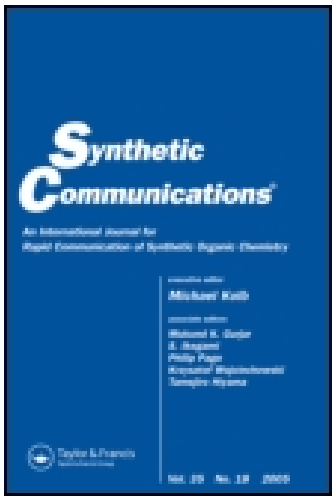

Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

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Published online: 16 Aug 2006.

To cite this article: Wiesław Szeja, Gabriela Pastuch, Ilona Wandzik, Nikodem Kuźnik & Grzegorz Grynkiewicz (2003) Synthesis of Selectively Protected Genistein Derivatives, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 33:23, 4111-4121, DOI: 10.1081/SCC-120026353

To link to this article: http://dx.doi.org/10.1081/SCC-120026353

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SYNTHETIC COMMUNICATIONS®
Vol. 33, No. 23, pp. 4111–4121, 2003

Synthesis of Selectively Protected Genistein Derivatives

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ABSTRACT

Differential functionalization of the phenolic groups in Genistein by sequential silylation/acylation reactions, involving some unexpected regioselective *O*-silyl group replacement, is described.

Key Words: Genistein; Silylation; Acylation.

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DOI: 10.1081/SCC-120026353 0039-7911 (Print); 1532-2432 (Online)

INTRODUCTION

Genistein **1** is a secondary metabolite of plant origin, belonging to the isoflavone family, which evokes great interest because of its pleiotropic biological activity and possible applications in therapy and chemoprevention.[1–4] While studies of the biological activity of **1** are plentiful (several 100 s of articles annually), its chemistry has attracted relatively little attention, possibly because of scarce availability of the substance. Although natural sources of **1** are rich and renewable (cultivation of soy; *Glycine max* Merril), inherent problems connected with the separation of complex mixtures of related natural products seem to favor chemical synthesis as a base for future product development. Nevertheless, general methods for isoflavone synthesis are not automatically applicable to polyphenolic products and genistein (a triphenol) is an example of the synthetic target for which temporary blocking of phenolic function is advisable for efficient construction of chromenone ring system.[5]

RESULTS AND DISCUSSION

Since the need for regioselective protection of phenolic group in multifunctional natural compounds is a recurrent theme in their synthesis as well as in subsequent derivatization, we were tempted to apply simple synthetic means, consisting of sequential silylation/acylation reactions for differentiation of phenolic functions in **1**. As a result of this approach a small collection of previously unreported derivatives of **1** (Figure 1), listed in the following Table 1, has been generated. In the course of the study we have observed unexpected differences in reactivity of regioisomeric *tert*-butyldimethylsilyl protecting groups, which shed new light on their possible application in chemistry of polyphenolic substrates.

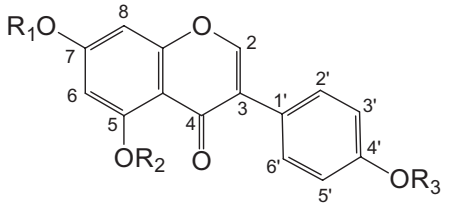


Figure 1. Genistein ($R_1 = R_2 = R_3 = H$) **1** and its derivatives.

Table 1. Summary of selectively functionalized derivatives of genistein (**1**).

Compound no.	R_1	R_2	R_3	
1	H	H	H	Genistein
2	*t*-BDMS	H	H	7-*O*-*t*-BDMS-**1**
3	H	H	*t*-BDMS	4′-*O*-*t*-BDMS-**1**
4	*t*-BDMS	H	*t*-BDMS	4′,7-Di-*O*-*t*-BDMS-**1**
5	Ac	Ac	*t*-BDMS	5,7-Di-OAc-4′-*O*-*t*-BDMS-**1**
6	Ac	Ac	H	5,7-Di-OAc-**1**
7	Ac	H	*t*-BDMS	7-OAc-4′-*O*-*t*-BDMS-**1**
8	*t*-BDMS	Ac	*t*-BDMS	5-OAc-4′,7-di-*O*-*t*-BDMS-**1**
9	*t*-BDMS	H	Ac	7-*O*-*t*-BDMS-4′-*O*-Ac-**1**
10	*t*-BDMS	Bz	*t*-BDMS	5-OBz-4′,7-di-*O*-*t*-BDMS-**1**
11	Bz	H	*t*-BDMS	7-OBz-4′-*O*-*t*-BDMS-**1**
12	Bz	Bz	*t*-BDMS	5,7-Di-OBz-4′-*O*-*t*-BDMS-**1**
13	Bz	Ac	*t*-BDMS	5-OAc-7-OBz-4′-*O*-*t*-BDMS-**1**

