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Concise Total Synthesis of (±)-Deguelin and (±)-Tephrosin Using a Vinyl Iodide as a Key Building Block

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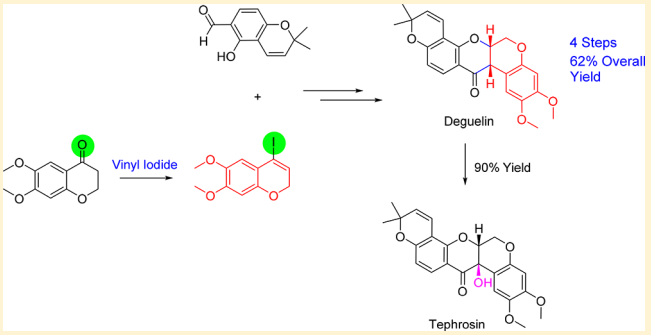
Supporting Information

ABSTRACT: A concise and protecting-group-free total synthesis of the antiproliferative natural product (±)-deguelin (**2**) was accomplished in four steps and 62% overall yield from commercially available precursors. The key transformation employed a vinyl iodide as the pivotal building block to construct the 4-acylchromene substructure present in deguelin. Subsequent Cu_2O-mediated α-hydroxylation of deguelin (**2**) afforded tephrosin (**3**) in 90% yield.



Rotenoids, members of a class of compounds isolated from *Derris* and *Lonchocarpus* species, exhibit significant pesticidal and antiproliferative properties.[1] A *cis*-fused tetrahydrochromeno[3,4-*b*]chromene core is often found in rotenoid natural products, such as rotenone (**1**), deguelin (**2**), and tephrosin (**3**) (Figure 1).[2] In particular, deguelin (**2**) displayed potent antiproliferative activity in several in vitro and in vivo studies and attracted considerable attention from biologists and chemists.[3] In recent years, the antitumor activity of deguelin (**2**) and its mechanism of action have been extensively studied. It was reported that deguelin (**2**) exhibited potent apoptotic and antiangiogenic activities against various human cancer cells, such as lung, prostate, head and neck, and stomach cancer cells.[4] The antitumor activity of deguelin (**2**) has been associated with cell-cycle arrest and induction of apoptosis mediated mainly through mitogen-activated protein kinase (MAPK) and phosphatidylinositol 3-kinase (PI3K)/Akt signal transduction cascades.[5] Recent studies showed that deguelin (**2**) binds to the ATP-binding pocket of heat shock protein 90 (Hsp90), causing the destabilization of various client Hsp90 proteins, such as CDK4, Akt, MEK, and hypoxia-inducible factor 1α (HIF-1α), and ultimately suppressed tumor growth.[6] The significant antiproliferative activity and specific mechanism of action of deguelin make it a compelling lead compound for therapeutic lead optimization and development.

Since its isolation from *Tephrosia vogelii* by Hanriot in 1907, several total syntheses of racemic deguelin (**2**) have already been reported.[7] Recently, an enantioselective synthesis of deguelin (**2**) was reported, and the biological evaluation of both enantiomers showed that the unnatural (+)-deguelin was slightly more potent than its enantiomer in some cancer cell lines.[8] However, for biological studies, deguelin (**2**) and its analogues are still usually prepared from the natural product rotenone (**1**) in four steps with 22% overall yield.[9] Although the semisynthesis of deguelin (**2**) starting from relatively inexpensive rotenone (**1**) facilitated the biological studies of deguelin and its simple analogues, extensive structure−activity relationship (SAR) studies of deguelin (**2**) for the development of potential antitumor agents were abandoned due to the lengthy and inefficient total synthesis.[10] Thus, it is essential to develop a concise and efficient synthetic route to deguelin (**2**) to accelerate the development of therapeutic lead compounds.

Tephrosin (**3**) is another rotenoid and, along with deguelin, is mainly isolated from plants of the genus *Derris*.[11] The anticancer activity and mechanism of action of deguelin (**2**) have been studied extensively, but biological studies on tephrosin (**3**) are rarely reported partly due to its limited availability. A few recent studies showed that tephrosin (**3**) inhibited mouse skin tumor promotion, invasion of cancer cells, and nuclear factor-κB (NF-κB) activity.[12] Nevertheless, the mechanism of its anticancer activity has not been defined. Although tephrosin (**3**) is the 12a-hydroxy analogue of deguelin (**2**), the direct α-C−H hydroxylation of the α-substituted carbonyl in deguelin to obtain α-substituted tephrosin is quite challenging. There has only been one reported de novo total synthesis of tephrosin (**3**).[13]

Our group is dedicated to the structure modification and SAR study of natural products, and a concise and efficient total synthesis of deguelin (**2**), tephrosin (**3**), and their structurally diverse analogues would be beneficial.

