HETEROCYCLES, Vol. 106, No. 8, 2023, pp. 1373 - 1384. © 2023 The Japan Institute of Heterocyclic Chemistry
Received, 22nd May, 2023, Accepted, 16th June, 2023, Published online, 19th June, 2023
DOI: 10.3987/COM-23-14868

SELECTIVE PROTECTION AND DE-PROTECTION OF PHENOLIC HYDROXY GROUPS OF NARINGENIN

Xiaolong Hu[1,2,3] and Guo-Chun Zhou[1,3]*

[1] School of Pharmaceutical Sciences, Nanjing Tech University, Nanjing 211816, Jiangsu, China

[2] College of Biotechnology and Pharmaceutical Engineering, Nanjing Tech University, Nanjing 211816, Jiangsu, China

[3] Xitaihu Lake Industrial College, Nanjing Tech University, Changzhou 213149, Jiangsu, China

* Corresponding author: gczhou@njtech.edu.cn

Abstract – Naringenin (**1**, Scheme 1) is a flavanone belonging to a part of a huge group of bioactive polyphenols. In order to selectively modify desired phenol/s, in this study, we developed some methods for selective protections of three hydroxy groups of **1**. The 1st method was to silylate two hydroxy groups of **1** and then selectively de-protect the silylation product followed by site-selective acetylation, or site-selective silylation of 7-OH and then acetylation of 4'-OH. The 2nd synthetic method was started from triacetyloxylated naringenin (**10**), which was conducted in specific solvents to remove the distinctive acetyl protection by TFA, TsOH or imidazole. After protection of 4',5-dihydroxynaringenin **(12)** by TBS at 7-OH to form 7-*t*-butyldimethylsilyloxy-4',5-diacetyloxynaringenin **(13)**, in the 3rd method, 4'-OAc or 5-OAc of **13** was selectively de-protected under acidic conditions to afford 4'-OH-5-OAc-7-OTBS naringenin (**14**) or 4'-OAc-5-OH-7-OTBS naringenin (**6**) as mixed protection derivatives. These methods have the advantages of mild reaction conditions, easily handled reagents and satisfactory yields.

Naringenin (**1**, Scheme 1), a flavanone (dihydrogen flavonoid) named as 4',5,7-trihydroxyflavanone, and its glycosylated forms exist in many natural plants such as grapefruit, sour orange, tart cherries, tomatoes, and grapes. It belongs to the group of flavonoids, which are a part of a huge group of polyphenols. Naringenin has a broad-spectrum bioactivity, such as anti-cancer,[1-4] skeletal protective effect,[5,6] anti-diabete,[3,7] anti-hypertension[3,7] anti-Alzheimer's disease (AD),[8-10] anti-Parkinson disease (PD),[9,10] treatment

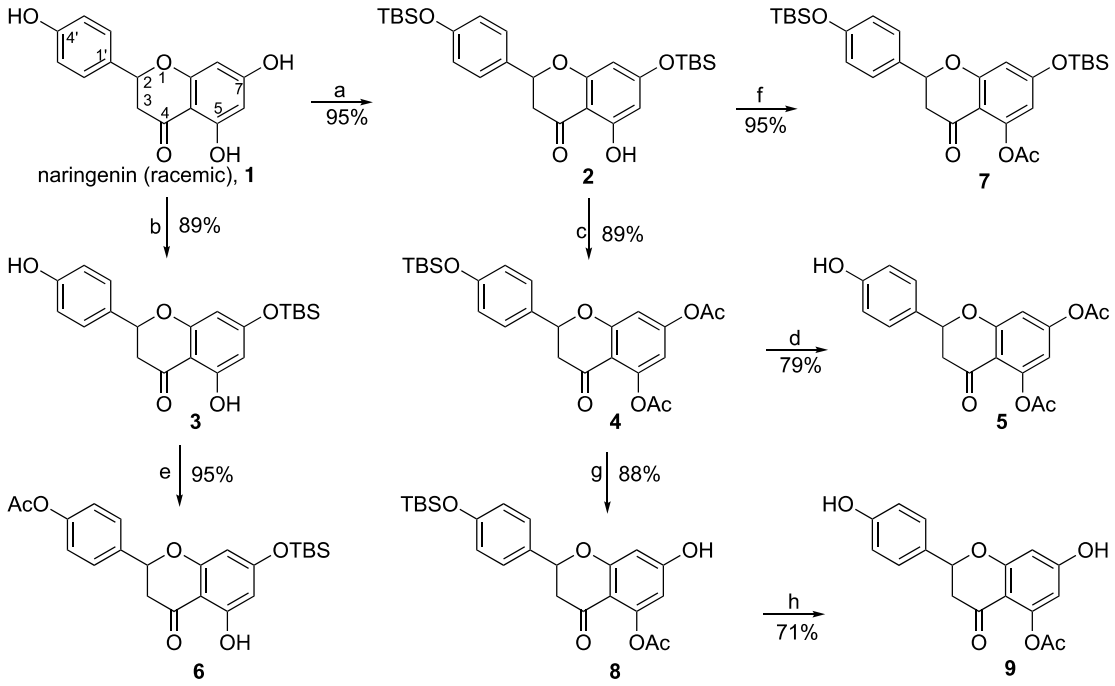
of non-alcoholic fatty liver disease,[11,12] anti-bacteria and anti-fungi.[13] Low bioavailability of naringenin has been a major drawback in optimally obtaining its beneficial effects,[3] which drove many studies to discover more potent naringenin derivatives with ideal bioavailability. Naturally abundant naringin is a 7-diglycosylated product of naringenin (4',5-dihydroxyflavanone-7-*O*-rhamnoglucoside) while prunin is a natural 7-glycosylated product of naringenin (4',5-dihydroxyflavanone-7-*O*-glucoside). Both of naringin and prunin are important bioactive flavonoids, such as antibacterial active agents.[14] Prunin can be practically converted from naringin by partial hydrolysis.[15] Prunin was recently discovered as an anti-HEVA-71 agent.[16] As a polyphenolic compound, modification at 4'-, 5- or/and 7-positions can produce many functionally specialized derivatives. (−)-Naringenin 4',7-dimethyl ether isolated from *Nardostachys jatamansi* DC, a traditional analgesic medicinal plant, was ascribed to its direct suppression of nociceptive neuron excitability;[17] synthesized 4'-, 7-, or 4',7-*O*-alkyl derivatives of naringenin showed antimicrobial activity against multidrug-resistant bacteria.[18] 4',5,7-*O*-Pyrazine methylene derivatives of naringenin showed anti-tumour effects.[19] 7-Benzylpiperazine substituted derivatives of naringenin can prevent glioblastoma invasion[20] while 4',7-*O*-alkylamine derivatives of naringenin were found to be multifunctional agents for the treatment of AD.[21] 4',7-Biscarbamate[22] and 4',5,7-tricarbamate[23] derivatives of naringenin can be as potential multifunctional agents for the treatment of AD. These reports indicate that modifications at different hydroxy groups of naringenin are important for the drug development of naringenin and how to selectively prepare one or two specific free hydroxy groups is the key.

