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The Garuganin and Garugamblin Diarylether Heptanoids: Total Synthesis and Determination of Chiral Properties Using Dynamic NMR

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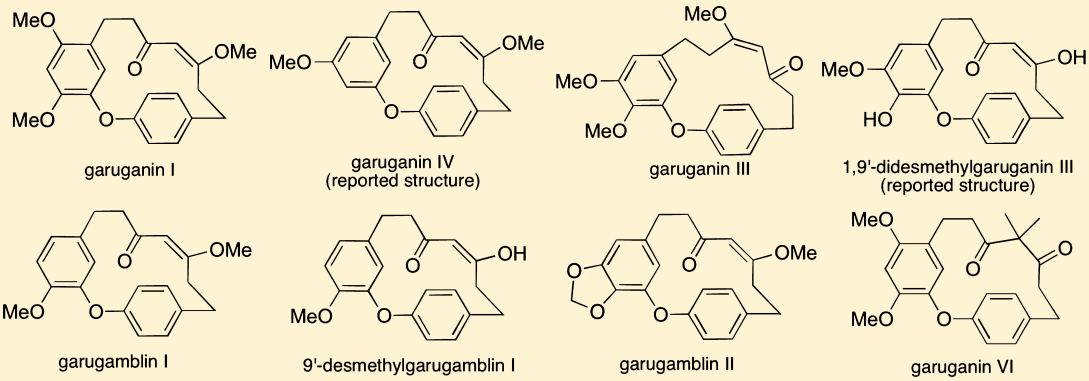
Supporting Information



ABSTRACT: The synthesis of the garuganin and garugamblin diarylether heptanoids using an intramolecular Ullmann coupling is reported. Alkene stereoisomers, vinylogous ester regioisomers, and β-diketone congeners are also synthesized. The chiral properties and free energies of activation for racemization of the garuganin and garugamblin diarylether heptanoids and congeners are determined using dynamic NMR methods. A combination of techniques including coalescence measurements, line shape analysis, and selective inversion experiments are used to measure racemization barriers. None of the garuganin or garugamblin diarylether heptanoids are chiral, despite their reported specific rotation values.

INTRODUCTION

Chirality is of paramount importance to medicine, biology, and chemistry.[1] When molecules contain sp^3 hybridized stereogenic centers, chirality can be readily identified. In molecules without stereogenic centers, the presence of chirality is not as easily recognized. Experimental determination of the presence or absence of chirality is not trivial, particularly when attempting to distinguish between racemic and achiral materials. It is our contention that the chiral properties of many cyclophane natural products are not well understood. Herein, we describe the use of dynamic NMR methods to experimentally determine the chiral properties of the garuganin and garugamblin diarylether heptanoid (DAEH) natural products.

Diarylether heptanoids (DAEHs) represent a class of natural products isolated from terrestrial woody plants.[2] DAEHs share a highly conserved oxa[1.7]metaparacyclophane architecture. These natural products display a range of biological activities[3] and have attracted interest from synthetic chemists.[4] Figure 1 shows the 16 natural DAEHs that do not possess a stereocenter and their specific rotation values. Interestingly, despite their highly conserved structures, some (though not all) DAEHs were isolated as optically active compounds.[5] We recently reported the synthesis, free energies of activation for racemization, and absolute stereochemistry of the DAEHs that display a heptanone ansa bridge, specifically **1**–**6**.[6] Myricatomentogenin, jugcathanin, galeon, and pterocarine are chiral molecules that undergo racemization at temperatures in excess of 200 °C with half-lives of several hours. However, acerogenin C and acerogenin L undergo rapid racemization at temperatures above −60 °C.[6]

The garuganin and garugamblin DAEHs (**7**–**14**) share a highly conserved molecular architecture. These compounds differ only in the substitution pattern at C2–C4 and the methylation pattern of the 1,3-diketone.[7] As shown in Figure 1, five of these compounds were reported to be optically active, suggesting that they are chiral nonracemic compounds. Three of these compounds were isolated without mention of optical activity or chirality, and it is unclear if they are achiral, racemic, or chiral nonracemic molecules. Nogradi and co-workers synthesized garuganin III, garugamblin I, and garugamblin II using a Wittig macrocyclization approach.[4a−c]

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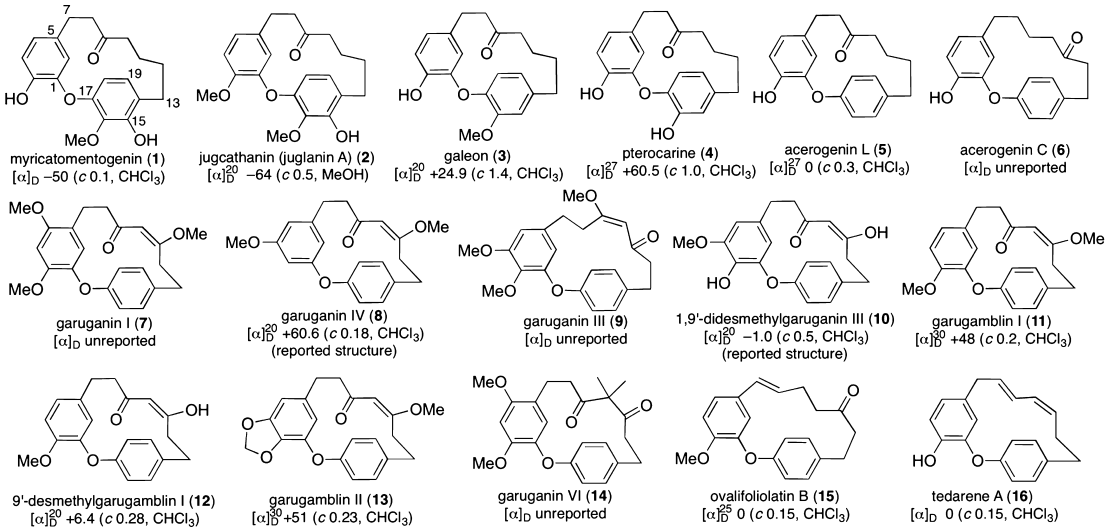
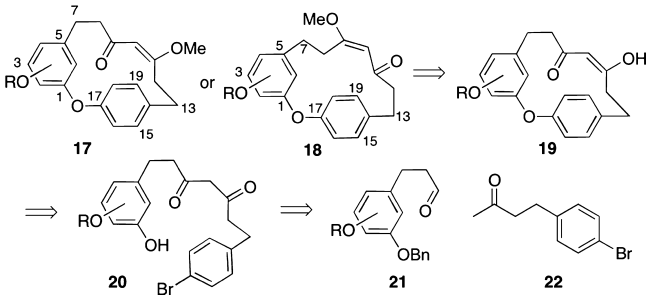


Figure 1. Diarylether heptanoid natural products that lack stereogenic centers.

RESULTS AND DISCUSSION

Synthesis of the Garuganin and Garugamblin Diarylether Heptanoids. We decided to prepare **7**–**14** to investigate their chiral properties. We envisioned the vinylogous ester DAEHs, exemplified by general structures **17** or **18**, arising from the corresponding vinylogous acid **19** (Scheme 1).

Scheme 1. Retrosynthetic Analysis of the Garuganin and Garugamblin DAEHs



Although this strategy would require regio- and stereoselective vinylogous ester formation, it would allow a unified strategy for the formation of all the garuganins and garugamblins, and it could provide access to isomeric DAEH structures for investigation. Moreover, we considered the possibility that the vinylogous esters had formed upon isolation of the vinylogous acids from hot methanolic extraction, and that they were the thermodynamically favored isomer or "stabilomer" (vide infra).

Simplification of the macrocycle by way of an intramolecular Ullmann coupling[8] leads to bromophenols **20**. Positioning the phenolic functional group on the more electron rich phenyl ring was anticipated to give a smoother cyclization than an alternative approach with an electron-rich bromoarene. The β-diketone functional group present in **20** suggested that it could be prepared via an aldol addition with subsequent oxidation, thus beginning with aldehyde **21** and methyl ketone **22**.[9]

The synthesis of garuganin I (**7**) began with hydrocinnamaldehyde derivative **23** (Scheme 2). Addition of **23** to the lithium enolate derived from **22** resulted in formation of aldol product **24**. Oxidation of the β-hydroxy ketone using IBX gave β-diketone **25**.[10] Debenzylation gave the Ullmann coupling substrate **26** in good yield.[11]

Compounds **27**–**31** were prepared using an analogous 3-step sequence. Note that Ullmann substrate **31** has the position of the bromide and the phenol reversed relative to its congeners. With the Ullmann substrates in hand, we then investigated the key macrocyclization (Table 1). Cyclization occurred using stoichiometric CuO in pyridine at elevated temperatures. The yields for the Ullmann reaction were good and quite sufficient for material throughput. Previously, this type of cyclization was predicted to be problematic.[4a]

The formation of **12** represents the synthesis of 9′-desmethylgarugamblin I. Spectral data for this compound

Scheme 2. Synthesis of the Ullmann Substrates

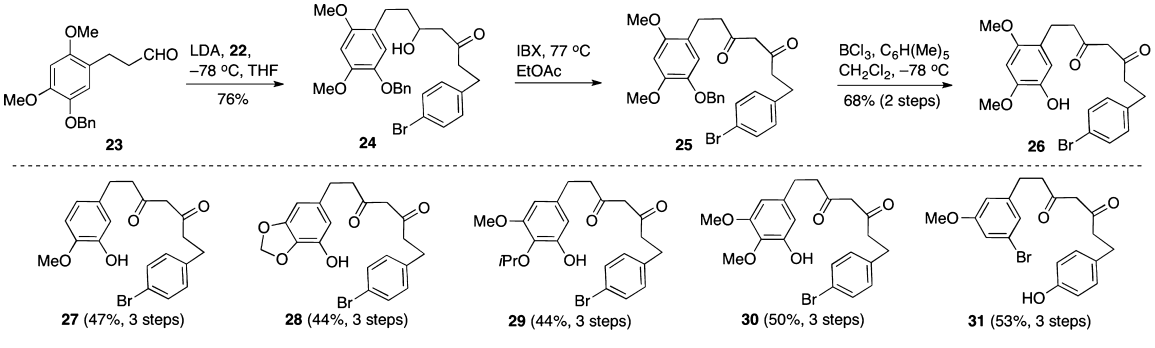


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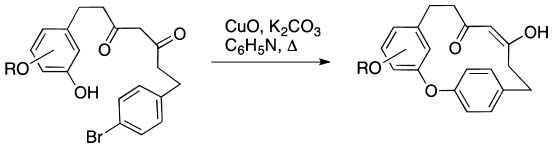
Table 1. Ullmann Cyclizations



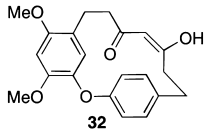
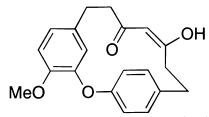
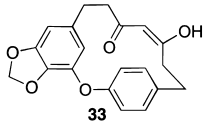
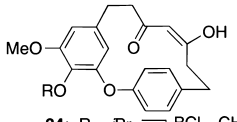
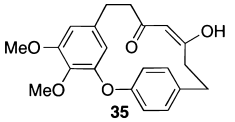
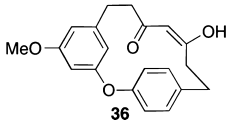
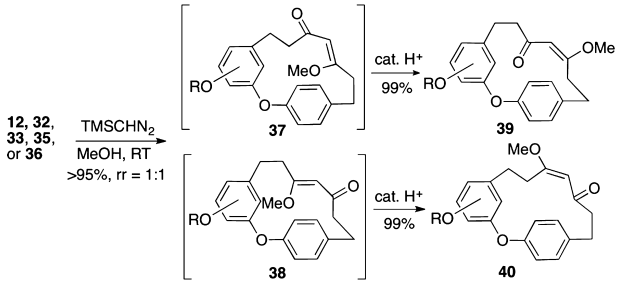
substrate	product	yield
26	 **32**	38%
27	 9'-desmethylgarugamblin I (**12**)	50%
28	 **33**	37%
29	 **34**: R = *i*Pr, **10**: R = H; BCl_3, CH_2Cl_2, 0 °C, 74%; 1,9'-didesmethylgaruganin III (reported structure)	37%
30	 **35**	51%
31	 **36**	40%

Table 2. Synthesis of the Garuganin and Garugamblin DAEHs



substrate	products	yield (ratio)
32	garuganin I (**7**); **41**	>95% (1:1)
12	garugamblin I (**11**); **42**	>95% (1:1)
33	garugamblin II (**13**); **43**	>95% (1:1)
35	**44**; garuganin III (**9**)	>95% (1:1)
36	garuganin IV (**8**) (reported structure); **45**	>95% (1:1)

matched those reported in the literature.[5g] Cleavage of the isopropyl ether of **34** gave the structure reported for 1,9′-didesmethylgaruganin III (**10**), which does not have spectral data consistent with that published for the natural compound, and we believe the structure of the natural product has been misassigned.[5h] The correct structure of the natural product and its verification through synthesis will be described in a forthcoming paper.[12]

We next investigated the methylation of the vinylogous acids **12**, **32**, **33**, **35**, and **36**. Methylation with (trimethylsilyl)-diazomethane was quantitative, giving a 1:1 mixture of vinylogous ester regioisomers with *Z*-configuration (see general structures **37** and **38**, Table 2).[4a−c] These conditions trap the dominant thermodynamic *Z* conformation of the vinylogous acid tautomer, leading to the *Z*-vinylogous esters. If desired, the regioisomeric *Z*-vinylogous esters can be separated by column chromatography, isolated, and observed by NMR in anhydrous base-treated $CDCl_3$. In practice, the *Z*-vinylogous esters were typically not isolated because quantitative isomerization to the *E*-configured esters (general structures **39** and **40**) is induced by treatment with weak acid (e.g., CSA, acetic acid, proline).

