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Total Synthesis of the Naturally Occurring Glycosylflavone Aciculatin

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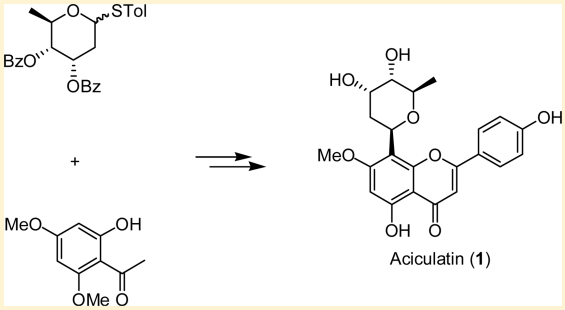
Supporting Information

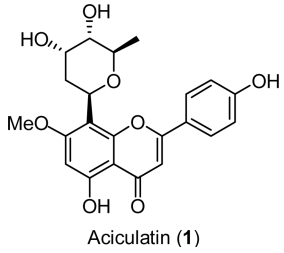
ABSTRACT: The new flavone-glycoside aciculatin (**1**), from *Chrysopogon aciculatus*, has been shown to have cytotoxic, anti-inflammatory, and antiarthritis activity. Further biological studies have been limited because of the limited availability of **1** from natural sources. Herein the first total synthesis of **1** in an overall yield of 8.3% is described. The synthesis involved the regio- and stereoselective glycosylation−Fries-type *O*-to-*C* rearrangement to construct the *C*-aryl glycosidic linkage, followed by a Baker−Venkataraman rearrangement and cyclodehydration to form the flavone scaffold.



Chrysopogon aciculatus is a traditional herbal medicine in widespread use for the treatment of swelling, the common cold, fever, and diarrhea. Some of the naturally occurring *C*-glycosylflavone extracts isolated from *C. aciculatus* were found to show cytotoxic activity against human cancer cell lines.[1−3] Aciculatin (**1**), a *β*-D-digitoxopyranosyl flavone, is a constituent of these extracts. Aciculatin itself was first reported to exhibit cytotoxic activity in 1991.[1] It also exerts a potent anti-inflammatory effect by inhibiting lipopolysaccharide-mediated inducible nitric oxide synthetase (iNOS) and cyclooxygenase-2 (COX-2) expression through regulation of the universal transcription factor NF-*κ*B and c-Jun N-terminal kinase (JNK)/p38 mitogen-activated protein kinase (MAPK) pathways.[4] The effects of aciculatin on anti-inflammatory arthritis via decreasing interleukin (IL)-1*β*-induced granulocyte-colony-stimulating factor (G-CSF) expression have been correlated with G-CSF-associated neutrophil maturation.[5] A recent study indicated that aciculatin (**1**) is a potent p53 inducer and a promising anticancer agent with low genotoxicity.[6] However, such studies are limited since aciculatin is available in only 0.26% (dry wt) yield from natural sources,[1] and hence an efficient, stereoselective total synthesis is urgently required. Herein, the first total synthesis of aciculatin is described. The key steps involve regio- and stereoselective digitoxosylation of the electron-rich phenol with thiodigitoxoside to construct the *C*-aryl glycosidic linkage via the Fries-type *O*-to-*C* rearrangement[7,8] and the formation of the flavone scaffold using the Baker−Venkataraman rearrangement, followed by cyclodehydration.[9,10]

RESULTS AND DISCUSSION

The retrosynthetic analysis, in which the target molecule aciculatin (**1**) is obtained from *β*-D-digitoxopyranosylflavone (**2**) via a series of functional-group transformations, is depicted in Scheme 1. Glycosylation of the electron-rich phenol acceptor (**5**) with the digitoxosyl donor (**4**) was anticipated to afford the



β-*C*-digitoxosyl derivative (**3**) with the correct regio- and stereoselectivity via a Fries-type *O*-to-*C* rearrangement. This process is well precedented in the construction of *α*-hydroxyaryl *C*-glycosyl linkages under acidic conditions, where electron-rich phenolic systems are used as acceptors.[7,8] Esterification of *β*-D-digitoxopyranosyl phenol (**3**) followed by a Baker−Venkataraman rearrangement and cyclodehydration should yield flavone (**2**).[9,10] The digitoxosyl donor (**4**), the key precursor of the synthesis, would be synthesized from methyl 2,3,4,6-tetra-*O*-trimethylsilyl-*α*-D-glucopyranoside (**6**) through one-pot protection and functional group conversions.

