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Structural Revision of Garuganin IV and 1,9′-Didesmethylgaruganin III through Total Synthesis

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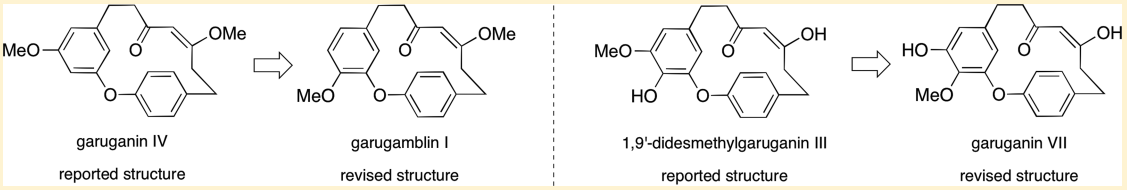
Supporting Information



ABSTRACT: The chemical structures of garuganin IV and 1,9′-didesmethylgaruganin III were misassigned. The structures were revised on the basis of analysis of the NMR data, and the revisions were verified through total synthesis.

The diarylether heptanoids (DAEHs) are a family of natural products characterized by an oxa[1.7]metaparacyclophane architecture. These natural products display a range of biological activities[1] and have attracted interest from synthetic chemists.[2] Sixteen DAEHs do not possess a stereocenter, but interestingly, some DAEHs are chiral.[3,4] We recently investigated the relationship between DAEH structure and chirality.[5] Two DAEHs, garuganin IV and 1,9′-didesmethylgaruganin III were independently isolated from *Garuga pinnata* as optically active compounds,[4g,h] and we recently published syntheses of the reported structures.[5] However, analysis of the ^{1}H and ^{13}C NMR spectra of these molecules revealed that the structures had been misassigned. We now report revised chemical structures for these two natural products. We have verified our assignments through total synthesis and established that the molecules are achiral.

The original assignment of garuganin IV (**1**) was based on chemical shift calculations and comparison with garugamblin I (**2**). The chemical shifts assigned to H_2 and H_4 were reported to be nearly the same (see Figure 1 for DAEH numbering[6]) and exhibited broadening at 250 and 500 MHz. As a result, values of the coupling constants were not reported. No information was given regarding how the assignments of the individual resonances were made.

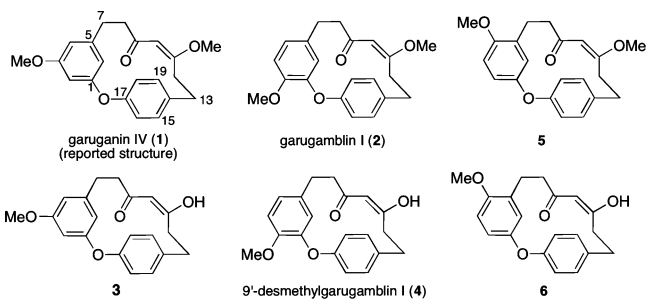


Figure 1. Reported structure of garuganin IV and congeners.

We prepared structure **1**[5] and found that the spectral data for the synthetic material did not match the data for the natural substance. In an attempt to deduce the true structure of garuganin IV, we considered the NMR data reported for the compound. Proton H_6 was present as evidenced by its diagnostic anisotropic upfield shift (δ 5.30 ppm) resulting from the ring current of the adjacent phenyl ring. The ^{1}H NMR data also showed the existence of a para-substituted phenyl ring, four methylenes, and a vinylogous methyl ester. Furthermore, the geminal methylene protons were chemical shift inequivalent, which only occurs for *E*-configured vinylogous esters with the C_9 carbonyl regioisomer.[5] Natural garguanin IV was hydrolyzed to the corresponding vinylogous acid and assigned as **3**,[4g] which established the presence of the vinylogous ester functional group. Since we determined experimentally that the structure of garuganin IV was not structure **1**, and since Sabata and co-workers reported that the structure was different than garugamblin I,[4g] we considered the only other isomeric possibility (**5**, Figure 1). We surmised that in the event that H_2 and H_3 were accidentally chemical shift equivalent, they would not experience *J* coupling, and this would explain the observed shifts and coupling patters reported. Synthetically, vinylogous ester **5** was envisioned to arise from vinylogous acid **6**, which would allow us to prepare regio- and stereoisomers of **5** and compare the spectral data of **6** with the data reported for the hydrolysis product of natural garuganin IV (and assigned as structure **3**).

To test this hypothesis, we prepared structure **5**. The synthesis begins with known benzaldehyde **7** (Scheme 1).[7] A standard three-step sequence gave hydrocinnamaldehyde **9**. Aldol addition of **9** to the lithium enolate derived from ketone