A convenient method for inducing quantitative and rapid isomerization involves dissolving the *Z*-configured ester in dry $CDCl_3$ that has not been treated with base. If desired, any of the *E*- and *Z*-configured esters can be recycled by hydrolysis to the corresponding diketones by treatment with aqueous acid. Note that natural products **7**, **8**, **11**, and **13** are exemplified by generic structure **39**, and garuganin III (**9**) is exemplified by generic structure **40**. All of the spectral data for the DAEHs matched those data reported for the natural samples, except for garuganin IV (**8**),[13] and we believe the structure of garuganin IV has been misassigned. The correct structure of the natural product and its verification through synthesis will be described in a forthcoming paper.[12]

DAEHs are commonly isolated by Soxhlet extraction with methanol, and we wondered if the vinylogous ester DAEHs were isolation artifacts arising from the corresponding diketone. To this end, we subjected **12** to hot acidic methanolic conditions (Table 3). After 72 h, the reaction mixture contained a 1:1 ratio of **12** and garugamblin I (**11**) *as a single regio- and stereoisomer*. These reaction conditions also gave a single regio- and stereoisomer of garuganin I (**7**), the reported structure of garuganin IV (**8**), and garugamblin II (**13**) in chemical yields of 17, 14, and 12%, respectively. The mass balance contained only unreacted starting material. Interestingly, treatment of **35** with acidic methanol led to the regioisomer of garuganin III (**44**) in 16% yield. Garuganin III

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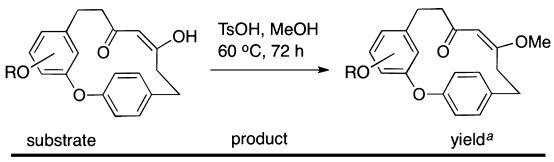
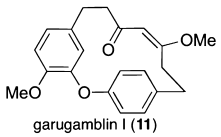
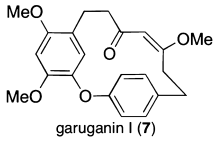
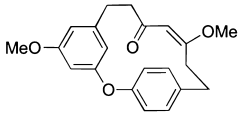
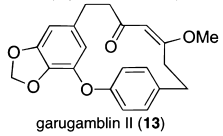
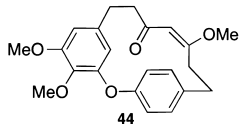
Table 3. Alternative Synthesis of the Garuganin and Garugamblin DAEHs

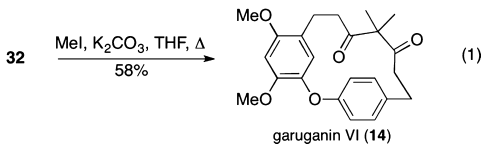


substrate	product	yield[a]
12	 garugamblin I (**11**)	50%
32	 garuganin I (**7**)	17%
36	 garuganin IV (**8**) (reported structure)	14%
33	 garugamblin II (**13**)	12%
35	 **44**	16%

[a]Yield determined by ^{1}H NMR of the crude reaction mixture.

(**9**) was not observed in the reaction mixture. This suggests that garuganin III is not an artifact of the isolation process.

Garuganin VI (**14**) displays geminal methyl groups, and it was prepared from **32** by methylation with MeI in hot basic THF (eq 1). Using the strategy discussed above, 10−100 mg quantities of the garuganins and garugamblins (**7**−**14**) were prepared for further study of their chiral properties.



(1)

Conformational Dynamics of the Garuganin and Garugamblin Diarylether Heptanoids. With **7**−**14** and regiosiomers **41**−**45** in hand, we attempted to determine which have stable isolable enantiomeric conformations. Note that all of the cyclophane molecules discussed in this study can be grouped into one of six structure types (type **A** through **E**, and garuganin VI; Figure 2). Analytical HPLC of **7**−**14** and **41**−**45** using chiral stationary phases showed a single peak regardless of chiral columns (OD, ODH, AY, OZ, IC), solvents, flow rate, or temperature (0 °C to rt). Of course, a single peak is consistent with a compound with enantiomeric conformations that interconvert rapidly on the HPLC time scale, or a compound with two stable enantiomers that have coincident retention times.

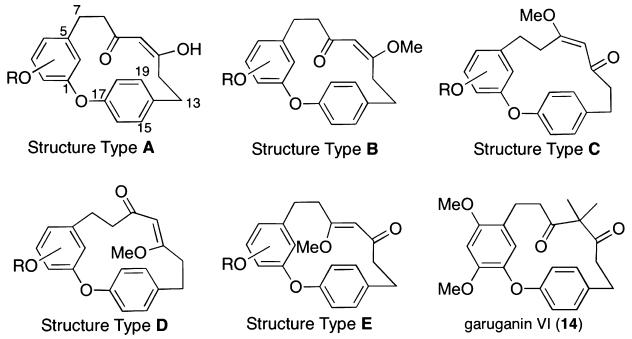


Figure 2. Garuganin and garugamblin structure types.

The 1D ^{1}H NMR spectra of **7**−**14** and congeners can be used to obtain qualitative information regarding the rate of interconversion of enantiomeric conformations. Figure 3 shows the room temperature ^{1}H NMR spectra of the garuganin I series of compounds (i.e., **32**, **7**, **41**, and **14**).[14] Only the spectrum of garuganin I (**7**), which displays the *E*-configured C_9-oxo structure[7] (structure type **B**) shows chemical shift inequivalent geminal methylene protons. Furthermore, symmetry-related protons H_{15}/H_{19} and H_{16}/H_{18} show chemical shift inequivalence in **7** only. The vinylogous acid **32** (structure type **A**), isomer **41** (strucuture type **C**), and garuganin VI (**14**) exhibit chemical shift equivalent geminal methylene (and symmetry-related phenyl) protons. This observation holds in the other garuganin and garugamblin series as well: only DAEHs of structure type **B** have chemical shift inequivalent geminal methylene and phenyl protons.[15] The chemical shift equivalence in structure types **A** and **C**−**E** suggests that enantiomeric conformations are interconverting rapidly at rt.[16]

Variable temperature (VT) NMR was next used to investigate the rate of interconversion of enantiomeric forms. Low temperature NMR spectra of molecules with structure type **A** (i.e., **12**, **32**, **33**, **35**, and **36**), structure type **C** (**41**−**43**, **9**, and **45**), and garuganin VI (**14**) were used to determine approximate rates of interconversion of enantiomeric conformations at cryogenic temperatures (see data for **32**, Figure 4). At low temperatures, racemization becomes slow relative to the NMR time scale, and decoalescence occurs.[17]

In two-site equally populated cases, the relationship $k_C = 2.22 \times \Delta\nu$ gives the rate constant for coalescence (k_C), where $\Delta\nu$ is the separation in Hz of the coalescing peaks at temperatures below coalescence.[18] We used this relationship to estimate the rate of conformational exchange in DAEHs that have coalescence temperatures below rt. For **32**, our estimated $\Delta\nu$ = 106 Hz gave k_C = 236 s^{-1}, an approximate $\Delta G^{\ddagger}_{rac}$ = 9.0 kcal/mol at −80 °C, and a half-life ($t_{1/2}$) of 0.003 s at −80 °C. All molecules with structure type **A** had nearly identical values (Table 4).

For structure **41**, we observed T_C = −10 °C and $\Delta\nu$ = 76 Hz giving k_C = 169 s^{-1}, an approximate $\Delta G^{\ddagger}_{rac}$ = 12.7 kcal/mol, and a half-life of 0.0041 s at −10 °C. All molecules with structure type **C** had nearly identical values (Table 4). Garuganin VI (**14**) showed T_C = −50 °C and $\Delta\nu$ = 31 Hz giving k_C = 68 s^{-1}, an approximate $\Delta G^{\ddagger}_{rac}$ = 11.1 kcal/mol, and a half-life of 0.0102 s at −50 °C. Thus, DAEHs with structure types **A**, **C**, and garuganin VI (**7**) are achiral molecules, despite any reported nonzero specific rotation values at room temperature.

Chemical shift inequivalence in structure type **B** indicates that the interconversion of enantiomeric conformations is slow

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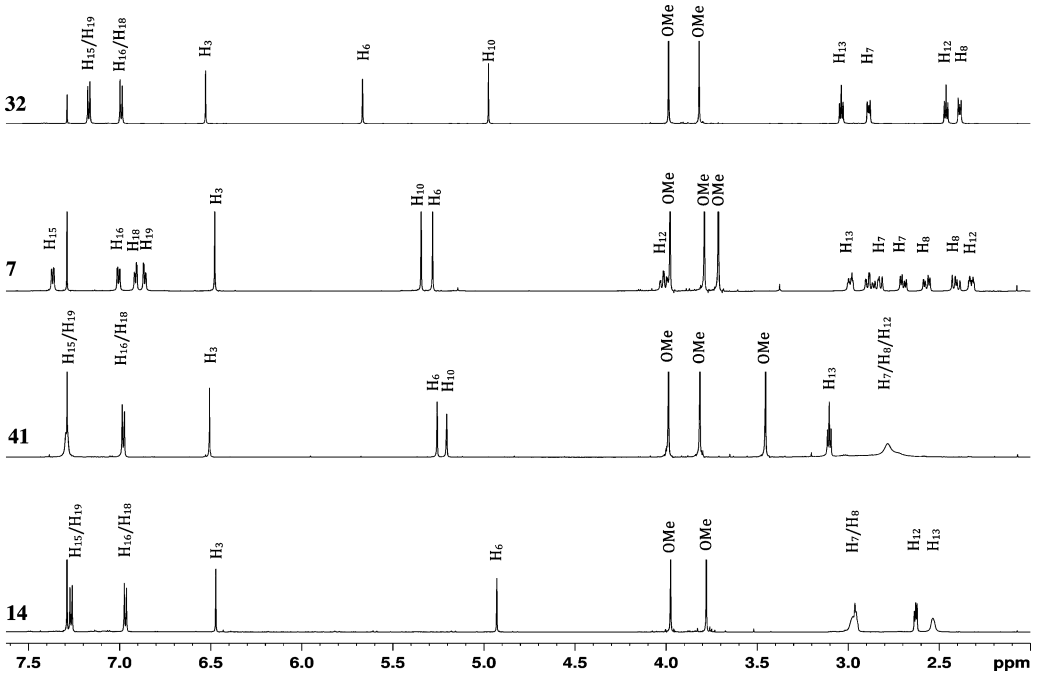

Figure 3. ^{1}H NMR spectra of **32**, **7**, **41**, and **14** ($CDCl_3$, 400 MHz).

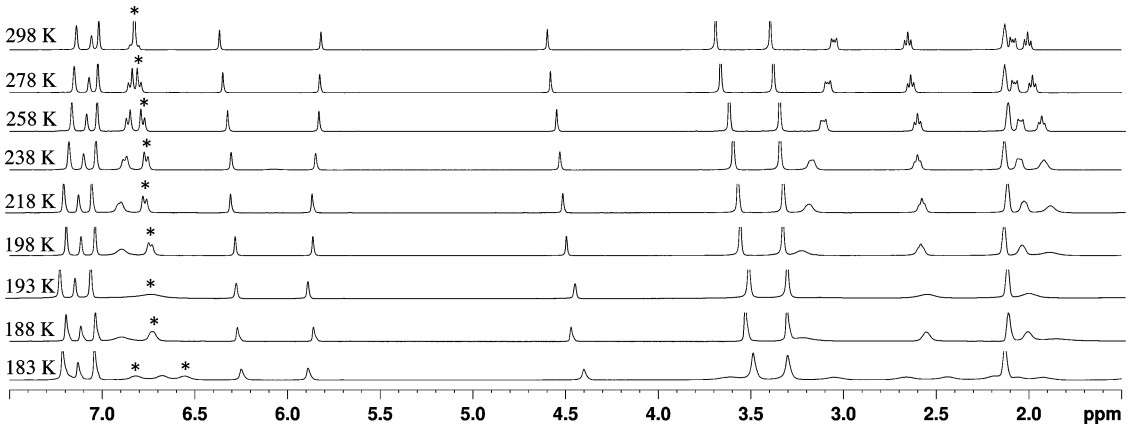

Figure 4. Low temperature NMR spectra of **32** (toluene-d_9, 400 MHz). *Indicates resonance used to determine T_C.

Table 4. Half-Lives of Molecules with Structure Types A, C, and Garuganin VI (14) at Cryogenic Temperatures

compound	structure-type	$\Delta\nu$ (Hz)	T_C (K)	k_C	ΔG (kcal/mol)	$t_{1/2}$ (s)
10	**A**	115	193	256	9.0	0.0027
12	**A**	94	193	208	9.1	0.0033
32	**A**	106	193	236	9.0	0.0029
33	**A**	146	193	324	8.9	0.0021
35	**A**	131	193	290	9.0	0.0024
36	**A**	128	193	285	9.0	0.0024
9	**C**	69	263	154	12.7	0.0045
41	**C**	76	263	169	12.6	0.0041
42	**C**	71	263	157	12.7	0.0044
43	**C**	70	263	155	12.7	0.0045
45	**C**	68	263	152	12.7	0.0046
14		31	223	68	11.1	0.0102

on the NMR time scale at rt. However, since the NMR time scale is faster than the laboratory time scale, this observation does not demonstrate that enantiomeric conformations of structure type **B** could be resolved at rt.

The ^{1}H NMR spectra of compounds with structure type **B** (i.e., **7**, **11**, **13**, **44**, **8**) were recorded at elevated temperatures (see data for **7**, Figure 5; Table 5). Coalescence of the geminal methylene protons and of the symmetry-related phenyl protons occurs at 90 °C. The coalescence temperature (T_C) and the separation between coalescing peaks below T_C can be used to determine k_C.[17] For **7**, $\Delta\nu$ = 180 Hz, giving a value of k_C = 400 s^{-1}. This results in an approximate free energy of activation for racemization ($\Delta G^{\ddagger}_{rac}$) of 17 kcal/mol at 90 °C. Of course, the free energy of activation for racemization at elevated temperatures does not give the half-life of an enantiomeric conformation at rt.

