C<u>H</u>$_3$)$_2$], 1.41 [6H, d, *J*=6.0 Hz, CH(C<u>H</u>$_3$)$_2$], 2.58 (3H, s, CH_3), 4.61 [1H, sep, *J*=6.0 Hz, O-C<u>H</u>(CH$_3$)$_2$], 4.64 [1H, sep, *J*=6.0 Hz, O-C<u>H</u>(CH$_3$)$_2$], 6.41 (1H, d, *J*=2.2 Hz, C_3-H), 6.47 (1H, dd, *J*=8.8, 2.2 Hz, C_5-H), 7.80 (1H, d, *J*=8.8 Hz, C_6-H). HRFAB-MS *m/z*: 237.1471 (Calcd for $C_{14}H_{21}O_3$: 237.1490). EI-MS *m/z*: 236 (M^+, 100%).

Methyl 2,4-Diisopropoxyphenylacetate (14). To a solution of TTN (10.1 g, 22.7 mmol) in MeOH (17.2 mL) was added 60% aq. $HClO_4$ (11.4 mL, 113 mmol) and a solution of acetophenone (**13**) (4.87 g, 20.6 mmol) in MeOH (84.5 mL), and the whole mixture was stirred at rt for 4.3 h under argon atmosphere. The reaction mixture was poured into water (500 mL) and extracted with AcOEt (3 x 200 mL). The organic layer was washed with water and brine, dried over $MgSO_4$ and evaporated to dryness *in vacuo* to yield a brown oil (5.67 g). The crude oil was purified by silica gel column chromatography (hexane-AcOEt, 5:1) to give a pale yellow oil (**14**) (4.48 g, 82%). IR ν_{max} (neat) cm^{-1}: 1741 (C=O). ^{1}H-NMR (500 MHz) δ: 1.29 [6H, d, *J*=6.1 Hz, CH-(C<u>H</u>$_3$)$_2$], 1.33 [6H, d, *J*=6.1 Hz, CH-(C<u>H</u>$_3$)$_2$], 3.52 (2H, s, Ar-C<u>H</u>$_2$-COOCH$_3$), 3.67 (3H, s, COO-CH$_3$), 4.49 and 4.51 [each 1H, sep, *J*=6.1 Hz, O-C<u>H</u>-(CH$_3$)$_2$], 6.41 (1H, dd, *J*=7.3, 2.4 Hz, C_5-H), 6.42 (1H, d, *J*=2.4 Hz, C_3-H), 7.04 (1H, d, *J*=7.3 Hz, C_6-H).

2,4-Diisopropoxyphenylacetic Acid (15). To a solution of ester (**14**) (4.25 g, 16.0 mmol) in MeOH (85

mL) was added 10% aq. NaOH (85 mL), and the whole mixture was stirred at rt for 1.5 h. The reaction mixture was poured into AcOEt (200 mL) and extracted with water (400 mL). The organic layer was extracted with10% aq. NaOH (2 x 100 mL). The combined alkaline solution was acidified (pH *ca*.1) with 10% aq. HCl and extracted with AcOEt (2 x 200 mL + 100 mL). The organic layer was washed with water and brine, dried over $MgSO_4$, and evaporated to dryness *in vacuo* to afford pale yellow prisms (3.70 g). The crude solid was washed with hexane to yield colorless prisms (**15**) (3.38 g, 84%, mp 81-83 ^oC), which were further purified by recrystallization from hexane to give **15** as colorless prisms (mp 80.5-82 ^oC). IR ν_{max} (Nujol) cm^{-1}: 3400-2400 (OH), 1709 (C=O). ^1H-NMR (500 MHz) δ: 1.31 and 1.33 [each 6H, d, *J*= 6.1 Hz, CH-(C<u>H</u>$_3$)$_2$], 3.56 (2H, s, Ar-C<u>H</u>$_2$-COOH), 4.51 and 4.53 [each 1H, sep, *J*= 6.1 Hz, O-C<u>H</u>-$(CH_3)_2$], 6.42 (1H, dd, *J*= 8.2, 2.4 Hz, C_5-H), 6.44 (1H, d, *J*= 2.4 Hz, C_3-H), 7.06 (1H, d, *J*= 8.2 Hz, C_6-H). *Anal*. Calcd for $C_{14}H_{20}O_4$: C, 66.64; H, 7.99. Found: C, 66.37; H, 7.93.

1,3-Diisopropoxybenzene[16] (16). To a mixture of 1,3-dihydroxybenzene (10.0 g, 90.9 mmol), K_2CO_3 (75.3 g, 545 mmol) and DMF (100 mL) was added *i*-PrBr (25.5 mL, 272 mmol), and the whole mixture was stirred at 55 ^oC for 12.5 h under argon atmosphere. The reaction mixture was poured into water (500 mL) and extracted with AcOEt (300 mL + 2 x 150 mL). The organic layer was washed with water (3 x 200 mL) and brine (200 mL), dried over $MgSO_4$, and evaporated to dryness *in vacuo* to afford a yellow oil (21.1 g). The crude oil was purified by distillation [bp 88-90 ^oC /6 mmHg (lit.[16] bp 89.5-95 ^oC /3 mmHg)] to give **16** as a colorless oil (13.6 g, 77%). ^1H-NMR (400 MHz) δ: 1.33 [12H, d, *J*=6.2 Hz, CH(C<u>H</u>$_3$)$_2$], 4.52 [2H, sep, *J*=6.2 Hz, O-C<u>H</u>$(CH_3)_2$], 6.44 (1H, d, *J*=2.2 Hz, C_2-H), 6.46 (2H, dd, *J*=7.9, 2.2 Hz, C_4-H and C_6-H), 7.14 (1H, t, *J*=7.9 Hz, C_5-H).

Friedel-Crafts Acylation of 2,4-Diisopropoxybenzene (16) with 2,4-Diisopropoxyphenylacetic Acid (15). A mixture of acid (**15**) (100 mg, 0.40 mmol) and $(COCl)_2$ (0.1 mL, 1.18 mmol) was stirred at rt for 2 h. The excess of $(COCl)_2$ was removed by evaporation *in vacuo* to yield 2,4-diisopropoxyphenylacetyl chloride as a yellow viscous liquid. [IR ν_{max} (neat) cm^{-1}: 1803 (C=O)].