Among the several total syntheses reported for deguelin (**2**),[7] the construction of the tetrahydrochromeno[3,4-*b*]chromene skeleton of deguelin (**2**) via 4-acylchromene **5** (Scheme 1)

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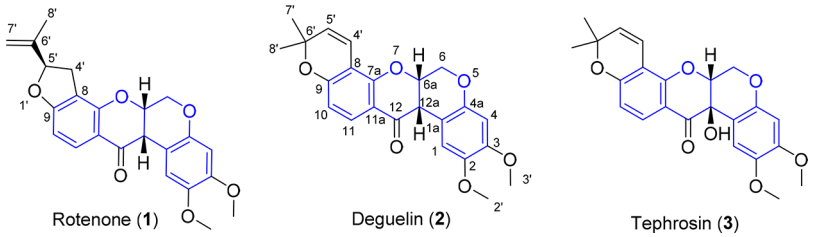
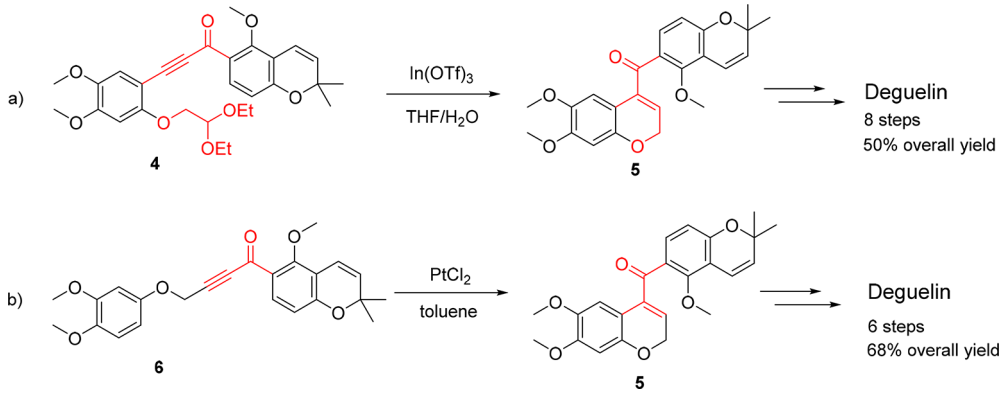
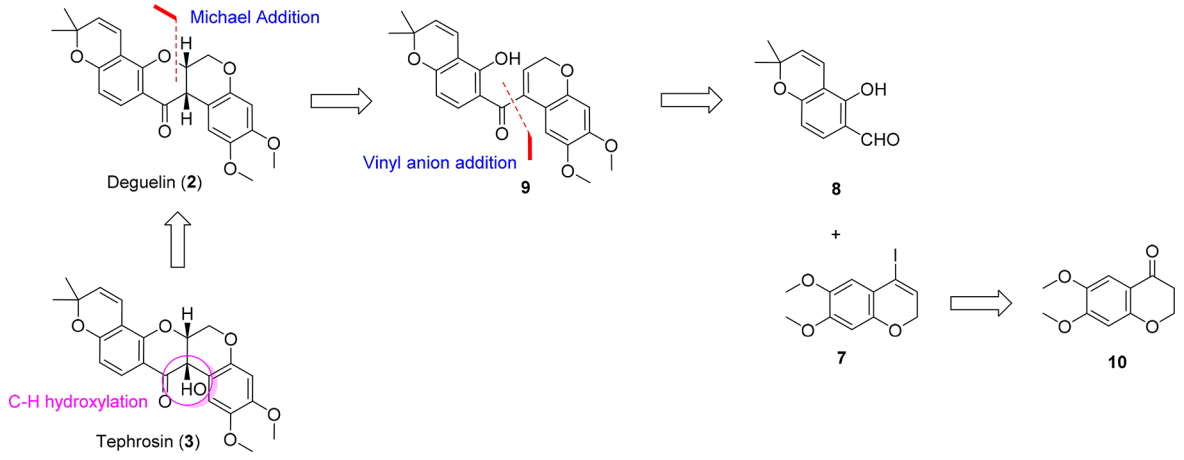


Figure 1. Structures of rotenone (**1**), deguelin (**2**), and tephrosin (**3**).