Line shape analysis using simulated spectra gives the rate of interconversion of enantiomers at temperatures below coalescence and is more accurate than using coalescence measurements.[19] Figure 6 shows experimental and simulated spectra for garuganin I (**7**). Analysis of these spectra give values of k = 5, 25, 60, and 110 s^{-1} at 35, 45, 55, and 65 °C,

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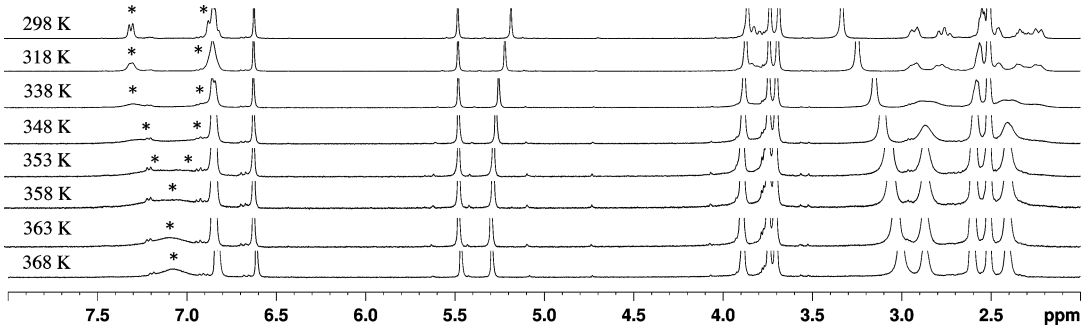

Figure 5. High temperature NMR spectra of 7 (DMSO-d_6, 400 MHz). *Indicates resonance used to determine T_C.

Table 5. Half-Lives of Molecules with Structure Types B at Elevated Temperatures

compound	structure-type	$\Delta\nu$ (Hz)	T_C (K)	k_C	ΔG (kcal/mol)	$t_{1/2}$ (s)
7	**B**	180	363	400	17.1	0.0017
8	**B**	189	363	419	17.0	0.0017
11	**B**	190	363	423	17.0	0.0016
13	**B**	192	363	426	17.0	0.0016
44	**B**	150	363	333	17.2	0.0021

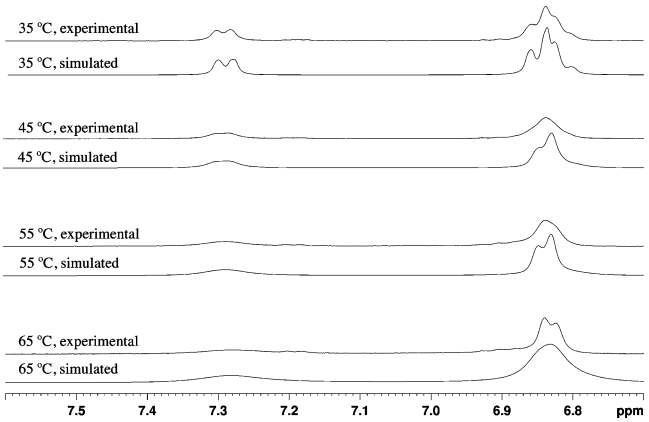

Figure 6. Experimental and simulated ^{1}H NMR spectra of 7.

respectively. Extrapolation of the data using Eyring analysis[20] gives a value of k = 2.4 s^{-1} at 25 °C, which corresponds to an approximate half-life of 0.29 s for each enantiomeric conformation. The calculated half-lives based on line shape analysis of compounds with structure type **B** were all quite similar (see Table 6, below).

Selective inversion recovery (SIR) describes a two-pulse NMR technique that can be used to obtain rates of processes that occur slowly on the NMR time scale.[21] Using this technique, selectively inverting one site leads to relaxation to equilibrium by normal T1 mechanisms and exchange with the noninverted site. The noninverted site shows a characteristic negative transient. These relaxations can be analyzed exactly, and the analysis results in accurate values of the interconversion rate. Use of SIR in combination with line shape analysis gives a very accurate measurement of rate.

Table 6. Room Temperature Half-Lives of Enantiomeric Conformations of Molecules with Structure Type B

compound	$t_{1/2}$ (s) from line shape analysis	$t_{1/2}$ (s) from SIR experiments
7	0.29	0.20
8	0.38	0.18
11	0.51	0.30
13	0.54	0.63
44	0.23	0.30

SIR experiments were performed on the molecules with structure type **B**. In these spectra, the signal for H_{15} was sufficiently well resolved to enable selective inversion using a soft pulse. The delay between pulses was varied between 0.001 and 10 s, and magnetization transfer to H_{19} was observed (see data for 7, Figure 7). Mathematical analysis of the delay-dependent integration of H_{15} and H_{19} was used to obtain the rate of exchange at rt. Using SIR, we found that the rate of interconversion of enantiomeric conformations of 7 is k_{rac} = 3.5 s^{-1}, giving a half-life of 0.20 s at 25 °C. This value corresponds well to the value obtained using line shape analysis (0.29 s). Moreover, we found that half-lives for enantiomeric conformations of compounds with structure type **B** at rt as determined from SIR experiments were quite similar and agreed well with the values obtained from line shape analysis (Table 6).

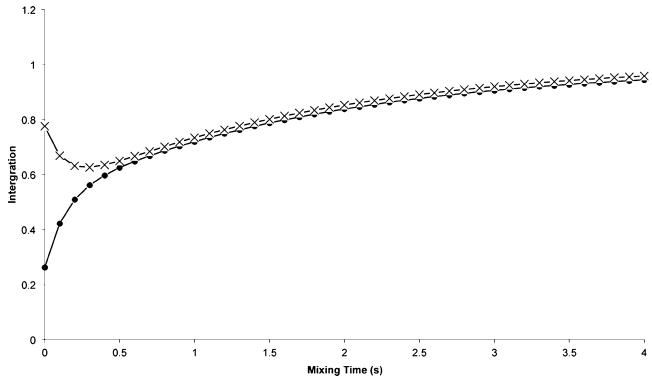

Figure 7. Selective inversion recovery experiments using 7. ● = data for H_{15}; × = data for H_{19}.

CONCLUSION

Garuganin and garugamblin DAEHs were synthesized using a key Ullmann bond-forming reaction to build the cyclophane molecular architecture of the natural products. Selective methylation of the vinylogous acid DAEHs (e.g., 9′-desmethylgarugamblin I, **12**) occurred in hot acidic methanol and produced a single isomer of the vinylogous ester DAEHs (e.g., garugamblin I, **11**). An unselective methylation using (trimethylsilyl)diazomethane, followed by acid-catalyzed isomerization, also gave access to the natural products along with

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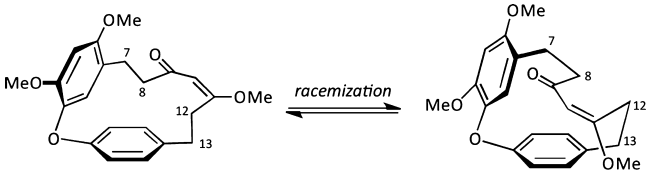
their corresponding regio- and stereoisomers. The overall synthesis proceeded with yields of 8−12% and conveniently produced 10−100 mg quantities of the natural products for study.

The racemization barriers of the garuganin and garugamblin DAEH natural products and congeners were measured. DAEHs that belong to the same structural class (**A**−**E**, see Figure 2) have nearly identical racemization barriers. Compounds with structure types **A** and **C** (e.g., 9′-desmethylgarugamblin I, garuganin III, and 1,9′-didesmethylgaruganin III) undergo racemization at cryogenic temperatures with half-lives on the order of milliseconds. Enantiomeric conformations of garuganin VI (**14**) have an approximate half-life of 0.01 s at −50 °C and cannot be resolved at rt. DAEHs with structure type **B** (e.g., garugamblin I, garugamblin II, garuganin I, and the reported structure of garuganin IV) have relatively higher barriers of racemization; however, resolution of enantiomeric conformations is not possible at rt. Line shape analysis and selective inversion recovery experiments indicate that the half-life of enantiomeric conformations of DAEHs with structure type **B** are less than 1 s at rt. Thus, all garuganin and garugamblin DAEHs are achiral, and they are not optically active.

Scheme 3 depicts the two enantiomeric conformations of garuganin I (**7**), which has structure type **B**. Racemization of

Scheme 3. Racemization of Garuganin I



this molecule requires conformational "flipping" of the seven carbon ansa loop over the para-substituted arene. Interestingly, molecules with structure type **B**, which display the C9 carbonyl, have a higher barrier than other garuganin and garugamblin structure types (i.e., **A** and **C**−**E**). Thus, both the geometry of the alkene and the location of the methyl group affect the rate of this conformational exchange. The racemization process may involve the rotation of the C7−C8 and C12−C13 sigma bonds, but whether this is a concerted movement or a stepwise process is currently unknown. We have initiated a DFT-based computational study of the precise mechanism of this process in all the DAEH natural products, and our results will be published in a forthcoming manuscript.

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. Flash column chromatography was carried out with SiliaFlash P60 silica gel. 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. 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 (^{1}H NMR and ^{13}C NMR) were recorded in deuterated chloroform ($CDCl_3$) unless otherwise noted at 700 or 400 MHz as indicated. Multiplicities are abbreviated as follows: s = singlet, d = doublet, t = triplet, q = quartet, sept = septet, br = broad, m = multiplet. Melting points are uncorrected.

The line shapes were simulated using the MEXICO suite of programs (available from ADB). The program simulates the line shape, given spectral parameters and a rate, and this simulated shape is compared to the experimental one using Bruker's TopSpin program. Chemical shifts and coupling constants were estimated by simulating the low-temperature spectrum with a very slow rate. At higher temperatures, the rate and the chemical shifts (which depend on temperature) were adjusted until a good fit of the spectrum was obtained. The estimated error of the rates is about ±10%.

Selective inversion recovery (SIR) data were analyzed using the CIFIT program (available from ADB). Intensities of the lines as a function of delay time were measured in Bruker's TopSpin program. Their time dependence is a sum of exponentials, so CIFIT does a fit to this functional form, using a Levenberg−Marquardt nonlinear least-squares algorithm. For data of the quality collected here, errors in rates are estimated to be less than 5%.

3-(5-(Benzyloxy)-2,4-dimethoxyphenyl)propanal (23). To a solution of ethyl 3-(2,4-dimethoxyphenyl)propanoate[22] (1.191 g, 5 mmol) in CH_2Cl_2 (20 mL, 0.25 M) at 0 °C were added acetyl chloride (535 μL, 7.5 mmol) and $AlC1_3$ (2 × 500 mg, 7.5 mmol).[1] After stirring for 2 h at 0 °C, the reaction mixture was poured into a mixture of ice (50 g) and aqueous HCl (10 mL, 1 M). The organic phase was separated. The aqueous phase was extracted with EtOAc (3 × 30 mL). The combined organic phases were dried with $MgSO_4$. Evaporation of the solvent gave ethyl 3-(5-acetyl-2,4-dimethoxyphenyl)propanoate (**S1**, 1.334 g, 4.76 mmol, 95% yield) as a white solid. Data for **S1**: R_f 0.41 (3:2 hexanes:EtOAc); mp = 90−92 °C; IR (thin film) 1723, 1656, 1605, 1570, 1262, 1234, 1208, 1171, 1020 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (s, 1 H), 6.42 (s, 1 H), 4.13 (q, J = 7.1 Hz, 2 H), 3.93 (s, 3 H), 3.90 (s, 3 H), 2.88 (t, J = 7.8 Hz, 2 H), 2.57 (s, 3 H), 2.56 (t, J = 7.8 Hz, 2 H), 1.26 (t, J = 7.1 Hz, 3 H); ^{13}C NMR (101 MHz, $CDCl_3$, HSQC, DEPT) δ *C* 197.6, 173.1, 162.2, 160.2, 121.1, 119.9; *C*H 132.1, 94.5, CH_2 60.3, 34.3, 25.2; *C*H_3 55.6, 55.5, 31.9, 14.2; HRMS (TOF MS ES+) calcd for $C_{15}H_{20}O_5Na$ [M + Na] 303.1208, found 303.1211.

To a solution of **S1** (1.682 g, 6 mmol) in CH_2Cl_2 (14 mL, 0.25 M) at 0 °C were added TsOH (52 mg, 0.3 mmol) and a solution of *m*CPBA (70%, 2.071 g, 8.4 mmol) in CH_2Cl_2 (10 mL) over a period of 30 min. The reaction mixture was stirred for 30 min at 0 °C and 4 h at rt. Subsequently, aqueous $Na_2S_2O_3$ (5 mL, 1 M) was added, and the suspension was stirred for 15 min at rt. Aqueous saturated $NaHCO_3$ was added until aqueous phase had pH 7. The organic phase was separated, and the aqueous phase was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic phases were dried with $MgSO_4$. Purification by flash column chromatography (hexanes:EtOAc = 5:1) gave ethyl 3-(5-acetoxy-2,4-dimethoxyphenyl)propanoate (**S2**, 1.25 g, 4.22 mmol, 70% yield) as a light yellow solid. Data for **S2**: R_f 0.42 (2:1 hexanes:EtOAc); mp = 33−35 °C; IR (thin film) 2939, 1764, 1732, 1619, 1515, 1371, 1319, 1197, 1034, 913 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.83 (s, 1 H), 6.51 (s, 1 H), 4.12 (q, J = 7.1 Hz, 2 H), 3.82 (s, 6 H), 2.85 (t, J = 7.7 Hz, 2 H), 2.56 (t, J = 7.7 Hz, 2 H), 2.28 (s, 3 H), 1.24 (t, J = 7.1 Hz, 3 H); ^{13}C NMR (101 MHz, $CDCl_3$, HSQC, DEPT) δ *C* 173.2, 169.4, 155.8, 150.0, 132.6, 120.8; *C*H 123.8, 96.8, CH_2 60.2, 34.2, 25.2; *C*H_3 56.1, 55.7, 20.6, 14.2; HRMS (TOF MS ES +) calcd for $C_{15}H_{20}O_6Na$ [M + Na] 319.1158, found 319.1151.