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Scheme 1. Synthesis of 5

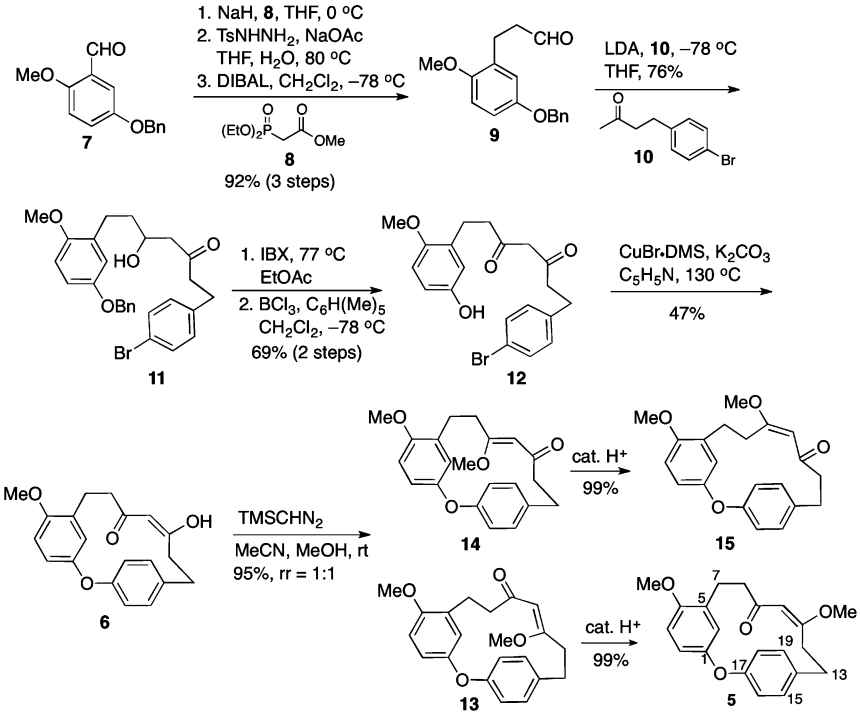

Table 1. ^{1}H NMR Chemical Shifts for Garuganin IV and Congeners

reported[a]	**1**[b]	**2**[b]	**5**[b]
7.36 d (8 Hz, 1 H)	7.35 dd (8.3, 1.3 Hz, 1 H)	7.37 d (8.2 Hz, 1 H)	7.33 dd (8.3, 2.0 Hz, 1 H)
7.05 d (8 Hz, 1 H)	7.01 dd (8.3, 1.8 Hz, 1 H)	7.06 d (8.1 Hz, 1 H)	6.94–6.90 m (2 H)
6.84 s (2 H)	6.84 dd (8.2, 1.4 Hz, 1 H)	6.85 br s (2 H)	6.87 dd (8.1, 2.3 Hz, 1 H)
6.72 d (8 Hz, 1 H)	6.83 dd (8.2, 1.9 Hz, 1 H)	6.73 d (8.1 Hz, 1 H)	6.84 dd (8.1, 2.0 Hz, 1 H)
6.58 d (8 Hz, 1 H)	6.53 t (2.2 Hz, 1 H)	6.60 dd (8.1, 2.1 Hz, 1 H)	6.71 d (8.8 Hz, 1 H)
5.30 s (1 H)	6.25 br s (1 H)	5.31 s (1 H)	5.32 s (1 H)
5.27 s (1 H)	5.30 s (1 H)	5.26 d (2.0 Hz, 1 H)	5.27 d (3.1 Hz, 1 H)
4.02/2.44 m (2 H)	4.83 br s (1 H)	4.02 td (12.9, 3.4 Hz, 1 H)	3.97 td (12.9, 3.4 Hz, 1 H)
3.94 s (3 H)	4.01 td (12.9, 3.4 Hz, 1 H)	3.93 s (3 H)	3.75 s (3 H)
3.67 s (3 H)	3.78 s (3 H)	3.68 s (3 H)	3.69 s (3 H)
3.19/2.91 m (2 H)	3.68 s (3 H)	3.20 dd (14.8, 11.6 Hz, 1 H)	2.96 dt (12.7, 4.0 Hz, 1 H)
3.19/2.26 m (2H)	3.26 dd (14.5, 11.7 Hz, 1 H)	2.97 dt (12.8, 4.0 Hz, 1 H)	2.86 td (13.0, 2.9 Hz, 2 H)
2.91/2.26 m (2 H)	2.96 dt (12.6, 3.9 Hz, 1 H)	2.89 td (12.9, 3.1 Hz, 1 H)	2.72 ddd (16.4, 7.1, 1.0 Hz, 1 H)
	2.90 td (12.9, 3.0 Hz, 1 H)	2.53 ddd (17.8, 7.3, 1.2 Hz, 1 H)	2.55 ddd (18.2, 7.0, 1.4 Hz, 1 H)
	2.50 ddd (17.8, 7.3, 1.5 Hz, 1 H)	2.42 ddd (17.9, 11.4, 0.8 Hz, 1 H)	2.42 ddd (18.2, 11.5, 1.1 Hz, 1 H)
	2.44 dd (17.6, 11.3 Hz, 1 H)	2.31 ddd (12.8, 4.4, 3.4 Hz, 1 H)	2.30 ddd (12.8, 4.4, 3.4 Hz, 1 H)
	2.32 dt (12.9, 3.8 Hz, 1 H)	2.27 dd (15.2, 7.0 Hz, 1 H)	
	2.27 dd (15.2, 7.0 Hz, 1 H)		

[a]$CDCl_3$, 500 MHz. [b]$CDCl_3$, 700 MHz.

10 produced adduct **11**. IBX-mediated oxidation[8] and removal of the benzyl ether[9] gives bromophenol **12**. Ullmann cyclization[10] of **12** gives **6**, which did not match the data reported for the hydrolysis product of the natural substance (assigned as **3**). Furthermore, an unselective kinetic methylation of **6** gave **13** and **14**.[2a−c,5] Neither *Z*-configured vinylogous ester **13** nor **14** matched the data reported for garuganin IV. Isomerization of **13** and **14** gave *E*-configured regioisomers **5** and **15**, respectively. Neither of these structures had NMR data that matched the reported data for garuganin IV.

We then revisited the NMR data for garuganin IV. Table 1 shows the ^{1}H NMR chemical shifts and multiplicities (in decreasing chemical shift order) reported for garuganin IV, along with the data for synthetic compounds **1**, **2**, and **5**. The aromatic region of the spectra (5.0−8.0 ppm) was most useful in the analysis because many of the signals upfield of 5.0 ppm were reported as overlapping multiplets. Inspection of the chemical shift values reveals that the compound isolated and named garuganin IV and garugamblin I (**2**) have ^{1}H chemical shifts that are nearly identical. Isomeric structures **1** and **5** do not match the reported data. Moreover, the ^{13}C NMR chemical shifts reported for garuganin IV match the shifts of **2**, and the reported data for 9′-desmethylgaruganin IV (originally assigned as **3**) matches that of **4**. We believe that the material isolated and reported as garuganin IV is garugamblin I (**2**). Although

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the natural sample was reported to be optically active, we have previously shown that this molecule is achiral.[5]

The assignment of 1,9′-didesmethylgaruganin III as structure **16** (Figure 2) was based on analysis of the 2D NMR data and

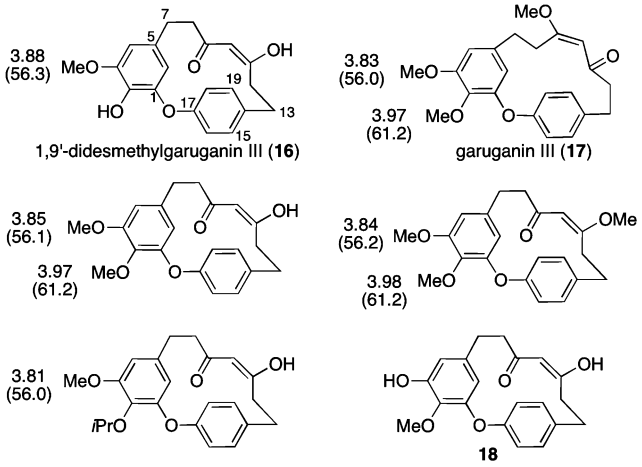

Figure 2. Reported structure of 1,9′-didesmethylgaruganin III and congeners. $CDCl_3$, 700 MHz; ^1H NMR chemical shifts for selected methyl groups; ^{13}C NMR chemical shifts in parentheses.

on comparison with garuganin III (**17**).[4h] Specifically, the methyl ether was assigned on the basis of the HMBC correlation of the methyl protons to C_3. We previously prepared structure **16** and found the data for the synthetic material did not match the natural product.

