The First Synthesis of Uralenol, 5′-Prenylated Quercetin, via Palladium-Catalyzed O-Dimethylallylation Reaction with Concurrent Acetyl Migration

Tomoyuki Kawamura,[a] Moemi Hayashi,[a] Rie Mukai,[b] Junji Terao,[b] Hisao Nemoto*[a]

[a] Department of Pharmaceutical Chemistry, Division of Heath Biosciences, Graduate School of the University of Tokushima, 1-78-1, Sho-machi, Tokushima 770-8505, Japan
Fax +81(88)6337284; E-mail: nem@ph.tokushima-u.ac.jp

[b] Department of Food Science, Institute of Health Biosciences, Graduate School of the University of Tokushima, 3-18-15, Kuramoto-cho, Tokushima 770-8503, Japan

Received: 18.09.2013; Accepted after revision: 25.10.2013

Abstract: The first synthesis of uralenol, 5′-prenylated quercetin, is described. The key step is a palladium-catalyzed O-1,1-dimethylallylation reaction, with concurrent acetyl migration to afford the desired intermediate as a major isomer, which was purified by recrystallization. Finally, Claisen rearrangement, followed by deprotection of all phenolic protecting groups, afforded uralenol in excellent yield.

Key words: palladium, prenylation, quercetin, flavonoids, rearrangement

The bioactivity of prenylated flavonoids is more attractive than that of unmodified flavonoids, since the changed conformation resulting from prenylation can have effects such as slowing down metabolism.[1] One such prenylated flavonoids, uralenol (**1**), which was first isolated from the leaves of *Glycyrrhiza uralensis* Fisch by Wang et al.,[1h] displays many types of biological activity[2] (Scheme 1).

In this paper, we report the first synthesis of uralenol. The key step was based on our recently reported procedure,[3] palladium-catalyzed 1,1-dimethylallylation (Kaiho's method,[4] step A) at O-4′ on the B ring, followed by prenylation at C-5′ via Claisen rearrangement in acetic anhydride[5] (step B). Although it was difficult to prepare an appropriate synthetic intermediate for uralenol as a single isomer due to the low energy gap for acetyl migration between the 3′- and 4′-positions, a combination of palladium-catalyzed O-dimethylallylation and acetyl migration predominantly afforded the desired synthetic intermediate for uralenol.

The synthetic strategy was as follows. Compound **4**, whose hydroxyl groups were protected except the one at 4′-position, is an important precursor. Once **4** can be prepared, our procedure for obtaining **2** from **4** via **3** is easily applicable to the introduction of a prenyl group at C-5′. Therefore, the most reactive acetyl group at C-7, the *para*-position of carbonyl functionality of the peracetylquercetin (**5**) can be deprotected, after which the resulting hydroxyl group is reprotected with an orthogonal protecting group to afford the compound such as **7** (Scheme 2). Because of a dipole moment interaction with the neighboring carbonyl group, deprotection of the acetyl groups at C-3 and C-5 proceeds more slowly than at the other acetyl groups. Accordingly, the key step is the discrimination of deprotection between the 4′- and 3′-acetyl group. Unfortunately, no appropriate method of discrimination was available[6] at the beginning of this synthetic study. However, we were ultimately successful in this regard by virtue of careful observation.