To a solution of **S2** (296 mg, 1 mmol) in EtOH (10 mL, 0.1 M) was added K_2CO_3 (415 mg, 3 mmol) at rt. The mixture was heated to 70 °C. After 2 h, BnBr (178 μL, 1.5 mmol) was added. The mixture was maintained at 70 °C for another 2 h. The mixture was cooled to rt and quenched by the addition of saturated aqueous NH_4Cl (20 mL). The resultant mixture was extracted with EtOAc (4 × 20 mL). The combined organic phases were dried with $MgSO_4$. Purification by flash column chromatography (hexanes:EtOAc = 6:1) gave ethyl 3-(5-(benzyloxy)-2,4-dimethoxyphenyl)propanoate (**S3**, 323 mg, 0.94 mmol, 94% yield) as a light yellow solid. Data for **S3**: R_f 0.57 (2:1 hexanes:EtOAc); mp = 41−43 °C; IR (thin film) 2937, 1731, 1614, 1513, 1455, 1374, 1208, 1034, 865 cm^{-1}; ^{1}H NMR (400 MHz,

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$CDCl_3$) δ 7.51−7.29 (m, 5 H), 6.79 (s, 1 H), 6.54 (s, 1 H), 5.08 (s, 2 H), 4.13 (q, J = 7.1 Hz, 2 H), 3.90 (s, 3 H), 3.83 (s, 3 H), 2.85 (t, J = 7.8 Hz, 2 H), 2.55 (t, J = 7.8 Hz, 2 H), 1.26 (t, J = 7.1 Hz, 3 H); ^{13}C NMR (101 MHz, $CDCl_3$, HSQC, DEPT) δ *C* 173.4, 152.4, 149.2, 141.8, 137.6, 120.6; *C*H 128.4, 127.8, 127.6, 118.1, 98.0, CH_2 72.5, 60.2, 34.6, 25.5; CH_3 56.5, 56.0, 14.3; HRMS (TOF MS ES+) calcd for $C_{20}H_{25}O_5$ [M + H] 345.1702, found 345.1686.

To a solution of **S3** (482 mg, 1.4 mmol) in CH_2Cl_2 (14 mL, 0.1 M) at −78 °C was added DIBAL-H (1.4 mL, 1.68 mmol, 1.2 M in toluene) over a period of 30 min. After the addition was complete, TLC indicated complete consumption of the starting material. The reaction was quenched with saturated aqueous Rochelle's salt (30 mL) at −78 °C. The mixture was warmed to rt. The organic phase was separated, and the inorganic phase was extracted with EtOAc (3 × 30 mL). The combined organic phases were dried with $MgSO_4$. Purification by flash column chromatography (hexanes:EtOAc = 5:1) gave **23** (366 mg, 1.22 mmol, 87% yield) as white solid. Data for **23**: R_f 0.33 (5:2 hexanes:EtOAc); mp = 80−82 °C; IR (thin film) 2936, 1713, 1607, 1519, 1462, 1402, 1310, 1219, 1027 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.77 (s, 1 H), 7.51−7.29 (m, 5 H), 6.75 (s, 1 H), 6.54 (s, 1 H), 5.08 (s, 2 H), 3.91 (s, 3 H), 3.82 (s, 3 H), 2.85 (t, J = 7.2 Hz, 2 H), 2.66 (t, J = 7.2 r4 Hz, 2 H); ^{13}C NMR (101 MHz, $CDCl_3$, HSQC, DEPT) δ *C* 152.2, 149.4, 141.8, 137.6, 120.1; *C*H 202.5, 128.5, 127.8, 127.6, 118.2, 98.0; CH_2 72.6, 44.2, 22.9; CH_3 56.5, 55.9; HRMS (TOF MS ES+) calcd for $C_{18}H_{20}O_4Na$ [M + Na] 323.1259, found 323.1263.

7-(5-(Benzyloxy)-2,4-dimethoxyphenyl)-1-(4-bromophenyl)-5-hydroxyheptan-3-one (24). To a solution of diisopropylamine (363 mg, 3.59 mmol) in THF (12 mL, 0.1 M) at 0 °C was added *n*-BuLi (2.24 mL, 3.59 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 **22**[9] (782 mg, 3.44 mmol) in THF (8 mL) was added over a period of 1 h. After stirring at −78 °C for 30 min, a solution of **23** (862 mg, 2.87 mmol) in THF (9 mL) was added over a period of 1 h. After stirring for 2 h, the reaction was quenched with saturated aqueous NH_4Cl (30 mL). The organic phase was separated, and the aqueous phase was extracted with EtOAc (3 × 30 mL). The combined organic phases were dried with $MgSO_4$. Purification by flash column chromatography (hexanes:EtOAc = 5:1 to 5:2) gave **24** (1.146 g, 2.17 mmol, 76% yield) as a white solid. Data for **24**: R_f 0.20 (2:1 hexanes:EtOAc); mp = 75−78 °C; IR (thin film) 3512 (br), 2933, 1708, 1511, 1454, 1404, 1315, 1203, 1072, 1035 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49−7.28 (m, 7 H), 7.06 (d, J = 8.3 Hz, 2 H), 6.74 (s, 1 H), 6.53 (s, 1 H), 5.08 (s, 2 H), 3.94 (m, 1 H), 3.90 (s, 3 H), 3.81 (s, 3 H), 3.00 (br s, 1 H), 2.86 (t, J = 7.3 Hz, 2 H), 2.78−2.44 (m, 6 H), 1.75−1.53 (m, 2 H); ^{13}C NMR (101 MHz, $CDCl_3$, HSQC, DEPT) δ *C* 210.2, 152.1, 149.0, 142.1, 139.9, 137.6, 121.5, 119.9; *C*H 131.6, 130.2, 128.5, 127.8, 127.6, 118.1, 98.2, 66.9; CH_2 72.4, 49.4, 44.8, 37.1, 28.8, 25.4; CH_3 56.5, 56.3; HRMS (TOF MS ES+) calcd for $C_{28}H_{32}BrO_5$ [M + H] 527.1433, found 527.1442.

1-(5-(Benzyloxy)-2,4-dimethoxyphenyl)-7-(4-bromophenyl)-heptane-3,5-dione (26). To a solution of **24** (106 mg, 0.2 mmol) in EtOAc (2 mL, 0.1 M) at rt was added IBX (168 mg, 0.6 mmol). The reaction mixture was heated to reflux until complete consumption of the starting material was observed (TLC, approximately 4 h). The reaction mixture was allowed to cool to rt, filtered through a short pad of silica gel, and concentrated to give the crude β-diketone **25**, which was used directly without further purification.

To a stirred solution of **25** (0.2 mmol, from previous step) in CH_2Cl_2 (4 mL, 0.05 M) were added pentamethylbenzene (89 mg, 0.6 mmol) and BCl_3 (0.8 mL, 0.8 mmol, 1 M in DCM) at −78 °C over a period of 10 min. After the addition was complete, TLC indicated complete consumption of the starting material. The reaction was quenched with MeOH (1 mL) at −78 °C. The resultant mixture was allowed to warm 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 (3 × 10 mL). The combined organic phases were dried with $MgSO_4$. Purification by flash column chromatography (hexanes:EtOAc = 5:1 to 3:1) gave **26** (59 mg, 0.136 mmol, 68% yield, 2 steps) as a light yellow solid. Data for **26**: R_f 0.40 (2:1 hexanes:EtOAc); mp = 69−71 °C; IR (thin film) 3455 (br), 2939, 1612, 1513, 1201, 1034 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, enol tautomer) δ 15.44 (br s, 1 H), 7.41 (d, J = 8.1 Hz, 2 H), 7.08 (d, J = 8.1 Hz, 2 H), 6.73 (s, 1 H), 6.49 (s, 1 H), 5.45 (s, 1 H), 5.24 (br s, 1 H), 3.90 (s, 3 H), 3.80 (s, 3 H), 2.95−2.71 (m, 4 H), 2.63−2.46 (m, 4 H); ^{13}C NMR (101 MHz, $CDCl_3$, HSQC, DEPT, enol tautomer) δ *C* 193.5, 192.8, 150.9, 145.1, 139.7, 139.2, 121.4, 120.0; *C*H 131.5, 130.1, 115.8, 99.5, 96.7; CH_2 39.8, 38.6, 30.8, 25.8; CH_3 56.3, 56.2; HRMS (TOF MS ES+) calcd for $C_{21}H_{24}BrO_5$ [M + H] 435.0807, found 435.0816.

4,6-Dimethoxy-2-oxatricyclo[13.2.2.1]^{3,7}[icosa-1(17),3,5,7-(20),15,18-hexene-10−12-dione (32). To a sealed tube were added **26** (21.8 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 to 120 °C. After 36 h, TLC indicated the complete consumption of the starting material. The reaction mixture was allowed to cool 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 (4 × 10 mL). The combined organic phases were dried with $MgSO_4$. Purification by flash column chromatography (hexanes:EtOAc = 8:1 to 6:1) gave **32** (7.9 mg, 0.0223 mmol, 45% yield) as a light yellow solid. Data for **32**: R_f 0.52 (2:1 hexanes:EtOAc); IR (thin film) 2933, 1604, 1520, 1504, 1392, 1318, 1209, 1030, 868 cm^{-1}; ^{1}H NMR (700 MHz, $CDCl_3$) δ 15.13 (br s, 1 H), 7.17 (d, J = 8.4 Hz, 2 H), 6.99 (d, J = 8.4 Hz, 2 H), 6.53 (s, 1 H), 5.67 (s, 1 H), 4.98 (s, 1 H), 3.99 (s, 3 H), 3.82 (s, 3 H), 3.04 (t, J = 6.8 Hz, 2 H), 2.89 (m, 2 H), 2.46 (t, J = 6.8 Hz, 2 H), 2.39 (m, 2 H); ^{13}C NMR (176 MHz, $CDCl_3$, HSQC, DEPT) δ *C* 197.3, 188.5, 155.6, 151.7, 146.8, 144.8, 136.2, 121.1; *C*H 130.6, 123.0, 115.2, 103.0, 97.3; CH_2 39.5, 36.8, 32.3, 20.8; CH_3 56.6, 56.2; HRMS (TOF MS ES+) calcd for $C_{21}H_{23}O_5$ [M + H] 355.1545, found 355.1555.

Garuganin I (7) and (10*E*)-4,6,12-Trimethoxy-2-oxatricyclo-[13.2.2.1^{3,7}]icosa-1(17),3,5,7(20),10,15,18-heptaen-12-one (41). To a solution of **32** (28.4 mg, 0.08 mmol) in CH_3CN and MeOH (8 mL, 0.01 M, 10:1 v/v) was added $TMSCHN_2$ (0.4 mL, 0.8 mmol, 2 M in hexanes). After stirring at rt for 4 h, the solvent was removed under reduced pressure. Purification by flash column chromatography (hexanes:EtOAc = 5:1 to 3:1) gave **37a** (14.1 mg, 0.0383 mmol, 48% yield, white solid, more polar) and **38a** (13.9 mg, 0.0377 mmol, 47% yield, white solid, less polar) in 1:1 regioselectivity. Treating **37a** and **38a** with dry acidic $CDCl_3$ ("old" $CDCl_3$ dried by 3 Å MS) at rt (approximately 5 min) gave garuganin I (**7**) and **41**, respectively in >95% yield. Data for garuganin I (**7**): white solid, R_f 0.46 (2:1 hexanes:EtOAc); IR (thin film) 2928, 1684, 1587, 1512, 1204, 1097, 1035 cm^{-1}; ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.37 (dd, J = 8.3, 1.8 Hz, 1 H), 7.01 (dd, J = 8.3, 2.3 Hz, 1 H), 6.91 (dd, J = 8.1, 2.3 Hz, 1 H), 6.86 (dd, J = 8.1, 1.8 Hz, 1 H), 6.48 (s, 1 H), 5.34 (s, 1 H), 5.28 (s, 1 H), 4.01 (td, J = 12.9, 3.3 Hz, 1 H), 3.98 (s, 3 H), 3.79 (s, 3 H), 3.71 (s, 3 H), 2.99 (dt, J = 12.9, 3.8 Hz, 1 H), 2.88 (td, J = 12.9, 2.9 Hz, 1 H), 2.83 (dd, J = 15.9, 11.6 Hz, 1 H), 2.70 (dd, J = 16.0, 6.8 Hz, 1 H), 2.57 (dd, J = 17.8, 6.8 Hz, 1 H), 2.41 (dd, J = 18.2, 11.5 Hz, 1 H), 2.32 (dt, J = 12.8, 3.8 Hz, 1 H); ^{13}C NMR (176 MHz, $CDCl_3$, HSQC, DEPT) δ *C* 197.2, 172.8, 156.0, 151.2, 146.3, 145.7, 137.8, 122.0; *C*H 131.1, 130.0, 124.4, 122.3, 117.1, 101.0, 97.5; CH_2 44.4, 33.9, 33.0, 19.1; CH_3 56.6, 56.5, 55.2; HRMS (TOF MS ES+) calcd for $C_{22}H_{25}O_5$ [M + H] 369.1702, found 369.1693.

Data for **41**: white solid, R_f 0.25 (2:1 hexanes:EtOAc); IR (thin film) 2928, 1664, 1562, 1515, 1504, 1441, 1394, 1203, 1034 cm^{-1}; ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.32−7.27 (m, 2 H), 6.98 (d, J = 8.5 Hz, 2 H), 6.51 (s, 1 H), 5.26 (s, 1 H), 5.20 (s, 1 H), 3.99 (s, 3 H), 3.81 (s, 3 H), 3.45 (s, 3 H), 3.10 (t, J = 7.0 Hz, 2 H), 3.08−2.40 (m, 6 H); ^{13}C NMR (176 MHz, $CDCl_3$, HSQC, DEPT) δ *C* 198.9, 174.2, 154.5, 151.4, 145.7, 145.2, 137.2, 121.1; *C*H 131.3, 123.5, 113.3, 102.0, 97.0; CH_2 44.3, 31.3, 28.3, 20.9; CH_3 56.6, 56.0, 55.6; HRMS (TOF MS ES +) calcd for $C_{22}H_{25}O_5$ [M + H] 369.1702, found 369.1697.

