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Total Synthesis of Lagerstannin C: Follow-up of the Khanbabaee's Synthesis

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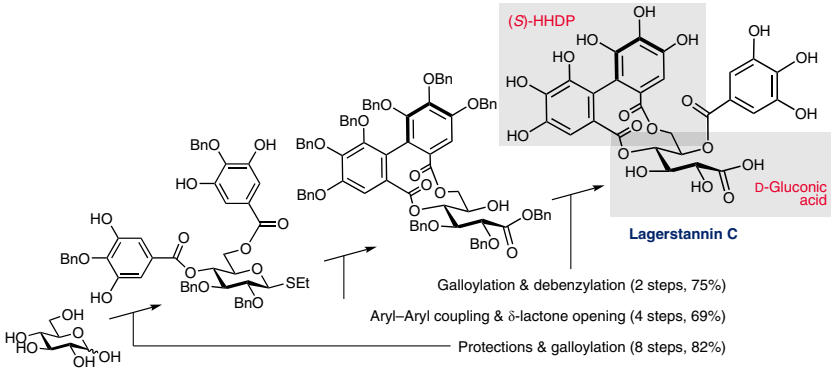


Received: 03.05.2017
Accepted after revision: 25.05.2017
Published online: 20.07.2017
DOI: 10.1055/s-0036-1588477; Art ID: ss-2017-f0296-op

Abstract This report describes the total synthesis of lagerstannin C, a natural ellagitannin that has D-gluconic acid in the molecule. The study presented here is the first synthesis of the gluconic acid containing ellagitannin. The key step in the synthesis is the opening of δ-lactone through transesterification to form the corresponding benzyl ester.

Key words total synthesis, natural products, ellagitannin, lagerstannin C, gluconic acid, transesterification

Lagerstannin C (**1**) is an ellagitannin isolated from leaves and fruits of *Lagerstroemia speciosa* (L.) PERS. (Lythraceae) along with lagerstannin A and B by Nonaka and co-workers.[1] The plant shows a hypoglycemic activity, and thus, is a potential natural medicine for diabetes.[2] In the same report, the authors reported its chemical structure **1** which bears respective (*S*)-hexahydroxydiphenoyl (HHDP) and galloyl groups at the 4,6- and 5-oxygens (4,6-*O* and 5-*O*) of D-gluconic acid (Figure 1).[1] Such gluconic acid based ellagitannins are a minor structural type of ellagitannin.

A synthetic study of **1** was reported by Khanbabaee and co-workers,[3,4] but the work is unfinished (Scheme 1). They condensed racemic and fully benzylated hexahydroxydiphenic acid **2** with glucose derivative **3**. In the condensation, termed double esterification, kinetic resolution affords single diastereomer **4** equipped with the desired (*S*)-HHDP bridge. They transformed **4** to the corresponding gluconolactone **6** through pyranose **5** by removal of the *o*-nitrobenzyl [Bn(*o*-NO_2)] groups followed by oxidation at the anomeric position. The opening of the δ-lactone ring of **6** was reported to proceed using silica gel to give carboxylic acid **7**. The successive methylation of the carboxylic acid and galloylation of the 5-*O* provided **8**. Chemoselective cleavage of the methyl ester in **8** in the presence of galloyl and HHDP esters furnished carboxylic acid **9**. Note that their study ended at **9** without mentioning the final deprotection step.