Ac—acetyl, *t*-BDMS—*tert*-butyldimetylsilyl, Bz—benzoyl.

Previous attempts at selective functionalization of **1** by action of electrophilic reagents exploited differences in acidity of 7-OH and 4′-OH and reversed nucleophilicity of the corresponding anions.[6,7] Although acidity constants for particular phenol groups in **1** seem to be a way apart in solution, (at least two orders of magnitude as calculated for 7-OH and 4′-OH) lack of solubility of genistein and some of its salts can complicate an issue of selective reactivity for example in the case of phase transfer reactions. In fact, it has been demonstrated with the help of X-ray crystallography and molecular modeling, that basic nitrogen interactions with less acidic phenolic groups also contribute significantly to the structure of molecular complexes between genistein and amines.[8,9]

In keeping with the above, our provisional notion that all three phenolic groups in **1** are sufficiently different in terms of ionization constants to be easily distinguishable by action of any electrophilic reagent was not supported by experiments. In fact upon direct action of acylating, alkylating, and glycosylating reagents on **1** in the presence of various basic reagents, low regioselectivity was observed, resulting in formation of at least two mono substituted derivatives, accompanied by a doubly functionalized product. Since such reaction mixtures proved rather difficult to separate, an idea of temporary protecting group securing complete regioselective placement of the desired substituent was put forward. *tert*-Butyldimethylsilyl group was chosen for our study on the ground of the well-known facility of its introduction and removal as well

as its compatibility with various derivatizing procedures.[10,11] Treatment of **1** with one molar equivalent of *tert*-butyldimethylsilyl chloride under a variety of conditions, including phase-transfer catalysis, resulted invariably in mixtures of 4′-*O*- and 7-*O*-substituted silyl derivatives of **1** (respectively **2** and **3**). Under more rigorous conditions degradation of the substrate was also observed, due to the isoflavone heterocyclic ring cleavage in the presence of strong bases. On the other hand, reaction of **1** with two molar equivalents of *tert*-butyldimethylsilyl chloride in the presence of imidazole in DMF as a solvent resulted in formation in good yield of a single derivative, which was identified as 7,4′-di-*O*-*t*-BDMS genistein **4**. This derivative is perceived as a suitable precursor for 5-*O*-acylated genistein derivatives, which are not available, by direct functionalization procedures.

Acetylation of **4** under standard conditions with acetic anhydride—pyridine gave unexpectedly selectively desilylated diacetyl derivative **5** and monoacetyl compound **7**, as summarized in Table 2. Using an excess of acetyl anhydride (4 equiv.) and prolonging the reaction time resulted in isolation of compound **5** as the only product in high yield (Entry 3). A similar result was observed in reaction of **4** with less reactive benzoic anhydride (Entry 5). The only product isolated was 7-monobenzoate **11** which after subsequent acetylation yielded protected compound **13** (Entry 7), providing an example of fully differentiated functionalization of all phenolic groups. Desilylation of **5** (Bu_4NF, THF) resulted in formation of genistein derivative **6**, with 4′-OH hydroxyl group unprotected (Sch. 1).

An attempt to acylate compound **4** by phthalic anhydride under analogous conditions was unsuccessful, leading to the product of regioselective deprotection of 7-OH, instead of expected hemiester. This procedure, an alternative for treatment with mildly acidic medium, offers an advantage for preparation of 4′-*O*-silylated genistein derivative **3** over direct equimolar silylation of **1**. Compound **3** was identified by NMR analysis of the monosilylation reaction mixture as the minor constituent, which could not be isolated in pure state. This compound is considered an important intermediate, allowing for selective 7-OH derivatization of **1**, due to much lower reactivity of the intramolecular bonded therefore noncompeting, 5-OH group.