During the course of our synthesis of the garuganin and garugamblin DAEHs, we prepared a variety of closely related chemical structures and acquired their ^1H and ^{13}C NMR spectra. Selected structures are shown in Figure 2 along with some of their chemical shift data. As evidenced by the tablulated data, the ^1H and ^{13}C chemical shift ranges of all C_3-bound methoxy groups are 3.81−3.88 and 56.0−56.3 ppm, respectively. Furthermore, the ^1H and ^{13}C chemical shifts of the C_2-bound methoxy groups are 3.97 and 61.2 ppm, respectively. The reported ^1H and ^{13}C chemical shifts of the methoxy group for the natural product assigned as 1,9′-didesmethylgaruganin III are 4.05 and 61.3 ppm, respectively. These data suggest that the true structure of the natural substance has the methoxy group at C_2, and the structure of the natural product is **18**. We decided to synthesize structure **18** to verify our prediction.

The synthesis of **18** begins with known gallic acid derivative **19** (Scheme 2).[11] Protection of the phenol and subsequent oxidation state change produced aldehyde **20**. Intermediate **20** underwent Horner−Wadsworth−Emmons reaction and reduction to yield hydrocinnamate **21**. Reduction, aldol addition, oxidation, and debenzylation gave bromophenol **22**. Cyclization of **22** and removal of the isopropyl group leads to structure **18**.

Gratifyingly, the spectral data for **18** matches the reported data for the natural product (Table 2).[12] The chemical shifts of the protons associated with the tetrasubstituted ring are the most diagnostic. Specifically, the two aryl protons (δ 6.37, 5.15 ppm) match the data of **18** nearly exactly. Furthermore, the chemical shift of the methyl group (δ 4.05 ppm) in **18** is a perfect match to the reported data. Finally, the reported ^{13}C NMR chemical shifts also match compound **18** and do not match the chemical shifts for **16**.

Since the natural product is not appropriately named 1,9′-didesmethylgaruganin III with any of the various diarylether

Scheme 2. Synthesis of 18

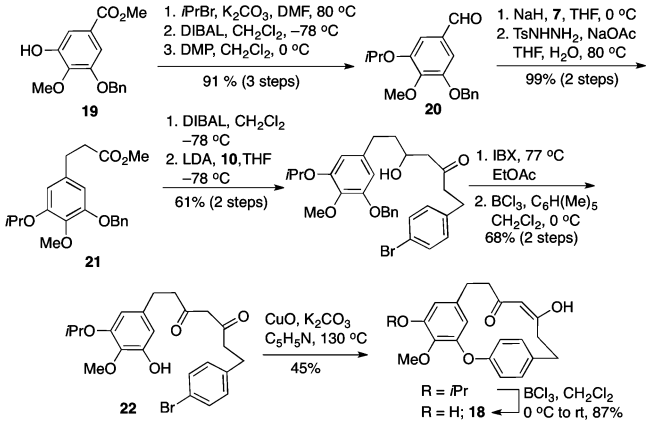

Table 2. ^1H NMR Chemical Shifts for 1,9′-Didesmethylgaruganin III, 16, and 18

reported[a]	16[b]	18[b]
7.18 d (8 Hz, 2 H)	15.17 br s (1 H)	15.17 br s (1 H)
6.98 d (8 Hz, 2 H)	7.17 d (8.3 Hz, 2 H)	7.18 d (8.5 Hz, 2 H)
6.36 d (1.2 Hz,1 H)	6.99 d (8.3 Hz, 2 H)	6.98 d (8.5 Hz, 2 H)
5.15 d (1.2 Hz,1 H)	6.31 br s (1 H)	6.37 m (1 H)
4.93 s (1 H)	5.51 br s (1 H)	5.78 s (1 H)
4.05 s (3 H)	5.25 d (1.7 Hz, 1 H)	5.15 d (2.0 Hz, 1 H)
3.04 t (6.6 Hz, 2 H)	4.94 s (1 H)	4.93 s (1 H)
2.87 m (2 H)	3.87 s (3 H)	4.05 s (3 H)
2.46 t (6.6 Hz, 2 H)	3.03 t (6.8 Hz, 2 H)	3.04 t (6.8 Hz, 2 H)
2.34 m (2 H)	2.90 m (2 H)	2.87 m (2 H)
	2.45 t (6.8 Hz, 2 H)	2.46 t (6.8 Hz, 2 H)
	2.35 m (2 H)	2.33 m (2 H)

[a]$CDCl_3$, 600 MHz. [b]$CDCl_3$, 700 MHz.

heptanoid numbering schemes, we propose the name garuganin VII for this natural product to avoid confusion. Additionally, despite reported optical activity, the molecule displays enantiotopic geminal methylene protons, which indicates that it is an achiral molecule.

In conclusion, we have determined that the natural product assigned as garuganin IV is garugamblin I. The natural product assigned as 1,9′-didesmethylgaruganin III has structure **18**, and we propose the name garuganin VII for structure **18**. Finally, we previously showed that garugamblin I is achiral, and since garuganin VII has enantiotopic geminal methylene protons, we conclude that this structure is also achiral, despite the optical activities reported for the natural substances.

EXPERIMENTAL SECTION

General Experimental Details. All reactions were carried out under an inert Ar atmosphere in oven-dried glassware. External bath temperatures were used to record all reaction mixture temperatures. All combined organic extracts were dried over $MgSO_4$. Column chromatography was carried out with SiliaFlash P60 silica gel. Thin layer chromatography was performed using Silica Gel 60 plates. Tetrahydrofuran (THF), methylene chloride (CH_2Cl_2) and acetonitrile (MeCN) were dried by passage through activated alumina columns. DMF and DMSO were stored over 3 Å molecular sieves. Pyridine (C_6H_5N) and diisopropylamine were distilled from CaH_2. All other reagents and solvents were used without further purification from commercial sources. FT-IR spectra were obtained as thin films on NaCl plates. Proton and carbon NMR spectra (^1H NMR and ^{13}C

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NMR) were recorded in deuterated chloroform ($CDCl_3$) at 700 or 400 MHz as indicated. Melting points are uncorrected.