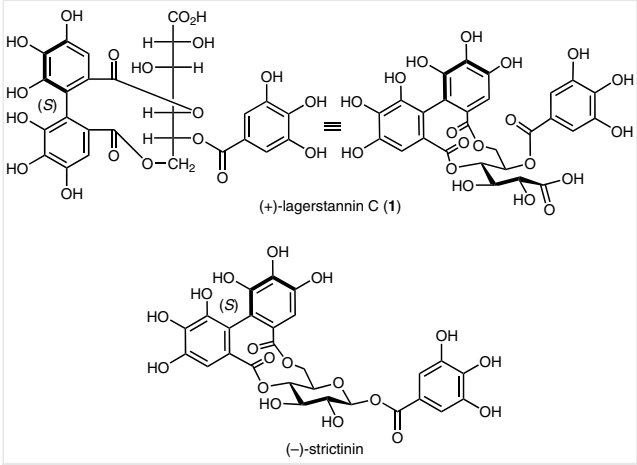
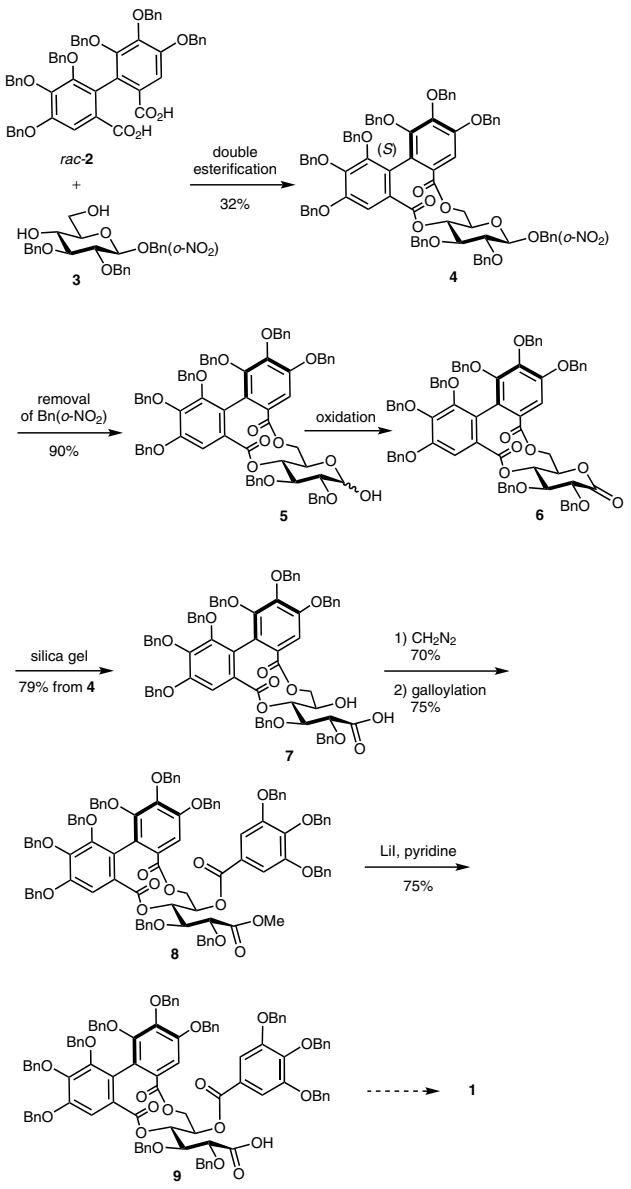