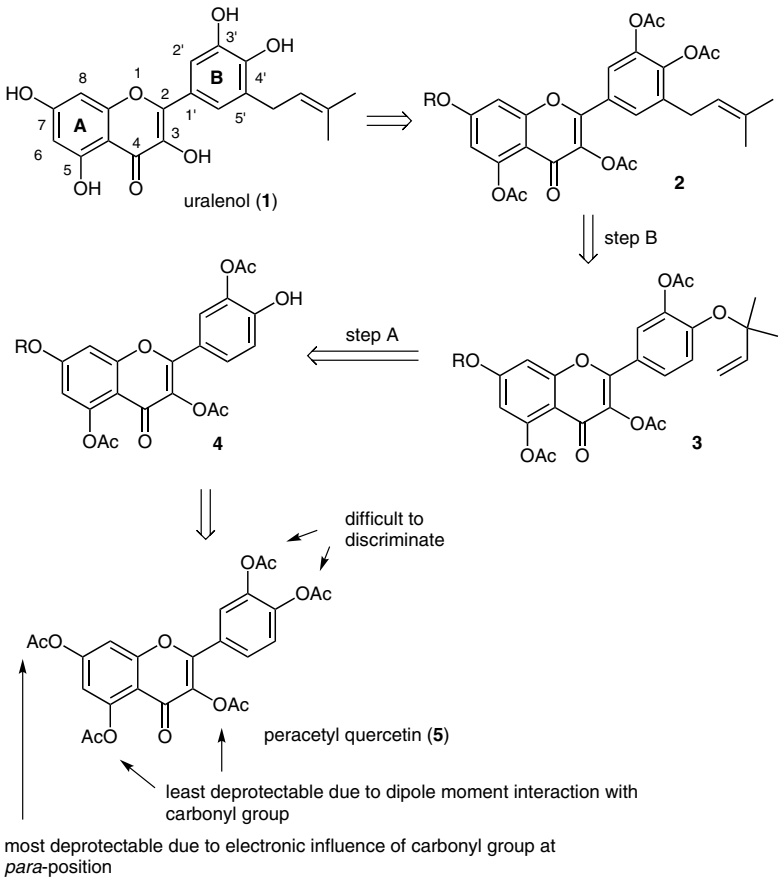
Synthesis was carried out as illustrated in Scheme 2. First, commercially available quercetin was acetylated to afford the peracetylated derivative **5**, which was transformed to mono-deacetylated compound **6** in 84% yield via a known procedure.[7] Treatment of **6** with chloromethyl methyl ether afforded **7** in 95% yield.

Next, the conversion of **7** into **8a** was examined using thiophenol with imidazole in *N*-methylpyrrolidone (NMP) by reference to a previous paper[8] to afford a mixture of **8a** and **8b** (ca. 76:24) in 92% combined yield without deacetylation at either the 3- or 5-position. The mixture of **8a** and **8b**[9] was treated with the carbonate **9** in the presence of a catalytic amount of tetrakis(triphenylphosphine)palladium to afford a mixture of **10a** and **10b** in reproducibly 92% yield. However, the molar ratio of **10a** and **10b** was irreproducible (approximately 70–80:30–20). It was concluded that the reason for this irreproducibility was the low-energy-gap equilibrium between **8a** and **8b** via 1,2-acetyl migration, although it is well known that the palladium-catalyzed reactions with carbonates, similar to that in step A, proceed under essentially neutral conditions.

We eventually noticed that the irreproducibility was due to the presence of trace amounts of residual imidazole, which had been used in the previous step. Therefore, we examined the reaction in the presence of 0.01 equivalent of various additives (Table 1).

As shown in entry 1, **10a** and **10b** were reproducibly obtained with a molar ratio of 71:29 when the imidazole was exhaustively removed.[10] When either 2,6-lutidine or 4-(dimethylamino)pyridine (DMAP) was used, the palladi-

SYNTHESIS 2014, 46, 0170–0174
Advanced online publication: 22.11.2013
DOI: 10.1055/s-0033-1338559; Art ID: SS-2013-F0630-OP



Scheme 1

um-catalyzed reaction was disrupted (Table 1, entries 2 and 3). In the presence of 4-toluenesulfonic acid monohydrate (*p*-TsOH·H_2O), the resulting molar ratio of **10a** and **10b** was 79:21 (entry 4). The most suitable ratio for the synthesis of uralenol was achieved using pyridine (entry 5) and diisopropylethylamine (*i*-Pr_2NEt) (entry 6). Because of the chemical yield, we chose pyridine as the most appropriate base, obtaining a mixture of **10a** and **10b** with a molar ratio of 87:13 in 92% yield. After a single recrystallization, pure **10a** was isolated in 79% overall yield from a mixture of **8a** and **8b**.