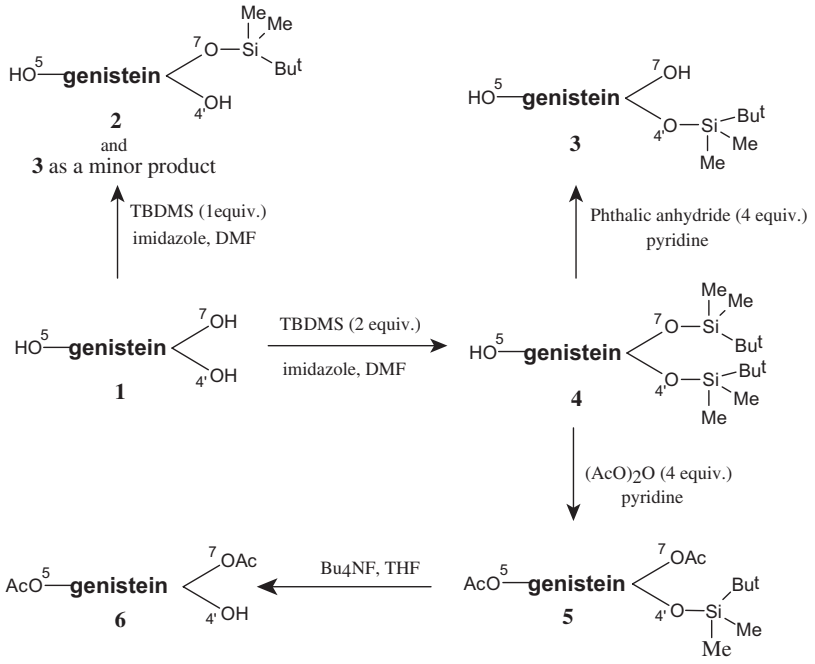
All described compounds were identified with the aid of ^{1}H NMR spectroscopy. The site of silyl substitution can be easily deduced from chemical shifts of singlet representing six protons of two methyl groups in silyl function. Mentioned protons in mono-7-*O*-*t*-BDMS genistein (**2**) resonate at lower field than those at mono 4′-*O*-*t*-BDMS genistein (**3**). Typical values are δ 0.275 and 0.215 ppm. Confirmation of the structure

Table 2. Acylation of silylated genistein derivatives **2**, **3**, **4**, and **11**.

Entry	Substrate	Acylating reagent	Reaction time (h)	Product	Yield (%)
1	**4**	$(AcO)_2O$ (2 equiv.)	24	**5** **7**	62 30
2	**4**	$(AcO)_2O$ (4 equiv.)	20	**5** **7**	55 27
3	**4**	$(AcO)_2O$ (4 equiv.)	96	**5**	85
4	**4**	AcCl (4 equiv.)	24	**8** **5**	49 12
5	**4**	$(BzO)_2O$ (2 equiv.)	24	**11**	64
6	**4**	BzCl (4 equiv.)	24	**10** **12**	51 29
7	**4**	Phthalic anh. (4 equiv.)	96	**3**	45
8	**2** (15% of **3**)	$(AcO)_2O$ (4 equiv.)	24	A mixture of acetylated **1**	—
9	**2** (15% of **3**)	AcCl (2 equiv.)	24	**9** **7**	80 11
10	**3**	$(AcO)_2O$ (4 equiv.)	96	**5**	82
11	**11**	$(AcO)_2O$ (3 equiv.)	24	**13**	51

of compound **3** was provided equivocally by X-ray crystallographic analysis (Fig. 2).[12]

Outcomes of acetylation reactions of both monosilylated derivatives of genistein with acetic anhydride differ dramatically. Thus **3** gave product **5**, whereas acetylation of **2** resulted in desilylation followed by esterification, providing a mixture of di- and tri-*O*-acetyl derivatives. Quite remarkably, the 7-*O*-silyl group in **2** can be exchanged or retained, depending on choice of the acetylating reagent. Thus, acetylation of **2** with acetyl chloride afforded derivative **9** in a good yield.



Scheme 1.