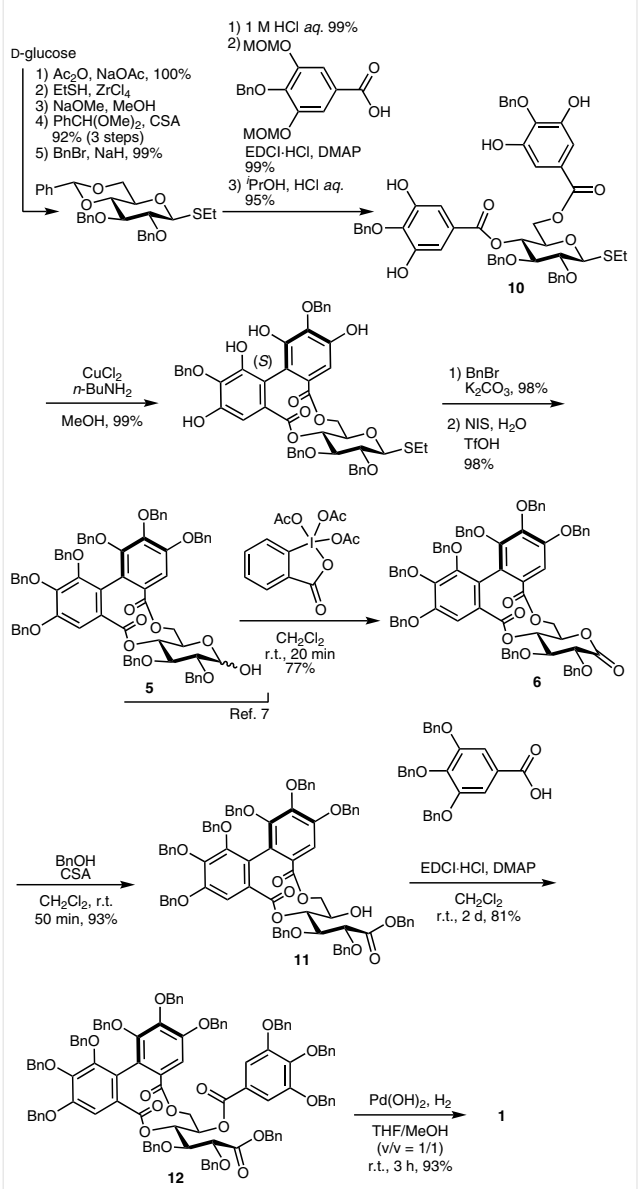
Figure 1 Structure of lagerstannin C and strictinin

As well as the incomplete synthesis, there are two more problems in their report. Firstly, the yield of **4** is 32% despite the perfect kinetic resolution in the double esterification. The reason for the poor yield might be a side reaction induced by (*R*)-**2**. The (*R*)-isomer, the unfavorable enantiomer in the kinetic resolution, tends to react with two equivalents of **3** at the less hindered 6-*O* to produce a HHDP compound equipped with two glucose moieties,[5,6] which expends **3**. Secondly, the chemoselective cleavage of the methyl ester of **8** is reported in their review;[4] therefore, no experimental detail and physical data for **9** are provided.

We here describe the total synthesis of lagerstannin C (**1**) with all experimental and spectral evidence for the first time. In our synthesis, the adoption of **6** (and its precursor **5**) as the intermediate is the same as in Khanbabaee's



Scheme 1 Khanbabaee's synthesis of protected lagerstannin C



Scheme 2 Total synthesis of lagerstannin C (**1**)

method, but our method for the preparation of **5** is different (Scheme 2). We previously used **5** in a high-yield synthesis of strictinin,[7] where the (*S*)-HHDP group was constructed through intramolecular and highly diastereoselective coupling of two galloyl groups of **10**. The overall yield to **5** is 82% from D-glucose (8 steps), the efficiency of which is much better than that of Khanbabaee's synthesis.[7] Hence, investigation of the synthesis of **1** commenced with the opening of the δ-lactone ring of **6** to form benzyl ester **11**. The new route through the benzyl ester **11** reduced the number of synthetic steps and made the final deprotection for obtaining unprotected natural product simpler than Khanbabaee's route. The details of the synthesis are given herein.

In our synthesis, the behavior of **6** against silica gel was different from that reported in Khanbabaee's results. In their synthesis, the lactone ring of **6** opened during column chromatography on silica gel eluted with a mixture of CH_2Cl_2 and MeOH (92:8).[3] On the other hand, we were able to isolate δ-lactone **6** after column chromatography on silica gel eluted with a mixture of hexane and ethyl acetate (3:1). We did not detect ring-opened **7** by means of this chromatography. In addition, we attempted to open the ring through chromatography on silica gel eluted with a mixture of CH_2Cl_2 and MeOH, which is the same eluent used in

Khanbabaee's experiment; however, no ring-opened compound **7** was obtained. Thus, we could not reproduce Khanbabaee's procedure. For confirmation, we treated **6** with silica gel in a mixture of CH_2Cl_2 and MeOH (92:8), but no reaction took place (Supporting Information 1).