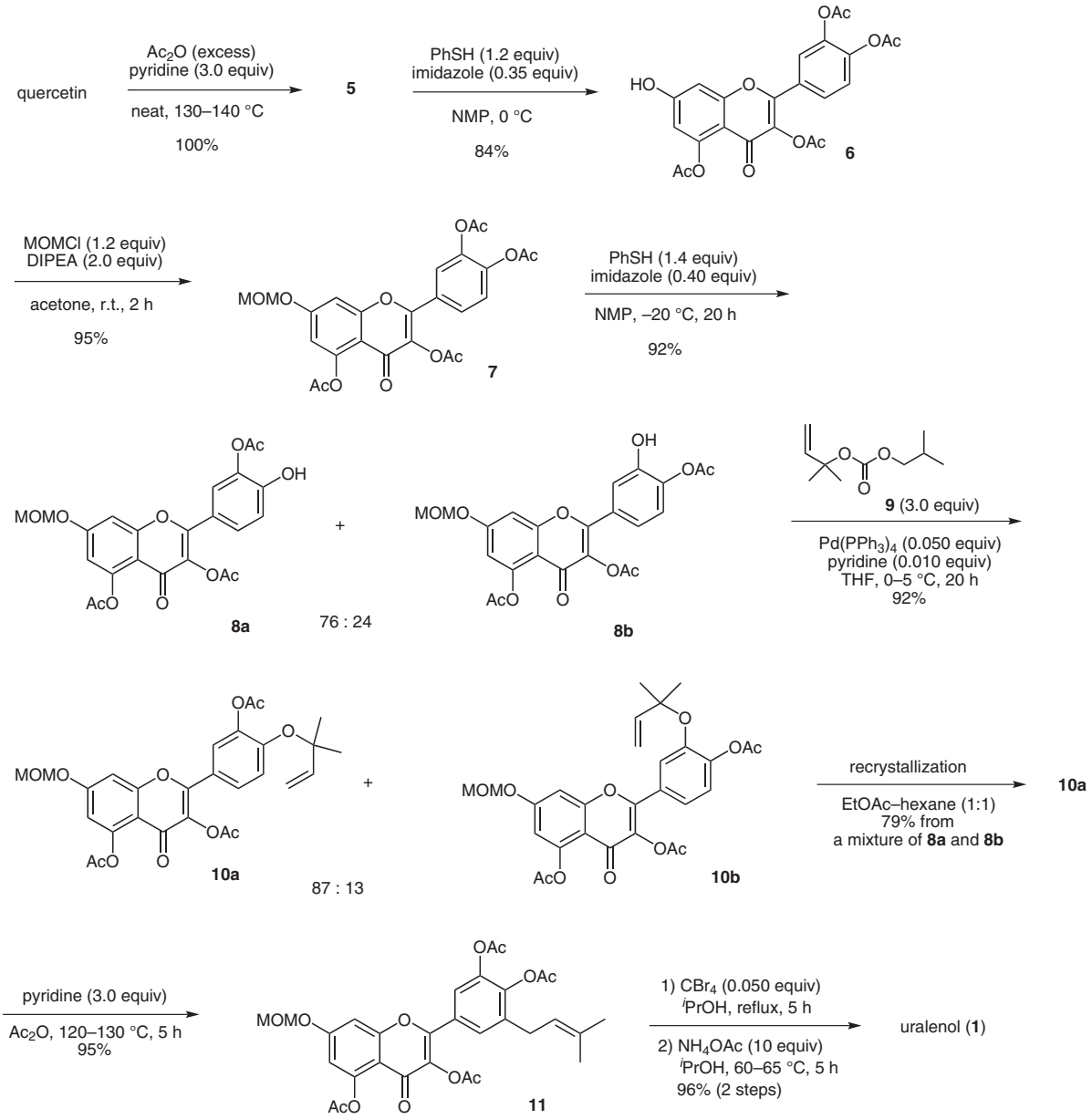
Table 1 Molar Ratio of **10a** and **10b** after Pd-Catalyzed O-Dimethylallylation from a Mixture of **8a** and **8b** (76:24) with Additives (0.01 equiv)

Entry	Additive	Molar ratio of **10a** and **10b**
1	–	71:29
2	DMAP	–
3	2,6-lutidine	–
4	*p*-TsOH·H_2O	79:21
5	pyridine	87:13
6	*i*-Pr_2NEt	84:17

Claisen rearrangement of purified **10a** smoothly proceeded in acetic anhydride[3] to afford the desired 5′-prenylated product **11** in 95% isolated yield. Finally, the methoxymethyl group was deprotected using carbon tetrabromide in isopropyl alcohol,[11] followed by deprotection of the other four acetyl groups by ammonium acetate to give uralenol (**1**) in 96% overall yield from **11**.