Selective modification of one or two hydroxy groups of a polyphenolic compound is a frequently encountered problem. Kim and co-workers[24] established methylation, benzoylation, silylation and corresponding de-protections of naringenin and apigenin. General modification on 4',5,7-triacetylated form of naringenin[25-27] is starting from site-selective de-protection of 7-acetyl (Ac) group. Looker et al.[28] reported imidazole-mediated de-acetylation of 7-OAc of 4',5,7-triacetylated naringenin in 1964. Imidazole alone[25] and the combination of imidazole with thiophenol (PhSH)[26] can successfully remove acetate group at 7-position. However, selective de-acetylation at 7-position by imidazole alone is sometimes not a complete reaction while PhSH is a very toxic and notorious chemical. The combination of K_2CO_3 in methanol (MeOH)/dichloromethane (DCM) (1/1)[27] is a good choice which can selectively make de-acetylation at 7-position of 4',5,7-triacetyloxynaringenin. Yamashita et al.[25] reported that de-acetylation at 7-position of 4',5,7-triacetyloxynaringenin was achieved in 80% yield by imidazole in dioxane; meanwhile, 82% yield of the 4'-free phenol-5,7-diacetyloxynaringenin from 4',5,7-triacetyloxynaringenin was conducted by Novozym 435 (*Candida antarctica* lipase B) in isopropanol and tetrahydrofuran (THF).[25] One report[29] for site-selective acylation of phenols of naringenin and similar natural products with BINOL-derived phosphoric acids provided 4'-OAc/7-OAc (1/7 ratio) products. It was previously reported that piperidine (2.0 eq)/potassium carbonate (0.1 eq) can selectively de-acetylate at 5-position of 4',5-diacetyloxy-7-

benzyloxynaringenin (1.0 eq)[30] to provide 5-free phenol-4',7-diacetyloxynaringenin (higher than 80% yield). In order to have more choices to modify at different position, in this study, we conduct our further study to develop and establish more methods to prepare one or two specific free phenol group/s.

The property of a distinctive phenol of naringenin is affected by its structural environment, such as electronic (inductive or/and conjugative) effects, stereo hindrance, hydrogen bond, and etc., which differentiate the acidity and accessibility of three phenolic OHs. Summarized from above references, the 7-OH is the most reactive one. Kim et al.[24] and Sugai et al.[31] discovered that 7-OH is the most active one for methylation and benzoylation. The *ortho*-electron-withdrawing group (EWG) of 4-carbonyl increases the acidity of *O<u>H</u>* of 5-OH group; however, 5-OH group is spatially available to form a very strong six-membered cyclic H-bond with 4-carbonyl group, which makes the reaction ability of 5-OH group be relatively weak and acetylated products relatively easily de-acetylated as reported by Sugai and colleagues.[31] Narender et al.[32] developed BF_3-mediated de-acetylation of 5-OAc in the above similar structures with the assistance of six-membered cyclic hydrogen bond formation. As 4'-OH has less hindrance and one *para*-electron-donating group (EDG) of alkyl, its reaction ability is between 7-OH group and 5-OH group. Kim and co-workers[24] reported that 4'-OH is more easily to be methylated than 5-OH.