As shown in Scheme 2, thiodigitoxoside (**4**) was synthesized starting from methyl 2,3,4,6-tetra-*O*-trimethylsilyl-*α*-D-glucopyranoside (**6**), from which methyl 4,6-*O*-benzylidene-2,3-di-*O*-tosyl-*α*-D-glucopyranoside (**7**) was prepared via a one-pot reaction in 71% yield.[11,12] Treatment of glucoside (**7**) with lithium triethylborohydride ($LiHBEt_3$) in THF gave **8** in 95% yield.[13] The proposed mechanism for this conversion is via the *α*-D-*allo*-2,3-epoxide intermediate followed by selective reductive ring opening. Alternatively, reductive cleavage was accomplished using methyl 4,6-*O*-benzylidene-2,3-di-*O*-mesyl-*α*-D-glucopyranoside as the substrate, but the yield was much lower (52%). Benzoylation of the resulting 3-axial hydroxy

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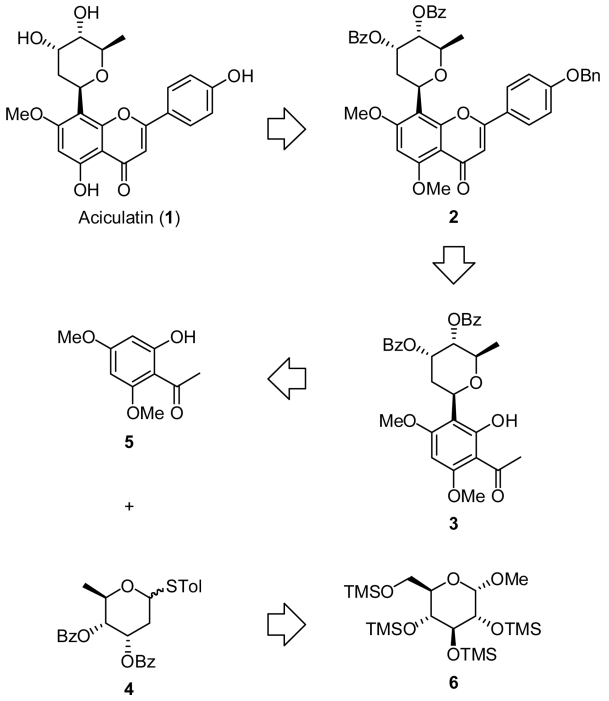
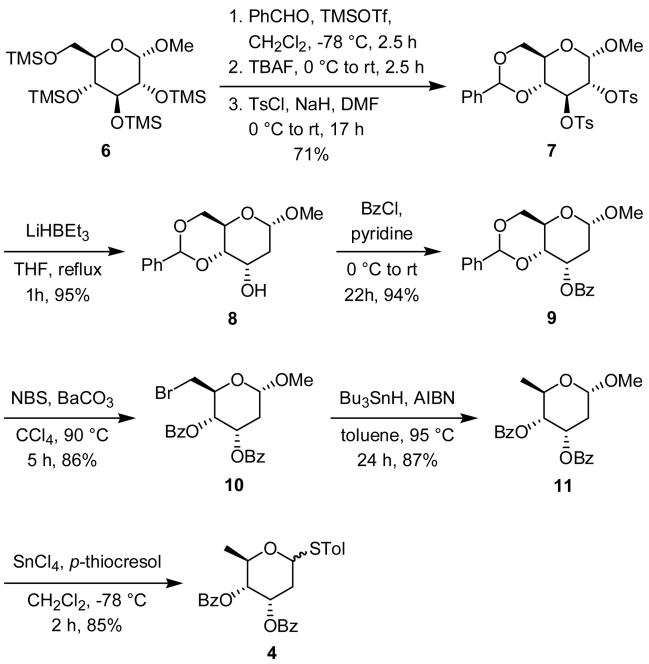
Scheme 1. Retrosynthetic Analysis of Aciculatin (1)



Scheme 2. Synthesis of 3,4-Di-*O*-Benzoylthiodigitoxoside (4)



group of **8** with BzCl in pyridine afforded methyl 3-*O*-benzoyl-4,6-*O*-benzylidene-2-deoxy-α-ribohexopyranoside (**9**) in 94% yield. The NBS-mediated fragmentation of the 4,6-benzylidene acetal via the Hanessian–Hullar reaction gave 3,4-di-*O*-benzoyl-6-bromo-2,6-deoxy-α-ribohexopyranoside (**10**) (86%) via a highly regioselective ring opening.[14−16] Compound **10** was then subjected to reductive debromination with AIBN and Bu_3SnH in toluene to afford the fully protected digitoxoside (**11**) (87%).[17] This was converted into the target donor 3,4-di-*O*-benzoylthiodigitoxoside (**4**) using *p*-thiocresol in the presence of $SnCl_4$ in 85% yield ($\alpha/\beta \approx 1/1$).[18]