Garuganin VI (14). To a solution of **32** (8 mg, 0.0226 mmol) in THF (2 mL, 0.0113 M) was added K_2CO_3 (31.2 mg, 0.226 mmol). After stirring at rt for 30 min, CH_3I (42 μL, 0.678 mmol) was added. The mixture was heated to reflux. After 24 h, another 42 μL of CH_3I

was added. After refluxing for another 24 h, TLC indicated the complete consumption of the starting material. The mixture was allowed to cool to rt and filtered through a short pad of Celite. Purification by flash column chromatography (hexanes:EtOAc = 10:1 to 6:1) gave **14** (5 mg, 0.0131 mmol, 58% yield) as a light yellow solid. Data for **14**: R_f 0.31 (3:1 hexanes:EtOAc); IR (thin film) 2925, 1691, 1606, 1453, 1318, cm^{-1}; ^1H NMR (700 MHz, $CDCl_3$) δ 7.27 (d, J = 8.5 Hz, 2 H), 6.97 (d, J = 8.5 Hz, 2 H), 6.47 (s, 1 H), 4.92 (s, 1 H), 3.98 (s, 3 H), 3.78 (s, 3 H), 3.04−2.92 (m, 4 H), 2.63 (t, J = 5.4 Hz, 2 H), 2.54 (br s, 2 H), 1.40 (s, 6 H); ^{13}C NMR (176 MHz, $CDCl_3$, HSQC, DEPT) δ *C* 207.6, 207.4 155.5, 151.2, 146.2, 145.9, 138.4, 121.1, 62.7; *C*H 131.1, 123.4, 115.7, 97.3; CH_2 41.4, 37.3, 28.8, 19.2; CH_3 56.6, 56.4, 22.8; HRMS (TOF MS ES+) calcd for $C_{23}H_{26}O_5Na$ [M + Na] 405.1678, found 405.1691.

1-(3-(Benzyloxy)-4-methoxyphenyl)-7-(4-bromophenyl)-heptane-3,5-dione (27). To a solution of diisopropylamine (468 mg, 4.62 mmol) in THF (15 mL, 0.1 M) at 0 °C was added *n*-BuLi (2.89 mL, 4.62 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 **22** (1.01 g, 4.44 mmol) in THF (11 mL) was added over a period of 30 min. After stirring at −78 °C for 30 min, a solution of 3-(3-(benzyloxy)-4-methoxyphenyl)propanal[23] (1 g, 3.7 mmol) in THF (11 mL) was added over a period of 30 min. After stirring for 2 h, the reaction was quenched with saturated aqueous NH_4Cl (40 mL). The organic phase was separated, and the aqueous phase was extracted with EtOAc (3 × 40 mL). The combined organic phases were dried with $MgSO_4$. Purification by flash column chromatography (hexanes:EtOAc = 5:1 to 3:1) gave 7-(3-(Benzyloxy)-4-methoxyphenyl)-1-(4-bromophenyl)-5-hydroxyheptan-3-one (**S4**, 1.325 g, 2.66 mmol, 72% yield) as white solid. Data for **S4**: R_f 0.29 (2:1 hexanes:EtOAc); mp = 96−98 °C; IR (thin film) 3504 (br), 2931, 1707, 1514, 1258, 1138, 1011 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.50−7.28 (m, 7 H), 7.06 (d, J = 8.4 Hz, 2 H), 6.84 (d, J = 8.0 Hz, 1 H), 6.79−6.71 (m, 2 H), 5.15 (s, 2 H), 3.99 (m, 1 H), 3.88 (s, 3 H), 2.91 (d, J = 3.4 Hz, 1 H), 2.86 (t, J = 7.4 Hz, 2 H), 2.77−2.47 (m, 6 H), 1.81−1.54 (m, 2 H); ^{13}C NMR (101 MHz, $CDCl_3$, HSQC, DEPT) δ *C* 210.5, 148.1, 148.0, 139.7, 137.3, 134.3, 120.0; *C*H 131.6, 130.1, 128.5, 127.8, 127.4, 121.0, 114.9, 112.1, 66.8; CH_2 71.1, 49.3, 44.7, 38.1, 31.2, 28.8; CH_3 56.2; HRMS (TOF MS ES+) calcd for $C_{27}H_{30}BrO_4$ [M + H] 497.1327, found 497.1327.

To a solution of **S4** (199 mg, 0.4 mmol) in EtOAc (4 mL, 0.1 M) at rt was added IBX (336 mg, 1.2 mmol). The reaction mixture was heated to reflux until complete consumption of the starting material was observed (TLC, approximately 6 h). The reaction mixture was allowed to cool to rt, filtered through a short pad of silica gel, and concentrated to give the crude **S5**, which was used directly without further purification.

To a solution of **S5** (0.4 mmol, from previous step) in CH_2Cl_2 (8 mL, 0.05 M) were added pentamethylbenzene (178 mg, 1.2 mmol) and BCl_3 (1.6 mL, 1.6 mmol, 1 M in DCM) over a period of 10 min at −78 °C. After the addition was complete, TLC indicated complete consumption of the starting material. The reaction was quenched with MeOH (1 mL) at −78 °C. The resultant mixture was allowed to warm to rt. Diluted aqueous $NaHCO_3$ was added until aqueous phase had pH 6. The organic phase was separated, and the aqueous phase was extracted with EtOAc (3 × 20 mL). The combined organic phases were dried with $MgSO_4$. Purification by flash column chromatography (hexanes:EtOAc = 6:1 to 4:1) gave **27** (105 mg, 0.26 mmol, 65% yield, 2 steps) as a light yellow solid. Data for **27**: R_f 0.41 (2:1 hexanes:EtOAc); mp = 54−56 °C; IR (thin film) 3445 (br), 2933, 1592, 1513, 1489, 1442, 1273, 1129, 1011 cm^{-1}; ^1H NMR (700 MHz, $CDCl_3$, enol tautomer) δ 15.42 (br s, 1 H), 7.42 (d, J = 8.4 Hz, 2 H), 7.08 (d, J = 8.4 Hz, 2 H), 6.81−6.75 (m, 2 H), 6.68 (dd, J = 8.2, 2.1 Hz, 1 H), 5.61 (br s, 1 H), 5.44 (s, 1 H), 3.89 (s, 3 H), 2.90 (t, J = 7.8 Hz, 2 H), 2.85 (t, J = 7.8 Hz, 2 H), 2.60−2.54 (m, 4 H); ^{13}C NMR (176 MHz, $CDCl_3$, HSQC, DEPT, enol tautomer) δ *C* 193.0, 192.8, 145.5, 145.0, 139.6, 133.9, 120.0; *C*H 131.6, 130.1, 119.7, 114.4, 110.6, 99.7; CH_2 40.0, 39.8, 30.9, 30.8; CH_3 56.0; HRMS (EI+) calcd for $C_{20}H_{21}BrO_4$ [M] 404.0623, found 404.0610.

9′-Desmethylgarugamblin I (12). To a sealed tube were added **27** (20.3 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 to 120 °C. After 24 h, TLC indicated the complete consumption of the starting material. The reaction mixture was allowed to cool 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 (4 × 10 mL). The combined organic phases were dried with $MgSO_4$. Purification by flash column chromatography (hexanes:EtOAc = 8:1 to 5:1) gave **12** (8.3 mg, 0.0256 mmol, 51% yield) as a light yellow solid. Data for **12**: R_f 0.54 (2:1 hexanes:EtOAc); IR (thin film) 2922, 2850, 1589, 1515, 1505, 1440, 1262, 1228, 1128 cm^{-1}; ^1H NMR (700 MHz, $CDCl_3$) δ 15.27 (br s, 1 H), 7.21 (d, J = 8.5 Hz, 2 H), 7.03 (d, J = 8.5 Hz, 2 H), 6.84 (d, J = 8.3 Hz, 1 H), 6.72−6.68 (m, 1 H), 5.63 (d, J = 2.2 Hz, 1 H), 4.98 (s, 1 H), 3.97 (s, 3 H), 3.07 (t, J = 6.8 Hz, 2 H), 2.95 (m, 2 H), 2.49 (t, J = 6.8 Hz, 2 H), 2.38 (m, 2 H); ^{13}C NMR (176 MHz, $CDCl_3$, HSQC, DEPT) δ *C* 196.9, 189.2, 154.3, 151.0, 146.6, 136.8, 133.8; *C*H 130.7, 123.3, 121.3, 113.5, 111.6, 103.1; CH_2 39.5, 38.1, 32.3, 27.5; CH_3 56.2; HRMS (TOF MS ES+) calcd for $C_{20}H_{21}O_4$ [M + H] 325.1440, found 325.1454.

Garugamblin I (11) and (10*E*)-4,10-Dimethoxy-2-oxatricyclo-[13.2.2.1]^{3,7}icosa-1(17),3,5,7(20),10,15,18-heptaen-12-one (42). To a solution of **12** (13 mg, 0.04 mmol) in a mixed solvent of CH_3CN and MeOH (4 mL, 0.01 M, 10:1 v/v) was added $TMSCHN_2$ (0.2 mL, 0.4 mmol, 2 M in hexanes). After stirring at rt for 4 h, the solvent was removed under reduced pressure. Purification by flash column chromatography (hexanes:EtOAc = 5:1 to 3:1) gave **37b** (6.5 mg, 0.0192 mmol, 48% yield, more polar) and **38b** (6.4 mg, 0.0189 mmol, 47% yield, less polar) in 1:1 ratio. Treating **37b** and **38b** with dry acidic $CDCl_3$ ("old" $CDCl_3$ dried by 3 Å MS) at rt (approximately 5 min) gave garugamblin I (**11**) and **42**, respectively in >99% yield. Data for garugamblin I (**11**): R_f 0.50 (2:1 hexanes:EtOAc); IR (thin film) 2933, 1681, 1589, 1515, 1432, 1259, 1210, 1128, 1097 cm^{-1}; ^1H NMR (700 MHz, $CDCl_3$) δ 7.40 (d, J = 8.5 Hz, 1 H), 7.11−7.06 (m, 1 H), 6.90−6.86 (m, 2 H), 6.76 (d, J = 8.1 Hz, 1 H), 6.63 (dd, J = 8.1, 2.1 Hz, 1 H), 5.34 (s, 1 H), 5.29 (d, J = 2.1 Hz, 1 H), 4.05 (td, J = 12.9, 3.4 Hz, 1 H), 3.95 (s, 3 H), 3.71 (s, 3 H), 3.23 (dd, J = 14.8, 11.6 Hz, 1 H), 3.00 (dt, J = 12.8, 4.0 Hz, 1 H), 2.92 (td, J = 12.9, 3.1 Hz, 1 H), 2.59−2.52 (m, 1 H), 2.49−2.42 (m, 1 H), 2.37−2.32 (m, 1 H), 2.30 (dd, J = 15.1, 7.0 Hz, 1 H); ^{13}C NMR (176 MHz, $CDCl_3$, HSQC, DEPT) δ *C* 197.2, 173.1, 155.1, 151.6, 146.3, 138.2, 135.0; *C*H 130.8, 130.5, 124.5, 122.3, 120.6, 115.4, 111.0, 101.2; CH_2 45.4, 33.9, 33.0, 26.7; CH_3 56.1, 55.2; HRMS (EI+) calcd for $C_{21}H_{22}O_4$ [M] 338.1518, found 338.1520.

Data for **42**: R_f 0.26 (2:1 hexanes:EtOAc); IR (thin film) 2929, 1668, 1566, 1515, 1504, 1442, 1266, 1226, 1127 cm^{-1}; ^1H NMR (700 MHz, $CDCl_3$) δ 7.33−7.27 (m, 2 H), 6.99 (d, J = 8.6 Hz, 2 H), 6.84 (d, J = 8.2 Hz, 1 H), 6.68 (dd, J = 8.2, 2.1 Hz, 1 H), 5.29 (d, J = 2.1 Hz, 1 H), 5.22 (s, 1 H), 3.96 (s, 3 H), 3.46 (s, 3 H), 3.11 (t, J = 7.0 Hz, 2 H), 3.08−2.40 (m, 6 H); ^{13}C NMR (176 MHz, $CDCl_3$, HSQC, DEPT) δ *C* 198.9, 174.0, 154.3, 151.1, 145.7, 137.5, 133.3; *C*H 131.3, 123.6, 121.0, 112.6, 111.7, 102.1; CH_2 44.3, 31.2, 28.6, 26.0; CH_3 56.2, 55.7; HRMS (TOF MS ES+) calcd for $C_{21}H_{23}O_4$ [M + H] 339.1596, found 339.1582.

1-(4-Bromophenyl)-7-(7-hydroxybenzo[d][1,3]dioxol-5-yl)-heptane-3,5-dione (28). To a slurry of NaH (312 mg, 7.8 mmol) in THF (10 mL, 0.195 M) at 0 °C was slowly added ethyl 2-(diethoxyphosphoryl)acetate (1.55 mL, 7.8 mmol) over a period of 10 min. After stirring at 0 °C for 30 min, a solution of 7-(benzyloxy)benzo[d][1,3]dioxole-5-carbaldehyde[24] (1.0 g, 3.9 mmol) in THF (10 mL) was added. The mixture was warmed to rt and stirred at rt for 30 min. The reaction was quenched with saturated NH_4Cl solution (30 mL). The organic phase was then separated, and the aqueous phase was extracted with EtOAc (3 × 30 mL). The combined organic phases were dried with $MgSO_4$. Purification by flash column chromatography (hexanes:EtOAc = 10:1 to 5:1) gave (*E*)-ethyl 3-(7-(benzyloxy)benzo[d][1,3]dioxol-5-yl)acrylate (**S6**, 1.27 g, 3.89 mmol, >99% yield) as a white solid. Data for **S6**: R_f 0.51 (4:1

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hexanes:EtOAc); mp = 115−118 °C; IR (thin film) 1698, 1511, 1434, 1279, 1235, 1130, 1090, 1034 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.54 (d, J = 15.9 Hz, 1 H), 7.49−7.30 (m, 5 H), 6.76 (s, 2 H), 6.26 (d, J = 15.9 Hz, 1 H), 6.02 (s, 2 H), 5.20 (s, 2 H), 4.27 (q, J = 7.1 Hz, 2 H), 1.35 (t, J = 7.1 Hz, 3 H); ^{13}C NMR (101 MHz, $CDCl_3$, HSQC, DEPT) δ *C* 167.1, 149.6, 142.6, 137.8, 136.4, 129.2; *C*H 144.3, 128.7, 128.2, 127.6, 116.8, 111.6, 101.4; *C*H_2 101.9, 71.6, 60.4; *C*H_3 14.4; HRMS (TOF MS ES+) calcd for $C_{19}H_{19}O_5$ [M + H] 327.1232, found 327.1229.