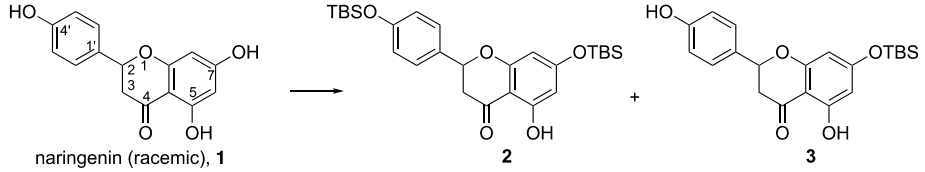
In order to meet diverse aims, the homo protections and the mixed protections for distinctive and useful diphenol protection were prepared. The determination of the product/s was according to the designation of ^{1}H NMR signal/s of proton/s of phenol/s. As three protons of phenols are situated on quite different environments, ^{1}H NMR signals of three O*<u>H</u>*s in DMSO-d_6 are distinguishable[33] that the signal of 5-O*<u>H</u>* is ~ 12 ppm, that of 7-O*<u>H</u>* is ~ 11 ppm and that of 4'-O*<u>H</u>* is ~ 10 ppm.



Scheme 1. Reagents and conditions: (a) 2.4 eq. TBSCl, 6.0 eq. imidazole, DCM, rt, 4 h, 95%; (b) 1.2 eq. TBSCl, 3.0 eq. TEA, DCM, rt, 3 h, 89%; (c) Ac_2O, pyridine (base and solvent), 0 ℃ for 5 min and then rt for 24 h, 89%; (d) KHF_2, THF, rt, 30 min, 79%; (e) 1.0 eq. Ac_2O, 2.0 eq. pyridine, DCM, 0 ℃ for 5 min and then rt for 3 h, 95%; (f) 4.0 eq. AcCl, 5.0 eq. pyridine , DCM, 0 ℃ for 5 min and then rt for 24 h, 18 h, 95%; (g) 2.0 eq. imidazole, MeOH/THF (v/v = 1/2), rt, 1 h, 88%; (h) 1.0 eq. CsF, MeCN, 0 ℃ for 5 min and then rt for 1 h, 71%.

As shown in **Scheme 1**, the silylation of racemic naringenin (**1**) was firstly selected as a primary protection as the large volume of *t*-butyldimethylsilyl (TBS) can possibly make the protection selectivity. At first, 3.6 eq. *t*-butyldimethylsilyl chloride (TBSCl) and triethylamine (TEA) (entry 1, **Table 1**) or pyridine (entry 2, **Table 1**) as a base and a solvent were applied, only 4',7-bis(OTBS)-5-free phenol product **2** (homo protections) was afforded by pyridine while the mixture of **2** and mono-silylated product **3**[34] was provided by TEA. No fully silylated product of naringenin was found. These results perhaps signifies that the volume of TBS is too large to introduce to 5-position and also the reaction conditions cannot break down the hydrogen bond between <u>*O*</u> of 4-carbonyl and <u>*H*</u> of 5-hydroxy.

Table 1. Silylation of naringenin (racemic, **1**)[a] under various reaction conditions



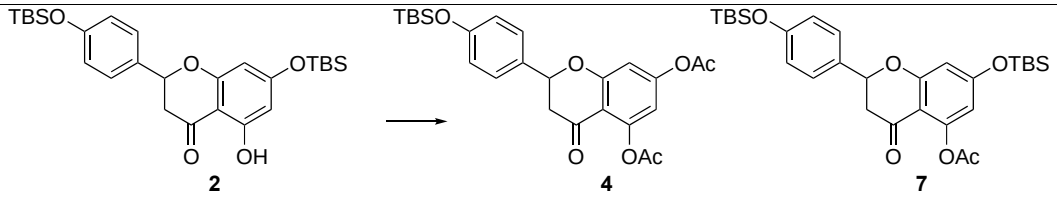
entry	Base (mL or eq.)	TBSCl (eq.)	DCM (mL)	Time (h)	Temp (°C)	yield (%)[b] of **2: 3: unreacted 1**
1[c]	TEA (0.75 mL)	3.6	0	5	25	1: 1: 0
2[d]	pyridine (0.75 mL)	3.6	0	40	40	1: 1: 0
3	TEA (9.0)	3.6	7.5	8	25	89: 0: 0
4	imidazole (9.0)	3.6	7.5	4	25	92: 0: 0
5	2,6-lutidine (9.0)	3.6	7.5	24	40	86: 0: 0
6	pyridine (9.0)	3.6	7.5	24	40	89: 0: 0
7[e]	TEA (6.0)	2.4	20	6	25	87: 0: 0
8	imidazole (6.0)	2.4	5.0	4	25	95: 0: 0
9	2,6-lutidine (6.0)	2.4	5.0	24	40	90: 0: 0
10	pyridine (6.0)	2.4	5.0	48	40	19: 47: 30
11[f]	TEA (3.0)	1.2	20	3	25	0: 89: 0
12	imidazole (3.0)	1.2	2.5	4	25	41: 34: 12
13	2,6-lutidine (3.0)	1.2	2.5	24	40	62: 14: 12
14	pyridine (3.0)	1.2	2.5	48	40	42: 13: 24

[a] 500 mg naringenin (**1**) was used except entries 1, 2, 7 and 11, and the reaction progress was monitored by thin layer chromatography (TLC). [b] isolated yields except TLC observations for entries 1 and 2. [c] 50 mg naringenin (**1**) was used and TEA was used as a base and a solvent. [d] 50 mg naringenin (**1**) was used and pyridine was used as a base and a solvent. [e] 1.0 g naringenin (**1**) was used. [f] 1.0 g naringenin (**1**) was used.