With the key intermediate **4** in hand, the synthesis of aciculatin (**1**) was pursued as outlined in Scheme 3. Glycosylation of the electron-rich phenol **5** with the digitoxosyl derivative **4** activated by NIS/TfOH afforded the β-D-digitoxopyranoside (**3**) in 81% yield, with good regio- and stereoselectivity.[19] An *in situ* $O \rightarrow C$ Fries-type rearrangement has been proposed to account for the formation of the hydroxy-*C*-glycosyl product.[7,8] Alternatively, compound **3** was isolated in slightly lower yield (63%) when the 3,4-di-*O*-benzoyldigitoxosyl imidate was used as the donor in the presence of a catalytic amount of TMSOTf. β-*C*-Digitoxoside (**3**) was susceptible to a 1-ethyl-3-(3-(dimethylamino)propyl)-carbodiimide (EDC)-mediated esterification with 4-benzyloxybenzoic acid to give the corresponding ester **12** in 98% yield. The 1,3-diketo intermediate was formed via Baker–Venkataraman rearrangement using NaH, in which enolate formation results in intramolecular acyl transfer.[9,10] When ^{t}BuOK or KOH was used as the base, the 1,3-diketo intermediate was accompanied by two major byproducts, as detected by thin-layer chromatography (TLC). The crude 1,3-diketone was converted into the flavone **2** in 59% over two steps using camphorsulfonic acid (CSA)-mediated cyclodehydration, significantly better than using *p*-toluenesulfonic acid (*p*TSA). Subsequently, the BBr_3-mediated selective de-*O*-methylation/de-*O*-benzylation of flavone **2** afforded the monomethoxy *C*-glycosyl compound **13** in 50% yield.[20,21] The BBr_3 and the selective nature of de-*O*-methylation result from the formation of a complex involving oxygen atoms of the 4-carbonyl and 5-methoxy groups.[21] Using the boron tribromide/dimethyl sulfide complex ($BBr_3{\cdot}SMe_2$)[22] resulted in a lower isolated yield of 42%. Finally, the benzoyl groups were removed by treatment with NaOMe to give aciculatin (**1**) in 88% yield. The spectroscopic data of synthetic **1** are in good agreement with those of natural aciculatin.[1]

In conclusion, the first total synthesis of aciculatin (**1**) has been accomplished in 12 steps with an overall yield of 8.3% starting from methyl 2,3,4,6-tetra-*O*-trimethylsilyl-α-D-glucopyranoside (**6**). The formation of the β-*C*-aryl glycosidic linkage by regio- and stereoselective glycosylation of the electron-rich phenol with thiodigitoxoside via a Fries-type *O*-to-*C* rearrangement and the use of a Baker–Venkataraman rearrangement/cyclodehydration to form the flavone are the key steps in the construction of the requisite skeleton. The efficient nature of this synthesis may provide sufficient quantities of aciculatin (**1**) for further biological studies.

EXPERIMENTAL SECTION

General Experimental Procedures. Unless otherwise stated, all reagents were purchased from commercial sources and used as supplied without further purification. Optical rotations were measured on a JASCO P-1020 digital polarimeter at 25 °C with a PTC-102T temperature controller; a sodium lamp with a wavelength of 589 nm was used as the light source. ^{1}H and ^{13}C NMR spectra were recorded on a Mercury-400 spectrometer, and chemical shifts are reported relative to the $CDCl_3$ signal (^{1}H, δ = 7.24; ^{13}C, δ = 77.00) or methanol-d_4 (^{1}H, δ = 3.31; ^{13}C, δ = 49.00). Splitting patterns are recorded as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; and ABq, AB quartet. HRFABMS data were obtained with a JEOL JMS-700 mass spectrometer, recorded as *m*/*z* values. Reactions were monitored by analytic TLC carried out on silica gel 60 F254 precoated glass-backed plates (Merck). The chromatograms were detected under UV irradiation (λ = 254 nm) followed by staining with a solution of