To a solution of **S6** (1.7 g, 5.21 mmol) in THF (40 mL, 0.065 M) were added 40 mL of H_2O, NaOAc (1.71 g, 20.84 mmol) and a solution of $TsNHNH_2$ (4.85 g, 26.05 mmol) in THF (40 mL) over a period of 30 min at 80 °C. After 24 h, TLC indicated the complete consumption of the starting material. The mixture was allowed to cool to rt. The organic phase was then separated, and the aqueous phase was extracted with EtOAc (3 × 40 mL). The combined organic phases were dried with $MgSO_4$. Purification by flash column chromatography (hexanes:EtOAc = 10:1 to 6:1) gave ethyl 3-(7-(benzyloxy)benzo[d]-[1,3]dioxol-5-yl)propanoate (**S7**, 1.7 g, 5.18 mmol, >99% yield) as a colorless solid. Data for **S7**: R_f 0.55 (4:1 hexanes:EtOAc); mp = 51−53 °C; IR (thin film) 2933, 1731, 1632, 1509, 1437, 1373, 1190, 1126, 1086, 1043 cm^{-1}; ^1H NMR (700 MHz, $CDCl_3$) δ 7.48−7.32 (m, 5 H), 6.45 (d, J = 1.4 Hz, 1 H), 6.42 (d, J = 1.4 Hz, 1 H), 5.96 (s, 2 H), 5.19 (s, 2 H), 4.15 (q, J = 7.1 Hz, 2 H), 2.86 (t, J = 7.8 Hz, 2 H), 2.58 (t, J = 7.8 Hz, 2 H), 1.27 (t, J = 7.1 Hz, 3 H); ^{13}C NMR (176 MHz, $CDCl_3$, HSQC, DEPT) δ *C* 172.8, 149.1, 142.5, 136.8, 135.1, 134.0; *C*H 128.6, 128.1, 127.6, 109.7, 102.7; *C*H_2 101.2, 71.5, 60.5, 36.2, 31.0; *C*H_3 14.3; HRMS (TOF MS ES+) calcd for $C_{19}H_{21}O_5$ [M + H] 329.1389, found 329.1405.

To a solution of **S7** (328 mg, 1 mmol) in CH_2Cl_2 (10 mL, 0.1 M) at −78 °C was added DIBAL-H (1 mL, 1.2 mmol, 1.2 M in toluene) over a period of 15 min. After the addition was complete, TLC indicated complete consumption of the starting material. The reaction was quenched with saturated aqueous Rochelle's salt (20 mL) at −78 °C. The mixture was allowed to warm to rt. The organic phase was separated, and the inorganic phase was extracted with EtOAc (3 × 20 mL). The combined organic phases were dried with $MgSO_4$. Purification by flash column chromatography (hexanes:EtOAc = 5:1) gave 3-(7-(benzyloxy)benzo[d][1,3]dioxol-5-yl)propanal (**S8**, 261 mg, 0.92 mmol, 92% yield) as a light yellow oil. Data for **S8**: R_f 0.58 (2:1 hexanes:EtOAc); IR (thin film) 2925, 1722, 1632, 1509, 1436, 1192, 1127, 1087, 1043 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.80 (t, J = 1.3 Hz, 1 H), 7.48−7.31 (m, 5 H), 6.42 (d, J = 1.3 Hz, 1 H), 6.40 (d, J = 1.3 Hz, 1 H), 5.96 (s, 2 H), 5.19 (s, 2 H), 2.86 (t, J = 7.4 Hz, 2 H), 2.72 (t, J = 7.4 Hz, 2 H); ^{13}C NMR (101 MHz, $CDCl_3$, HSQC, DEPT) δ *C* 149.2, 142.5, 136.8, 134.8, 134.1; *C*H 201.4, 128.6, 128.1, 127.6, 109.9, 102.7; *C*H_2 101.2, 71.6, 45.4, 28.1; HRMS (TOF MS ES +) calcd for $C_{17}H_{17}O_4$ [M + H] 285.1127, found 285.1124.

To a solution of diisopropylamine (223 mg, 2.2 mmol) in THF (8 mL, 0.1 M) was added *n*-BuLi (1.38 mL, 2.2 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 **22** (479 mg, 2.11 mmol) in THF (5 mL) was added over a period of 30 min. After stirring at −78 °C for 30 min, a solution of **S8** (500 mg, 1.76 mmol) in THF (5 mL) was added over a period of 30 min. After stirring for 2 h, the reaction was quenched with saturated aqueous NH_4Cl (20 mL). The organic phase was separated, and the aqueous phase was extracted with EtOAc (3 × 20 mL). The combined organic phases were dried with $MgSO_4$. Purification by flash column chromatography (hexanes:EtOAc = 5:1 to 3:1) gave 7-(7-(benzyloxy)benzo[d][1,3]dioxol-5-yl)-1-(4-bromophenyl)-5-hydroxyheptan-3-one (**S9**, 511 mg, 1 mmol, 57% yield) as a white solid. Data for **S9**: R_f 0.26 (3:1 hexanes:EtOAc); mp = 113−115 °C; IR (thin film) 3468 (br), 2928, 1707, 1631, 1508, 1489, 1436, 1191, 1125, 1073, 1042 cm^{-1}; ^1H NMR (700 MHz, $CDCl_3$) δ 7.48−7.32 (m, 7 H), 7.07 (d, J = 8.4 Hz, 2 H), 6.43 (d, J = 1.2 Hz, 1 H), 6.41 (d, J = 1.2 Hz, 1 H), 5.95 (s, 2 H), 5.19 (s, 2 H), 4.02 (m, 1 H), 2.95 (br s, 1 H), 2.87 (t, J = 7.5 Hz, 2 H), 2.74 (t, J = 7.5 Hz, 2 H), 2.73−2.67 (m, 1 H), 2.62−2.49 (m, 3 H), 1.79−1.72 (m, 1 H), 1.65−1.58 (m, 1 H); ^{13}C NMR (176 MHz, $CDCl_3$, HSQC, DEPT) δ *C* 210.5, 149.0, 142.4, 139.7, 136.9, 136.2, 133.8, 120.0; *C*H 131.6, 130.1, 128.6, 128.0, 127.6, 109.9, 102.8, 66.6; *C*H_2 101.2, 71.5, 49.3, 44.7, 38.1, 31.7, 28.8; HRMS (TOF MS ES+) calcd for $C_{27}H_{28}BrO_5$ [M + H] 511.1120, found 511.1125.

To a solution of **S9** (199 mg, 0.39 mmol) in EtOAc (4 mL, 0.1 M) at rt was added IBX (328 mg, 1.17 mmol). The reaction mixture was heated to reflux until complete consumption of the starting material was observed (TLC, approximately 6 h). The reaction mixture was allowed to cool to rt, filtered through a short pad of silica gel, and concentrated to give the crude **S10**, which was used directly without further purification.

To a solution of **S10** (approximately 0.39 mmol, from previous step) in CH_2Cl_2 (8 mL, 0.05 M) were added pentamethylbenzene (173 mg, 1.17 mmol) and BCl_3 (0.78 mL, 0.78 mmol, 1 M in DCM) over a period of 10 min at −78 °C. After addition is completed, TLC indicated complete consumption of the starting material. The reaction was quenched with MeOH (2 mL) at −78 °C. The resultant mixture was allowed to warm 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 (3 × 20 mL). The combined organic phases were dried with $MgSO_4$. Purification by flash column chromatography (hexanes:EtOAc = 6:1 to 4:1) gave 1-(4-bromophenyl)-7-(7-hydroxybenzo[d][1,3]dioxol-5-yl)heptane-3,5-dione (**28**, 125 mg, 0.3 mmol, 76% yield, 2 steps) as a light yellow solid. Data for **28**: R_f 0.38 (2:1 hexanes:EtOAc); mp = 89−91 °C; IR (thin film) 3400 (br), 2925, 1621, 1505, 1488, 1446, 1070 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, enol tautomer) δ 15.37 (s, 1 H), 7.42 (d, J = 8.1 Hz, 2 H), 7.07 (d, J = 8.1 Hz, 2 H), 6.33 (s, 2 H), 5.94 (s, 2 H), 5.43 (s, 1 H), 5.22 (br s, 1 H), 2.94−2.74 (m, 4 H), 2.62−2.50 (m, 4 H); ^{13}C NMR (101 MHz, $CDCl_3$, HSQC, DEPT, enol tautomer) δ *C* 193.0, 192.8, 148.8, 139.6, 139.1, 135.3, 132.5, 120.0; *C*H 131.6, 130.1, 110.6, 101.9, 99.8; *C*H_2 101.3, 40.0, 39.7, 31.3, 30.9; HRMS (TOF MS ES+) calcd for $C_{20}H_{20}BrO_5$ [M + H] 419.0494, found 419.0486.

2,5,7-Trioxatetracyclo[16.2.2.1^{3,10}.0^{4,8}]tricosa-1(20),3,8,10-(23)18,21-hexaene-3,15-dione (33). To a sealed tube were added **28** (21.8 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 to 130 °C. After 24 h, TLC indicated the complete consumption of the starting material. The reaction mixture was allowed to cool 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 (4 × 10 mL). The combined organic phases were dried with $MgSO_4$. Purification by flash column chromatography (hexanes:EtOAc = 8:1 to 6:1) gave **33** (6.4 mg, 0.0189 mmol, 38% yield) as a light yellow solid. Data for **33**: R_f 0.63 (2:1 hexanes:EtOAc); IR (thin film) 1635, 1600, 1504, 1435, 1210, 1192, 1064 cm^{-1}; ^1H NMR (700 MHz, $CDCl_3$) δ 15.19 (br s, 1 H), 7.21 (d, J = 8.5 Hz, 2 H), 7.04 (d, J = 8.5 Hz, 2 H), 6.33 (m, 1 H), 6.03 (s, 2 H), 5.21 (m, 1 H), 4.96 (s, 1 H), 3.06 (t, J = 6.8 Hz, 2 H), 2.91 (m, 2 H), 2.48 (t, J = 6.8 Hz, 2 H), 2.37 (m, 2 H); ^{13}C NMR (176 MHz, $CDCl_3$, HSQC, DEPT) δ *C* 197.0, 188.7, 154.1, 148.9, 144.8, 137.0, 135.4, 133.1; *C*H 130.6, 123.0, 107.7, 103.1, 102.8; *C*H_2 101.6, 39.4, 38.0, 32.2, 28.0; HRMS (EI+) calcd for $C_{20}H_{18}O_5$ [M] 338.1154, found 338.1138.

Garugamblin II (13) and (13*E*)-13-Methoxy-2,5,7-trioxatetracyclo[16.2.2.1^{3,10}.0^{4,8}]tricosa-1(20),3,8,10-(23),13,18,21-heptaen-15-one (43). To a solution of **33** (13.5 mg, 0.04 mmol) in a mixed solvent of CH_3CN and MeOH (4 mL, 0.01 M, 10:1 v/v) was added $TMSCHN_2$ (0.2 mL, 0.4 mmol, 2 M in hexanes). After stirring at rt for 4 h, the solvent was removed under reduced pressure. Purification by flash column chromatography (hexanes:EtOAc = 5:1 to 3:1) gave **37c** (6.7 mg, 0.019 mmol, 48% yield, white solid, more polar) and **38c** (6.8 mg, 0.0193 mmol, 48% yield, white solid, less polar) in 1:1 ratio. Treating **37c** and **38c** with dry acidic $CDCl_3$ ("old" $CDCl_3$ dried by 3 Å MS) at rt (approximately 5 min) gave garugamblin II (**13**) and **43**, respectively in >99% yield. Data for garugamblin II (**13**): R_f 0.58 (2:1 hexanes:EtOAc); IR (thin film) 2932, 1681, 1634, 1587, 1505, 1438, 1192, 1097, 1061 cm^{-1}; ^1H NMR (700 MHz, $CDCl_3$) δ 7.39 (dd, J = 8.3, 2.0 Hz, 1 H), 7.08 (dd, J = 8.3, 2.3 Hz, 1 H), 6.90 (dd, J = 8.1, 2.3 Hz, 1 H), 6.87 (dd, J = 8.1, 2.0 Hz,

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1 H), 6.27 (m, 1 H), 6.02−5.99 (m, 2 H), 5.33 (s, 1 H), 4.90 (br s, 1 H), 4.03 (td, J = 12.9, 3.5 Hz, 1 H), 3.72 (s, 3 H), 3.21 (dd, J = 15.1, 11.3 Hz, 1 H), 3.00 (dt, J = 12.8, 4.0 Hz, 1 H), 2.91 (td, J = 12.9, 3.1 Hz, 1 H), 2.57−2.51 (m, 1 H), 2.49−2.42 (m, 1 H), 2.36−2.32 (m, 1 H), 2.25 (dd, J = 15.4, 6.9 Hz, 1 H); ^{13}C NMR (176 MHz, $CDCl_3$, HSQC, DEPT) δ *C* 197.0, 173.1, 154.8, 148.4, 145.6, 138.5, 136.4, 132.5; *C*H 130.8, 130.3, 124.3, 122.1, 109.7, 102.6, 101.2; *C*H$_2$ 101.4, 45.4, 33.9, 33.0, 27.2; *C*H$_3$ 55.3; HRMS (TOF MS ES+) calcd for $C_{21}H_{21}O_5$ [M + H] 353.1389, found 353.1373.