Scheme 1. Reported Approaches to the Synthesis of (±)-Deguelin (2) via 4-Acylchromene (5)



Scheme 2. Retrosynthetic Analysis for the Synthesis of Deguelin (2) and Tephrosin (3)



proved to be a relatively efficient strategy.[7c,d] As shown in Scheme 1, Kim and Nayak completed a formal synthesis of deguelin (**2**) in eight steps by constructing the 4-acylchromene moiety via an intramolecular alkyne−carbonyl metathesis in the presence of $In(OTf)_3$.[7d] Pastine and Sames reported a concise total synthesis of deguelin (**2**) with a linear sequence of six steps in 68% yield through a hydroarylation of an alkynone intermediate using a platinum catalyst.[7c] However, the use of a noble metal catalyst and/or multiple steps limits the broad application of these synthetic methods. Thus, a search for a more concise transition-metal-free method to establish the complex 4-acylchromene functionality was undertaken.

Considering that vinyl halides have been extensively used in organic synthesis, such as in Sonogashira couplings, Nozaki−Hiyama−Kishi reactions, and Kumada couplings,[14] the addition of the vinyl anion derived from vinyl iodide **7** to benzaldehyde **8** could generate the bis-chromene **9** (Scheme 2). Indeed, some examples of vinyl iodides being used in the total syntheses of natural products for the preparation of unsaturated ketones have been disclosed.[15] With this key strategy in mind, the retrosyntheses of deguelin (**2**) and tephrosin (**3**) were designed as shown in Scheme 2. The direct α-C−H hydroxylation of deguelin (**2**) would afford tephrosin (**3**), and deguelin (**2**) could be generated through the cyclization of bis-chromene **9**. In previous reports, the phenolic group of 2,2-dimethylchromene is often protected as the *O*-methyl ether, and the subsequent demethylation step was inefficient due to selectivity problems arising from the presence of two other methoxy groups in intermediates such as **5**.[7c,d,8] In the proposed scheme, it is anticipated that the *o*-hydroxy-4-acylchromene **9** could be cyclized directly. Bis-chromene **9** could be assembled by the coupling of intermediates **7** and **8**, and the common building block **8** is commercially available. Vinyl iodide **7** could be synthesized via the oxidation of a hydrazone by iodine in the presence of a base.

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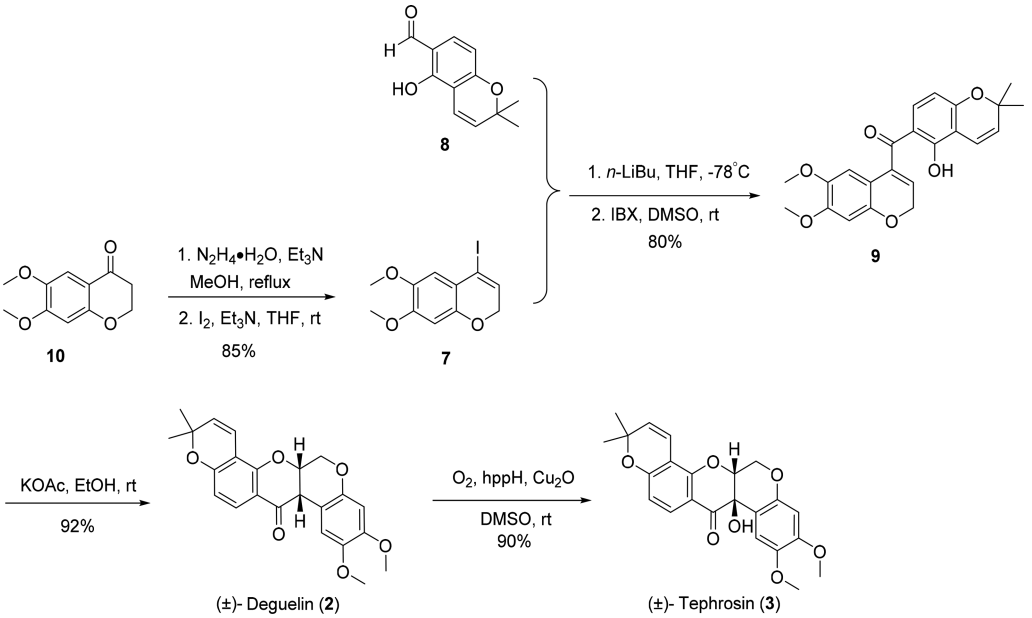
Scheme 3. Total Syntheses of (±)-Deguelin (2) and (±)-Tephrosin (3)