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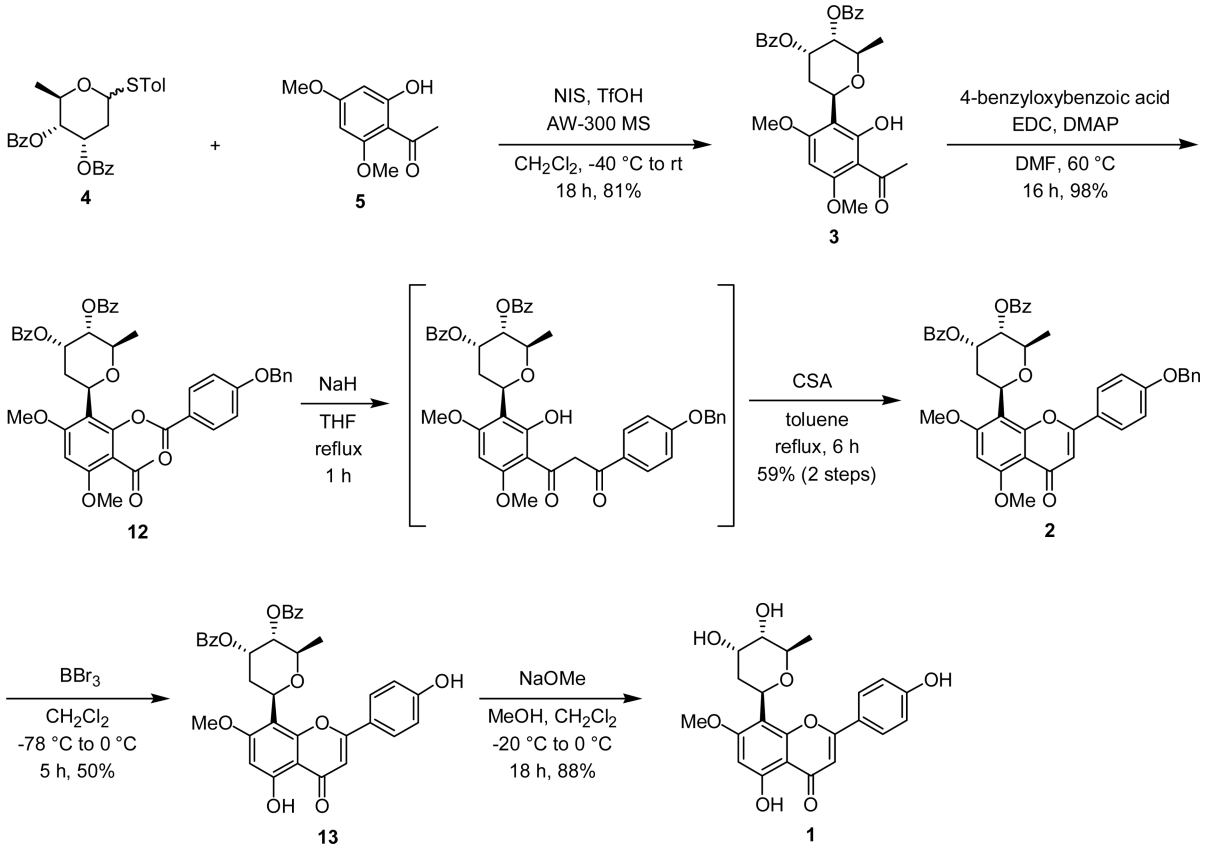
Scheme 3. Synthesis of Aciculatin (1)



$Ce(NH_4)_2(NO_3)_6$, $(NH4)_6Mo_7O_{24}$, and H_2SO_4 in water. Column chromatography was performed using SiliaFlash P60 silica gel of 230–400 mesh size. Purity of synthesized aciculatin (**1**) was determined by a Hitachi 2000 series HPLC system using a C_{18} reversed-phase column (Agilent ZORBAX Eclipse XDB-C18 5 μm, 4.6 mm × 150 mm). The elution system consisted of a MeCN (mobile phase A) and 10 mM NH_4OAc aqueous solution containing 0.1% formic acid (mobile phase B). The analysis was carried out in gradient conditions starting from A/B = 10/90% to A/B = 90/10% in 45 min at a flow rate of 0.5 mL/min.

Methyl 4,6-*O*-Benzylidene-2,3-di-*O*-(*p*-tolylsulfonyl)-α-D-glucopyranoside (7). TMSOTf (18 μL, 0.097 mmol) was added to a solution of **6** (315 mg, 0.651 mmol), PhCHO (80 μL, 0.782 mmol), and 3 Å molecular sieves (470 mg) in CH_2Cl_2 (3 mL) at −78 °C under $Ar_{(g)}$. After 2.5 h stirring, the reaction mixture was warmed to 0 °C, and TBAF (1 M solution in THF, 2.6 mL, 2.6 mmol) was added. The mixture was gradually warmed to room temperature, and stirring was maintained. After 2.5 h, the solution was cooled to 0 °C and diluted with DMF (2.0 mL). A solution of *p*-toluenesulfonyl chloride (994 mg, 5.213 mmol) in DMF (2.0 mL) and NaH (365 mg, 9.123 mmol) were sequentially added. The reaction mixture was allowed to warm to room temperature and stirred overnight. The reaction was quenched with H_2O at 0 °C, and the resulting mixture was extracted with CH_2Cl_2 (3 × 25 mL). The organic layer was dried over $MgSO_4$, filtered, concentrated under reduced pressure, and purified by column chromatography (EtOAc/*n*-hexane = 1/3) to provide **7** (272 mg, 71%) as a white solid. The spectroscopic data of compound **7** were in agreement with literature data.[13b]