3-(5-(Benzyloxy)-2-methoxyphenyl)propanal (9). To a slurry of NaH (216 mg, 5.4 mmol) in THF (10 mL, 0.2 M) at 0 °C was slowly added methyl 2-(diethoxyphosphoryl)acetate (991 μL, 5.4 mmol) over a period of 10 min. After stirring at 0 °C for 30 min, a solution of 5-(benzyloxy)-2-methoxybenzaldehyde[13] (872 mg, 3.6 mmol) in THF (8 mL) was added. The mixture was warmed to rt and stirred at rt for 30 min. To the above reaction mixture were added H_2O (18 mL), NaOAc (1.181 g, 14.4 mmol) and a solution of $TsNHNH_2$ (2.011 g, 10.8 mmol) in THF (18 mL) over a period of 30 min at 80 °C. The mixture was stirred for 24 h and then allowed to cool to rt. The organic phase was separated, and the aqueous phase was extracted with EtOAc. Purification by flash column chromatography (hexanes:EtOAc = 10:1 to 8:1) gave methyl 3-(5-(benzyloxy)-2-methoxyphenyl)propanoate (**S1**, 1.07 g, 3.56 mmol, 99% yield, 2 steps) as a light yellow solid. Data for **S1**: R_f 0.54 (3:1 hexanes:EtOAc); mp = 41−43 °C, IR (thin film) 2949, 1737, 1501, 1223, 1042 cm^{-1}; ^1H NMR (700 MHz, $CDCl_3$) δ 7.44 (d, J = 7.6 Hz, 2 H), 7.39 (t, J = 7.6 Hz, 2 H), 7.33 (t, J = 7.3 Hz, 1 H), 6.85 (d, J = 2.9 Hz, 1 H), 6.80 (dd, J = 8.8, 2.9 Hz, 1 H), 6.76 (d, J = 8.8 Hz, 1 H), 5.01 (s, 2 H), 3.79 (s, 3 H), 3.68 (s, 3 H), 2.93 (t, J = 7.9 Hz, 2 H), 2.62 (t, J = 7.9 Hz, 2 H); ^{13}C NMR (176 MHz, $CDCl_3$, HSQC, DEPT) δ *C* 173.7, 152.5, 151.9, 137.3, 129.9; *C*H 128.5, 127.8, 127.4, 117.3, 112.6, 110.9; CH_2 70.5, 33.9, 26.2; CH_3 55.7, 51.5; HRMS (TOF MS ES+) calcd for $C_{18}H_{20}O_4Na$ [M + Na] 323.1259, found 323.1260.

To a solution of methyl 3-(5-(benzyloxy)-2-methoxyphenyl)-propanoate (901 mg, 3 mmol) in CH_2Cl_2 (30 mL, 0.1 M) at −78 °C was added DIBAL-H (3 mL, 3.6 mmol, 1.2 M in toluene) over a period of 60 min. The reaction was quenched with saturated aqueous Rochelle's salt at −78 °C. The mixture was warmed to rt. The organic phase was separated, and the inorganic phase was extracted with EtOAc. Purification by flash column chromatography (hexanes:EtOAc = 5:1) gave **9** (730 mg, 2.7 mmol, 90% yield) as light yellow oil. Data for **9**: R_f 0.46 (3:1 hexanes:EtOAc); IR (thin film) 2834, 1723, 1500, 1222, 1038 cm^{-1}; ^1H NMR (700 MHz, $CDCl_3$) δ 9.80 (t, J = 1.6 Hz, 1 H), 7.43 (d, J = 7.5 Hz, 2 H), 7.38 (t, J = 7.6 Hz, 2 H), 7.32 (t, J = 7.3 Hz, 1 H), 6.82 (d, J = 2.9 Hz, 1 H), 6.79 (dd, J = 8.8, 2.9 Hz, 1 H), 6.76 (d, J = 8.8 Hz, 1 H), 5.00 (s, 2 H), 3.78 (s, 3 H), 2.92 (t, J = 7.5 Hz, 2 H), 2.71 (td, J = 7.5, 1.6 Hz, 2 H); ^{13}C NMR (176 MHz, $CDCl_3$, HSQC, DEPT) δ *C* 152.6, 151.8, 137.2, 129.8; *C*H 202.4, 128.5, 127.9, 127.5, 117.4, 112.6, 111.0; CH_2 70.6, 43.8, 23.6; CH_3 55.6; HRMS (TOF MS ES+) calcd for $C_{17}H_{19}O_3$ [M + H] 271.1334, found 271.1324.

7-(5-(Benzyloxy)-2-methoxyphenyl)-1-(4-bromophenyl)-5-hydroxyheptan-3-one (11). To a solution of diisopropylamine (316 mg, 3.12 mmol) in THF (13 mL, 0.1 M) at 0 °C was added *n*-BuLi (1.95 mL, 3.12 mmol, 1.6 M in hexane) over a period of 10 min. After stirring at 0 °C for 30 min, the mixture was cooled to −78 °C. A solution of 4-(4-bromophenyl)butan-2-one[14] (681 mg, 3 mmol) in THF (6 mL) was added over a period of 30 min. After stirring at −78 °C for 30 min, a solution of aldehyde **9** (676 mg, 2.5 mmol) in THF (6 mL) was added over a period of 30 min. After stirring for 2 h, the reaction was quenched with saturated aqueous NH_4Cl. The organic phase was separated, and the inorganic phase was extracted with EtOAc. Purification by flash column chromatography (hexanes:EtOAc = 5:1 to 5:2) gave **11** (946 mg, 1.9 mmol, 76% yield) as a white solid. Data for **11**: R_f 0.43 (2:1 hexanes:EtOAc); mp = 62−64 °C, IR (thin film) 3500 (br), 2928, 1709, 1499, 1222, 1042 cm^{-1}; ^1H NMR (700 MHz, $CDCl_3$) δ 7.44−7.36 (m, 6 H), 7.32 (t, J = 7.3 Hz, 1 H), 7.04 (d, J = 8.4 Hz, 2 H), 6.82 (d, J = 2.5 Hz, 1 H), 6.77 (dd, J = 8.8, 2.6 Hz, 1 H), 6.76 (d, J = 8.8 Hz, 1 H), 5.00 (s, 2 H), 3.99 (m, 1 H), 3.77 (s, 3 H), 3.09 (br s, 1 H), 2.84 (t, J = 7.3 Hz, 2 H), 2.76−2.67 (m, 4 H), 2.57−2.49 (m, 2 H), 1.78−1.71 (m, 1 H), 1.69−1.63 (m, 1 H); ^{13}C NMR (176 MHz, $CDCl_3$, HSQC, DEPT) δ *C* 210.2, 152.8, 151.7, 139.8, 137.2, 131.1, 119.9; *C*H 131.5, 130.1, 128.5, 127.8, 127.5, 117.4, 112.3, 111.2, 66.9; CH_2 70.5, 49.3, 44.8, 36.7, 28.7, 26.0; CH_3 55.9; HRMS (TOF MS ES+) calcd for $C_{27}H_{30}BrO_4$ [M + H] 497.1327, found 497.1321.