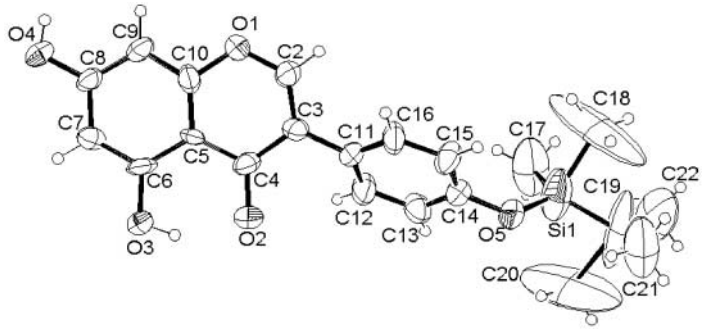


Figure 2. X-ray structure of **3**.

In summary, although direct selective monosilylation of genistein proved rather difficult to achieve under standard conditions, it has been demonstrated that complete differentiation of all three phenolic groups in **1** is possible, in a stepwise manner, via 7,4′-di-*O*-silyl derivative **4**.

The described direct and regioselective transformation of 7-*O*-silyl group under treatment of **4** with acyl anhydrides in pyridine, is to our knowledge, without a precedent. It is worth noting that this new transformation opens a simple way for the preparation of various selectively substituted derivatives of genistein.

EXPERIMENTAL

Elemental analyses were performed on a Perkin–Elmer 2400 analyzer. ^{1}H NMR spectra were recorded for solutions in $CDCl_3$, or $(CD_3)_2SO$ (internal Me_4Si) on Varian 300 MHz spectrometer. Melting points were determined in capillaries and are uncorrected. Reactions were monitored by TLC on precoated plates of silica gel 60 (70–230 mesh, Merck), components were indicated with ultraviolet light after heating. Chromatographic purification was performed on silica gel 60, Merck (0.063–0.2 mm).

Silylation of Genistein (1)

Imidazole (2.72 g, 40 mmol) and *tert*-butyldimethylsilyl chloride (3.3 g, 22 mmol) were added to a solution of genistein **1** (2.7 g, 10 mmol) in anhydrous DMF (30 mL). The mixture was stirred for 1.5 h at room temperature. Then the reaction mixture was diluted with toluene (200 mL) and washed with water (2×50 mL). The water layer was additionally extracted with methylene chloride (50 mL). All organic extracts were dried (magnesium sulfate), filtered, and concentrated under diminished pressure. Purification by column chromatography (hexane/ethyl acetate, 20:1, v/v) of the resulting yellow solid (5.34 g) gave product **4** (4.19 g, 84% yield) and mixture of **2** and **3** (0.26 g, 6% yield).

7-*t*-Butyldimethylsilyloxy-5-hydroxy-3-(4′-hydroxyphenyl)-chromen-4-one (2). ^{1}H NMR ($CDCl_3$) δ: 0.28 (s, 6H, CH_3), 0.99 (s, 9H, $(CH_3)_3C$), 5.29 (s, 1H, 4′-OH), 12.92 (s, 1H, 5-OH).

5,7-Dihydroxy-3-[4′-(*t*-butyldimethylsilyloxy)phenyl]-chromen-4-one (3). Yellow crystals. M.p.: 199–201°C. Anal. calcd. for $C_{21}H_{24}O_5Si$ (384.50): C, 65.60; H, 6.29. Found: C, 65.45; H, 6.27. ^{1}H NMR ($CDCl_3$) δ: 0.22 (s, 6H, CH_3), 0.99 (s, 9H, $(CH_3)_3C$), 6.03 (s, 1H, 7-OH), 12.92 (s, 1H, 5-OH).

7-*t*-Butyldimethylsilyloxy-5-hydroxy-3-[4′-(*t*-butyldimethylsilyloxy)-phenyl]-chromen-4-one (4). Yellow crystals. M.p.: 86–88°C. Anal. calcd. for $C_{27}H_{38}O_5Si_2$ (498.76): C, 65.02; H, 7.68. Found: C, 65.17;

H, 7.42. ^{1}H NMR ($CDCl_3$) δ 0.23 (s, 6H, CH_3), 0.28 (s, 6H, CH_3), 0.99 (s, 18H, $(CH_3)_3C$), 6.31 (d, 1H, H-6, $J = 2.2$ Hz), 6.35 (d, 1H, H-8, $J = 2.2$ Hz), 6.91 (d, 2H, H-3′, H-5′, $J = 8.6$ Hz), 7.39 (d, 2H, H-2′, H-6′, $J = 8.6$ Hz), 7.86 (s, 1H, H-2), 12.82 (s, 1H, 5-OH).