Then we explored silylation of **1** at various reaction conditions and the results are summarized in **Table 1**. The quantity of a base was reduced and DCM was used as a solvent to dilute the reactants. The reaction of 3.6 eq. TBSCl with 9 eq. bases (entries 3 to 6, **Table 1**) in DCM afforded > 86% yields of **2** and no tri-silylated product was isolated. Compared entry 3 (**Table 1**) with entry 1 (**Table 1**), it seems that the dilution of reactants by DCM makes 4'-silylation more easily. The reactions (entries 7-9, **Table 1**) of 2.4 eq. TBSCl in DCM treated with 6.0 eq. TEA, imidazole and 2,6-lutidine also provided excellent yields for 4',7-bis(OTBS) product **2**. Whereas, the reaction of 2.4 eq. TBSCl in DCM at 40 °C for 48 h (entry 10, **Table 1**) did not proceed smoothly in the presence of 6.0 eq. pyridine, in which the mixture of **2** and **3** with unreacted **1** was received. In summary, imidazole is here the best base for the production of 4',7-bis(OTBS) product **2** with the highest yield, room temperature and the shortest reaction time (entry 8, **Table 1**). Furthermore, the combinations of 1.2 eq. TBSCl with 3.0 eq. bases of imidazole (entry 12, **Table 1**), 2,6-lutidine (entry 13, **Table 1**) and pyridine (entry 14, **Table 1**) in DCM gave a mixture of **2** and **3** with unreacted **1**. However, the reaction conducted by 1.2 eq. TBSCl with 3.0 eq. TEA in DCM provided 89%

yield of **3** (entry 11, **Table 1**). It is noted that monitoring reaction progress is very important as 4',7-bis(OTBS) product **2** appears after longer reaction time. These results indicates that TEA is an optimal base for the formation of mono-silylated product **3**.

Table 2. Acetylation of compound **2**[a,b,c]

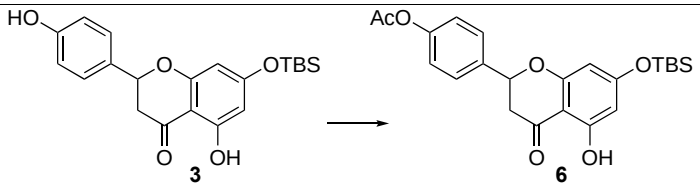


entry	Base (eq.)	Ac agent (eq.)	DCM (mL)	Time (h)	Isolated yield (%) of **4**: **7**
1	pyridine (6.0 mL)	Ac_2O (5.0)	0	24	89: 0
2	pyridine (1.2 mL)	AcCl (4.0)	0	12	6: 86
3	pyridine (5.0)	AcCl (4.0)	6.0	18	0: 95
4	TEA (5.0)	AcCl (4.0)	1.2	8	78: 10

[a] 500 mg compound **2** was used for entries 1 and 3 while 100 mg compound **2** was used for entries 2 and 4. [b] all reactions were maintained at 0 °C for 5 min after addition and then moved to 25 °C for further reaction time. [c] the reaction progress was indicated by TLC.

It is interesting that acetylation of **2** at 0 to 25 °C by acetic anhydride (Ac_2O) and pyridine, which was used as a base and a solvent, afforded 4'-OTBS-5,7-diacetyloxynaringenin (**4**) (entry 1, **Table 2**) in 89% yield, indicating that de-silylation and then acetylation at 7-position happened. Whereas, a combination of pyridine as a base and a solvent and acetyl chloride (AcCl) as an acetylating agent (entry 2, **Table 2**) made the reaction mode inversed that bis(OTBS) product **7** was a major product and 7-desilylated and acetylated product **4** was a minor product. In contrast, the reaction in DCM, the combination of pyridine and AcCl produced the product **7** in 95% yield. Next, the reaction by TEA and AcCl in DCM afforded 7-desilylated and then acetylated product **4** as a major product while bis(OTBS) **7** was a minor product. These results revealed that 7-desilylation and acetylation depends on the combination of a base, an acetylating agent and a solvent such as DCM or a base as a solvent. As shown in **Scheme 1**, de-silylation of TBS of **4** by potassium bifluoride (KHF_2) in THF at rt for 30 min yielded a homo protected compound **5**[25] of 4'-free phenol-5,7-diacetyloxynaringenin, which is a starting material for modification at 4'-position.