1-(4-Bromophenyl)-7-(5-hydroxy-2-methoxyphenyl)-heptane-3,5-dione (12). To a solution of **11** (763 mg, 1.48 mmol) in EtOAc (15 mL, 0.1 M) at rt was added IBX (1.243 g, 4.44 mmol). The reaction mixture was heated to reflux for 4 h. The reaction mixture was cooled to rt, filtered through a pad of silica gel, and concentrated to give 1-(5-(benzyloxy)-2-methoxyphenyl)-7-(4-bromophenyl)heptane-3,5-dione, which was used directly without further purification.

To a stirred solution of 1-(5-(benzyloxy)-2-methoxyphenyl)-7-(4-bromophenyl)heptane-3,5-dione (approximately 1.48 mmol) in CH_2Cl_2 (15 mL, 0.1 M) were added pentamethylbenzene (658 mg, 4.44 mmol) and BCl_3 (5.9 mL, 5.92 mmol, 1 M in DCM) at −78 °C over a period of 10 min. The reaction was quenched with MeOH at −78 °C. The mixture was warmed to rt. Diluted aqueous $NaHCO_3$ was added until the aqueous phase had pH 6. The organic phase was separated, and the aqueous phase was extracted with EtOAc. Purification by flash column chromatography (hexanes:EtOAc = 5:1 to 3:1) gave **12** (413 mg, 1.02 mmol, 69% yield, 2 steps) as a light yellow solid. Data for **12**: R_f 0.46 (2:1 hexanes:EtOAc); mp = 58−60 °C, IR (thin film) 3380 (br), 1609, 1504, 1439, 1286, 1221, 1033, 1011 cm^{-1}; ^1H NMR (700 MHz, $CDCl_3$, enol tautomer) δ 15.42 (br s, 1 H), 7.42 (d, J = 8.2 Hz, 2 H), 7.07 (d, J = 8.3 Hz, 2 H), 6.75−6.63 (m, 3 H), 5.46 (s, 1 H), 5.31 (br s, 1 H), 3.78 (s, 3 H), 2.92−2.76 (m, 4 H), 2.60−2.54 (m, 4 H); ^{13}C NMR (176 MHz, $CDCl_3$, HSQC, DEPT, enol tautomer) δ *C* 193.8, 192.7, 151.5, 149.2, 139.6, 119.9; *C*H 131.5, 130.0, 117.1, 113.3, 111.4, 99.6; CH_2 39.7, 38.1, 30.8, 26.5; CH_3 55.8; HRMS (TOF MS ES+) calcd for $C_{20}H_{22}BrO_4$ [M + H] 405.0701, found 405.0688.

6-Methoxy-2-oxatricyclo[13.2.2.1^{3,7}]icosa-1(17),3,5,7-(20),15,18-hexaene-10,12-dione (6). To a sealed tube were added **12** (20.3 mg, 0.05 mmol), $CuBr{\cdot}Me_2S$ (25.7 mg, 0.125 mmol) and K_2CO_3 (13.8 mg, 0.1 mmol). The tube was evacuated and backfilled with Ar, followed by the addition of pyridine (10 mL, 0.005 M). The tube was then sealed and heated to 130 °C for 48 h. The mixture was cooled to rt. After evaporation of the solvent, aqueous HCl (1 mL, 1 M) and H_2O (5 mL) were added. The mixture was extracted with EtOAc. Purification by flash column chromatography (hexanes:EtOAc = 8:1 to 6:1) gave **6** (7.6 mg, 0.0234 mmol, 47% yield) as a light yellow solid. Data for **6**: R_f 0.66 (2:1 hexanes:EtOAc); IR (thin film) 2930, 1598, 1495, 1215 cm^{-1}; ^1H NMR (700 MHz, $CDCl_3$) δ 15.06 (br s, 1 H), 7.14 (d, J = 8.5 Hz, 2 H), 6.97 (dd, J = 8.8, 3.0 Hz, 1 H), 6.94 (d, J = 8.5 Hz, 2 H), 6.74 (d, J = 8.8 Hz, 1 H), 5.65 (d, J = 3.0 Hz, 1 H), 4.96 (s, 1 H), 3.78 (s, 3 H), 3.01 (t, J = 6.8 Hz, 2 H), 2.91 (m, 2 H), 2.44 (t, J = 6.8 Hz, 2 H), 2.39 (m, 2 H); ^{13}C NMR (176 MHz, $CDCl_3$, HSQC, DEPT) δ *C* 197.2, 188.2, 155.8, 155.4, 151.8, 136.1, 130.0; *C*H 130.5, 122.8, 114.8, 114.5, 110.6, 103.0; CH_2 39.5, 36.4, 32.2, 21.6; CH_3 55.8; HRMS (TOF MS ES+) calcd for $C_{20}H_{21}O_4$ [M + H] 325.1440, found 325.1437.

***E*-6,12-Dimethyl-2-oxatricyclo[13.2.2.1^{3,7}]icosa-1(17),3,5,7-(20),11,15,18-heptaen-10-one (5).** To a solution of **6** (16.2 mg, 0.05 mmol) in a mixed solvent of CH_3CN and MeOH (5 mL, 0.01 M, 10:1 v/v) was added $TMSCHN_2$ (0.25 mL, 0.5 mmol, 2 M in hexanes). After 4 h, the solvent was removed under reduced pressure. Purification by flash column chromatography (hexanes:EtOAc = 5:1 to 3:1) gave **13** (8.1 mg, 0.0239 mmol, 48% yield, white solid, more polar) and **14** (8.0 mg, 0.0236 mmol, 47% yield, white solid, less polar). Treating **13** and **14** with dry acidic $CDCl_3$ ("old" $CDCl_3$ dried by 3 Å MS) at rt (about 5 min) gave **5** and **15**, respectively, in >99% yield. Data for **5**: white solid, R_f 0.63 (2:1 hexanes:EtOAc); IR (thin film) 2934, 1683, 1587, 1496, 1212, 1097 cm^{-1}; ^1H NMR (700 MHz, $CDCl_3$) δ 7.33 (dd, J = 8.3, 2.0 Hz, 1 H), 6.94−6.90 (m, 2 H), 6.87 (dd, J = 8.1, 2.3 Hz, 1 H), 6.84 (dd, J = 8.1, 2.0 Hz, 1 H), 6.71 (d, J = 8.8 Hz, 1 H), 5.32 (s, 1 H), 5.27 (d, J = 3.1 Hz, 1 H), 3.97 (td, J = 12.9, 3.4 Hz, 1 H), 3.75 (s, 3 H), 3.69 (s, 3 H), 2.96 (dt, J = 12.7, 4.0 Hz, 1 H), 2.86 (td, J = 13.0, 2.9 Hz, 2 H), 2.72 (ddd, J = 16.4, 7.1, 1.0 Hz, 1 H), 2.55 (ddd, J = 18.2, 7.0, 1.4 Hz, 1 H), 2.42 (ddd, J = 18.2, 11.5, 1.1 Hz, 1 H), 2.30 (ddd, J = 12.8, 4.4, 3.4 Hz, 1 H); ^{13}C NMR (176 MHz, $CDCl_3$, HSQC, DEPT) δ *C* 196.9, 172.8, 156.3, 156.2, 151.3, 137.6, 130.8; *C*H 131.2, 129.9, 124.2, 122.1, 116.8, 113.8, 110.9, 101.0; CH_2 43.9, 33.9, 33.0, 19.9; CH_3 56.1, 55.2; HRMS (TOF MS