To a solution of the acyl chloride in CH_2Cl_2 (4.8 mL) was added a solution of 2,4-diisopropoxybenzene (**16**) (76.6 mg, 0.39 mmol) in CH_2Cl_2 (4.8 mL) under ice-cooling, then added 1.0 M $SnCl_4$ / CH_2Cl_2 (0.44 mL, 0.44 mmol) at -78 ^oC. The whole mixture was stirred at -78 ^oC for 18.5 h. The reaction mixture was poured into water (30 mL) and extracted with AcOEt (3 x 70 mL). The organic layer was washed with sat. aq. $NaHCO_3$ and water, dried over K_2CO_3 and evaporated to dryness *in vacuo* to afford a yellow oil (151 mg). The crude product was purified by silica gel column chromatography (hexane-AcOEt, 20:1 to 2:1) to

give **17** (75.6 mg, 45%) as a pale yellow oil. Further elution gave recovery of starting 1,3-diisopropoxybenzene (**16**) (22.7 mg, 30%), lactone (**18**) (9.7 mg, 13%), dimer (**19**) (6.0 mg, 6.3%), and trimer **20** (10.0 mg, 7.0%).

i) 2,4-Diisopropoxyphenyl 2',4'-Diisopropoxybenzyl Ketone (17). A pale yellow oil. IR ν_{max} (neat) cm^{-1}: 1672 (C=O). ^{1}H-NMR (500 MHz) δ: 1.20, 1.32, 1.35 and 1.39 [each 6H, d, *J*=6.1 Hz, O-CH-(C<u>H</u>$_3$)$_2$], 4.17 (2H, s, CO-CH_2), 4.44, 4.50, 4.60 and 4.64 [each 1H, sep, *J*= 6.1 Hz, O-C<u>H</u>-(CH_3)$_2$], 6.40-6.43 (3H, m, $C_{3,3'\text{ and }5'}$-H), 6.47 (1H, dd, *J*= 8.9, 2.1 Hz, C_5-H), 7.02 (1H, d, *J*= 8.9 Hz, $C_{6'}$-H), 7.73 (1H, d, *J*= 8.9 Hz, C_6-H).

ii) 2,3-Dihydro-6-isopropoxybenzo[*b*]furan-2-one (18). A brown powder. ^{1}H-NMR (500 MHz) δ: 1.34 [6H, d, *J*=6.1 Hz, CH(C<u>H</u>$_3$)$_2$], 3.67 (2H, s, -CO-CH_2), 4.52 [1H, sep, *J*=6.1 Hz, O-C<u>H</u>(CH_3)$_2$], 6.65 (1H, dd, *J*=8.2, 2.4 Hz, C_5-H), 6.67 (1H, d, *J*=2.4 Hz, C_7-H), 7.14 (1H, d, *J*=8.2 Hz, C_4-H).

iii) 2,4-Diisopropoxy-5-[(2',4'-diisopropoxyphenyl)acetyl]phenylacetic Acid (19). A pale yellow oil. ^{1}H-NMR (600 MHz) δ: 1.20, 1.31, 1.35, 1.40 [each 6H, d, *J*=6.1 Hz, CH(C<u>H</u>$_3$)$_2$], 3.55 (2H, s, ArCH_2-COOH), 4.16 (2H, s, ArCH_2COAr'), 4.44, 4.50, 4.60, 4.64 [each 1H, sep, *J*=6.1 Hz, O-C<u>H</u>(CH_3)$_2$], 6.39-6.42 (3H, m, Ar-H), 7.01 (1H, d, *J*=7.4 Hz, $C_{6'}$-H), 7.63 (1H, s, C_6-H), no signal for COO<u>H</u>.

iv) 2,4-Diisopropoxyphenyl 2',4'-Diisopropoxy-5'-[(2",4"-Diisopropoxyphenyl)acetyl]benzyl Ketone (20). A pale yellow oil. ^{1}H-NMR (500 MHz) δ: 1.22, 1.25, 1.32, 1.35, 1.39, 1.40 [each 6H, d, *J*=6.1 Hz, CH(C<u>H</u>$_3$)$_2$], 4.16, 4.19 (each 2H, s, ArCH_2COAr'), 4.41-4.68 [6H, m, O-C<u>H</u>(CH_3)$_2$], 6.39-6.50 (5H, m, Ar-H), 6.99 (1H, d, *J*=8.0 Hz, $C_{6"}$-H), 7.61 (1H, s, $C_{6'}$-H), 7.70 (1H, d, *J*=8.8 Hz, C_6-H).

Methyl 5-Bromo-2,4-diisopropoxyphenylacetate (20). To a solution of phenylacetate (**14**) (1.00 g, 3.76 mmol) in $CHCl_3$ (30 mL) was added SiO_2 (Micro Bead 3A, Fuji Silysia) (3.30 g) and NBS (0.669 g, 3.76 mmol), and the whole mixture was stirred at rt for 70 min. After filtration of SiO_2 and washing with $CHCl_3$ (120 mL), the combined organic layer was washed with 10% aq. $Na_2S_2O_3$ (60 mL), dried over $MgSO_4$ and evaporated to dryness *in vacuo* to afford **20** (1.29 g, 99%) as a labile yellow oil, which was used for the next step without further purification. IR ν_{max} (neat) cm^{-1}: 1736 (C=O). ^{1}H-NMR (500 MHz) δ: 1.30 [6H, d, *J*=6.0 Hz, CH-(C<u>H</u>$_3$)$_2$], 1.37 [6H, d, *J*=6.0 Hz, CH-(C<u>H</u>$_3$)$_2$], 3.50 (2H, s, CO-CH_2-), 3.68 (3H, s, O-CH_3), 4.48 [2H, sep, *J*=6.0 Hz, O-C<u>H</u>-(CH_3)$_2$], 6.48 (1H, s, C_3-H), 7.29 (1H, s, C_6-H).