Table 3. Acetylation of 7-OTBS diphenol **3**[a]

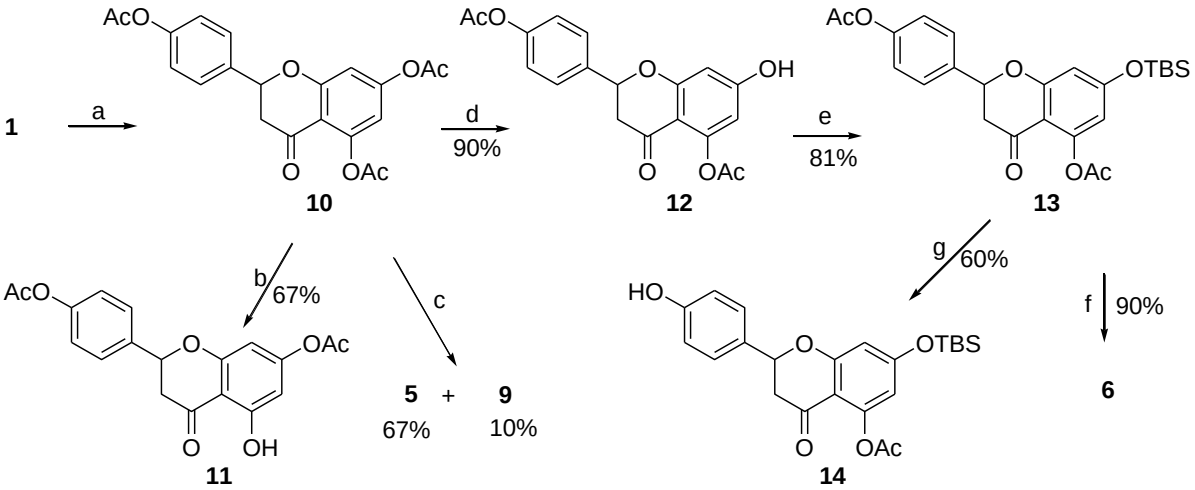


entry	Base (eq.)	Ac agent (eq.)	DCM (mL)	Time (h)	Temperature (°C)	Yield of 6 (%)
1	TEA (2.0)	AcCl (1.0)	4.0	1	0	74
2	pyridine (2.0)	Ac_2O (1.0)	4.0	3	0 to 25 [b]	95
3	TEA (2.0)	Ac_2O (1.0)	4.0	3	0 to 25	63
4	pyridine (2.0)	AcCl (1.0)	4.0	1	0	54
5	pyridine (1.2)	Ac_2O (1.1)	4.0	3	0 to 25	92
6	pyridine (5.0)	Ac_2O (2.2)	4.0	3	0 to 25	87

[a] 100 mg compound **3** was used. [b] The reactions were maintained at 0 °C for 5 min after addition and then moved to 25 °C for further reaction time.

On the other hand, 4',5-diol compound **3** was selectively acetylated at 4'-position (**Table 3**) by acetyl chloride (AcCl) or Ac_2O in the presence of pyridine or TEA to generate 5-OH-4'-OAc-7-OTBS compound **6** (mixed protections). The combination of pyridine and Ac_2O in DCM provided higher than 92% isolated yield (entries 2 and 5, **Table 3**). Compound **6** is an alternative 5-free phenol naringenin derivative to compound **2**. Furthermore, Ac group of 7-OAc of compound **4** was removed by imidazole in MeOH/THF (v/v = 1/2)[28] at rt in 1 h to produce **8**, which was then conducted de-silylation of 4'-OTBS to form **9**. Compound **8** with mixed protections is a 7-OH-4',5-protected derivative, which has flexible de-protection choices in further application.

Next, as shown in **Scheme 2**, full acetylation of naringenin and then selective de-acetylation and silylation were explored. Full acetylated naringenin was conducted according to the references[25-27] to afford compound **10**. The de-acetylation reaction at 5-position of compound **10**[25-27] by trifluoroacetic acid (TFA) in 1,2-dichloroethane (DCE) at 40 °C for 6 h generated 67% yield of a homo protected compound **11** of 5-OH-4',7-diacetyloxynaringenin.[35] Compound **11** is the same 5-free phenol intermediate as compounds **2** and **6**. Meanwhile, **10** was hydrolysed by $TsOH \cdot H_2O$ in AcOH/MeOH (v/v = 1/2) into separable compounds of 4'-OH **5** (67%) and 4',7-diphenol **9** (10%). This is an alternative method to prepare the homo protected compound **5**.



Scheme 2. Reagents and conditions: (a) Ac_2O, pyridine, 0 ℃ for 5 min and then to rt, 5 h; (b) TFA, DCE, 40 ℃, 6 h, 67%; (c) $TsOH·H_2O$, AcOH/MeOH (v/v = 1/2); (d) imidazole, MeOH/THF (v/v = 1/2), 40 ℃, 1 h, 90%; (e) TBSCl, imidazole, DCM, rt, 6 h, 81%; (f) TFA, 40 ℃, DCM, 1 h, 90%; (g) $TsOH·H_2O$, MeOH, rt, 6 h, 60%.