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ES+) calcd for $C_{21}H_{23}O_4$ [M + H] 339.1596, found 339.1581. Data for **15**: white solid, R_f 0.37 (2:1 hexanes:EtOAc); IR (thin film) 2935, 1668, 1564, 1496, 1214 cm^{-1}; ^1H NMR (700 MHz, $CDCl_3$) δ 7.30−7.25 (m, 2 H), 6.95−6.89 (m, 3 H), 6.71 (d, J = 8.8 Hz, 1 H), 5.23 (d, J = 3.0 Hz, 1 H), 5.18 (s, 1 H), 3.77 (s, 3 H), 3.43 (s, 3 H), 3.08 (t, J = 7.0 Hz, 2 H), 3.06−2.40 (m, 6 H); ^{13}C NMR (176 MHz, $CDCl_3$, HSQC, DEPT) δ *C* 198.8 174.1, 155.9, 154.6, 151.6, 137.2, 130.1; *CH* 131.3, 123.4, 112.9, 112.7, 110.2, 101.9; CH_2 44.3, 31.2, 28.1, 21.6; CH_3 55.7, 55.6; HRMS (TOF MS ES+) calcd for $C_{21}H_{23}O_4$ [M + H] 339.1596, found 339.1583.

3-(Benzyloxy)-5-isopropoxy-4-methoxybenzaldehyde (20). To a solution of methyl 3-(benzyloxy)-5-hydroxy-4-methoxybenzoate[15] (577 mg, 2 mmol) in DMF (20 mL, 0.1 M) was added K_2CO_3 (415 mg, 3 mmol) and 2-bromopropane (284 μL, 3 mmol). The mixture was heated to 80 °C for 6 h. The mixture was cooled to rt and poured into 50 mL of H_2O. The resultant mixture was extracted with Et_2O. Purification by flash column chromatography (hexanes:EtOAc = 8:1) gave methyl 3-(benzyloxy)-5-isopropoxy-4-methoxybenzoate (**S2**, 648 mg, 1.96 mmol, 98% yield) as a white solid. Data for **S2**: R_f 0.64 (2:1 hexanes:EtOAc); mp = 76−78 °C, IR (thin film) 2978, 1721, 1588, 1500, 1428, 1327, 1117, 1009 cm^{-1}; ^1H NMR (700 MHz, $CDCl_3$) δ 7.48−7.29 (m, 7 H), 5.15 (s, 2 H), 4.61 (sept, J = 6.1 Hz, 1 H), 3.90 (s, 3 H), 3.88 (s, 3 H), 1.37 (d, J = 6.1 Hz, 6 H); ^{13}C NMR (176 MHz, $CDCl_3$, HSQC, DEPT) δ *C* 166.7, 152.3, 151.4, 144.3, 136.7, 124.9; *CH* 128.5, 128.0, 127.4, 110.7, 108.6, 71.6; CH_2 71.0; CH_3 60.8, 52.2, 22.1; HRMS (EI+) calcd for $C_{19}H_{22}O_5$ [M] 330.1467, found 330.1464.

To a solution of methyl 3-(benzyloxy)-5-isopropoxy-4-methoxybenzoate (661 mg, 2 mmol) in CH_2Cl_2 (20 mL, 0.1 M) at −78 °C was added DIBAL-H (4 mL, 4.8 mmol, 1.2 M in toluene) over a period of 10 min. The mixture was warmed to rt and quenched with saturated aqueous Rochelle's salt. The organic phase was separated, and the inorganic phase was extracted with EtOAc. Concentration gave (3-(benzyloxy)-5-isopropoxy-4-methoxyphenyl)methanol, which was used without further purification.

To a solution of (3-(benzyloxy)-5-isopropoxy-4-methoxyphenyl)-methanol (from above, about 2 mmol) in CH_2Cl_2 (10 mL, 0.2 M) at 0 °C was added DMP (1.272 g, 3 mmol). After stirring at 0 °C for 30 min, the reaction was quenched with diluted aqueous $NaHCO_3$ (20 mL, to pH 7). The organic phase was separated. The aqueous phase was extracted with EtOAc. Purification by flash column chromatography (hexanes:EtOAc = 8:1) gave **20** (560 mg, 1.86 mmol, 93% yield, 2 steps) as a light yellow oil. Data for **20**: R_f 0.69 (2:1 hexanes:EtOAc); IR (thin film) 2978, 1694, 1583, 1496, 1440, 1385, 1323, 1235, 1116, 1006 cm^{-1}; ^1H NMR (700 MHz, $CDCl_3$) δ 9.80 (s, 1 H), 7.47−7.31 (m, 5 H), 7.14 (d, J = 1.8 Hz, 1 H), 7.13 (d, J = 1.8 Hz, 1 H), 5.18 (s, 2 H), 4.63 (sept, J = 6.1 Hz, 1 H), 3.94 (s, 3 H), 1.39 (d, J = 6.1 Hz, 6 H); ^{13}C NMR (176 MHz, $CDCl_3$, HSQC, DEPT) δ *C* 153.0, 152.2, 145.8, 136.6, 131.6; *CH* 191.0, 128.6, 128.1, 127.3, 110.6, 108.6, 71.8; CH_2 71.2; CH_3 60.8, 22.1; HRMS (EI+) calcd for $C_{18}H_{20}O_4$ [M] 300.1362, found 300.1372.

Methyl 3-(3-(benzyloxy)-5-isopropoxy-4-methoxyphenyl)-propanoate (21). To a slurry of NaH (180 mg, 4.5 mmol, 60% oil dispersion) in THF (8 mL, 0.2 M) at 0 °C was slowly added methyl 2-(diethoxyphosphoryl)acetate (826 μL, 4.5 mmol) over a period of 10 min. After stirring at 0 °C for 30 min, a solution of **20** (901 mg, 3 mmol) in THF (7 mL) was added. The mixture was warmed to rt and stirred for 30 min. The reaction was quenched with H_2O (15 mL).