5-Bromo-2,4-diisopropoxyphenylacetic Acid (21). To a solution of bromophenylacetate (**20**) (1.29 g, 3.72 mmol) in MeOH (14 mL) was added 10% aq. NaOH (14 mL, 3.50 mmol), and the whole mixture

was stirred at rt for 3.5 h. After evaporation of MeOH the residue was dissolved in AcOEt (70 mL). The organic layer was extracted with water (50 mL + 3 x 30 mL) and 10% aq. NaOH (3 x 30 mL). The combined aqueous solution was acidified (pH 1) with conc. HCl and extracted with AcOEt (150 mL + 2 x 100 mL). The organic layer was washed with water and brine (each 100 mL), dried over $MgSO_4$ and evaporated to dryness *in vacuo* to afford pale yellow prisms (1.09 g), which were recrystallized from hexane to give acid (**21**) (0.961 g, 78%) as colorless prisms (mp 98-100 ^oC). IR ν_{max} (Nujol) cm^{-1}: 3100-2500 (OH), 1704 (C=O). ^{1}H-NMR (400 MHz) δ: 1.32 [6H, d, *J*=6.0 Hz, CH-(C<u>H</u>$_3$)$_2$], 1.38 [6H, d, *J*=6.2 Hz, CH-(C<u>H</u>$_3$)$_2$], 3.54 (2H, s, CH_2-CO-), 4.48 [1H, sep, *J*=6.0 Hz, O-C<u>H</u>$(CH_3)_2$], 4.50 [1H, sep, *J*=6.2 Hz, O-C<u>H</u> $(CH_3)_2$], 6.49 (1H, s, C_3-H), 7.32 (1H, s, C_6-H), no signal of hydroxy proton was observed. *Anal.* Calcd for $C_{14}H_{19}O_4Br$: C, 50.77; H, 5.78. Found: C, 50.82; H, 5.90.

Friedel-Crafts Acylation of 1,3-Diisopropoxybenzene (16) with 5-Bromo-2,4-diisopropoxyphenyl-acetic Acid (21). A mixture of bromoacid (**21**) (0.653 g, 1.97 mmol) and $(COCl)_2$ (0.47 mL, 5.55 mmol) was stirred at rt for 2.5 h. The excess of $(COCl)_2$ was removed by evaporation *in vacuo* to afford 5-bromo-2,4-diisopropoxyphenylacetyl chloride as a pale green solid. [IR ν_{max} (Nujol) cm^{-1}: 1786 (C=O)]. To a solution of the acyl chloride in CH_2Cl_2 (3.7 mL) was added at -78 ^oC 1,3-diisopropoxybenzene (**16**) (0.389 g, 2.00 mmol) followed by 1.0 M solution of $SnCl_4$ in CH_2Cl_2 (8.1 mL, 8.1 mmol), and the whole mixture was stirred at -78 ^oC for 65 min. The reaction mixture was poured into water (200 mL) and extracted with AcOEt (100 mL + 2 x 70 mL). The organic layer was washed with sat. aq. $NaHCO_3$ and water (each 70 mL), dried over K_2CO_3, and evaporated to dryness *in vacuo* to give a dark green oil (1.01 g). The crude product was purified by silica gel column chromatography (hexane-AcOEt, 20:1 to 2:1) to afford **22** (0.707 g, 71%) and lactone (**23**) (0.0974 g, 18%).

i) 5'-Bromo-2',4'-diisopropoxybenzyl 2,4-Diisopropoxyphenyl Ketone (22). A pale yellow oil. IR ν_{max} (neat) cm^{-1}: 1671(C=O). ^{1}H-NMR (400 MHz) δ: 1.22 [6H, d, *J*=6.0 Hz, O-CH-(C<u>H</u>$_3$)$_2$], 1.36 [6H, d, *J*=6.0 Hz, O-CH-(C<u>H</u>$_3$)$_2$], 1.37 [6H, d, *J*=6.0 Hz, O-CH-(C<u>H</u>$_3$)$_2$], 1.40 [6H, d, *J*=6.0 Hz, O-CH-(C<u>H</u>$_3$)$_2$], 4.14 (2H, s, CO-CH_2), 4.42, 4.46, 4.60, 4.65 [each 1H, sep, *J*=6.0 Hz, O-C<u>H</u>-$(CH_3)_2$], 6.42 (1H, d, *J*=2.2 Hz, C_3-H), 6.47 (1H, dd, *J*=8.8, 2.2 Hz,C_5-H), 6.49 (1H, s, $C_{3'}$-H), 7.28 (1H, s, $C_{6'}$-H), 7.74 (1H, d, *J*=8.8 Hz, C_6-H).

ii) 5-Bromo-2,3-dihydro-6-isopropoxybenzo[*b*]furan-2-one (23). A yellow powder. ^{1}H-NMR (400 MHz) δ: 1.40 [6H, d, *J*=6.0 Hz, CH(C<u>H</u>$_3$)$_2$], 3.693 (1H, d, *J*=1.1 Hz, C_3-H_a), 3.694 (1H, d, *J*=1.1 Hz, C_3-H_b), 4.53 [1H, sep, *J*=6.0 Hz, O-C<u>H</u>$(CH_3)_2$], 6.73 (1H, s, C_7-H), 7.44 (1H, t, *J*=1.1 Hz, C_4-H).