General Procedures for the Acylation

Procedure A

Acyl anhydride:acetic, benzoic, or phthalic (2–4 equiv. as listed in Table 2) was added to a solution of genistein derivative **2**, **3**, **4**, or **11** (2 mmol) in anhydrous pyridine (5 mL). The mixture was stirred for 20–96 h at room temperature (as listed in Table 2). The reaction mixture was then diluted with toluene (30 mL) and washed with cold water (3×15 mL). Organic layer was dried (magnesium sulfate), filtered and concentrated under diminished pressure. The resulting solid was chromatographed on a column of silica gel (hexane/ethyl acetate, 15:1, v/v). The following compounds were obtained:

7-Acetoxy-5-acetoxy-3-[4′-(*t*-butyldimethylsilyloxy)phenyl]-chromen-4-one (5). White crystals. M.p.: 126–128°C. Anal. calcd. for $C_{25}H_{28}O_7Si$ (468.57): C, 64.08; H, 6.02. Found: C, 64.16; H, 6.25. ^{1}H NMR ($CDCl_3$) δ: 0.21 (s, 6H, CH_3), 0.99 (s, 9H, $(CH_3)_3C$), 2.34 (s, 3H, CH_3CO), 2.42 (s, 3H, CH_3CO), 6.84 (d, 1H, H-8, $J = 2.4$ Hz), 6.87 (d, 2H, H-3′, H-5′, $J = 8.6$ Hz), 7.23 (d, 1H, H-6, $J = 2.4$ Hz), 7.34 (d, 2H, H-2′, H-6′, $J = 8.6$ Hz), 7.85 (s, 1H, H-2).

7-Acetoxy-5-hydroxy-3-[4′-(*t*-butyldimethylsilyloxy)phenyl]-chromen-4-one (7). Light yellow crystals. M.p.: 145–147.5°C. Anal. calcd. for $C_{23}H_{26}O_6Si$ (426.53): C, 64.77; H, 6.14. Found: C, 64.48; H, 6.02. ^{1}H NMR ($CDCl_3$) δ: 0.23 (s, 6H, CH_3), 1.00 (s, 9H, $(CH_3)_3C$), 2.33 (s, 3H, CH_3CO), 6.58 (d, 1H, H-6, $J = 2.2$ Hz), 6.75 (d, 1H, H-8, $J = 2.2$ Hz), 6.92 (d, 2H, H-3′, H-5′, $J = 8.6$ Hz), 7.40 (d, 2H, H-2′, H-6′, $J = 8.6$ Hz), 7.94 (s, 1H, H-2), 12.85 (s, 1H, 5-OH).

7-Benzoyloxy-5-hydroxy-3-[4′-(*t*-butyldimethylsilyloxy)phenyl]-chromen-4-one (11). Light yellow crystals. M.p.: 164–166°C. Anal. calcd. for $C_{28}H_{28}O_6Si$ (488.60): C, 68.83; H, 5.78. Found: C, 68.99; H, 5.54. ^{1}H NMR ($CDCl_3$) δ: 0.23 (s, 6H, CH_3), 1.00 (s, 9H, $(CH_3)_3C$), 6.71 (d, 1H, H-6, $J = 2.0$ Hz), 6.87 (d, 1H, H-8, $J = 2.0$ Hz), 6.92 (d, 2H, H-3′, H-5′, $J = 8.4$ Hz), 7.41 (d, 2H, H-2′, H-6′, $J = 8.4$ Hz), 7.51 (m, 2H, *m*-C_6H_5), 7.65 (m, 1H, *p*-C_6H_5), 7.94 (s, 1H, H-2), 8.18 (m, 2H, *o*-C_6H_5), 12.89 (s, 1H, 5-OH).