Adopted the method of the reference,[25] 4’,5,7-triacetyloxynaringenin **10** was treated with imidazole in 1,4-dioxane at 40 ^oC for 4 h provided about 82% yield of 7-OH homo protected compound **12**; after optimization, MeOH/THF (v/v = 1/2) as mixed reaction solvents, the reaction yield of 7-free phenol compound **12** reached 90% and the reaction was complete in 1 h at the same reaction temperature. Then, 7-OH compound **12** was easily transformed into 7-*t*-butyldimethylsilyloxy-4’,5-diacetyloxynaringenin **13**[36] in 81% yield, which can be used for further study to generate 5-OH **6** and 4’-OH **14** (mixed protections) under different acidic conditions. TFA removed 5-acetyl protection of **13** to produce 5-free phenol compound **6** in 90% yield in DCM at 40 ^oC for 1 h; while $TsOH·H_2O$ selectively de-protected 4’-acetyl group of **13** in methanol at rt for 6 h afforded 60% yield of 4’-free phenol compound **14**. Both of compounds **6** and **14** have mixed protections of Ac and TBS, which give us more choices for further de-protection and modifications after desired free phenol is used.

In summary, in this study, we have developed some new and convenient synthetic methods for the synthesis of diverse selectively phenol-protecting derivatives of naringenin with one or two free phenols, which can meet for different modification goals. The seven intermediates with one free phenol were prepared, including four homo protecting intermediates of **2** and **11** (5-OH), **5** (4’-OH), and **12** (7-OH) while three mixed protecting intermediates of **6** (5-OH), **8** (7-OH) and **14** (4’-OH). Both of the mixed protections and the homo protections are convenient for further multiple modifications. In addition, two intermediates **3** and **9** with two free phenols were prepared, which can be used for simultaneous modification at two phenols. Briefly, both of TBS and Ac can be removed under basic and acidic conditions; however, de-protection of TBS by fluoride and acidic conditions is more easily operated. On the other hand, homo-protections at two

OHs can be de-protected simultaneously, it is convenient for following modification at these two OHs; while it is reliable to site-selective removal of one protection in mixed protections at two OHs. With the advantages of mild reaction conditions, easily handled reagents and satisfactory yields, our synthetic methods have practical application to be used in drug R&D of naringenin and similar polyphenolic compounds.

EXPERIMENTAL

General information. All materials were reagent grade and used without further purification if no specific indication. Representative experiments are provided in the following while full details of experiments are presented in Supporting Information.

Key experimental procedure for (+/-)-4',7-bis(*t*-butyldimethylsilyloxy)-5-hydroxynaringenin (2) from 1. 1.0 g (3.7 mmol) of racemic naringenin (**1**) was dissolved in DCM (20 mL) and then 2.1 mL (22.0 mmol) of TEA and 1.33 g (8.9 mmol) of TBSCl were successively added to the solution at rt. The reaction was stirred at rt for 6 h by monitoring of thin layer chromatography (TLC). The reaction was diluted by EtOAc (EA) and treated with sat. aq. $NaHCO_3$ solution. The organic phase was washed by brine and then dried over anhydrous Na_2SO_4. After filtered and evaporated, the residue was silica gel column chromatography to provide 1.6 g (87% yield) of compound **2**: white solid; mp 107.2-107.5 ^oC; ^1H NMR (400 MHz, Chloroform-*d*) δ 11.99 (s, 1H), 7.37 – 7.32 (m, 2H), 6.94 – 6.88 (m, 2H), 6.08 – 5.97 (m, 2H), 5.37 (dd, *J* = 13.3, 2.9 Hz), 3.12 (dd, *J* = 17.2, 13.3 Hz), 2.80 (dd, *J* = 17.2, 3.0 Hz), 1.02 (s, 9H), 0.99 (s, 9H), 0.27 (s, 6H), 0.24 (s, 6H); ^1H NMR (400 MHz, DMSO-d_6) δ 12.06 (s, 1H), 7.48 – 7.40 (m, 2H), 6.94 – 6.88 (m, 2H), 6.04 – 5.94 (m, 2H), 5.57 (dd, *J* = 13.1, 2.9 Hz, 1H), 3.39 (d, *J* = 13.8 Hz, 1H), 2.76 (dd, *J* = 17.1, 3.0 Hz, 1H), 0.97 (s, 9H), 0.94 (s, 9H), 0.24 (s, 6H), 0.21 (s, 6H); ^{13}C NMR (101 MHz, Chloroform-*d*) δ 196.27, 164.98, 163.98, 162.92, 156.29, 131.05, 127.68 (2C), 120.40 (2C), 103.65, 101.27, 99.90, 79.04, 43.38, 25.68 (3C), 25.51 (3C), 18.22 (2C), -4.33 (2C), -4.38 (2C); HRMS (ESI) *m*/*z* 501.2489 $[M+H]^+$, calculated for $C_{27}H_{40}O_5Si_2$, 501.2487.