As shown in Scheme 3, the synthesis of deguelin (**2**) started from the preparation of the key vinyl iodide building block **7**, which was carried out by the conversion of chromanone **10** into the hydrazone by heating with $N_2H_4{\cdot}H_2O$ in refluxing MeOH. Oxidation of the hydrazone by iodine in the presence of base gave the vinyl iodide in 85% yield.[16] Initially, vinyl iodide **7** was obtained in only 21% yield over two steps. The mechanism proposed by Barton suggests that the hydrazone is oxidized by iodine to the diazo compound first. Nucleophilic attack on the iodine and subsequent loss of nitrogen afford an iodocarbocation. Elimination of HI finally affords the vinyl iodide.[17] Thus, a variety of conditions (solvent, base, molar ratio, and temperature) were screened to increase the yield of **7**. The reaction proceeded smoothly in anhydrous tetrahydrofuran (THF) with tetraethylamine (TEA) as a base and provided **7** in 85% yield. Next the assembly of 4-acylchromene **9** from **7** and commercially available benzaldehyde **8** was investigated. *n*-BuLi-induced metal−halogen exchange generated a vinylic anion that adds to benzaldehyde **8** to link the two chromene moieties.[18] The resulting crude product was oxidized by 2-Iodoxybenzoic acid (IBX) to afford ketone **9** in 80% yield. Intermediate **9** was transformed into deguelin (**2**) in 92% yield by a base-catalyzed intramolecular oxo-Michael addition. Thus, deguelin (**2**) was prepared in four linear steps in 62% overall yield.

Having established a robust route to deguelin, the synthesis of tephrosin (**3**) from deguelin (**2**) was attempted. As a 12a-hydroxy analogue of deguelin, tephrosin can be obtained by oxidation of the deguelin enolate.[19] In recent years, α-C−H hydroxylation of α-substituted carbonyl compounds to obtain α-hydroxy carbonyl compounds has received considerable attention, and transition-metal catalysis with molecular O_2 for selective C−H hydroxylation of carbonyl compounds has been widely applied.[20] Schoenebeck and co-workers developed an efficient method using a metal oxide (Cu_2O) and the base hppH (1,3,4,6,7,8-hexahydro-2*H*-pyrimido[1,2-*a*]pyrimidine) for C−H hydroxylation.[21] Following optimization of the reaction conditions, the reaction of deguelin with O_2 using a catalytic amount of Cu_2O in the presence of hppH proceeded smoothly to afford tephrosin (**3**) in 90% yield. The spectroscopic data for the synthesized deguelin (**2**) and tephrosin (**3**) matched those reported for the natural products (Supporting Information).[9b]

In summary, short, efficient, protecting-group-free total syntheses were developed for (±)-deguelin (**2**) and (±)-tephrosin (**3**) in four steps with 62% overall yield and five steps with 54% overall yield, respectively. The synthesis employed a vinyl iodide to concisely construct the 4-acylchromene skeleton of the rotenoids. Importantly, the small number of steps and the high overall yield make it a potentially viable option for both the scalable preparation of deguelin (**2**) and tephrosin (**3**) as well as the synthesis of their analogues to facilitate further medicinal chemistry studies.

EXPERIMENTAL SECTION

General Experimental Procedures. ^{1}H NMR and ^{13}C NMR spectra were obtained using a Bruker AV-300 or AV-500 spectrometer (Bruker Company, Germany) in the indicated solvents ($CDCl_3$ or DMSO-d_6 with tetramethylsilane as the internal standard). The values of the chemical shifts are expressed in δ values (ppm), and the coupling constants (J) are reported in Hz. ESIMS and HRESIMS data were collected on a Finnigan MAT 95 spectrometer (Finnigan, Germany). Flash column chromatography was carried out on 200−300 mesh silica gel purchased from Qingdao Haiyang Chemical Co. Ltd. (Qingdao, People's Republic of China). Reactions were monitored by thin-layer chromatography on 0.25 mm silica gel plates (GF254) and visualized under UV light.