7-Benzoyloxy-5-acetoxy-3-[4′-(*t*-butyldimethylsilyloxy)phenyl]-chromen-4-one (13). White crystals. M.p.: 117–120°C. Anal. calcd. for $C_{30}H_{30}O_7Si$ (530.64): C, 67.90; H, 5.70. Found: C, 68.28; H, 6.07. ^{1}H NMR ($CDCl_3$) δ: 0.22 (s, 6H, CH_3), 1.00 (s, 9H, $(CH_3)_3C$), 2.44 (s, 3H, CH_3CO), 6.89 (d, 2H, H-3′, H-5′, $J = 8.8$ Hz), 6.99 (d, 1H, H-6, $J = 2.2$ Hz), 7.36 (m, 3H, H-8, H-2′, H-6′), 7.55 (m, 2H, *m*-C_6H_5), 7.69 (m, 1H, *p*-C_6H_5), 7.88 (s, 1H, H-2), 8.20 (m, 2H, *o*-C_6H_5).

Procedure B

Acyl chloride: acetyl or benzoyl (2–4 equiv. as listed in Table 2) was added to a solution of genistein derivative **2** or **4** (2 mmol) in anhydrous pyridine (5 mL). The mixture was stirred for 24 h at room temperature. The reaction mixture was then diluted with toluene (30 mL) and washed with cold water (3×15 mL). Organic layer was dried (magnesium sulfate), filtered, and concentrated under diminished pressure. The resulting solid was chromatographed on a column of silica gel (hexane/ethyl acetate, 15:1, v/v). The following compounds were obtained:

7-*t*-Butyldimethylsilyloxy-5-acetoxy-3-[4′-(*t*-butyldimethylsilyloxy)-phenylo]-chromen-4-one (8). White crystals. M.p.: 91–94°C. Anal. calcd. for $C_{29}H_{40}O_6Si_2$ (540.80): C, 64.41; H, 7.46. Found: C, 64.67; H, 7.39. ^{1}H NMR ($CDCl_3$) δ: 0.21 (s, 6H, CH_3), 0.28 (s, 6H, CH_3), 0.99 (s, 18H, $(CH_3)_3C$), 2.41 (s, 3H, CH_3CO), 6.53 (d, 1H, H-6, $J = 2.4$ Hz), 6.74 (d, 1H, H-8, $J = 2.4$ Hz), 6.86 (d, 2H, H-3′, H-5′, $J = 8.6$ Hz), 7.33 (d, 2H, H-2′, H-6′, $J = 8.6$ Hz), 7.78 (s, 1H, H-2).

7-*t*-Butyldimethylsilyloxy-5-hydroxy-3-(4′-acetoxyphenyl)-chromen-4-one (9). Light yellow crystals. M.p.: 119–121°C. Anal. calcd. for $C_{23}H_{26}O_6Si$ (426.53): C, 64.77; H, 6.14. Found: C, 64.60; H, 6.28. ^{1}H NMR ($CDCl_3$) δ: 0.27 (s, 6H, CH_3), 0.99 (s, 9H, $(CH_3)_3C$), 2.32 (s, 3H, CH_3CO), 6.32 (d, 1H, H-6, $J = 2.4$ Hz), 6.36 (d, 1H, H-8, $J = 2.0$ Hz), 7.16 (d, 2H, H-3′, H-5′, $J = 8.6$ Hz), 7.54 (d, 2H, H-2′, H-6′, $J = 8.6$ Hz), 7.88 (s, 1H, H-2), 12.73 (s, 1H, 5-OH).

7-*t*-Butyldimethylsilyloxy-5-benzoyloxy-3-[4′-(*t*-butyldimethylsilyloxy) phenyl]-chromen-4-one (10). White crystals. M.p.: 148–152°C. Anal. calcd. for $C_{34}H_{42}O_6Si_2$ (602.86): C, 67.74; H, 7.02. Found: C, 68.32; H, 7.39. ^{1}H NMR ($CDCl_3$) δ: 0.17 (s, 6H, CH_3), 0.30 (s, 6H, CH_3), 0.96 (s, 9H, $(CH_3)_3C$), 1.01 (s, 9H, $(CH_3)_3C$), 6.65 (d, 1H, H-6, $J = 2.4$ Hz), 6.78 (d, 1H, H-8, $J = 2.4$ Hz), 6.80 (d, 2H, H-3′, H-5′, $J = 8.5$ Hz), 7.30 (d, 2H, H-2′, H-6′, $J = 8.5$ Hz), 7.44-7.64 (m, 3H, *m*-C_6H_5, *p*-C_6H_5), 7.79 (s, 1H, H-2), 8.22–8.26 (m, 2H, *o*-C_6H_5).