2-Hydroxy-4-isopropoxyphenyl 2,4-Diisopropoxybenzyl Ketone (26). To a solution of ketone (**17**) (75.6 mg, 0.176 mmol) in toluene (4.5 mL) was added $MgI_2 \cdot 6H_2O$ (79.5 mg, 0.206 mmol). The whole mixture was refluxed using Dean-Stark apparatus for 20 h (bath temperature 150 ^oC). The reaction mixture was poured into water (30 mL) and extracted with AcOEt (3 x 70 mL). The organic layer was washed with water and brine, dried over $MgSO_4$ and evaporated to dryness *in vacuo* to give a brown oil (80.8 mg). The crude product was purified by silica gel column chromatography (hexane-AcOEt, 20:1) to afford 2-hydroxy ketone (**26**) as a pale yellow oil (48.9 mg, 72%). IR ν_{max} (neat) cm^{-1}: 1629 (C=O). ^{1}H-NMR (600 MHz) δ: 1.25 [6H, d, *J*= 6.0 Hz, CH-(C<u>H</u>$_3$)$_2$], 1.32 [6H, d, *J*= 6.0 Hz, CH-(C<u>H</u>$_3$)$_2$], 1.35 [6H, d, *J*= 6.0 Hz, CH-(C<u>H</u>$_3$)$_2$], 4.08 (2H, s, CO-CH_2), 4.50 [2H, sep, *J*= 6.0 Hz, O-C<u>H</u>-$(CH_3)_2$], 4.59 [1H, sep, *J*= 6.0 Hz, O-C<u>H</u>-$(CH_3)_2$], 6.30-6.48 (4H, m, $C_{3,\ 5,\ 3'\ and\ 5'}$-H), 7.09 (1H, d, *J*= 8.5 Hz, $C_{6'}$-H), 7.86 (1H, d, *J*= 9.3 Hz, C_6-H), 12.81 (1H, s, -OH).

5'-Bromo-2',4'-diisopropoxybenzyl 2-Hydroxy-4-isopropoxyphenyl Ketone (27). A mixture of ketone (**22**) (0.325 g, 0.64 mmol), conc. H_2SO_4 (0.82 mL, 14.9 mmol) and AcOH (26 mL) was stirred at 50 ^oC for 4 h. The reaction mixture was poured into water (50mL) and extracted with AcOEt (3 x 30 mL). The organic layer was washed with 5% aq. $NaHCO_3$ (30 mL) and 2% aq. NaOH (3 x 30 mL + 10 mL), dried over $MgSO_4$, and evaporated to dryness *in vacuo* to afford a brown oil (0.348 g). The crude product was purified by silica gel column chromatography (hexane-AcOEt, 30:1) to give pale yellow crystals (0.213 g, 71%) which were recrystallized from hexane to afford **27** as colorless prisms (mp 89-90.5 ^oC). IR ν_{max} (Nujol) cm^{-1}: 1625 (C=O). ^{1}H-NMR (400 MHz) δ: 1.25 [6H, d, *J*=6.8 Hz, CH(C<u>H</u>$_3$)$_2$], 1.36 [6H, d, *J*=6.8 Hz, CH(C<u>H</u>$_3$)$_2$], 1.39 [6H, d, *J*=6.2 Hz, CH(C<u>H</u>$_3$)$_2$], 4.07 (2H, s, CO-CH_2), 4.44-4.52 [2H, m, O-C<u>H</u>-$(CH_3)_2$], 4.60 [1H, sep, *J*=6.2 Hz, O-C<u>H</u>-$(CH_3)_2$], 6.38-6.41 (2H, m, Ar-H), 6.49 (1H, s, $C_{3'}$-H), 7.35 (1H, s, $C_{6'}$-H), 7.81 (1H, d, *J*= 9.7 Hz, C_6-H), 12.71 (1H, s, -OH). *Anal.* Calcd for $C_{23}H_{29}O_5Br$: C, 59.36; H, 6.28. Found: C, 59.54; H, 6.27.

Ethyl 5'-Bromo-7,2',4'-triisopropoxyisoflavone-2-carboxylate (28). To a solution of ketone (**27**) (1.256 g, 2.70 mmol) in pyridine (12.8 mL) was added $ClOCCO_2Et$ (1.27 mL, 11.21 mmol) under ice-cooling. The whole mixture was heated at 120 ^oC for 7.5 h. The reaction mixture was poured into water (200 mL) and extracted with $CHCl_3$ (150 mL + 2 x 70 mL). The organic layer was washed with 10% HCl (200 mL), dried over $MgSO_4$, and evaporated to dryness *in vacuo* to afford brown oil (2.093 g). The crude product was separated by silica gel column chromatography (hexane-AcOEt, 20:1 to 2:1, then AcOEt) to afford two fractions:

i) From the less polar fraction: a yellow solid (**28**) (0.525 g, 36%), which was recrystallized from ether-hexane to give isoflavone (**28**) as pale yellow prisms (mp 140-141 ^{o}C). IR ν_{max} (Nujol) cm^{-1}: 1733, 1648 (C=O). ^{1}H-NMR (400 MHz) δ: 1.07 (3H, t, *J*=7.1 Hz, OCH_2-C$\underline{H}_3$), 1.14 [3H, d, *J*=6.0 Hz, CH(C$\underline{H}_3$)$_2$], 1.22 [3H, d, *J*=6.0 Hz, CH(C$\underline{H}_3$)$_2$], 1.40-1.42 [12H, m, CH(C$\underline{H}_3$)$_2$], 4.11-4.23 (2H, m, O$C\underline{H}_2CH_3$), 4.35 [1H, sep, *J*=6.0 Hz, O-C$\underline{H}$-$(CH_3)_2$], 4.53 [1H, sep, *J*=6.0 Hz, O-C$\underline{H}$-$(CH_3)_2$], 4.67 [1H, sep, *J*=6.1 Hz, O-C$\underline{H}(CH_3)_2$], 6.53 (1H, s, $C_{3'}$-H), 6.94-6.97 (2H, m, C_6-H, C_8-H), 7.38 (1H, s, $C_{6'}$-H), 8.11 (1H, d, *J*=8.6 Hz, C_5-H). *Anal*. Calcd for $C_{27}H_{31}O_7Br$: C, 59.24; H, 5.71. Found: C, 59.12; H, 5.68.
ii) From the polar fraction: a brown solid (**29**) (0.469 g, 33%), which was identical with the sample described below.