Methyl 4,6-*O*-Benzylidene-2-deoxy-α-D-ribohexopyranoside (8). To a stirred solution of compound **7** (57 mg, 0.097 mmol) in THF (1.0 mL) was added $LiHBEt_3$ (1 M solution in THF, 0.6 mL, 0.6 mmol) at 0 °C under $Ar_{(g)}$. The reaction mixture was heated under reflux for 1 h, and the excess reducing agent was quenched with EtOAc. The mixture was diluted with saturated aqueous NH_4Cl and extracted with CH_2Cl_2 (3 × 15 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (EtOAc/*n*-hexane = 1/2) to provide **8** (24.1 mg, 95%) as a white solid. The spectroscopic data of compound **8** were in agreement with literature data.[13b]

Methyl 3-*O*-Benzoyl-4,6-*O*-benzylidene-2-deoxy-α-D-ribohexopyranoside (9). Benzoyl chloride (2.2 mL, 18.94 mmol) was added to a stirred solution of **8** (4.8 g, 18.01 mmol) in pyridine (60 mL) at 0 °C under $Ar_{(g)}$. The reaction mixture was gradually warmed to room temperature and stirred overnight (22 h). Water was added, and the mixture was extracted with CH_2Cl_2 (3 × 100 mL). The organic layer was washed with 1 N HCl, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (EtOAc/*n*-hexane = 1/8) to provide **9** (6.3 g, 94%) as a white solid. The spectroscopic data of compound **9** were in agreement with literature data.[16]

Methyl 3,4-Di-*O*-benzoyl-6-bromo-2,6-dideoxy-α-D-ribohexopyranoside (10). *N*-Bromosuccinimide (2.5 g, 14.05 mmol) and $BaCO_3$ (3.9 g, 19.76 mmol) were added to a stirred solution of **9** (4.9 g, 13.22 mmol) in CCl_4 (95 mL) at 90 °C under $Ar_{(g)}$. The reaction mixture was heated under reflux for 5 h and then cooled to room temperature. The mixture was filtered, and H_2O was added to the filtrate. The aqueous layer was extracted with CH_2Cl_2 (3 × 100 mL), and the organic layer was washed with saturated aqueous $NaHCO_3$, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (EtOAc/*n*-hexane = 1/5) to provide **10** (5.1 g, 86%) as a white solid. The spectroscopic data of compound **10** were in agreement with literature data.[16]

Methyl 3,4-Di-*O*-benzoyl-2,6-dideoxy-α-D-ribohexopyranoside (11). Azobis(isobutyronitrile) (1.9 g, 11.57 mmol) and Bu_3SnH (5.6 mL, 20.71 mmol) were added to a stirred solution of **10** (5.2 g, 11.57 mmol) in toluene (50 mL) at room temperature under $Ar_{(g)}$. The reaction mixture was heated at 95 °C for 24 h and then concentrated under reduced pressure to remove the solvent. The residue was purified by column chromatography (*n*-

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hexane → toluene/Et_2O = 9/1) to give **11** (3.72 g, 87%) as a white solid. The spectroscopic data of compound **11** were in agreement with literature data.[16]

4-Methylphenyl 3,4-Di-*O*-benzoyl-2,6-dideoxy-1-thio-D-ribohexopyranoside (4). A solution of $SnCl_4$ (0.19 mL, 1.607 mmol) in CH_2Cl_2 (2.0 mL) was added dropwise to a mixture of **11** (541 mg, 1.461 mmol), *p*-thiocresol (218 mg, 1.755 mmol), and AW-300 MS (540 mg) in CH_2Cl_2 (7.0 mL) at −78 °C under $Ar_{(g)}$. The reaction mixture was stirred at −78 °C for 2 h; then CH_2Cl_2 (150 mL), saturated aqueous $NaHCO_3$ (25 mL), and saturated aqueous potassium sodium tartrate solution (25 mL) were added sequentially to the solution at 0 °C and stirred for another 1 h at room temperature. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (EtOAc/*n*-hexane = 1/10) to afford **4** (577 mg, 85%, $\alpha/\beta \approx 1/1$) as a colorless solid. **4α**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24−8.21 (m, 2H), 7.88−7.86 (m, 2H), 7.60−7.56 (m, 1H), 7.52−7.40 (m, 5H), 7.35−7.31 (m, 2H), 7.14 (d, *J* = 7.6 Hz, 2H), 5.80 (q, *J* = 3.2 Hz, 1H), 5.49 (dd, *J* = 6.4, 1.2 Hz, 1H), 5.04 (dd, *J* = 9.6, 3.2 Hz, 1H), 4.97−4.90 (m, 1H), 2.63 (ddd, *J* = 15.2, 6.4, 3.2 Hz, 1H), 2.48 (ddd, *J* = 15.2, 3.2, 1.2 Hz, 1H), 2.33 (s, 3H), 1.31 (d, *J* = 6.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.8 (C), 165.5 (C), 137.4 (C), 133.2 (CH), 132.7 (C), 131.8 (CH), 130.1 (CH), 129.8 (C), 129.7 (CH), 129.5 (C), 128.4 (CH), 128.3 (CH), 83.2 (CH), 72.9 (CH), 66.9 (CH), 63.4 (CH), 35.3 (CH_2), 21.1 (CH_3), 17.5 (CH_3); **4**: HRFABMS *m*/*z* 462.1507 $[M]^+$ (calcd for $C_{27}H_{26}O_5S$, 462.1501).