In conclusion, the first synthesis of uralenol (**1**) was accomplished in 8 steps and in 53% overall yield from quercetin. It is noted that even the mild palladium-catalyzed reaction with carbonates under essentially neutral conditions could not prevent the 1,2-acetyl migration between the *ortho*-phenolic groups. However, this disadvantage was finally utilized to increase the selectivity and overall chemical yield of the reaction via the newly examined concerted acetyl migration and palladium-catalyzed O-1,1-dimethylallylation using an amine purposely added as a base.

Melting points were obtained on a Yanagimoto-model 20 melting point apparatus and were uncorrected. IR spectra were recorded on a Jasco FT-IR 6200 spectrophotometer. ^1H NMR spectra were recorded in $CDCl_3$ or CD_3OD and referenced to TMS using Jeol JNM-AL 300 (300 MHz), Jeol JNM-AL 400 (400 MHz), or Bruker AV400N (400 MHz) spectrometers. ^{13}C NMR were recorded in $CDCl_3$ or acetone-d_6 and referenced to $CDCl_3$ ($\delta = 77.0$) or CD_3OD ($\delta = 49.9$) using a Jeol JNM-AL 300 (75 MHz) spectrometer. Column chromatography was performed on silica gel (Kanto Kagaku



Scheme 2

N-60). TLC was performed on precoated plates (0.25 mm, silica gel Merck Kieselgel $60F_{254}$). All reactions were performed in oven-dried glassware under positive pressure of argon, unless otherwise noted. Reaction mixtures were stirred magnetically. MeOH was distilled over Mg. NMP was distilled over CaH_2. Anhydrous THF and Ac_2O were purchased from Wako Chemicals Co. Inc.

4-[3,5-Diacetoxy-7-(methoxymethoxy)-4-oxo-4*H*-chromen-2-yl]-1,2-phenylene Diacetate (7)

To a solution of tetraacetylated quercetin **6**[6] (10.0 g, 21.3 mmol, 1.00 equiv) and *i*-Pr_2NEt (5.6 mL, 31.9 mmol, 1.50 equiv) in acetone (85 mL, 0.25 M) was added chloromethyl methyl ether (1.9 mL, 25.5 mmol, 1.2 equiv) at 0 °C, and the mixture was stirred for 2 h at r.t. The resulting mixture was diluted with EtOAc (1.0 L), and the EtOAc layer was washed with aq 1 M HCl (300 mL) and brine (300 mL). The organic phase was dried (Na_2SO_4) and concentrated in vacuo. The residue was recrystallized from EtOAc–hexane (2:1) to give **7** as a white powder; yield: 10.4 g (20.2 mmol, 95%); mp 173–174 °C.

FT-IR (KBr): 3503, 2943, 1773, 1636, 1506, 1442, 1372, 1264, 1201, 1083, 1023, 936, 871, 847, 814, 793, 676, 601, 552, 498, 468 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.73 (dd, *J* = 8.4, 2.0 Hz, 1 H), 7.69 (d, *J* = 2.0 Hz, 1 H), 7.34 (d, *J* = 8.4 Hz, 1 H), 7.06 (d, *J* = 2.4 Hz, 1 H), 6.74 (d, *J* = 2.4 Hz, 1 H), 5.26 (s, 2 H), 3.50 (s, 3 H), 2.43 (s, 3 H), 2.34 (s, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.1 (C), 169.5 (C), 168.0 (C), 167.8 (C), 167.7 (C), 161.4 (C), 157.8 (C), 153.2 (C), 150.6 (C), 144.2 (C), 142.1 (C), 133.8 (C), 128.0 (C), 126.4 (CH), 123.8 (CH), 123.7 (CH), 111.7 (C), 109.9 (CH), 101.5 (CH), 94.5 (CH_2), 56.5 (CH_3), 21.1 (CH_3), 20.7 (2 × CH_3), 20.5 (CH_3).

2-(3-Acetoxy-4-hydroxyphenyl)-7-(methoxymethoxy)-4-oxo-4*H*-chromene-3,5-diyl Diacetate (8a)/2-(4-Acetoxy-3-hydroxyphenyl)-7-(methoxymethoxy)-4-oxo-4*H*-chromene-3,5-diyl Diacetate (8b)