Data for **43**: R_f 0.33 (2:1 hexanes:EtOAc); IR (thin film) 2919, 1667, 1636, 1567, 1504, 1440, 1190, 1064 cm^{-1}; ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.33−7.27 (m, 2 H), 7.00 (d, J = 8.6 Hz, 2 H), 6.29 (d, J = 1.2 Hz, 1 H), 6.01 (s, 2 H), 5.21 (s, 1 H), 4.87 (br s, 1 H), 3.46 (s, 3 H), 3.11 (t, J = 6.9 Hz, 2 H), 3.08−2.40 (m, 6 H); ^{13}C NMR (176 MHz, $CDCl_3$, HSQC, DEPT) δ *C* 198.8, 173.9, 153.8, 148.9, 145.0, 137.8, 134.9, 132.2; *C*H 131.2, 123.4, 106.5, 102.2, 102.1; *C*H$_2$ 101.4, 44.3, 31.2, 28.6, 26.8; *C*H$_3$ 55.7; HRMS (TOF MS ES+) calcd for $C_{21}H_{21}O_5$ [M + H] 353.1389, found 353.1374.

1-(4-Bromophenyl)-7-(3-hydroxy-4-isopropoxy-5-methoxyphenyl)heptane-3,5-dione (29). To a solution of 3-(benzyloxy)-4-hydroxy-5-methoxybenzaldehyde[25] (1.162 g, 4.5 mmol) in DMF (45 mL, 0.1 M) was added K_2CO_3 (933 mg, 6.75 mmol) and 2-bromopropane (634 μL, 6.75 mmol) at 80 °C. After 1 h, TLC indicated complete consumption of the starting material. The reaction mixture was allowed to cool to rt and poured into 100 mL of H_2O. The resultant mixture was extracted with Et_2O (4 × 50 mL). The combined organic phases were dried with $MgSO_4$. Purification by flash column chromatography (hexanes:EtOAc = 6:1) gave 3-(benzyloxy)-4-isopropoxy-5-methoxybenzaldehyde (**S11**, 1.334 g, 4.44 mmol, 99% yield) as a white solid. Data for **S11**: R_f 0.43 (3:1 hexanes:EtOAc); mp = 57−59 °C; IR (thin film) 2976, 1693, 1585, 1493, 1429, 1383, 1326, 1233, 1119 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.85 (s, 1 H), 7.50−7.31 (m, 5 H), 7.20 (d, J = 1.7 Hz, 1 H), 7.16 (d, J = 1.7 Hz, 1 H), 5.18 (s, 2 H), 4.60 (sept, J = 6.2 Hz, 1 H), 3.92 (s, 3 H), 1.34 (d, J = 6.2 Hz, 6 H); ^{13}C NMR (101 MHz, $CDCl_3$, HSQC, DEPT) δ *C* 154.6, 153.3, 142.7, 136.6, 131.5; *C*H 191.1, 128.6, 128.0, 127.3, 109.1, 106.6, 76.1; *C*H$_2$ 71.2; *C*H$_3$ 56.2, 22.6; HRMS (TOF MS ES+) calcd for $C_{18}H_{21}O_4$ [M + H] 301.1440, found 301.1441.

To a slurry of NaH (276 mg, 6.9 mmol) in THF (10 mL, 0.3 M) at 0 °C was added ethyl 2-(diethoxyphosphoryl)acetate (1.37 mL, 6.9 mmol) over a period of 10 min. After stirring at 0 °C for 30 min, a solution of **S11** (1.382 g, 4.6 mmol) in THF (5 mL) was added. The mixture was warmed to rt and stirred at rt for 30 min. The reaction was quenched with saturated aqueous NH_4Cl (30 mL). The organic phase was then separated, and the aqueous phase was extracted with EtOAc (3 × 30 mL). The combined organic phases were dried with $MgSO_4$. Purification by flash column chromatography (hexanes:EtOAc = 10:1 to 5:1) gave (*E*)-ethyl 3-(3-(benzyloxy)-4-isopropoxy-5-methoxyphenyl)acrylate (**S12**, 1.7 g, 4.59 mmol, >99% yield) as a colorless solid. Data for **S12**: R_f 0.47 (3:1 hexanes:EtOAc); mp = 66−68 °C; IR (thin film) 2977, 1710, 1636, 1579, 1500, 1425, 1274, 1246, 1175, 1156, 1116 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (d, J = 15.9 Hz, 1 H), 7.51−7.30 (m, 5 H), 6.82 (d, J = 1.5 Hz, 1 H), 6.79 (d, J = 1.5 Hz, 1 H), 6.33 (d, J = 15.9 Hz, 1 H), 5.14 (s, 2 H), 4.50 (sept, J = 6.2 Hz, 1 H), 4.28 (q, J = 7.1 Hz, 2 H), 3.88 (s, 3 H), 1.39−1.30 (m, 9 H); ^{13}C NMR (101 MHz, $CDCl_3$, HSQC, DEPT) δ *C* 167.0, 154.3, 153.1, 139.1, 136.9, 129.6; *C*H 144.7, 128.5, 127.9, 127.3, 117.2, 107.8, 105.5, 75.8; *C*H$_2$ 71.2, 60.5; *C*H$_3$ 56.1, 22.6, 14.4; HRMS (TOF MS ES+) calcd for $C_{22}H_{27}O_5$ [M + H] 371.1858, found 371.1842.

To a solution of **S12** (1.482 g, 4 mmol) in THF (20 mL, 0.1 M) were added H_2O (20 mL), NaOAc (1.312 g, 16 mmol) and a solution of $TsNHNH_2$ (2.235 g, 12 mmol) in THF (20 mL) over a period of 40 min at 80 °C. After 18 h, TLC indicated the complete consumption of the starting material. The mixture was allowed to cool to rt. The organic phase was then separated, and the aqueous phase was extracted with EtOAc (3 × 30 mL). The combined organic phases were dried with $MgSO_4$. Purification by flash column chromatography (hexanes:EtOAc = 10:1 to 6:1) gave ethyl 3-(3-(benzyloxy)-4-isopropoxy-5-methoxyphenyl)propanoate (**S13**, 1.49 g, 4 mmol, >99% yield) as a colorless oil. Data for **S13**: R_f 0.40 (5:1 hexanes:EtOAc); IR (thin film) 2976, 1732, 1588, 1502, 1454, 1428, 1375, 1236, 1117, 936 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50−7.29 (m, 5 H), 6.50 (d, J = 1.3 Hz, 1 H), 6.46 (d, J = 1.3 Hz, 1 H), 5.10 (s, 2 H), 4.39 (sept, J = 6.2 Hz, 1 H), 4.15 (q, J = 7.1 Hz, 2 H), 3.84 (s, 3 H), 2.89 (t, J = 7.8 Hz, 1 H), 2.61 (t, J = 7.8 Hz, 1 H), 1.31 (d, J = 6.2 Hz, 6 H), 1.26 (t, J = 7.1 Hz, 3 H); ^{13}C NMR (101 MHz, $CDCl_3$, HSQC, DEPT) δ *C* 172.9, 154.0, 152.9, 137.4, 135.8, 135.4; *C*H 128.4, 127.7, 127.3, 107.7, 105.9, 75.3; *C*H$_2$ 71.2, 60.4, 36.0, 31.3; *C*H$_3$ 56.1, 22.6, 14.2; HRMS (TOF MS ES+) calcd for $C_{22}H_{29}O_5$ [M + H] 373.2015, found 373.2025.

To a solution of **S13** (1.594 g, 4.28 mmol) in CH_2Cl_2 (43 mL, 0.1 M) at −78 °C was added DIBAL-H (4.28 mL, 5.14 mmol, 1.2 M in toluene) over a period of 1 h. After the addition was complete, TLC indicated complete consumption of the starting material. The reaction was quenched with saturated aqueous Rochelle's salt (100 mL) at −78 °C. The mixture was allowed to warm to rt. The organic phase was separated, and the inorganic phase was extracted with EtOAc (3 × 100 mL). The combined organic phases were dried with $MgSO_4$. Purification by flash column chromatography (hexanes:EtOAc = 5:1) gave 3-(3-(benzyloxy)-4-isopropoxy-5-methoxyphenyl)propanal (**S14**, 1.14 g, 3.47 mmol, 81% yield) as a white solid. Data for **S14**: R_f 0.50 (2:1 hexanes:EtOAc); mp = 60−62 °C; IR (thin film) 2974, 1723, 1587, 1503, 1454, 1428, 1235, 1117, 933 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.81 (m, 1 H), 7.50−7.29 (m, 5 H), 6.47 (d, J = 1.8 Hz, 1 H), 6.44 (d, J = 1.8 Hz, 1 H), 5.10 (s, 2 H), 4.39 (sept, J = 6.2 Hz, 1 H), 3.84 (s, 3 H), 2.89 (t, J = 7.4 Hz, 2 H), 2.76 (t, J = 7.4 Hz, 2 H), 1.31 (d, J = 6.2 Hz, 6 H); ^{13}C NMR (101 MHz, $CDCl_3$, HSQC, DEPT) δ *C* 154.1, 153.0, 137.4, 135.6, 135.4; *C*H 201.6, 128.4, 127.8, 127.3, 107.8, 105.9, 75.4; *C*H$_2$ 71.2, 45.3, 28.4; *C*H$_3$ 56.1, 22.6; HRMS (TOF MS ES+) calcd for $C_{20}H_{25}O_4$ [M + H] 329.1753, found 329.1755.

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 **22** (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 **S14** (657 mg, 2 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 (30 mL). The organic phase was separated, and the aqueous phase was extracted with EtOAc (3 × 30 mL). The combined organic phases were dried with $MgSO_4$. Purification by flash column chromatography (hexanes:EtOAc = 5:1 to 3:1) gave 7-(3-(benzyloxy)-4-isopropoxy-5-methoxyphenyl)-1-(4-bromophenyl)-5-hydroxyheptan-3-one (**S15**, 891 mg, 1.6 mmol, 80% yield) as a colorless oil. Data for **S15**: R_f 0.26 (2:1 hexanes:EtOAc); IR (thin film) 3490 (br), 2932, 1708, 1588, 1503, 1454, 1431, 1236, 1115, 935 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50−7.29 (m, 7 H), 7.06 (d, J = 8.3 Hz, 2 H), 6.48 (d, J = 1.5 Hz, 1 H), 6.44 (d, J = 1.5 Hz, 1 H), 5.10 (s, 2 H), 4.39 (sept, J = 6.2 Hz, 1 H), 4.05 (m, 1 H), 3.83 (s, 3 H), 3.02 (br s, 1 H), 2.87 (t, J = 7.4 Hz, 2 H), 2.80−2.47 (m, 6 H), 1.86−1.58 (m, 2 H), 1.31 (d, J = 6.2 Hz, 6 H); ^{13}C NMR (101 MHz, $CDCl_3$, HSQC, DEPT) δ *C* 210.5, 154.0, 152.8, 139.7, 137.5, 137.0, 135.1, 120.0; *C*H 131.6, 130.1, 128.4, 127.7, 127.3, 107.9, 106.0, 75.3, 66.9; *C*H$_2$ 71.2, 49.4, 44.7, 38.1, 32.1, 28.8; *C*H$_3$ 56.1, 22.6; HRMS (TOF MS ES+) calcd for $C_{30}H_{36}BrO_5$ [M + H] 555.1746, found 555.1749.

To a solution of **S15** (805 mg, 1.45 mmol) in EtOAc (14.5 mL, 0.1 M) at rt was added IBX (1.218 g, 4.35 mmol). The reaction mixture was heated to reflux until complete consumption of the starting material was observed (TLC, approximately 4−8 h). The reaction mixture was allowed to cool to rt, filtered through a short pad of silica gel and concentrated. Purification by flash column chromatography (hexanes:EtOAc = 5:1) gave 1-(3-(benzyloxy)-4-isopropoxy-5-methoxyphenyl)-7-(4-bromophenyl)heptane-3,5-dione (**S16**, 640 mg, 1.16 mmol, 80% yield) as a light yellow oil. Data for **S16**: R_f 0.67 (2:1 hexanes:EtOAc); IR (thin film) 2973, 1590, 1503, 1489, 1453, 1232, 1117, 1011, 931 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, enol tautomer) δ 15.44 (br s, 1 H), 7.50−7.30 (m, 7 H), 7.07 (d, J = 8.3 Hz, 2 H), 6.48 (d, J = 1.6 Hz, 1 H), 6.43 (d, J = 1.6 Hz, 1 H), 5.41 (s, 1 H), 5.10 (s, 2 H), 4.40 (sept, J = 6.2 Hz, 1 H), 3.83 (s, 3 H), 2.94−2.75

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(m, 4 H), 2.62−2.51 (m, 4 H), 1.32 (d, J = 6.2 Hz, 6 H); ^{13}C NMR (101 MHz, $CDCl_3$, HSQC, DEPT, enol tautomer) δ *C* 192.9, 192.8, 154.0, 152.9, 139.6, 137.4, 135.8, 135.4, 120.0; *C*H 131.6, 130.1, 128.4, 127.8, 127.3, 107.8, 105.9, 99.8, 75.3; CH_2 71.2, 40.0, 39.7, 31.9, 30.8; CH_3 56.1, 22.6; HRMS (TOF MS ES+) calcd for $C_{30}H_{33}BrO_5Na$ [M + Na] 575.1409, found 575.1415.