We opened the lactone ring of **6** by transesterification with BnOH. In this conversion, 3.0 and 30 equivalents of CSA and BnOH were used, respectively. After completion of the reaction, evaporative removal of excess BnOH (bp 205 °C) from the reaction mixture was difficult, but purification of **11** by silica gel column chromatography was simple despite close R_f values of BnOH and **11** (R_f = 0.45 and 0.32, respectively, when eluted with hexane/EtOAc 2:1). Usually, opening of δ-lactone by transesterification is difficult. Khanbabaee mentioned that the opening of the glucono-δ-lactone was induced by strain energy.[3] Actually, the 11-membered ring including the HHDP group contains six sp^2 carbons. In consequence, the conformation is unexpectedly rigid and this adds distortional instability to the lactone ring. Nonetheless, ring opening of fully *O*-acetylated and fully *O*-benzylated glucono-δ-lactones has also been reported to proceed with good to excellent yield.[8,9] Therefore, the strain induced by the HHDP bridge might be a reason for the easy ring-opening, but it would not be the main cause. Incidentally, the employment of BnOH for the opening of glucono-δ-lactone derivative is the first.

The following two steps completed the total synthesis of **1** (Scheme 2). The steps were the introduction of the galloyl group to the unprotected 5-*O* using EDCI and DMAP to provide **12**, and hydrogenolytic removal of all benzyl groups catalyzed by $Pd(OH)_2$. The ^{1}H NMR spectrum of synthesized **1** was identical to that of natural lagerstannin C. Although the chemical shift of 6-H is reported at δ = 4.16 in the literature,[1] re-observation of the stocked and purified natural product at 400 MHz indicated δ = 4.03 for 6-H.

In summary, we achieved the total synthesis of lagerstannin C (**1**). The key step in the synthesis was the opening of δ-lactone **6** to form the corresponding benzyl ester **11**, which made the synthetic route shorter than Khanbabaee's. With the efficiency of preparation of the starting material **5**, the route became practical at a laboratory level. The synthesis confirmed the structure of natural lagerstannin C, and demonstrated that the gluconic acid type ellagitannins can be supplied synthetically.

All commercially available reagents were used without further purification. All moisture and air sensitive reactions were performed in glassware equipped with rubber septa (or a septum) under the positive pressure of argon or N_2. When necessary, the glassware was dried under reduced pressure by heating with a heat-gun and solvents were distilled prior to use. The substrates were azeotropically dried if needed by evaporation of their benzene solution several times to remove trace water that may be contained to the substrates. The reaction mixture was magnetically stirred. Concentration was performed under reduced pressure. The reactions were monitored by TLC and MS. Anhyd $MgSO_4$ was used to dry organic layers after extraction, and it was removed by filtration through a cotton pad. The filtrate was concentrated and subjected to further purification protocols if necessary. This sequence was represented as 'the general drying procedure' in the following experimental methods. TLC was performed on Merck precoated silica gel 60 F-254 plates. Spots were visualized by exposure to UV light, or by immersion into a solution of 2% anisaldehyde, 5% H_2SO_4 in EtOH followed by heating at ca. 200 °C. Column chromatography was performed on Kanto Chemical silica gel 60 N (Spherical, neutral, 40–50 or 63–210 μm). The other carrier materials were noted in each case.

The melting points were determined using a Yanagimoto micro-melting point apparatus and uncorrected. Optical rotations were determined using a Jasco DIP-370 polarimeter with a 100-mm cell at 589 nm. IR spectra were recorded with a spectrophotometer equipped with an attenuated total reflectance (ATR) sampling unit. HRMS were obtained on a Jeol JMS-T100LC spectrometer for electrospray ionization (ESI). The data are reported in units of mass to charge.