5'-Bromo-7,2',4'-triisopropoxyisoflavone-2-carboxylic Acid (29). To a solution of ester (**28**) (0.171 g, 0.31 mmol) in EtOH (6 mL) was added 5% aq. Na_2CO_3 (6.64 mL, 3.13 mmol), and the whole mixture was heated at 50 ^{o}C for 4.5 h and 70 ^{o}C for 1.5 h. The reaction mixture was dissolved in ether (80 mL) and extracted with water (50 mL) and 10% aq. NaOH (40 mL + 2 x 20 mL). The combined aqueous layer was acidified (pH 1) with conc. HCl and extracted with AcOEt (100 mL + 2 x 70 mL). The orgnic layer was washed with water and brine (each 70 mL), dried over $MgSO_4$, and evaporated to dryness *in vacuo* to afford acid (**29**) (0.157 g, 96%) as pale yellow prisms. This compound was used for the next step without further purification. A part of the sample was recrystallized from ether-hexane to give pale yellow prisms (mp 216-220.5 ^{o}C). IR ν_{max} (Nujol) cm^{-1}: 1742, 1625 (C=O). ^{1}H-NMR (500 MHz) δ: 1.16 [3H, d, *J*=6.1 Hz, CH(C$\underline{H}_3$)$_2$], 1.24 [3H, d, *J*=6.1 Hz, CH(C$\underline{H}_3$)$_2$], 1.35-1.43 [12H, m, CH(C$\underline{H}_3$)$_2$], 4.39 [1H, sep, *J*=5.8 Hz, O-C$\underline{H}(CH_3)_2$], 4.54 [1H, sep, *J*=5.8 Hz, O-C$\underline{H}(CH_3)_2$], 4.67 [1H, sep, *J*=6.1 Hz, O-C$\underline{H}(CH_3)_2$], 6.53 (1H, s, $C_{3'}$-H), 6.94 (1H, d, *J*=2.1 Hz, C_8-H), 6.97 (1H, dd, *J*=8.9, 2.1 Hz, C_6-H), 7.40 (1H, s, $C_{6'}$-H), 8.11 (1H, d, *J*=8.9 Hz, C_5-H), no signal for COOH. *Anal.* Calcd for $C_{25}H_{27}O_7Br$: C, 57.81; H, 5.24. Found: C, 57.79; H, 5.27.

5'-Bromo-7,2',4'-triisopropoxyisoflavone (30)

i) Decarboxylation of acid 29. Acid (**29**) (0.201 g, 0.39 mmol) was heated at 230 ^{o}C for 0.5 h. The crude brown oil (0.185 g) was purified by silica gel column chromatography (hexane-AcOEt, 20:1 to 2:1) to afford pale yellow prisms (**30**) (0.158 g, 86%, mp 116.5-121.5 ^{o}C). A part of the sample was recrystallized from cyclohexane-hexane to give **30** as pale yellow prisms (mp 119.5-120 ^{o}C). IR ν_{max} (Nujol) cm^{-1}: 1638 (C=O). ^{1}H-NMR (600 MHz) δ: 1.25 [6H, d, *J*=6.0Hz, CH(C$\underline{H}_3$)$_2$], 1.41 and 1.42 [each 6H, d, *J*=6.0 Hz, CH(C$\underline{H}_3$)$_2$], 4.41 [1H, sep, *J*=6.0 Hz, C$\underline{H}(CH_3)_2$], 4.53 [1H, sep, *J*=6.0 Hz, O-C$\underline{H}(CH_3)_2$],

4.67 [1H, sep, *J*=4.4 Hz, O-C<u>H</u>$(CH_3)_2$], 6.57 (1H, s, $C_{3'}$-H), 6.83 (1H, d, *J*=2.2 Hz, C_8-H), 6.94 (1H, dd, *J*=9.0, 2.2 Hz, C_6-H), 7.54 (1H, s, $C_{6'}$-H), 7.91 (1H, s, C_2-H), 8.17 (1H, d, *J*=9.0 Hz, C_5-H). *Anal.* Calcd for $C_{24}H_{27}O_5Br$: C, 60.64; H, 5.72. Found: C, 60.68; H, 5.71.

ii) One pot synthesis from 27. To a solution of ketone (**27**) (3.00 g, 6.45 mmol) in dry benzene (135 mL) was added $Me_2CH(OMe)_2$ (1.7 mL, 12.8 mmol), and the whole mixture was heated at 100 ^oC for 3 h under argon atmosphere. After disappearance of the starting ketone (**27**) on TLC, silica gel (FL100D, 15.00 g) was added to the reaction mixture, and the whole was stirred at rt for 2.3 h. The insoluble material was removed by filtration and washed with AcOEt. The combined filtrate was washed with 3.3% aq. HCl (2 x 60 mL), water (60 mL), and brine (60 mL), dried over $MgSO_4$, and evaporated to dryness *in vacuo* to afford **30** (3.07 g, 100%) as a yellow powder (mp 113-119 ^oC). This compound was identical with the sample prepared from **29** described above.

7,2',4'-Triisopropoxyisoflavone (33). To a solution of 5'-bromoisoflavone (**30**) (0.443 g, 0.93 mmol) and AIBN (0.019 g, 0.12 mmol) in dry toluene (5.3 mL) was added Bu_3SnH (0.43 mL, 1.60 mmol) and the whole mixture was heated at 115 ^oC for 5 h and at 140 ^oC for 1.5 h. For completing the reaction additional reagent was added as follows: Bu_3SnH (0.08 mL, 0.30 mmol) and a trace amount of AIBN in toluene (0.2 mL), 3.5 h, then Bu_3SnH (0.25 mL, 0.93 mmol), AIBN in toluene (2 mL), 1 h. The reaction mixture was diluted with pentane (10 mL) and the soluble fraction was evaporated to dryness *in vacuo* to give a yellow oil (1.406 g). The crude product was purified by column chromatography (hexane, benzene, benzene-AcOEt, 20:1 to 2:1) to yield a pale yellow oil (**33**) (0.358 g, 97%). IR ν_{max} cm^{-1} (neat): 1641(C=O). ^{1}H-NMR (400 MHz) δ: 1.25 [6H, d, *J*=6.0 Hz, CH(C<u>H</u>$_3)_2$], 1.36 [6H, d, *J*=6.0 Hz, CH(C<u>H</u>$_3)_2$], 1.40 [6H, d, *J*=6.0 Hz, CH(C<u>H</u>$_3)_2$], 4.45 [1H, sep, *J*=6.0 Hz, O-C<u>H</u>$(CH_3)_2$], 4.56 [1H, sep, *J*=6.0 Hz, O-C<u>H</u>$(CH_3)_2$], 4.66 [1H, sep, *J*=6.0 Hz, O-C<u>H</u>$(CH_3)_2$], 6.52 (1H, s, $C_{3'}$-H), 6.53 (1H, d, *J*=8.0 Hz, $C_{5'}$-H), 6.83 (1H, d, *J*=2.4 Hz, C_8-H), 6.93 (1H, dd, *J*=8.8, 2.4 Hz, C_6-H), 7.30 (1H, d, *J*=8.0 Hz, $C_{6'}$-H), 7.93 (1H, s, C_2-H), 8.18 (1H, d, *J*=8.8 Hz, C_5-H). HRFAB-MS *m/z*: 397.2024 (Calcd for $C_{24}H_{29}O_5$: 397.2015). EI-MS *m/z*: 396 (M^+, 100%).