To the above mixture were added NaOAc (984 mg, 12 mmol) and a solution of $TsNHNH_2$ (1.676 g, 9 mmol) in THF (15 mL) over a period of 30 min. The mixture was heated to 80 °C for 24 h. The mixture was cooled to rt. The organic phase was then separated, and the inorganic phase was extracted with EtOAc. Purification by flash column chromatography (hexanes:EtOAc = 10:1 to 8:1) gave **21** (1.07 g, 2.99 mmol, >99% yield, 2 steps) as a colorless oil. Data for **21**: R_f 0.69 (2:1 hexanes:EtOAc); IR (thin film) 2976, 1738, 1588, 1503, 1435, 1237, 1117, 1010 cm^{-1}; ^1H NMR (700 MHz, $CDCl_3$) δ 7.46−7.28 (m, 5 H), 6.44 (d, J = 1.9 Hz, 1 H), 6.43 (d, J = 1.9 Hz, 1 H), 5.10 (s, 2 H), 4.51 (sept, J = 6.1 Hz, 1 H), 3.84 (s, 3 H), 3.66 (s, 3 H), 2.83 (t, J = 7.8 Hz, 2 H), 2.57 (t, J = 7.8 Hz, 2 H), 1.35 (d, J = 6.1 Hz, 3 H); ^{13}C NMR (176 MHz, $CDCl_3$, HSQC, DEPT) δ *C* 173.3, 152.6, 151.7, 138.9, 137.3, 135.8; *CH* 128.5, 127.7, 127.2, 109.8, 107.9, 71.6; CH_2 71.2, 35.8, 31.1; CH_3 60.7, 51.6, 22.2; HRMS (EI+) calcd for $C_{21}H_{26}O_5$ [M] 358.1780, found 358.1789.

1-(4-Bromophenyl)-7-(3-hydroxy-5-isopropoxy-4-methoxyphenyl)heptane-3,5-dione (22). To a solution of **21** (1.326 g, 3.7 mmol) in CH_2Cl_2 (37 mL, 0.1 M) at −78 °C was added DIBAL-H (3.7 mL, 4.44 mmol, 1.2 M in toluene) over a period of 60 min. The reaction was quenched with saturated aqueous Rochelle's salt at −78 °C and warmed to rt. The organic phase was separated, and the inorganic phase was extracted with EtOAc. Purification by flash column chromatography (hexanes:EtOAc = 5:1) gave 3-(3-(benzyloxy)-5-isopropoxy-4-methoxyphenyl)propanal (**S3**, 1.022 g, 3.11 mmol, 84% yield) as a light yellow oil. Data for **S3**: R_f 0.61 (2:1 hexanes:EtOAc); IR (thin film) 2976, 1723, 1588, 1503, 1435, 1237, 1117, 1010 cm^{-1}; ^1H NMR (700 MHz, $CDCl_3$) δ 9.78 (t, J = 1.4 Hz, 1 H), 7.46−7.29 (m, 5 H), 6.43 (s, 2 H), 5.10 (s, 2 H), 4.52 (sept, J = 6.1 Hz, 1 H), 3.84 (s, 3 H), 2.84 (t, J = 7.5 Hz, 2 H), 2.71 (td, J = 7.5, 1.1 Hz, 2 H), 1.35 (d, J = 6.1 Hz, 6 H); ^{13}C NMR (176 MHz, $CDCl_3$, HSQC, DEPT) δ *C* 152.6, 151.7, 138.9, 137.2, 135.6; *CH* 201.4, 128.4, 127.7, 127.2, 109.9, 108.0, 71.6; CH_2 71.2, 45.2, 28.2; CH_3 60.6, 22.2; HRMS (EI+) calcd for $C_{20}H_{24}O_4$ [M] 328.1675, found 328.1672.

To a solution of diisopropylamine (253 mg, 2.5 mmol) in THF (8 mL, 0.1 M) was added *n*-BuLi (1.56 mL, 2.5 mmol, 1.6 M in hexane) over a period of 10 min at 0 °C. After stirring at 0 °C for 30 min, the mixture was cooled to −78 °C. A solution of 4-(4-bromophenyl)-butan-2-one (545 mg, 2.4 mmol) in THF (6 mL) was added over a period of 30 min. After stirring at −78 °C for 30 min, a solution of 3-(3-(benzyloxy)-5-isopropoxy-4-methoxyphenyl)propanal (657 mg, 2 mmol) in THF (6 mL) was added over a period of 30 min. After 2 h, the reaction was quenched with saturated aqueous NH_4Cl. The organic phase was separated, and the inorganic phase was extracted with EtOAc. Purification by flash column chromatography (hexanes:EtOAc = 5:1 to 3:1) gave 7-(3-(benzyloxy)-5-isopropoxy-4-methoxyphenyl)-1-(4-bromophenyl)-5-hydroxyheptan-3-one (**S4**, 808 mg, 1.45 mmol, 73% yield) as a colorless oil. Data for **S4**: R_f 0.29 (2:1 hexanes:EtOAc); IR (thin film) 3501 (br), 2975, 2931, 1709, 1587, 1501, 1489, 1434, 1237, 1116, 1011 cm^{-1}; ^1H NMR (700 MHz, $CDCl_3$) δ 7.44 (d, J = 7.4 Hz, 2 H), 7.41−7.34 (m, 4 H), 7.30 (t, J = 7.4 Hz, 1 H), 7.04 (d, J = 8.3 Hz, 2 H), 6.43 (s, 2 H), 5.10 (s, 2 H), 4.52 (sept, J = 6.1 Hz, 1 H), 4.00 (m, 1 H), 3.84 (s, 3 H), 3.02 (br s, 1 H), 2.84 (t, J = 7.5 Hz, 2 H), 2.75−2.65 (m, 3 H), 2.58−2.46 (m, 3 H), 1.77−1.70 (m, 1 H), 1.63−1.56 (m, 1 H), 1.35 (dd, J = 6.1, 1.4 Hz, 6 H); ^{13}C NMR (176 MHz, $CDCl_3$, HSQC, DEPT) δ *C* 210.6, 152.5, 151.5, 139.6, 138.4, 137.3, 137.0, 119.9; *CH* 131.5, 130.0, 128.4, 127.7, 127.2, 109.8, 107.8, 71.4, 66.7; CH_2 71.0, 49.2, 44.6, 37.9, 31.8, 28.7; CH_3 60.7, 22.2; HRMS (TOF MS ES+) calcd for $C_{30}H_{36}BrO_5$ [M + H] 555.1746, found 555.1730.

To a solution of 7-(3-(benzyloxy)-5-isopropoxy-4-methoxyphenyl)-1-(4-bromophenyl)-5-hydroxyheptan-3-one (389 mg, 0.7 mmol) in EtOAc (7 mL, 0.1 M) at rt was added IBX (588 mg, 2.1 mmol). The reaction mixture was heated to reflux for 4 h. The mixture was cooled to rt, filtered through a pad of silica gel, and concentrated to give 1-(3-(benzyloxy)-5-isopropoxy-4-methoxyphenyl)-7-(4-bromophenyl)-heptane-3,5-dione, which was used without further purification.