(1*R*)-1-(3-Acetyl-2-hydroxy-4,6-dimethoxyphenyl)-1,5-anhydro-3,4-di-*O*-benzoyl-2,6-dideoxy-D-ribohexitol (3). NIS (260 mg, 1.155 mmol) and TfOH (0.5 M solution in Et_2O, 0.30 mL, 0.150 mmol) were added sequentially to a mixture of **4** (492 mg, 1.064 mmol), **5** (180 mg, 0.917 mmol), and AW-300 MS (1 g) in CH_2Cl_2 (11 mL) at −40 °C. After stirring for 1 h, the reaction mixture was warmed to room temperature gradually and stirred overnight. The reaction was quenched with Et_3N at 0 °C and filtered through a pad of Celite. The filtrate was washed with an aqueous solution of $Na_2S_2O_3$, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (EtOAc/*n*-hexane = 1/5 → 1/3) to provide **3** (395 mg, 81%) as a white solid: $[\alpha]^{25}_D$ +20 (*c* 0.3, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12−8.09 (m, 2H), 7.91−7.88 (m, 2H), 7.61−7.57 (m, 1H), 7.51−7.46 (m, 3H), 7.34−7.30 (m, 2H), 5.94 (s, 1H), 5.84 (q, *J* = 3.2 Hz, 1H), 5.63 (dd, *J* = 12.0, 2.4 Hz, 1H), 5.11 (dd, *J* = 10.0, 3.2 Hz, 1H), 4.34 (dq, *J* = 10.0, 6.0 Hz, 1H), 3.90 (s, 3H), 3.89 (s, 3H), 3.13 (ddd, *J* = 14.4, 12.0, 3.2 Hz, 1H), 2.58 (s, 3H), 1.93 (ddd, *J* = 14.4, 3.2, 2.4 Hz, 1H), 1.28 (d, *J* = 6.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.4 (C),165.69 (C), 165.66 (C), 164.8 (C), 164.7 (C), 163.3 (C), 133.01 (CH), 132.98 (CH), 130.5 (C), 129.8 (C), 129.69 (CH), 129.65 (CH), 128.5 (CH), 128.3 (CH), 107.4 (C), 106.0 (C), 86.4 (CH), 73.9 (CH), 71.2 (CH), 69.3 (CH), 66.3 (CH), 55.7 (CH_3), 55.4 (CH_3), 33.2 (CH_3), 33.1 (CH_2), 18.4 (CH_3); HRFABMS *m*/*z* 535.1968 $[M + H]^+$ (calcd for $C_{30}H_{31}O_9$, 535.1968).

(1*R*)-1-(3-Acetyl-2-{[4-(benzyloxy)benzoyl]oxy}-4,6-dimethoxyphenyl)-1,5-anhydro-3,4-di-*O*-benzoyl-2,6-dideoxy-D-ribohexitol (12). A mixture of **3** (41 mg, 0.077 mmol), 4-benzyloxybenzoic acid (35 mg, 0.153 mmol), EDC (44 mg, 0.230 mmol), and DMAP (19 mg, 0.156 mmol) in DMF (1.0 mL) was stirred at 60 °C for 16 h. After completion, H_2O was added to the mixture, and the aqueous layer was extracted with EtOAc (3 × 10 mL). The organic layer was washed with an aqueous solution of NaCl, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (EtOAc/*n*-hexane = 1/1) to provide **12** (56 mg, 98%) as a white solid. $[\alpha]^{25}_D$ +24 (*c* 0.3, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12−8.07 (m, 2H), 7.93 (dd, *J* = 8.4, 1.2 Hz, 2H), 7.79 (dd, *J* = 8.4, 1.6 Hz, 2H), 7.54−7.23 (m, 11H), 7.04−7.01 (m, 2H), 6.37 (s, 1H), 5.77 (q, *J* = 2.8 Hz, 1H), 5.39 (dd, *J* = 12.0, 2.4, 1H), 5.16, 5.14 (ABq, *J* = 12.0 Hz, 2H), 4.65 (dd, *J* = 10.0, 2.8, 1H), 4.09 (dq, *J* = 10.0, 6.4 Hz, 1H), 3.87 (s, 3H), 3.83 (s, 3H), 2.77 (ddd, *J* = 14.4, 12.0, 2.8 Hz, 1H), 2.45 (s, 3H), 2.08 (ddd, *J* = 14.4, 2.8, 2.4 Hz, 1H), 0.86 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.1 (C), 165.5 (C), 165.3 (C), 164.6 (C), 163.0 (C), 159.6 (C), 158.2 (C), 147.8 (C), 136.3 (C), 133.0 (CH), 132.9 (CH), 132.3 (CH), 130.3 (C), 129.7 (C), 129.6 (CH), 129.5 (CH), 128.7 (CH), 128.4 (CH), 128.23 (CH), 128.16 (CH), 127.5 (CH), 121.8 (C), 118.9 (C), 114.9 (CH), 114.2 (C), 93.2 (CH), 73.4 (CH), 71.1 (CH), 70.2 (CH_2), 68.7 (CH), 67.4 (CH), 56.0 (CH_3), 55.9 (CH_3), 34.2 (CH_2), 31.7 (CH_3), 17.8 (CH_3); HRFABMS *m*/*z* 744.2576 $[M]^+$ (calcd for $C_{44}H_{40}O_{11}$, 744.2571).