5'-Acetyl-7,2',4'-triisopropoxyisoflavone (34). To a solution of isoflavone (**33**) (0.468 g, 1.18 mmol) in CH_2Cl_2 (1.4 mL) was added Ac_2O (0.33 mL, 3.5 mmol) followed by a solution of $SnCl_4$ (0.41 mL, 3.50 mmol) in CH_2Cl_2 (0.7 mL) at -78 ^oC, and the whole mixture was stirred at -40 ^oC for 3 h and at -25 ^oC for 1.5 h. The reaction mixture was poured into water (20 mL) and extracted with CH_2Cl_2 (30 mL, 2 x 10 mL). The organic layer was washed with water (15 mL) and brine (15 mL), dried over $MgSO_4$, and

evaporated to dryness *in vacuo* to afford a yellow solid (0.477 g, 92%). Recrystallization from ether gave acetyl compound (**34**) (0.330 g, 64%) as pale a yellow powder (mp 138-140 ^{o}C). IR ν_{max} cm^{-1} (KBr): 1657, 1639 (C=O). ^{1}H-NMR (400 MHz) δ: 1.30 [6H, d, *J*=6.0 Hz, CH(C<u>H</u>$_3$)$_2$], 1.41 [6H, d, *J*=6.0 Hz, CH(C<u>H</u>$_3$)$_2$], 1.45 [6H, d, *J*=6.0 Hz, CH(C<u>H</u>$_3$)$_2$], 2.60 (3H, s, CO-CH$_3$), 4.56 [1H, sep, *J*=6.0 Hz, O-C<u>H</u>(CH$_3$)$_2$], 4.67 [1H, sep, *J*=6.0 Hz, O-C<u>H</u>(CH$_3$)$_2$], 4.69 [1H, sep, *J*=6.0 Hz, O-C<u>H</u>(CH$_3$)$_2$], 6.48 (1H, s, C$_{3'}$-H), 6.83 (1H, d, *J*=2.4 Hz, C$_8$-H), 6.93 (1H, dd, *J*=9.0, 2.4 Hz, C$_6$-H), 7.78 (1H, s, C$_2$- or C$_{6'}$-H), 7.83 (1H, s, C$_{6'}$- or C$_2$-H), 8.15 (1H, d, *J*=9.0 Hz, C$_5$-H). EI-MS *m/z*: 438 (M$^+$, 29%), 297(100%). *Anal*. Calcd for $C_{26}H_{30}O_6$: C, 71.21; H, 6.90. Found: C, 71.36; H, 7.00.

5'-Hydroxy-7,2',4'-triisopropoxyisoflavone (31)

i) Baeyer-Villiger oxidation. A mixture of 98% HCOOH (0.20 mL, 5.19 mmol) and 30% H_2O_2 (0.14 mL, 1.23 mmol) was stirred at 0 ^{o}C for 1 h. A solution of 5'-acetyisoflavone (**34**) (0.093 g, 0.21 mmol) in 98% HCOOH (0.4 mL) was added to the above solution under ice-cooling, and the whole mixture was stirred at 0 ^{o}C for 4 h. The reaction mixture was poured into a solution of Na_2SO_3 (0.32 g) in water (8 mL) and extracted with ether (3 x 10 mL). The organic layer was washed with water (2 x 10 mL + 2 x 30 mL) and brine (10 mL), dried over $MgSO_4$, and evaporated to dryness *in vacuo* to give acetate (**35**) (0.085 g, 88%) as a yellow oil.

ii) Hydrolysis of acetate (35). To a solution of 5'-acetoxyisoflavone (**35**) (14.4 mg, 0.032 mmol) in anhydrous MeOH (1.8 mL) was added K_2CO_3 (17.5 mg, 0.13 mmol) and the whole mixture was stirred at rt for 3.3 h. The reaction mixture was poured into water (10 mL), acidified (pH 1) with 10% aq. HCl (5 mL) and extracted with AcOEt (3 x 10 mL). The organic layer was washed with water (10 mL) and brine (10 mL), dried over $MgSO_4$, and evaporated to dryness *in vacuo* to afford phenol (**31**) (8.2 mg, 63%) as a pale yellow powder (mp128-136 ^{o}C). Recrystallization from ether gave **31** as colorless prisms (mp 135.5-137 ^{o}C). IR ν_{max} cm^{-1} (Nujol): 3195 (OH), 1637 (C=O). ^{1}H-NMR (400 MHz) δ: 1.18 [6H, d, *J*=6.1 Hz, CH(C<u>H</u>$_3$)$_2$], 1.39 [6H, d, *J*=6.1 Hz,-CH(C<u>H</u>$_3$)$_2$], 1.41 [6H, d, *J*=6.1 Hz, CH(C<u>H</u>$_3$)$_2$], 4.19 [1H, sep, *J*=6.1 Hz, O-C<u>H</u>(CH$_3$)$_2$], 4.56 [1H, sep, *J*=6.1 Hz, O-C<u>H</u>(CH$_3$)$_2$], 4.67 [1H, sep, *J*=6.1 Hz, O-C<u>H</u>(CH$_3$)$_2$], 5.36 (1H, s, OH), 6.58 (1H, s, C$_{3'}$-H), 6.83 (1H, d, *J*=2.2 Hz, C$_8$-H), 6.94 (1H, dd, *J*=8.8, 2.4 Hz, C$_6$-H), 6.98 (1H, s, C$_{6'}$-H), 7.93 (1H, s, C$_2$-H), 8.18 (1H, d, *J*=8.8 Hz, C$_5$-H). EI-MS *m/z*: 412 (M$^+$, 58%), 328 (100%). *Anal.* Calcd for $C_{24}H_{28}O_6$: C, 69.89; H, 6.84. Found: C, 69.73; H, 6.77.