NMR spectra were recorded on Jeol JNM-ECX-400, at 400 MHz for ^{1}H and 100 MHz for ^{13}C, respectively. Chemical shifts in NMR spectra were calibrated by using the internal standard or solvent residual peaks [TMS in $CDCl_3$ (δ = 0.0) and acetone (δ = 2.04) for ^{1}H NMR, and $CHCl_3$ (δ = 77.16) and acetone (δ = 29.84) for ^{13}C NMR]. For ^{13}C NMR (100 MHz) the multiplicities are abbreviated as follows: s, C; d, CH; t, CH_2; and q, CH_3.

2,3-Di-*O*-benzyl-4,6-*O*-[(*S*)-hexabenzyloxydiphenoyl]-D-glucono-δ-lactone (6)

A solution of pyranose **5** (99.9 mg, 83.0 μmol) and Dess–Martin periodinane (42.3 mg, 99.7 μmol) in CH_2Cl_2 (5 mL) was stirred for 20 min at r.t. The reaction was quenched with sat. aq $NaHCO_3$ (5 mL). The aqueous mixture was extracted with EtOAc. The combined organic layers were washed with H_2O and brine. After the general drying procedure, the crude product was purified by column chromatography (silica gel, 3 g, hexane/EtOAc 1:0 to 3:1 to 0:1) to afford lactone **6** (77.2 mg, 64.3 μmol, 77%) as a yellow amorphous solid, whose ^{1}H NMR data was identical to the literature data.[3]

Benzyl 2,3-Di-*O*-benzyl-4,6-*O*-[(*S*)-hexabenzyloxydiphenoyl]-D-gluconate (11)

A solution of lactone **6** (134 mg, 112 μmol), BnOH (348 μL, 3.35 mmol), and CSA (77.7 mg, 335 μmol) in CH_2Cl_2 (3 mL) was stirred for 50 min at r.t. The reaction was quenched with water (5 mL). The aqueous mixture was extracted with EtOAc, and the combined organic layers were successively washed with H_2O and brine. After the general drying procedure, the crude product was purified by column chromatography (silica gel, 10 g, hexane/EtOAc 5:1 to 0:1) to afford ester **11** (156 mg, 104 μmol, 93%) as a pale yellow solid; mp 163–164 °C; $[\alpha]_D^{23}$ +3.1 (*c* 0.42, $CHCl_3$).

IR (neat): 3500–3100, 3065, 3031, 2957, 2951, 2927, 1742, 1592, 1454, 1369, 1339, 1252, 1193, 1095, 1028, 904, 772, 745 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 7.54 (d, *J* = 7.1 Hz, 2 H), 7.42–7.21 (m, 33 H), 7.14–7.09 (m, 6 H), 7.01–6.99 (m, 4 H), 6.95 (s, 1 H), 6.85 (s, 1 H), 5.31 (dd, *J* = 7.8, 4.6 Hz, 1 H), 5.22 (d, *J* = 11.9 Hz, 1 H), 5.21 (d, *J* = 11.4 Hz, 1 H), 5.10 (d, *J* = 11.4 Hz, 1 H), 5.05–4.99 (m, 6 H), 4.91–4.85 (m, 3 H), 4.80 (d, *J* = 10.8 Hz, 1 H), 4.77–4.66 (m, 5 H), 4.47 (br m, 1 H), 4.42 (d, *J* = 11.2 Hz, 1 H), 4.32 (d, *J* = 4.6 Hz, 1 H), 4.24 (dd, *J* = 4.6, 4.6 Hz, 1 H), 3.89 (d, *J* = 12.2 Hz, 1 H), 2.80 (d, *J* = 4.8 Hz, 1 H).