4-Iodo-6,7-dimethoxy-2*H*-chromene (7). Compound **10** (500 mg, 2.4 mmol, 1.0 equiv), freshly distilled hydrazine hydrate (98%, 720 mg, 14.4 mol, 6.0 equiv), and triethylamine (0.5 mL, 3.6 mmol, 1.5 equiv) were heated in refluxing MeOH (25 mL) for 2.5 h. After completion of the nucleophilic addition, the mixture was poured onto H_2O and extracted with EtOAc (50 mL). The combined organic phase was washed with brine (20 mL) and H_2O (20 mL) and dried over anhydrous $MgSO_4$. After evaporation of the solvent, the crude hydrazone was obtained and used without further purification. Triethylamine (3 mL, 22.5 mmol, 9.3 equiv) in THF (24 mL) was added via cannula over 2 min to a stirred solution of iodine (1.71 g, 6.75 mmol, 2.8 equiv) in THF (20 mL) at 0 °C. A solution of hydrazone in THF (10 mL) was added via cannula over 5 min. The mixture was kept at room temperature for 2 h, and the suspension was

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filtered through sintered glass. The solid phase was washed with EtOAc (5 × 3 mL), and the combined organic layers were washed with saturated aqueous $Na_2S_2O_3$ (2 × 20 mL). The organic phase was concentrated in vacuo. Purification of the crude product by flash column chromatography (silica gel, 1:20 EtOAc/petroleum ether) yielded **7** as a yellow solid (647 mg, 85%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.74 (1H, s), 6.30 (1H, s), 6.28 (1H, t, J = 4.1 Hz), 4.58 (2H, d, J = 4.1 Hz), 3.81 (3H, s), 3.78 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.71, 148.16, 143.79, 129.29, 115.53, 114.67, 100.25, 92.95, 67.58, 56.60, 56.14; HRESIMS m/z 316.9671 $[M - H]^-$ (calcd for $C_{11}H_{10}IO_3$, 316.9680).

(6,7-Dimethoxy-2*H*-chromen-4-yl)(5-hydroxy-2,2-dimethyl-2*H*-chromen-6-yl)methanone (9). *n*-BuLi (0.744 mL, 1.86 mmol, 2.5 mol/L, 3.0 equiv) was added to freshly distilled THF (20 mL) at −78 °C. Compound **7** (200 mg, 0.62 mmol, 1.0 equiv) was added, and the reaction mixture was stirred until the temperature reached 25 °C, at which point **8** (128 mg, 0.62 mmol, 1.0 equiv) was added. After stirring for 1 h, the reaction was quenched with saturated NH_4Cl, and the product was extracted with EtOAc (30 mL), washed with brine, dried over anhydrous $MgSO_4$, and evaporated under reduced pressure. The crude product was added to a well-stirred solution of IBX (212 mg, 0.75 mmol, 1.2 equiv) in dry DMSO (20 mL) at room temperature. After stirring for 20 min, a solution of 10% saturated aqueous $NaHCO_3$ (10 mL) was added. The product was extracted with EtOAc (20 mL), the organic layer was washed with brine and dried over anhydrous $MgSO_4$, and the solvent was removed under reduced pressure to afford the crude product. Purification by flash column chromatography (silica gel, 1:10 EtOAc/petroleum ether) yielded **9** as a yellow solid (198 mg, 80%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.56 (1H, s), 7.11 (1H, d, J = 8.8 Hz), 6.97 (1H, s), 6.62 (1H, d, J = 10.1 Hz), 6.51 (1H, d, J = 9.9 Hz), 6.35 (1H, d, J = 8.8 Hz), 5.86−5.80 (1H, m), 5.78 (1H, d, J = 10.1 Hz), 4.59 (2H, m), 3.79 (3H, s), 3.62 (3H, s), 1.41 (6H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.28, 159.71, 159.31, 146.54, 145.67, 144.21, 133.95, 127.54, 123.50, 121.42, 121.27, 117.95, 115.36, 114.63, 111.78, 108.46, 108.11, 77.48, 65.09, 61.34, 56.25, 29.30, 28.10; HRESIMS m/z 395.1498 $[M + H]^+$ (calcd for $C_{23}H_{23}O_6$, 395.1489).