5'-(3-Methyl-2-butenyloxy)-7,2',4'-triisopropoxyisoflavone (36). To a mixture of 5'-hydroxyisoflavone (**31**) (0.199 g, 0.48 mmol), K_2CO_3 (0.173 g, 1.25 mmol) and acetone (5 mL) was added

4-bromo-2-methyl-2-butene (0.17 mL, 1.42 mmol), and the whole mixture was stirred at rt for 17 h under argon atmosphere. The reaction mixture was poured into water (10 mL) and extracted with ether (20 mL + 2 x 10 mL). The organic layer was washed with 2% aq. NaOH (10 mL) and water (10 mL), dried over K_2CO_3, and evaporated to dryness *in vacuo* to afford a brown oil (0.239 g). Recrystallization from pentane gave a pale yellow powder (**36**) (0.177 g, 76%, mp 48-52 ^oC). ^1H-NMR (400 MHz) δ: 1.20 [6H, d, *J*=6.0 Hz, CH(C$\underline{H}_3$)$_2$], 1.36 [6H, d, *J*=6.0 Hz, CH(C$\underline{H}_3$)$_2$], 1.41 [6H, d, *J*=6.0 Hz, CH(C$\underline{H}_3$)$_2$], 1.70 (3H, s, $C_{4''}H_3$), 1.77 (3H, d, *J*=0.7 Hz, $C_{5''}H_3$), 4.26 [1H, sep, *J*=6.0 Hz, O-C$\underline{H}$(CH$_3$)$_2$], 4.51 (2H, d, *J*=6.0 Hz, $C_{1''}H_2$), 4.52 [1H, sep, *J*=6.0 Hz, O-C$\underline{H}$(CH$_3$)], 4.67 [1H, sep, *J*=6.0 Hz, O-C$\underline{H}$(CH$_3$)$_2$], 5.49-5.53 (1H, m, $C_{2''}$-H), 6.61 (1H, s, $C_{3'}$-H), 6.84 (1H, d, *J*=2.4 Hz, C_8-H), 6.95 (1H, dd, *J*=8.9, 2.4 Hz, C_6-H), 7.04 (1H, s, $C_{6'}$-H), 7.99 (1H, s, C_2-H), 8.19 (1H, d, *J*=9.0 Hz, C_5-H). EI-MS *m/z*: 480 (M^+, 24%), 327 (100%).

3'-Hydroxy-2'-(3-methyl-2-butenyl)-7,4',6'-triisopropoxyisoflavone (37). A mixture of isoflavone (**36**) (0.526 g, 1.09 mmol), montmorillonite KSF clay (0.527 g) and dry benzene (11 mL) was stirred at rt for 9.5 days under argon atmosphere. The catalyst was filtered off and washed with AcOEt and MeOH. The combined organic solution was evaporated to dryness *in vacuo* to give a yellow oil (0.549 g). The crude product was purified by silica gel column chromatography (hexane, benzene, benzene-AcOEt, 20:1 to 2:1) to give a colorless powder (**37**) (0.165 g, 31%) together with starting ether (**36**) (0.056 g, 11%) and 5'-hydroxyisoflavone (**31**) (0.161g, 41%). ^1H-NMR (400 MHz) δ: 1.06 [3H, d, *J*=6.1 Hz, CH(C$\underline{H}_3$)$_2$], 1.16 [3H, d, *J*=5.8 Hz, CH(C$\underline{H}_3$)$_2$], 1.35-1.45 [18H, m, CH(C$\underline{H}_3$)$_2$, $C_{4''}H_3$ and $C_{5''}H_3$], 3.04 (1H, dd, *J*=14.3, 7.9 Hz, $C_{1''}$H), 3.39 (1H, dd, *J*=14.3, 6.1 Hz, $C_{1''}$H), 4.13 [1H, sep, *J*=6.1 Hz, O-C$\underline{H}$(CH$_3$)$_2$], 4.55 [1H, sep, *J*=6.1 Hz, O-C$\underline{H}$(CH$_3$)$_2$], 4.68 [1H, sep, *J*=6.1 Hz, O-C$\underline{H}$(CH$_3$)$_2$], 5.08 (1H, br t, *J*=6.5 Hz, $C_{2''}$-H), 5.50 (1H, s, OH), 6.46 (1H, s, $C_{5'}$-H), 6.84 (1H, d, *J*=2.1 Hz, C_8-H), 6.94 (1H, dd, *J*=8.9, 2.1 Hz, C_6-H), 7.74 (1H, s, C_2-H), 8.17 (1H, d, *J*=8.9 Hz, C_5-H). FAB-MS *m/z*: 481 ($[M+H]^+$).