^{13}C NMR ($CDCl_3$): δ = 170.3 (s), 168.2 (s), 167.1 (s), 152.8 (s), 152.6 (s), 152.5 (s), 152.4 (s), 144.7 (s), 144.3 (s), 138.0 (s), 137.9 (s), 137.7 (s), 137.6 (s), 137.2 (s), 136.7 (s), 136.6 (s, 2 C), 134.9 (s), 129.5 (s), 128.9–127.6 (overlapping 44 d and 1 s: 15 peaks were observed), 127.1 (d), 123.9 (s), 122.8 (s), 108.8 (d), 107.7 (d), 79.1 (d), 78.8 (d), 75.7 (t, 2 C), 75.2 (t), 75.1 (t), 74.3 (t), 73.5 (t), 73.0 (d), 71.2 (t), 71.2 (t), 69.2 (d), 67.6 (t), 66.6 (t).

HRMS (ESI-TOF): *m*/*z* [M + Na]$^+$ calcd for $C_{83}H_{72}O_{15}Na$: 1331.4769; found: 1331.4740.

Benzyl 2,3-Di-*O*-benzyl-4,6-*O*-[(*S*)-hexabenzyloxydiphenoyl]-5-*O*-(3,4,5-tri-*O*-benzylgalloyl)-D-gluconate (12)

To a stirred solution of alcohol **11** (5.5 mg, 4.2 μmol) in CH_2Cl_2 (1.25 mL) were added 3,4,5-tri-*O*-benzylgallic acid (2.1 mg, 4.8 μmol), EDCI·HCl (3.2 mg, 17 μmol), and DMAP (2.1 mg, 17 μmol) at r.t. The mixture was stirred for 2 d, and then to the mixture was added sat. aq NH_4Cl (2 mL). The aqueous mixture was extracted with EtOAc, and the combined organic layers were successively washed with H_2O and brine. After the general drying procedure, the crude product was purified by column chromatography (silica gel, 0.7 g, hexane/EtOAc 4:1 to 0:1) to afford ester **12** (5.9 mg, 3.4 μmol, 81%) as a white solid; mp 53–55 °C; $[\alpha]_D^{21}$ –9.4 (*c* 0.5, $CHCl_3$).

IR (neat): 3067, 3019, 2960, 2933, 2877, 1741, 1718, 1594, 1498, 1451, 1110, 1095, 970, 750 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 7.46–7.10 (m, 60 H), 7.04–6.96 (m, 2 H), 6.94 (s, 1 H), 6.90 (s, 1 H), 5.78 (br dd, *J* = 7.9, 2.5 Hz, 1 H), 5.63 (dd, *J* = 7.9, 3.0 Hz, 1 H), 5.19 (d, *J* = 12.0 Hz, 1 H), 5.15–4.95 (m, 14 H), 4.91 (d, *J* = 11.0 Hz, 1 H), 4.86 (d, *J* = 11.0 Hz, 1 H), 4.86 (d, *J* = 11.0 Hz, 1 H), 4.79 (dd, *J* = 13.2, 2.5 Hz, 1 H), 4.77 (d, *J* = 11.5 Hz, 1 H), 4.73–4.68 (m, 3 H), 4.51 (d, *J* = 11.5 Hz, 1 H), 4.42 (d, *J* = 11.0 Hz, 1 H), 4.35 (d, *J* = 5.3 Hz, 1 H), 4.21 (d, *J* = 13.2, 1 H), 4.19 (dd, *J* = 5.3, 3.0 Hz, 1 H).

^{13}C NMR ($CDCl_3$): δ = 170.5 (s), 168.0 (s), 167.4 (s), 165.1 (s), 152.7 (s), 152.6 (s, 3 C), 152.5 (s), 152.4 (s), 144.8 (s), 144.4 (s), 142.9 (s), 138.0 (s), 137.8 (s), 137.7 (s), 137.6 (s, 2 C), 137.5 (s), 137.1 (s), 136.7 (s, 2 C), 136.6 (s), 136.5 (s), 135.0 (s), 129.2 (s), 128.7–127.6 (overlapping 60 d: 19 peaks were observed), 127.1 (s), 124.5 (s), 123.8 (s), 123.1 (s), 109.4 (d, 2 C), 108.4 (d), 107.6 (d), 80.0 (d), 77.4 (d), 75.6 (t), 75.6 (t), 75.2 (t), 75.2 (t), 75.1 (t), 74.1 (t), 73.7 (t), 71.6 (d), 71.3 (t, 2 C), 71.1 (t), 71.0 (t), 70.9 (d), 67.4 (t), 64.4 (t).