Key experimental procedure for (+/-)-4'-(*t*-butyldimethylsilyloxy)-5,7-diacetyloxynaringenin (4) from 2. To the ice-water bath cooled solution of 500 mg (1.0 mmol) of compound **2** dissolved in 6 mL of pyridine, 0.47 mL (5.0 mmol) of acetic anhydride was added dropwise and then slowly warmed to the ambient temperature. The reaction was stirred at the same temperature for 24 h before the reaction was complete. Treated with EA and successively washed by sat. aq. $NaHCO_3$ solution and brine, the organic phase was dried over anhydrous Na_2SO_4. After filtered and distilled off in vacuum the solvents, silica gel column chromatography gave 420 mg (89% yield) of compound **4**: white solid; mp 54.0-54.6 ^oC; ^1H NMR (400 MHz, Chloroform-*d*) δ 7.34 – 7.27 (m, 2H), 6.93 – 6.85 (m, 2H), 6.77 (d, *J* = 2.3 Hz, 1H), 6.52 (d, *J* = 2.3 Hz, 1H), 5.42 (dd, *J* = 13.7, 2.7 Hz, 1H), 3.06 (dd, *J* = 16.7, 13.7 Hz, 1H), 2.74 (dd, *J* = 16.7, 2.7 Hz,

1H), 2.38 (s, 3H), 2.29 (s, 3H), 0.99 (s, 9H), 0.21 (s, 6H); ^{13}C NMR (101 MHz, Chloroform-*d*) δ 189.47, 169.30, 168.00, 163.42, 156.36, 155.86, 151.22, 130.64, 127.67 (2C), 120.38 (2C), 111.76, 110.41, 109.14, 79.45, 45.01, 25.66 (3C), 21.19, 21.08, 18.22, -4.38 (2C). HRMS (ESI) *m*/*z* 471.1835 $[M+H]^+$, calculated for $C_{25}H_{30}O_7Si$, 471.1835.

Key experimental procedure for (+/-)-7-(*t*-butyldimethylsilyloxy)-4',5-diacetyloxynaringenin (14) from 13. The solution of 1.0 g (2.1 mmol) of compound **13** in MeOH (30 mL) was treated with 750 mg (4.2 mmol) of $TsOH\cdot H_2O$ at rt for about 6 h. After the reaction was complete, diluted with EA and sat. aq. $NaHCO_3$ solution, the organic phase was washed with sat. aq. $NaHCO_3$ solution and brine, followed by dried over anhydrous Na_2SO_4. Filtered and distilled to dryness, purification of the residue by silica gel column chromatography afford 540 mg (60% yield) of compound **14**: white solid; mp 165.2-165.4 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.62 (s, 1H), 7.38 – 7.30 (m, 2H), 6.85 – 6.74 (m, 2H), 6.40 (d, *J* = 2.4 Hz, 1H), 6.29 (dd, *J* = 6.9, 2.3 Hz, 1H), 5.53 –5.42 (m, 1H), 3.19 (dd, *J* = 16.6, 13.2 Hz, 1H), 2.58 (dd, *J* = 16.6, 2.8 Hz, 1H), 2.26 (d, *J* = 4.8 Hz, 3H), 0.94 (s, 9H), 0.24 (s, 6H); ^{13}C NMR (101 MHz, Chloroform-*d*) δ 189.96, 170.08, 164.25, 162.65, 156.67, 151.75, 130.09, 127.99, 115.72, 109.59, 108.45, 106.26, 79.21, 44.80, 25.47, 21.22, 18.18, -4.39; HRMS (ESI) *m*/*z* 429.1728 $[M+H]^+$, calculated for $C_{23}H_{28}O_6Si$, 429.1728.

SUPPORTING INFORMATION

Additional supporting information including full experimental details and copies of ^{1}H and ^{13}CNMR and HRMS of compounds can be found in the online version, at URL: https://www.heterocycles.jp/newlibrary/downloads/PDFsi/27969/106/8

REFERENCES

1. M. U. Rehman, M. U. Mir, A. Farooq, S. M. Rashid, B. Ahmad, S. B. Ahmad, R. Ali, I. Hussain, M. Masoodi, S. Muzamil, H. Madkhali, and M. A. Ganaie, *Environ. Toxicol.*, 2018, **33**, 422.
2. I. A. Mir and A. B. Tiku, *Nutr. Cancer*, 2015, **67**, 27.
3. K. Patel, G. K. Singh, and D. K. Patel, *Chin. J. Integr. Med.*, 2018, **24**, 551.
4. M. Motallebi, M. Bhia, H. F. Rajani, I. Bhia, H. Tabarraei, N. Mohammadkhani, M. Pereira-Silva, M. S. Kasaii, S. Nouri-Majd, A. L. Mueller, F. J. B. Veiga, A. C. Paiva-Santos, and M. Shakibaei, *Life Sci.*, 2022, **15**, 120752.
5. M. L. Nor Muhamad, S. O. Ekeuku, S. K. Wong, and K. Y. Chin, *Nutrients*, 2022, **14**, 4851.
6. X. Luo, L. Zhang, M. Yang, J. Xu, and X. Xu, *Chin. J. Tissue Eng. Res.*, 2022, **26**, 1051.
7. R. Ortiz-Andrade, J. A. Araujo León, J. C. Sánchez-Salgado, A. Sánchez-Recillas, P. Vazquez-Garcia, and E. Hernández-Núñez, *Molecules*, 2022, **27**, 7933.