(1*R*)-1,5-Anhydro-3,4-di-*O*-benzoyl-1-{2-[4-(benzyloxy)-phenyl]-5,7-dimethoxy-4-oxo-4*H*-chromen-8-yl}-2,6-dideoxy-D-ribohexitol (2). To a stirred solution of **12** (72 mg, 0.097 mmol) in THF (1.5 mL) was added 60% NaH (8 mg, 0.193 mmol) at 0 °C. After stirring for 10 min at this temperature, the mixture was stirred at 80 °C for 1 h. The reaction was quenched with H_2O, and the mixture was extracted with EtOAc (3 × 10 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure to afford a crude extract of the 1,3-diketone, which was used for the next reaction without further purification.

A mixture of the crude extract of the 1,3-diketone (72 mg, 0.097 mmol) and CSA (6 mg, 0.024 mmol) in toluene (1.0 mL) was stirred at 130 °C under $Ar_{(g)}$. After 5 h, a further portion of CSA (12 mg, 0.048 mmol) was added, and the resulting mixture was stirred at 130 °C for another 1 h. The reaction mixture was cooled to 0 °C and neutralized with saturated aqueous $NaHCO_3$. The aqueous layer was extracted with EtOAc (3 × 10 mL), and the organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (EtOAc/*n*-hexane = 3/1 → EtOAc/CH_2Cl_2/THF = 1/6/1) to afford **2** (41.2 mg, 59%) as a yellowish solid: $[\alpha]^{25}_D$ −25 (*c* 0.2, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (dd, *J* = 8.4, 1.2 Hz, 2H), 7.96 (d, *J* = 8.8 Hz, 2H), 7.93 (dd, *J* = 8.4, 1.2 Hz, 2H), 7.64−7.60 (m, 1H), 7.53−7.32 (m, 10H), 7.07 (d, *J* = 8.4 Hz, 2H), 6.60 (s, 1H), 6.39 (s, 1H), 5.85−5.82 (m, 2H), 5.34 (dd, *J* = 10.0, 2.8 Hz, 1H), 5.14, 5.12 (ABq, *J* = 11.6 Hz, 2H), 4.45 (dq, *J* = 10.0, 6.4 Hz, 1H), 3.98 (s, 3H), 3.93 (s, 3H), 3.01−2.94 (m, 1H), 2.09 (ddd, *J* = 14.8, 2.8, 2.8 Hz, 1H), 1.37 (*J* = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.9 (C), 165.6 (C), 161.4 (C), 161.3 (C), 161.0 (C), 160.9 (C), 157.4 (C), 136.3 (C), 133.2 (CH), 130.4 (C), 129.7 (CH), 129.6 (C), 128.64 (CH), 128.57 (CH), 128.4 (CH), 128.2 (CH), 127.9 (CH), 127.6 (CH), 124.3 (C), 115.3 (CH), 109.2 (C), 107.8 (C), 107.1 (CH), 91.6 (CH), 73.3 (CH), 71.8 (CH), 70.2 (CH_2), 69.2 (CH), 66.9 (CH), 56.4 (CH_3), 56.1 (CH_3), 34.0 (CH_2), 18.4 (CH_3); HRFABMS *m*/*z* 727.2547 $[M + H]^+$ (calcd for $C_{44}H_{39}O_{10}$, 727.2543).