HRMS (ESI-TOF): *m*/*z* [M + Na]$^+$ calcd for $C_{111}H_{94}O_{19}Na$: 1753.6287; found: 1753.6274.

Lagerstannin C (1)

A mixture of benzyl ether **12** (33.2 mg, 19.2 μmol) and $Pd(OH)_2$ on carbon (20 wt%, 6.9 mg, 4.9 μmol) in THF/MeOH (1:1, 1 mL) was stirred for 10 h at r.t. under a H_2 atmosphere. The mixture was filtered through a cotton-Celite pad to remove $Pd(OH)_2$ on carbon, which was washed with MeOH. The filtrate and MeOH used for the washing was combined, and it was concentrated to afford lagerstannin C (10.0 mg, 17.8 μmol, 93%) as a gray amorphous solid, whose ^{1}H, ^{13}C NMR data, and mass spectrum were identical to the literature data.[1] The gray amorphous solid was further purified by a series of chromatography, which are cellulose column chromatography (cellulose, 1.5 g, H_2O/AcOH 49:1 then H_2O/MeOH 9:1), chelate resin column chromatography (DIAION CR-20, 1.5 g, H_2O/MeOH 1:0 to 3:1), and Sephadex column chromatography (Sephadex LH-20, 1.5 g, H_2O/acetone 1:0 to 3:7), to afford **1** as white amorphous solid; $[\alpha]_D^{19}$ +34 (*c* 0.4, MeOH).

IR (neat): 3603–3070, 3033, 3006, 2959, 2927, 2871, 1710, 1649, 1599, 1498, 1424, 1363, 1225, 1194, 1157, 1093, 1031, 913, 741, 698 cm^{-1}.

^{1}H NMR (acetone-d_6): δ = 7.17 (s, 2 H), 6.84 (s, 1 H), 6.56 (s, 1 H), 5.76 (dd, *J* = 8.2, 3.0 Hz, 1 H), 5.47 (dd, *J* = 8.2, 2.7 Hz, 1 H), 4.92 (dd, *J* = 13.2, 3.0 Hz, 1 H), 4.27 (d, *J* = 2.5 Hz, 1 H), 4.14 (dd, *J* = 2.7, 2.5 Hz, 1 H), 4.03 (d, *J* = 13.2 Hz, 1 H).

^{13}C NMR (acetone-d_6): δ = 174.5 (s), 168.9 (s), 167.6 (s), 166.1 (s), 146.1 (s, 2 C), 145.2 (s), 145.2 (s), 144.5 (s), 144.3 (s), 139.3 (s), 136.5 (s), 136.0 (s), 127.4 (s), 126.4 (s), 121.1 (s), 115.8 (s), 115.2 (s), 110.1 (d, 2 C), 109.1 (d), 107.6 (d), 73.1 (d), 72.2 (d), 71.5 (d), 71.3 (d), 64.8 (t).

HRMS (ESI-TOF): *m*/*z* [M – H]$^-$ calcd for $C_{27}H_{21}O_{19}$: 649.0677; found: 649.0665.

Funding Information

The Ministry of Education, Culture, Sports Science & Technology in Japan supported the program for the Strategic Research Foundation at Private Universities (S1311046), JSPS KAKENHI (Grant Number JP15K13650, JP16H01163 in Middle Molecular Strategy, and JP16KT0061) partly supported this work. We thank Osaka Synthetic Chemical Laboratories, Inc. for provision of EDCI·HCl

Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0036-1588477.

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