8. A. Calderaro, G. T. Patanè, E. Tellone, D. Barreca, S. Ficarra, F. Misiti, and G. Laganà, *Int. J. Mol. Sci.*, 2022, **23**, 14835.
9. M.-Z. Sun, J. Li, L.-C. Zhang, C.-F. Ding, S.-D. Yang, H.-F. Yu, and W.-Y. Hu, *Heliyon*, 2022, **8**, e11440.
10. A. Goyal, A. Verma, N. Dubey, J. Raghav, and A. Agrawal, *J. Food Biochem.*, 2022, **15**, e14415.
11. X. Ma, T. Chen, and H. Xiao, *Chin. J. Diabetes*, 2022, **13**, 1094.
12. Y. Du, J. Ma, Y. Fan, X. Wang, S. Zheng, J. Feng, J. Li, Z. Fan, G. Li, and Q. Ye, *Oxid. Med. Cell Longev.*, 2021, **2021**, 210675.
13. A. Duda-Madej, J. Stecko, J. Sobieraj, N. Szymańska, and J. Kozłowska, *Antibiotics* (Basel), 2022, **11**, 1628.
14. G. Céliz, M. Daz, and M. C. Audisio, *J. Appl. Microbiol.*, 2011, **111**, 731.
15. K. Kurahayashi, K. Hanaya, S. Higashibayashi, and T. Sugai, *Biosci. Biotechnol. Biochem.*, 2018, **82**, 1463.
16. S. Gunaseelan, K. Z. Wong, N. Min, J. Sun, N. K. B. M. Ismail, Y. J. Tan, R. C. H. Lee, and J. J. H. Chu, *Sci. Transl. Med.*, 2019, **11**, eaar5759.
17. R. R. Gu, X. H. Meng, Y. Zhang, H. Y. Xu, L. Zhan, Z. B. Gao, J. L. Yang, and Y. M. Zheng, *Molecules*, 2022, **27**, 1735.
18. A. Duda-Madej, J. Kozłowska, P. Krzyżek, M. Anioł, A. Seniuk, K. Jermakow, and E. Dworniczek, *Molecules*, 2020, **25**, 3642.
19. H. Wang, W. Zhang, Y. Cheng, X. Zhang, N. Xue, G. Wu, M. Chen, K. Fang, W. Guo, F. Zhou, H. Cui, T. Ma, P. Wang, and H. Lei, *Molecules*, 2018, **23**, 314.
20. Ö. Zaim, O. Doğanlar, Z. B. Doğanlar, H. Özcan, M. M. Zreigh, and K. Kurtdere, *Bioorg. Chem.*, 2022, **129**, 106209.
21. J. Yang, Y. Zhou, Y. Ban, J. Mi, Y. He, X. Li, Z. Liu, K. Wang, G. Zhu, W. Liu, Z. Tan, and Z. Sang, *J. Enzyme Inhib. Med. Chem.*, 2022, **37**, 792.
22. J. Wu, X. Kou, H. Ju, H. Zhang, A. Yang, and R. Shen, *Bioorg. Med. Chem. Lett.*, 2021, **49**, 128316.
23. J. Mi, Y. He, J. Yang, Y. Zhou, G. Zhu, A. Wu, W. Liu, and Z. Sang, *Bioorg. Med. Chem. Lett.*, 2022, **60**, 128574.
24. J. Kim, K.-S. Park, C. Lee, and Y.Chong, *Bull. Korean Chem. Soc.*, 2007, **28**, 2527.
25. Y. Yamashita, K. Hanaya, M. Shoji, and T. Sugai, *Chem. Pharm. Bull.*, 2016, **64**, 961.
26. T. Kawamura, M. Hayashi, R. Mukai, J. Terao, and H. Nemoto, *Synthesis*, 2012, 1308.
27. Z. Zheng, Z. Han, L. Cai, D. Zhou, B. R. Chavis, C. Li, Q. Sui, K. Jiang, and Q. Gao, *Tetrahedron Lett.*, 2018, **59**, 17.
28. J. H. Looker, M. J. Holm, J. L. Minor, and S. A. Kagal, *J. Heterocycl. Chem.*, 1964, **1**, 253.

29. J. Li, S. Grosslight, S. J. Miller, M. S. Sigman, and F. D. Toste, *ACS Catal.*, 2019, **9**, 9794.
30. G. Gu and G.-C. Zhou, *Indian J. Heterocycl. Chem.*, 2022, **32**, 278.
31. T. Sugai, K. Hanaya, and S. Higashibayashi, *Biosci. Biotechnol. Biochem.*, 2021, **85**, 143.
32. T. Narender, K. Papi Reddy, and B. Kumar, *Tetrahedron Lett.*, 2008, **49**, 4409.
33. (a) J.-t. Liu, L. Li, J.-l. Dong, B.-n. Jiao, and X.-s. Su, *J. Instrum. Anal.*, 2020, **39**, 190; (b) L.-j. Sun, X.-f. Hu, X. Cheng, L.-t. Luo, H.-b. Liu, and L. Chen, *Chin. J. Magn. Reson.*, 2017, **34**, 465.
34. K. i. Oyama and T. Kondo, *Tetrahedron*, 2004, **60**, 2025.
35. S. Gester, P. Metz, O. Zierau, and G. Vollmer, *Tetrahedron*, 2001, **57**, 1015.
36. C. Shang, C. Zhao, P. Nie, J. Liu, and Y. Du, *Tetrahedron*, 2021, **91**, 132216.