Deguelin (2). Compound **9** (50 mg, 0.126 mmol) was dissolved in a saturated solution of KOAc in EtOH (0.5 mL), and the mixture was stirred at rt for 1 h. EtOAc and H_2O were added to the reaction mixture. The layers were separated, and the aqueous layer was extracted with EtOAc (2 × 20 mL). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The crude residue was filtered through silica gel (petroleum ether/EtOAc, 4:1) to yield (±)-deguelin (**2**) as a white solid (46 mg, 92%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.75 (1H, d, J = 8.7 Hz, H-11), 6.80 (1H, s, H-1), 6.65 (1H, d, J = 10.1 Hz, H-4′), 6.46 (1H, d, J = 8.7 Hz, H-10), 6.46 (1H, s, H-4), 5.56 (1H, d, J = 10.1 Hz, H-5′), 4.92 (1H, dd, J = 3.2, 4.2 Hz, H-6a), 4.64 (1H, dd, J = 12.0, 3.2 Hz, H-6), 4.19 (1H, d, J = 12.0 Hz, H-6′), 3.84 (1H, d, J = 4.2 Hz, H-12a), 3.81 (3H, s, H-3′), 3.78 (3H, s, H-2′), 1.46 (3H, s, H-8′), 1.39 (3H, s, H-7′); ^{13}C NMR (75 MHz, $CDCl_3$) δ 189.13 (C-12), 159.99 (C-9), 156.83 (C-7a), 149.36 (C-4a), 147.32 (C-3), 143.75 (C-2), 128.56 (C-5′), 128.44 (C-11), 115.64 (C-4′), 112.64 (C-11a), 111.36 (C-10), 110.34 (C-1), 109.03 (C-8), 104.66 (C-1a), 100.84 (C-4), 77.59 (C-6′), 72.33 (C-6a), 66.19 (C-6), 56.21 (C-2′), 55.75 (C-3′), 44.28 (C-12a), 28.40 (C-8′), 28.05 (C-7′); HRESIMS m/z 395.1505 $[M + H]^+$ (calcd for $C_{23}H_{23}O_6$, 395.1489).

Tephrosin (3). To a solution of deguelin (**2**) (40 mg, 0.1 mmol) and Cu_2O (2 mg, 0.014 mmol, 0.14 equiv) in anhydrous DMSO (1 mL) was added hppH (15 mg, 0.11 mmol, 1.1 equiv). The reaction vessel was sealed, evacuated, refilled with oxygen gas, and stirred at room temperature for 5 h under an oxygen atmosphere that was maintained with an O_2-filled balloon. The reaction mixture was extracted with EtOAc (3 × 20 mL). The combined organic phases were dried over anhydrous $MgSO_4$ and purified by flash column chromatography (petroleum ether/EtOAc, 4:1) to yield (±)-tephrosin (**3**), white solid (36 mg, 90%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.72 (1H, d, J = 8.7 Hz, H-11), 6.60 (1H, d, J = 10.1 Hz, H-4′), 6.57 (1H, s, H-1), 6.48 (1H, s, H-4), 6.45 (1H, d, J = 8.7 Hz, H-10), 5.55 (1H, d, J = 10.1 Hz, H-5′), 4.63 (1H, dd, J = 12.1, 2.4 Hz, H-6), 4.58−4.56 (1H, m, H-6a), 4.49 (1H, dd, J = 12.1, 1.1 Hz, H-6), 4.42 (1H, s, OH-12a), 3.81 (3H, s, H-3′), 3.73 (3H, s, H-2′), 1.45 (3H, s, H-8′), 1.39 (3H, s, H-7′); ^{13}C NMR (75 MHz, $CDCl_3$) δ 191.40 (C-12), 160.79 (C-9), 156.70 (C-7a), 151.22 (C-4a), 148.48 (C-3), 144.05 (C-2), 128.85 (C-5′), 128.58 (C-11), 115.45 (C-4′), 111.91 (C-10), 111.18 (C-11a), 109.59 (C-1), 109.17 (C-8), 108.74 (C-1a), 101.19 (C-4), 78.03 (C-6′), 76.34 (C-6a), 67.51 (C-12a), 63.91 (C-6), 56.46 (C-2′), 55.90 (C-3′), 28.58 (C-8′), 28.35 (C-7′); HRESIMS m/z 433.1273 $[M + Na]^+$ (calcd for $C_{23}H_{22}NaO_7$, 433.1258).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.jnatprod.7b00794.

Additional information (PDF)

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Notes

The authors declare no competing financial interest.

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