3'-Methoxy-2'-(3-methyl-2-butenyl)-7,4',6'-triisopropoxyisoflavone (38). To a mixture of 3'-hydroxyisoflavone (**37**) (24.6 mg, 0.051 mmol) and K_2CO_3 (141.7 mg, 1.03 mmol) was added a solution of Me_2SO_4 (0.05 mL, 0.53 mmol) in DMF (0.25 mL), and the whole mixture was stirred at rt for 4 h and heated at 50 ^oC for 18 h. The reaction mixture was poured into 5% aq. NH_3 (1 mL) and stirred at rt for 15 min. After dilution with water (10 mL) the reaction mixture was extracted with AcOEt (3 x 10 mL). The orgnic layer was washed with water (15 mL + 2 x 10 mL) and brine (10 mL), dried over $MgSO_4$, and evaporated to dryness *in vacuo* to give oil (28.3 mg). The crude product was purified by preparative TLC (hexane-AcOEt, 7:1) to afford a pale yellow oil (**38**) (22.0 mg, 87%). IR ν_{max} cm^{-1} (neat): 1647

(C=O). ^{1}H-NMR (400 MHz) δ: 1.12 [3H, d, *J*=6.0 Hz, CH(C<u>H</u>$_3$)$_2$], 1.18 [3H, d, *J*=6.0 Hz, CH(C<u>H</u>$_3$)$_2$], 1.38 [6H, d, *J*=5.2 Hz, CH(C<u>H</u>$_3$)$_2$], 1.41 (3H, s, $C_{4''}$-H or $C_{5''}$-H), 1.41 [6H, d, *J*=7.6 Hz, CH(C<u>H</u>$_3$)$_2$], 1.55 (3H, s, $C_{4''}$-H or $C_{5''}$-H), 3.04 (1H, dd, *J*=14.5, 7.5 Hz, $C_{1''}$-H), 3.35 (1H, dd, *J*=14.5, 6.0 Hz, $C_{1''}$-H), 3.79 (3H, s, OMe), 4.26 [1H, sep, *J*=6.0 Hz, O-C<u>H</u>(CH$_3$)$_2$], 4.54 [1H, sep, *J*=6.0 Hz, O-C<u>H</u>(CH$_3$)$_2$], 4.67 [1H, sep, *J*=6.0 Hz, O-C<u>H</u>(CH$_3$)$_2$], 5.01 (1H, br t, *J*=6.0 Hz, $C_{2''}$-H), 6.45 (1H, s, $C_{5'}$-H), 6.83 (1H, d, *J*=2.4 Hz, C_8-H), 6.93 (1H, dd, *J*=9.0, 2.4 Hz, C_6-H), 7.62 (1H, s, C_2-H), 8.16 (1H, d, *J*=9.0 Hz, C_5-H). HRFAB-MS *m/z*: 494.2625 (Calcd for $C_{30}H_{38}O_6$: 494.2669). EI-MS *m/z*: 494 (M^+, 100%).

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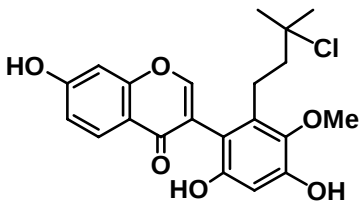
15. Trials for deisopropylation of **38**: i) With 0.1 M BCl_3 / CH_2Cl_2: HCl-adduct (**39**). A pale pink powder. ^{1}H-NMR (400 MHz) δ: 1.42 (3H, s, -CH_3), 1.48 (3H, s, -CH_3), 1.79 (1H, m, $C_{2''}$-H), 1.88 (1H, m, $C_{2''}$-H), 2.63 (1H, m, $C_{1''}$-H), 2.73 (1H, m, $C_{1''}$-H), 3.80 (3H, s, -OCH_3), 6.42 (1H, s, $C_{3'}$-H), 6.85 (1H, s, C_8-H), 6.92 (1H, m, C_6-H), 7.82 (1H, s, C_2-H), 8.09 (1H, d, *J*=8.8 Hz, C_5-H); ii) With 0.1 M BCl_3 / CH_2Cl_2 and 2-methyl-2-butene: partially deprotected product (**40**). A pale yellow powder. ^{1}H-NMR (400 MHz) δ: 1.39-1.43 [12H, m, CH(C<u>H</u>$_3$)$_2$], 1.49 [3H, s, C=C(CH_3)$_2$], 1.58 [3H, s, C=C(CH_3)$_2$], 3.16 (1H, dd, *J*=15.4, 7.1 Hz, $C_{1''}$-H_a), 3.36 (1H, dd, *J*=15.4, 4.2 Hz, $C_{1''}$-H_b), 4.56 [1H, sep, *J*=5.9 Hz, O-C<u>H</u>(CH_3)$_2$], 4.70 [1H, sep, *J*=5.9 Hz, O-C<u>H</u>(CH_3)$_2$], 5.10 (1H, dd, *J*=7.1, 4.2 Hz, $C_{2''}$-H), 6.55 (1H, s, $C_{5'}$-H), 6.88 (1H, d, *J*=2.4 Hz, C_8-H), 7.00 (1H, dd, *J*=9.0, 2.4 Hz, C_6-H), 7.87 (1H, s, C_2-H), 8.21 (1H, d, *J*=9.0 Hz, C_5-H); iii) With $MeSO_3H$: chroman (**41**). A yellow powder. ^{1}H-NMR (400 MHz, $CDCl_3$ + CD_3OD) δ: 1.28 (3H, s, CH_3), 1.30 (3H, s, CH_3), 1.68 (2H, t, *J*=6.7 Hz, C_3-H), 2.46 (2H, t, *J*=6.7 Hz, C_4-H), 6.39 (1H, s, C_7-H), 6.80 (1H, d, *J*=2.2 Hz, C_8-H), 6.87 (1H, dd, *J*=8.8, 2.2 Hz, C_6-H), 7.78 (1H, s, C_2-H), 8.03 (1H, d, *J*=8.8 Hz, C_5-H). EI-MS *m/z*: 354 (M^+, 49%), 137 (100%).

    It was noteworthy that in ^{1}H-NMR spectra these products (**39**) and (**41**) were identical with the compounds obtained from kwakhurin (**5**) with hydrochloric acid by Tahara and Ingham.[3b)]



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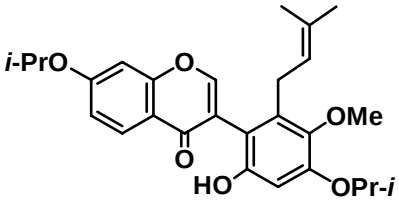

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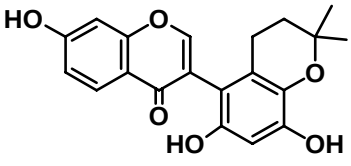

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