7-Benzoyloxy-5-benzoyloxy-3-[4′-(*t*-butyldimethylsilyloxy)phenyl]-chromen-4-one (12). White crystals. M.p.: 97–100°C. Anal. calcd. for $C_{35}H_{32}O_7Si$ (592.71): C, 70.92; H, 5.44. Found: C, 71.23; H, 5.11. ^{1}H NMR ($CDCl_3$) δ: 0.17 (s, 6H, CH_3), 0.97 (s, 9H, $(CH_3)_3C$), 6.83 (d, 2H, H-3′, H-5′, $J = 8.6$ Hz), 7.11 (d, 1H, H-8, $J = 2.4$ Hz), 7.33 (d, 2H, H-2′, H-6′, $J = 8.6$ Hz), 7.42 (d, 1H, H-6, $J = 2.4$ Hz), 7.47–7.71 (m, 6H, *m*-C_6H_5, *p*-C_6H_5), 7.88 (s, 1H, H-2), 8.20–8.28 (m, 4H, *o*-C_6H_5).

Desilylation of Genistein Derivative 5

Seventy-Five percent water solution of Bu_4NF (0.53 mL, 1.6 mmol) was added to a solution of genistein derivative **5** (0.8 g, 1.6 mmol) in THF (20 mL). The mixture was stirred 2 min at room temperature. Then the reaction mixture was diluted with methylene chloride (50 mL) and washed with water (20 mL). Organic layer was dried (magnesium sulfate), filtered, and concentrated under diminished pressure. Purification by column chromatography (hexane/ethyl acetate, 5:1, v/v) of the resulting solid gave product **6** (0.3 g, 53% yield) as white crystals.

5,7-Diacetoxy-3-(4′-hydroxyphenyl)-chromen-4-one (6). White crystals. M.p.: 189–192°C. Anal. calcd. for $C_{19}H_{14}O_7$ (354.31): C, 64.41; H, 3.98. Found: C, 64.18, H, 4.22. ^{1}H NMR ($(CD_3)_2SO$) δ: 2.28 (s, 3H, CH_3CO), 2.29 (s, 3H, CH_3CO), 6.60 (d, 1H, H-6, $J = 2.4$ Hz), 6.80 (d, 1H, H-8, $J = 2.4$ Hz), 7.21 (d, 2H, H-3′, H-5′, $J = 8.6$ Hz), 7.50 (d, 2H, H-2′, H-6′, $J = 8.6$ Hz), 8.36 (s, 1H, H-2), 11.19 (s, 1H, 4′-OH).

ACKNOWLEDGMENT

Partial financial support of the State Committee for Scientific Research (KBN, grant 4 T09A 075 23) is gratefully acknowledged.

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12. Crystallographic data for **3**: $C_{21}H_{24}O_5Si$, $M = 385.50$, monoclinic, space group $P2_1/n$, $a = 8.152(2)$, $b = 7.819(2)$, $c = 33.453(7)$ Å, $\beta = 92.25(3)^\circ$, $U = 2130.7(7)$ Å^3, $Z = 4$, $T = 293(2)$ K, $\mu(Mo\text{-}K\alpha) = 0.14$ mm^{-1}, $D_c = 1.20$, 2630 reflections measured, of which 2576 independent ($R_{int} = 0.1573$) $R_f = 0.0560$ [657 data $F_o > 4\sigma(F_o)$], $wR(F^2) = 0.1643$, $S = 0.856$. Largest residual density peak (0.30 eÅ^{-3}) is located close to atom Si1 (0.33 Å). Crystallographic data for the structure reported in this article have been deposited with the Cambridge Crystallographic Data Centre as deposition No. CCDC 200812. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, U.K. [Fax: +44(0)1223 336033; E-mail: deposit@ccdc.cam.ac.uk].

Received in Poland April 17, 2003

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