To a suspension of **7** (10.0 g, 19.4 mmol, 1.00 equiv) in NMP (40 mL, 0.50 M) were added imidazole (0.528 g, 7.76 mmol, 0.400 equiv) and thiophenol (2.8 mL, 27.2 mmol, 1.40 equiv) at –20 °C,

and the mixture was stirred for 20 h at the same temperature. The resulting mixture was diluted with EtOAc (1.0 L) and washed with aq 1 M HCl (0.50 L), H_2O (0.50 L), and brine (0.50 L). The organic phase was dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by column chlomatography (silica gel, hexane–EtOAc, 2:3) to give a mixture of **8a** and **8b** (8.43 g, 17.8 mmol, 92%, 76:24) as a pale yellow amorphous powder. Although pure **8a** was obtained by recrystallization of the mixture of **8a** and **8b**, it was difficult to record the spectral data of **8a** because **8a** was converted into a mixture of **8a** and **8b** within a short time. Only ^{1}H NMR was available.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.59–7.55 (m, 2 H), 7.00 (d, *J* = 3.2 Hz, 1 H), 6.97 (d, *J* = 11.2 Hz, 1 H), 6.72 (d, *J* = 3.2 Hz, 1 H), 6.50 (s, phenolic OH, 1 H), 5.27 (s, 2 H), 3.51 (s, 3 H), 2.44 (s, 3 H), 2.35 (s, 3 H), 2.33 (s, 3 H).

2-{3-Acetoxy-4-[(2-methylbut-3-en-2-yl)oxy]phenyl}-7-(methoxymethoxy)-4-oxo-4*H*-chromene-3,5-diyl Diacetate (10a)

To a solution of **8a**/**8b** (8.00 g, 16.9 mmol, 1.00 equiv) in THF (170 mL, 0.10 M) were added pyridine (14 mL, 0.169 mmol, 0.01 equiv), the mixed carbonate **9** (90 wt%, 10.5 g, 50.7 mmol, 3.00 equiv), and $Pd(PPh_3)_4$ (0.976 g, 0.845 mmol, 0.05 equiv) at 0–5 °C, and the mixture was stirred for 20 h at the same temperature. The resulting mixture was filtered through a Celite pad, and the residue was then washed with EtOAc (3 × 100 mL). The combined eluents were concentrated in vacuo. The residue was purified by column chromatography (silica gel, hexane–EtOAc, 1:1) to give a mixture of **10a** and **10b** (8.40 g, 15.5 mmol, 92%, **10a**/**10b** = 87:13) as a pale yellow amorphous powder. The mixture was recrystallized from EtOAc–hexane (1:1) to give the single isomer **10a** as a white powder; yield: 7.22 g (13.4 mmol, 79% from **8a**/**8b**); mp 124–125 °C.

FT-IR (KBr): 3446, 2987, 1773, 1633, 1506, 1434, 1365, 1286, 1203, 1076, 1021, 948, 858, 793, 697, 600 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.60 (dd, *J* = 8.8, 2.0 Hz, 1 H), 7.54 (d, *J* = 2.0 Hz, 1 H), 7.22 (d, *J* = 8.8 Hz, 1 H), 7.05 (d, *J* = 2.4 Hz, 1 H), 6.72 (d, *J* = 2.4 Hz, 1 H), 6.13 (dd, *J* = 17.6, 10.8 Hz, 1 H), 5.27 (d, *J* = 17.6 Hz, 1 H), 5.26 (s, 2 H), 5.22 (d, *J* = 10.8 Hz, 1 H), 3.50 (s, 3 H), 2.43 (s, 3 H), 2.34 (s, 3 H), 2.33 (s, 3 H), 1.52 (s, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.3 (C), 169.7 (C), 168.7 (C), 168.1 (C), 161.3 (C), 157.9 (C), 154.0 (C), 150.8 (C), 150.7 (C), 143.4 (CH), 142.4 (C), 133.3 (C), 126.3 (CH), 122.8 (CH), 122.6 (C), 119.5 (CH), 114.4 (CH_2), 111.7 (C), 109.7 (CH), 101.5 (CH), 94.5 (CH_2), 81.6 (C), 56.4 (CH_3), 26.9 (2 × CH_3), 21.0 (CH_3), 20.5 (2 × CH_3).

2-[3,4-Diacetoxy-5-(3-methylbut-2-enyl)phenyl]-7-(methoxymethoxy)-4-oxo-4*H*-chromene-3,5-diyl Diacetate (11)

A solution of **10a** (7.00 g, 13.0 mmol, 1.00 equiv) in Ac_2O (130 mL, 0.10 M) and pyridine (3.2 mL, 39.0 mmol, 3.00 equiv) was heated to 120–130 °C and stirred for 5 h at the same temperature. After cooling to r.t., the resulting mixture was concentrated in vacuo. The residue was recrystallized from EtOAc and hexane (2:1) to give **11** as a white powder; yield: 7.19 g (12.4 mmol, 95%); mp 152–154 °C).