To a stirred solution of 1-(3-(benzyloxy)-5-isopropoxy-4-methoxyphenyl)-7-(4-bromophenyl)heptane-3,5-dione (from above, approximately 0.7 mmol) in CH_2Cl_2 (14 mL, 0.05 M) were added pentamethylbenzene (311 mg, 2.1 mmol) and BCl_3 (2.8 mL, 2.8 mmol, 1 M in DCM) at −78 °C over a period of 10 min. The reaction was quenched with MeOH at −78 °C. The mixture was warmed to rt. Diluted aqueous $NaHCO_3$ was added until the aqueous phase had pH 6. The organic phase was separated, and the aqueous phase was extracted with EtOAc. Purification by flash column chromatography (hexanes:EtOAc = 5:1 to 3:1) gave **22** (227 mg, 0.49 mmol, 70% yield, 2 steps) as a light yellow oil. Data for **22**: R_f 0.56 (2:1 Hexanes:EtOAc); IR (thin film) 3432 (br), 2976, 2932, 1592, 1507, 1489, 1368, 1330, 1195, 1115, 1073, 1011 cm^{-1}; ^1H NMR (700 MHz, $CDCl_3$, enol tautomer) δ 15.41 (br s, 1 H), 7.39 (d, J = 8.3 Hz, 2 H), 7.05 (d, J = 8.3 Hz, 2 H), 6.40 (d, J = 1.9 Hz, 1 H), 6.28 (d, J = 1.9 Hz,

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1 H), 5.80 (br s, 1 H), 5.42 (s, 1 H), 4.57−4.49 (m, 1 H), 3.87 (s, 3 H), 2.89−2.73 (m, 4 H), 2.58−2.51 (m, 4 H); ^{13}C NMR (176 MHz, $CDCl_3$, HSQC, DEPT, enol tautomer) δ *C* 192.9, 192.7, 150.2, 149.3, 139.5, 136.5, 134.8, 119.9; *C*H 131.5, 130.0, 107.3, 107.1, 99.7, 70.7; *C*H$_2$ 39.8, 39.7, 31.5, 30.8; *C*H$_3$ 60.7, 22.1; HRMS (TOF MS ES+) calcd for $C_{23}H_{26}BrO_4$ [M + H − H_2O] 445.1014, found 445.1020.

Garuganin VII (18). To a sealed tube were added **22** (23.2 mg, 0.05 mmol), CuO (9.9 mg, 0.125 mmol) and K_2CO_3 (13.8 mg, 0.1 mmol). The tube was evacuated and backfilled with Ar, followed by the addition of pyridine (10 mL, 0.005 M). The tube was then sealed and heated at 130 °C for 48 h. The mixture was cooled to rt. After evaporation of the solvent, aqueous HCl (1 mL, 1 M) and H_2O (5 mL) were added. The mixture was extracted with EtOAc. Purification by flash column chromatography (hexanes:EtOAc = 8:1 to 6:1) gave isopropylgaruganin VII (**S5**, 8.6 mg, 0.0225 mmol, 45% yield) as a light yellow solid. Data for **S5**: R_f 0.64 (2:1 Hexanes:EtOAc); IR (thin film) 2974, 2931, 1587, 1504, 1436, 1215, 1113, 1064 cm^{-1}; ^{1}H NMR (700 MHz, $CDCl_3$) δ 15.15 (s, 1 H), 7.16 (d, *J* = 8.4 Hz, 2 H), 6.98 (d, *J* = 8.4 Hz, 2 H), 6.32 (d, *J* = 1.7 Hz, 1 H), 5.23 (d, *J* = 2.0 Hz, 1 H), 4.94 (s, 1 H), 4.52 (sept, *J* = 6.1 Hz, 1 H), 3.95 (s, 3 H), 3.03 (t, *J* = 6.8 Hz, 2 H), 2.89 (m, 2 H), 2.45 (t, *J* = 6.8 Hz, 2 H), 2.35 (m, 2 H), 1.36 (d, *J* = 6.1 Hz, 6 H); ^{13}C NMR (176 MHz, $CDCl_3$, HSQC, DEPT) δ *C* 196.9, 188.7, 155.2, 154.8, 151.4, 137.4, 136.5, 136.2; *C*H 130.5, 123.1, 109.3, 107.0, 103.1, 71.5; *C*H$_2$ 39.4, 37.6, 32.2, 28.0; *C*H$_3$ 61.0, 22.2; HRMS (TOF MS ES+) calcd for $C_{23}H_{27}O_5$ [M + H] 383.1858, found 383.1866.

To a solution of isopropylgaruganin VII (8.4 mg, 0.022 mmol) in DCM (2 mL, 0.011 M) was added BCl_3 (33 μL, 0.033 mmol) at 0 °C. The mixture was allowed to warm to rt. The reaction was then quenched with MeOH and stirred for 10 min. The solvent was evaporated under reduced pressure. Purification by flash column chromatography (hexanes:EtOAc = 6:1 to 4:1) gave garuganin VII (6.5 mg, 0.0191 mmol, 87% yield) as a white solid. Data for garuganin VII: R_f 0.51 (2:1 hexanes:EtOAc); IR (thin film) 3346 (br), 2932, 1587, 1504, 1347, 1215, 1044, 995 cm^{-1}; ^{1}H NMR (700 MHz, $CDCl_3$) δ 15.17 (br s, 1 H), 7.18 (d, *J* = 8.5 Hz, 2 H), 6.98 (d, *J* = 8.5 Hz, 2 H), 6.37 (m, 1 H), 5.78 (s, 1 H), 5.15 (d, *J* = 2.0 Hz, 1 H), 4.93 (s, 1 H), 4.05 (s, 3 H), 3.04 (t, *J* = 6.8 Hz, 2 H), 2.87 (m, 2 H), 2.46 (t, *J* = 6.8 Hz, 2 H), 2.33 (m, 2 H); ^{13}C NMR (176 MHz, $CDCl_3$, HSQC, DEPT) δ *C* 196.9, 188.7, 154.2, 153.8, 149.0, 137.1, 136.8, 133.6; *C*H 130.6, 123.0, 108.2, 106.2, 103.1; *C*H$_2$ 39.4, 37.7, 32.2, 27.8; *C*H$_3$ 61.3; HRMS (TOF MS ES+) calcd for $C_{20}H_{21}O_5$ [M + H] 341.1389, found 341.1390.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Depiction of ^{1}H and ^{13}C NMR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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