(1*R*)-1,5-Anhydro-3,4-di-*O*-benzoyl-2,6-dideoxy-1-[5-hydroxy-2-(4-hydroxyphenyl)-7-methoxy-4-oxo-4*H*-chromen-8-yl]-D-ribohexitol (13). To a stirred solution of **2** (26.4 mg, 0.036 mmol) in CH_2Cl_2 (1.0 mL) was added BBr_3 (1 M solution in CH_2Cl_2, 75 μL, 0.072 mmol) at −78 °C under $Ar_{(g)}$. The reaction mixture was gradually warmed to 0 °C and stirred for 5 h. Ice water was added to quench the reaction, and the mixture was extracted with EtOAc (3 × 5 mL). The organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (MeOH/CH_2Cl_2 = 1/100) to give **13** (11.3 mg, 50%) as a yellowish solid: $[\alpha]^{25}_D$ −61 (*c* 0.1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (dd, *J* = 8.0, 1.2 Hz, 2H), 7.96 (d, *J* = 8.8 Hz, 2H), 7.91 (dd, *J* = 8.0, 1.2 Hz, 2H), 7.66−7.62 (m, 1H), 7.54−7.49 (m, 3H), 7.36 (d, *J* = 8.0 Hz, 1H), 7.34 (d, *J* = 7.6 Hz, 1H), 7.01 (d, *J* = 8.4 Hz, 2H), 6.58 (s, 1H), 6.38 (s, 1H), 5.83 (q, *J* = 2.8 Hz, 1H), 5.76 (dd, *J* = 12.0, 2.4 Hz, 1H), 5.34 (dd, *J* = 10.0, 2.8, 1H), 4.44 (dq, *J* = 10.0, 6.0 Hz, 1H), 3.87 (s, 3H), 2.89 (ddd, *J* = 14.8, 12.0, 2.8 Hz, 1H), 2.09 (ddd, *J* = 14.8, 2.8, 2.4 Hz, 1H), 1.36 (d, *J* = 6.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 182.9 (C), 165.9 (C), 165.6 (C), 164.3 (C), 162.5 (C), 159.3 (C), 155.5 (C), 133.31 (CH), 133.29 (CH), 130.3 (C), 129.7 (CH), 129.5 (C), 128.61 (CH), 128.58 (CH), 128.4 (CH), 123.9 (C), 116.3 (CH), 106.0 (C), 105.5 (C), 103.7 (CH), 95.3 (CH), 73.4 (CH), 71.7 (CH), 69.1 (CH), 66.8 (CH), 56.3 (CH_3), 34.3 (CH_2), 18.4 (CH_3); HRFABMS *m*/*z* 623.1915 $[M + H]^+$ (calcd for $C_{36}H_{31}O_{10}$, 623.1917).

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Aciculatin (1). To a stirred solution of **13** (20 mg, 0.032 mmol) in $MeOH/CH_2Cl_2$ (1/1, 1.0 mL) was added NaOMe (30% in MeOH, 20 μL, 0.096 mmol) at −20 °C under $Ar_{(g)}$. The reaction mixture was warmed to 0 °C gradually and stirred for 18 h. After completion of the reaction, the mixture was diluted with MeOH, neutralized by the addition of acidic Dowex 50W2-200, and filtered. The filtrate was concentrated under reduced pressure, and the residue was purified by column chromatography ($MeOH/CH_2Cl_2$ = 1/20 → 1/10) to afford aciculatin (**1**) (11.7 mg, 88%) as a yellowish solid. The spectroscopic data of the synthetic **1** were in agreement with literature data.[1] $[\alpha]^{25}_D$ +52 (*c* 0.4, MeOH); lit. $[\alpha]^{25}_D$ +51 (*c* 0.5, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$/methanol-d_4 = 1/1) δ 7.95−7.92 (m, 2H), 6.94−6.91 (m, 2H), 6.55 (s, 1H), 6.40 (s, 1H), 5.61 (dd, *J* = 12.0, 2.0 Hz, 1H), 4.13−4.11 (m, 1H), 3.96−3.90 (m, 1H), 3.90 (s, 3H), 3.45 (dd, *J* = 9.6, 3.2 Hz, 1H), 2.57 (ddd, *J* = 14.4, 12.0, 2.4 Hz, 1H), 1.82 (ddd, *J* = 14.4, 2.4, 2.0 Hz, 1H), 1.35 (d, *J* = 6.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$/methanol-d_4 = 1/1) δ 182.6 (C), 164.8 (C), 162.4 (C), 161.1 (C), 160.8 (C), 155.2 (C), 128.2 (CH), 121.8 (C), 115.3 (CH), 106.8 (C), 104.6 (C), 102.1 (CH), 94.6 (CH), 72.9 (CH), 72.4 (CH), 67.1 (CH), 65.2 (CH), 55.4 (CH_3), 35.7 (CH_2), 17.6 (CH_3); HRFABMS *m*/*z* 415.1389 $[M + H]^+$ (calcd for $C_{22}H_{23}O_8$, 415.1393); HPLC purity = 99.28%, t_R = 22.16 min.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.jnatprod.5b01051.

^{1}H NMR spectra for all previously reported compounds; ^{1}H and ^{13}C NMR spectra for all new compounds and aciculatin (**1**) (PDF)

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Notes

The authors declare no competing financial interest.

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