FT-IR (KBr): 3503, 2913, 1771, 1621, 1488, 1443, 1372, 1290, 1178, 1079, 1012, 950, 842, 788, 680, 604, 521, 472 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.57 (d, *J* = 2.0 Hz, 1 H), 7.53 (d, *J* = 2.0 Hz, 1 H), 7.05 (d, *J* = 2.4 Hz, 1 H), 6.73 (d, *J* = 2.4 Hz, 1 H), 5.27 (s, 1 H), 5.20–5.25 (m, 1 H), 3.51 (s, 1 H), 3.31 (d, *J* = 6.8 Hz, 2 H), 2.43 (s, 3 H), 2.34 (s, 3 H), 2.31 (s, 6 H), 1.77 (s, 3 H), 1.71 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.4 (C), 169.8 (C), 168.3 (2 × C), 168.0 (C), 161.6 (C), 158.1 (C), 153.9 (C), 150.9 (C), 143.0 (C), 142.8 (C), 136.6 (C), 134.9 (C), 134.0 (CH), 127.9 (C), 127.2 (CH), 121.5 (CH), 120.5 (CH), 112.0 (C), 110.0 (CH), 101.8 (CH), 94.7 (CH_2), 56.6 (CH_3), 28.8 (CH_2), 25.8 (CH_3), 21.2 (CH_3), 20.8 (CH_3), 20.5 (CH_3), 20.4 (CH_3), 17.9 (CH_3).

Urarenol (1)

To a suspension of **11** (7.00 g, 12.0 mmol, 1.00 equiv) in *i*-PrOH (120 mL, 0.10 M) was added CBr_4 (0.199 g, 0.60 mmol, 0.05 equiv) at r.t. and the mixture was stirred for 5 h at reflux. After cooling to r.t., NH_4OAc (9.25 g, 120 mmol, 10.0 equiv) was added to the resulting solution and the mixture was stirred for 5 h at 60 °C. After cooling to r.t., the mixture was concentrated in vacuo, and the residue was recrystallized from MeOH–H_2O (85:15) to give **1** as pale yellow needles; yield: 4.27 g (11.5 mmol, 96%); mp 176–178 °C.

FT-IR (KBr): 3462, 1734, 1653, 1559, 1522, 1457, 1339, 1161 cm^{-1}.

^{1}H NMR (400 MHz, CD_3OD): δ = 7.61 (d, *J* = 2.0 Hz, 1 H), 7.55 (d, *J* = 2.0 Hz, 1 H), 6.36 (d, *J* = 2.0 Hz, 1 H), 6.18 (d, *J* = 2.0 Hz, 1 H), 5.34–5.39 (m, 1 H), 3.37 (d, *J* = 7.6 Hz, 2 H), 1.76 (s, 6 H).

^{13}C NMR (75 MHz, CD_3OD): δ = 177.5 (C), 165.7 (C), 162.7 (C), 158.4 (C), 148.5 (C), 146.9 (C), 145.9 (C), 137.3 (C), 133.4 (C), 129.6 (CH), 123.9 (C), 123.3 (C), 122.1 (CH), 113.5 (CH), 104.6 (CH), 99.3 (CH), 94.4 (CH), 29.3 (CH_2), 25.9 (CH_3), 17.9 (CH_3).

Acknowledgment

This work was supported by the Program for Promotion of Basic and Applied Researches for Innovations in Bio-oriented Industry (Japan).

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis.

References

(1) (a) Yazaki, K.; Sasaki, K.; Tsurumaru, Y. *Phytochemistry* **2009**, *70*, 1739. (b) Nomura, T. *Yakugaku Zasshi* **2001**, *121*, 535; *Chem. Abstr.* **2001**, *135*, 119570. (c) Ren, Y.; Kardono, L. B. S.; Riswan, S.; Chai, H.; Farnsworth, N. R.; Soejarto, D. D.; Carcache-Blanco, E. J.; Kinghorn, A. D. *J. Nat. Prod.* **2010**, *73*, 949. (d) Huang, Y.-C.; Hwang, T.-L.; Chang, C.-S.; Yang, Y.-L.; Shen, C.-N.; Liao, W.-Y.; Chen, S.-C.; Liaw, C.-C. *J. Nat. Prod.* **2009**, *72*, 1273. (e) Tabopda, T. K.; Ngoupayo, J.; Awoussong, P. K.; Mitaine-Offer, A.-C.; Ali, M. S.; Ngadjui, B. T.; Lacaille-Dubois, M.-A. *J. Nat. Prod.* **2008**, *71*, 2068. (f) Meragelman, K. M.; MaKee, T. C.; Boyd, M. R. *J. Nat. Prod.* **2001**, *64*, 546. (g) Conseil, G.; Decottignies, A.; Jault, J-M.; Comte, G.; Barron, D.; Goffeau, A.; Pietro, A. D. *Biochemistry* **2000**, *39*, 6910. (h) Jia, S. S.; Ma, C. M.; Wang, J. M. *Acta. Pharm. Sin.* **1990**, *25*, 758. (i) Fukai, T.; Wang, Q.-H.; Takayama, M.; Nomura, T. *Heterocycles* **1990**, *31*, 373.

(2) (a) Zheng, Z.-P.; Cheng, K.-W.; Chao, J.; Wu, J.; Wang, M. *Food Chem.* **2008**, *106*, 529. (b) Chen, R. M.; Hu, L. H.; An, T. Y.; Li, J.; Shen, Q. *Bioorg. Med. Chem.* **2002**, *12*, 3387.

(3) Kawamura, T.; Hayashi, M.; Mukai, R.; Terao, J.; Nemoto, H. *Synthesis* **2012**, *44*, 1308.

(4) (a) Kaiho, T.; Miyamoto, M.; Nobori, T.; Katakami, T. *Yuki Gosei Kagaku Kyokaishi* **2004**, *62*, 27. (b) Kaiho, T.; Yokoyama, T.; Mori, H.; Fujiwara, J.; Nobori, T.; Odaka, H.; Kamiya, J.; Maruyama, M.; Sugawara, T. Japanese Patent JP 06-128238, **1994**; *Chem. Abstr.* **1995**, *123*, 55900.

(5) When acetic anhydride was used as the solvent, the chemical yield and chemoselectivity of Claisen rearrangement were dramatically improved; see ref. 3.

(6) Differentiation of C-4′ from C-3′ with migratory group such as acetyl group has not been reported prior to our result reported herein. In contrast, selective O-methylation of C-4′ of quercetin via six steps was reported: Li, N.-G.; Shi, Z.-H.;

Tang, Y.-P.; Yang, J.-P.; Duan, J.-A. *Beilstein J. Org. Chem.* **2009**, *5*, No. 60.
(7) (a) Picq, M.; Prigent, A. F.; Nemoz, G.; Andre, A. C.; Pacheco, H. *J. Med. Chem.* **1982**, *25*, 1192. (b) Li, M.; Han, X.; Yu, B. *J. Org. Chem.* **2003**, *68*, 6842.
(8) Peng, W.; Li, Y.; Zhu, C.; Han, X.; Yu, B. *Carbohydr. Res.* **2005**, *340*, 1682.
(9) In fact, pure **8a** was isolated from a mixture of **8a** and **8b** by recrystallization. Unfortunately, however, the purified **8a** reverted to a mixture of **8a** and **8b** after a short time. Furthermore, even when Pd-catalyzed O-dimethylallylation was carried out immediately after isolation of pure **8a**, a mixture of **10a** and **10b** was obtained. Incidentally, isomerization from **8b** to **8a** was also observed during recrystallization, because recrystallization of a mixture of **8a** and **8b** (76:24) afforded pure **8a** in 84% (which is greater than 76%) yield. Accordingly, the best purification point in the synthesis of uralenol was after obtaining a mixture of **10a** and **10b** because **10** has no phenolic proton.
(10) Pd-catalyzed O-dimethylallylation at the 7-position of tetraacetylated quercetin was reported in our recent paper (see, ref. 3). During the reaction, no acetyl migration was detected probably because the phenolic hydroxide was not located at the *ortho*-position of any of the acetoxy groups in the starting materials.
(11) Shinozuka, T.; Yamamoto, Y.; Hasegawa, T.; Saito, K.; Naito, S. *Tetrahedron Lett.* **2008**, *49*, 1619.