To a solution of **S16** (166 mg, 0.3 mmol) in EtOAc (15 mL, 0.02 M) was added 20% Pd/C (16.6 mg, 10% w/w). Hydrogen gas was applied (balloon), and the mixture was stirred at rt until complete consumption of the starting material (carefully monitored by TLC, approximately 30 min−2 h). The reaction was quenched by filtering through a short pad of silica gel. Purification by flash column chromatography (hexanes:EtOAc = 10:1 to 8:1) gave 1-(4-bromophenyl)-7-(3-hydroxy-4-isopropoxy-5-methoxyphenyl)heptane-3,5-dione (**29**, 95 mg, 0.205 mmol, 68% yield) as a yellow oil. Data for **29**: R_f 0.39 (3:1 hexanes:EtOAc); IR (thin film) 3445 (br), 2974, 1704, 1602, 1508, 1489, 1459, 1357, 1197, 1107, 1011, 929 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, enol tautomer) δ 15.42 (br s, 1 H), 7.41 (d, J = 8.2 Hz, 2 H), 7.07 (d, J = 8.2 Hz, 2 H), 6.45 (d, J = 1.6 Hz, 1 H), 6.30 (d, J = 1.6 Hz, 1 H), 5.82 (br s, 1 H), 5.43 (s, 1 H), 4.53 (sept, J = 6.2 Hz, 1 H), 3.82 (s, 3 H), 2.93−2.75 (m, 4 H), 2.62−2.51 (m, 4 H), 1.31 (d, J = 6.2 Hz, 6 H); ^{13}C NMR (101 MHz, $CDCl_3$, HSQC, DEPT, enol tautomer) δ *C* 192.9, 192.8, 152.3, 150.0, 139.6, 136.5, 120.0; *C*H 131.6, 130.1, 107.4, 104.2, 99.7, 75.1; CH_2 39.9, 39.7, 31.6, 30.8; CH_3 55.8, 22.6; HRMS (TOF MS ES+) calcd for $C_{23}H_{26}BrO_4$ [M + H − H_2O] 445.1014, found 445.1006.

5-Methoxy-4-(propan-2yloxy)-2-oxatricyclo[13.2.2.1^{3,7}]-icosa-1(17),3,5,7(20),15,18-hexaene-10,12-dione (34). To a sealed tube were added **29** (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 to 130 °C. After 72 h, the reaction mixture was allowed to cool 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 (4 × 10 mL). The combined organic phase was dried with $MgSO_4$. Purification by flash column chromatography (hexanes:EtOAc = 8:1 to 6:1) gave **34** (7.1 mg, 0.0186 mmol, 37% yield) as a light yellow solid. Data for **34**: R_f 0.41 (3:1 hexanes:EtOAc); IR (thin film) 3450 (br), 2973, 1590, 1505, 1433, 1216, 1092, 934 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), 6.99 (d, J = 8.5 Hz, 2 H), 6.33 (d, J = 1.9 Hz, 1 H), 5.26 (d, J = 1.9 Hz, 1 H), 4.98 (s, 1 H), 4.50 (sept, J = 6.2 Hz, 1 H), 3.84 (s, 3 H), 3.05 (t, J = 6.8 Hz, 2 H), 2.95 (m, 2 H), 2.48 (t, J = 6.8 Hz, 2 H), 2.39 (m, 2 H), 1.41 (d, J = 6.2 Hz, 6 H); ^{13}C NMR (176 MHz, $CDCl_3$, HSQC, DEPT) δ *C* 197.2, 188.6, 155.5, 155.0, 153.7, 136.4, 136.0, 134.0; *C*H 130.5, 123.2, 106.9, 105.5, 103.2, 75.6; CH_2 39.4, 37.6, 32.3, 28.1; CH_3 56.1, 22.6; HRMS (TOF MS ES+) calcd for $C_{23}H_{27}O_5$ [M + H] 383.1858, found 383.1865.

Reported Structure of 1,9′-Didesmethylgaruganin III (10). To a solution of **34** (5 mg, 0.013 mmol) in DCM (1 mL, 0.013 M) was added BCl_3 (39 uL, 0.039 mmol) at 0 °C. The mixture was allowed to warm to rt. After 5 min, TLC indicated consumption of starting material. The reaction was then quenched with MeOH (1 mL) 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 **10** (3.2 mg, 0.0097 mmol, 74% yield) as a light yellow solid. Data for **10**: R_f 0.20 (3:1 hexanes:EtOAc); IR (thin film) 3441 (br), 2939, 1603, 1518, 1454, 1436, 1213, 1083, 860 cm^{-1}; ^{1}H NMR (700 MHz, $CDCl_3$) δ 15.19 (br s, 1 H), 7.20 (d, J = 8.4 Hz, 2 H), 7.02 (d, J = 8.4 Hz, 2 H), 6.34 (br s, 1 H), 5.53 (s, 1 H), 5.28 (d, J = 1.7 Hz, 1 H), 4.97 (s, 1 H), 3.90 (s, 3 H), 3.06 (t, J = 6.8 Hz, 2 H), 2.93 (m, 2 H), 2.48 (t, J = 6.8 Hz, 2 H), 2.38 (m, 2 H); ^{13}C NMR (176 MHz, $CDCl_3$, HSQC, DEPT) δ *C* 197.0, 188.8, 154.7, 148.9, 147.2, 136.8, 132.6, 132.0; *C*H 130.6, 123.2, 106.7, 105.0, 103.2; CH_2 39.5, 37.9, 32.2, 28.0; CH_3 56.3; HRMS (TOF MS ES+) calcd for $C_{20}H_{21}O_5$ [M + H] 341.1389, found 341.1380.

1-(4-Bromophenyl)-7-(3-hydroxy-4,5-dimethoxyphenyl)-heptane-3,5-dione (30). To a slurry of NaH (360 mg, 9 mmol) in THF (10 mL, 0.3 M) was added ethyl 2-(diethoxyphosphoryl)acetate (1.79 mL, 9 mmol) over a period of 10 min at 0 °C. After stirring at 0 °C for 30 min, a solution of 3-(benzyloxy)-4,5-dimethoxybenzaldehyde[5] (1.634 g, 6 mmol) in THF (10 mL) was added. The mixture was warmed to rt and stirred at rt for 30 min. The reaction was quenched with saturated aqueous NH_4Cl (30 mL). The organic phase was then separated, and the aqueous phase was extracted with EtOAc (3 × 30 mL). The combined organic phases were dried with $MgSO_4$. Purification by flash column chromatography (hexanes:EtOAc = 10:1 to 5:1) gave (*E*)-ethyl 3-(3-(benzyloxy)-4,5-dimethoxyphenyl)acrylate (**S17**, 2.038 g, 5.95 mmol, >99% yield) as a white solid. Data for **S17**: R_f 0.51 (3:1 hexanes:EtOAc); mp = 67−69 °C; IR (thin film) 2940, 1709, 1636, 1581, 1504, 1425, 1275, 1176, 1152, 1120, 1005 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (d, J = 15.9 Hz, 1 H), 7.49−7.31 (m, 5 H), 6.81 (d, J = 1.8 Hz, 1 H), 6.78 (d, J = 1.8 Hz, 1 H), 6.32 (d, J = 15.9 Hz, 1 H), 5.15 (s, 2 H), 4.27 (q, J = 7.1 Hz, 2 H), 3.92 (s, 3 H), 3.89 (s, 3 H), 1.35 (t, J = 7.1 Hz, 3 H); ^{13}C NMR (101 MHz, $CDCl_3$, HSQC, DEPT) δ *C* 166.9, 153.6, 152.5, 140.8, 136.8, 129.9; *C*H 144.5, 128.6, 128.0, 127.3, 117.5, 107.7, 105.4; CH_2 71.2, 60.5; CH_3 61.0, 56.2, 14.4; HRMS (TOF MS ES+) calcd for $C_{20}H_{23}O_5$ [M + H] 343.1545, found 343.1528.

To a solution of **S17** (1.883 g, 5.5 mmol) in THF (28 mL, 0.1 M) were added H_2O (28 mL), NaOAc (1.805 g, 22 mmol) and a solution of $TsNHNH_2$ (3.072 g, 16.5 mmol) in THF (27 mL) over a period of 1 h at 80 °C. After 24 h, TLC indicated the complete consumption of the starting material. The mixture was allowed to cool to rt. The organic phase was then separated, and the aqueous phase was extracted with EtOAc (3 × 30 mL). The combined organic phases were dried with $MgSO_4$. Purification by flash column chromatography (hexanes:EtOAc = 10:1 to 6:1) gave ethyl 3-(3-(benzyloxy)-4,5-dimethoxyphenyl)propanoate (**S18**, 1.88 g, 5.46 mmol, >99% yield) as a colorless oil. Data for **S18**: R_f 0.39 (4:1 hexanes:EtOAc); IR (thin film) 2940, 1732, 1590, 1508, 1454, 1429, 1239, 1120, 1011 cm^{-1}; ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.49−7.31 (m, 5 H), 6.50 (d, J = 1.8 Hz, 1 H), 6.46 (d, J = 1.8 Hz, 1 H), 5.14 (s, 2 H), 4.15 (q, J = 7.1 Hz, 2 H), 3.88 (s, 3 H), 3.87 (s, 3 H), 2.89 (t, J = 7.8 Hz, 2 H), 2.60 (t, J = 7.8 Hz, 2 H), 1.27 (t, J = 7.1 Hz, 3 H); ^{13}C NMR (176 MHz, $CDCl_3$, HSQC, DEPT) δ *C* 172.9, 153.3, 152.3, 137.2, 137.1, 136.3; *C*H 128.5, 127.9, 127.3, 107.5, 105.6; CH_2 71.1, 60.5, 36.0, 31.3; CH_3 60.9, 56.1, 14.3; HRMS (TOF MS ES+) calcd for $C_{20}H_{25}O_5$ [M + H] 345.1702, found 345.1699.

To a solution of **S18** (344 mg, 1 mmol) in CH_2Cl_2 (10 mL, 0.1 M) at −78 °C was added DIBAL-H (1 mL, 1.2 mmol, 1.2 M in toluene) over a period of 15 min. After the addition was complete, TLC indicated complete consumption of the starting material. The reaction was quenched with saturated aqueous Rochelle's salt (20 mL) at −78 °C. The mixture was warmed to rt. The organic phase was separated, and the inorganic phase was extracted with EtOAc (3 × 30 mL). The combined organic phases were dried with $MgSO_4$. Purification by flash column chromatography (hexanes:EtOAc = 5:1) gave 3-(3-(benzyloxy)-4,5-dimethoxyphenyl)propanal (**S19**, 246 mg, 0.82 mmol, 82% yield) as a colorless oil. Data for **S19**: R_f 0.49 (2:1 hexanes:EtOAc); IR (thin film) 2937, 1722, 1589, 1507, 1453, 1429, 1239, 1119, 1008 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.80 (br s, 1 H), 7.49−7.29 (m, 5 H), 6.47 (d, J = 1.6 Hz, 1 H), 6.44 (d, J = 1.6 Hz, 1 H), 5.13 (s, 2 H), 3.87 (s, 3 H), 3.86 (s, 3 H), 2.88 (t, J = 7.4 Hz, 2 H), 2.74 (t, J = 7.4 Hz, 2 H); ^{13}C NMR (101 MHz, $CDCl_3$, HSQC, DEPT) δ *C* 153.4, 152.4, 137.3, 137.2, 136.0; *C*H 201.5, 128.5, 127.9, 127.3, 107.7, 105.8; CH_2 71.2, 45.3, 28.4; CH_3 60.9, 56.1; HRMS (TOF MS ES+) calcd for $C_{18}H_{21}O_4$ [M + H] 301.1440, found 301.1449.

To a solution of diisopropylamine (190 mg, 1.88 mmol) in THF (6 mL, 0.1 M) was added *n*-BuLi (1.17 mL, 1.88 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 **22** (409 mg, 1.8 mmol) in THF (4 mL) was added over a period of 30 min. After stirring at −78 °C for 30 min, a solution of **S19** (451 mg, 1.5 mmol) in THF (5 mL) was added over a period of 30 min. After stirring for 2 h, the reaction was quenched with saturated aqueous NH_4Cl (20 mL). The organic phase was separated, and the aqueous phase was extracted with EtOAc (3 × 20 mL). The combined organic phases were dried with $MgSO_4$. Purification by flash column chromatography (hexanes:EtOAc = 5:1 to 3:1) gave 7-(3-(benzyloxy)-4,5-dimethoxyphenyl)-1-(4-

bromophenyl)-5-hydroxyheptan-3-one (**S20**, 554 mg, 1.05 mmol, 70% yield) as a colorless oil. Data for **S20**: R_f 0.21 (2:1 hexanes:EtOAc); IR (thin film) 3500 (br), 2934, 1707, 1590, 1505, 1489, 1330, 1239, 1118, 1010 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.50−7.29 (m, 7 H), 7.06 (d, J = 8.3 Hz, 2 H), 6.48 (br s, 1 H), 6.45 (br s, 1 H), 5.13 (s, 2 H), 4.04 (m, 1 H), 3.88 (s, 3 H), 3.86 (s, 3 H), 3.06 (brs, 1 H), 2.86 (t, J = 7.3 Hz, 2 H), 2.80−2.47 (m, 6 H), 1.84−1.57 (m, 2 H); ^{13}C NMR (101 MHz, $CDCl_3$, HSQC, DEPT) δ *C* 210.5, 153.3, 152.3, 139.7, 137.4, 137.3, 137.0, 120.0; *C*H 131.6, 130.1, 128.5, 127.8, 127.3, 107.8, 105.9, 66.8; CH_2 71.1, 49.4, 44.7, 38.1, 32.0, 28.8; CH_3 60.9, 56.1; HRMS (TOF MS ES+) calcd for $C_{28}H_{32}BrO_5$ [M + H] 527.1433, found 527.1429.

To a solution of **S20** (448 mg, 0.85 mmol) in EtOAc (8.5 mL, 0.1 M) at rt was added IBX (714 mg, 2.55 mmol). The reaction mixture was heated to reflux until complete consumption of the starting material was observed (TLC, approximately 4−8 h). The reaction mixture was allowed to cool to rt, filtered through a short pad of silica gel, and concentrated to give the crude **S21**, which was used directly without further purification.

To a solution of **S21** (approximately 0.85 mmol, from previous step) in CH_2Cl_2 (17 mL, 0.05 M) were added pentamethylbenzene (378 mg, 2.55 mmol) and BCl_3 (3.4 mL, 3.4 mmol, 1 M in DCM) over a period of 10 min at −78 °C. After the addition was complete, TLC indicated complete consumption of the starting material. The reaction was quenched with MeOH (2 mL) at −78 °C. The resultant mixture was allowed to warm 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 (3 × 20 mL). The combined organic phases were dried with $MgSO_4$. Purification by flash column chromatography (hexanes:EtOAc = 6:1 to 4:1) gave 1-(4-bromophenyl)-7-(3-hydroxy-4,5-dimethoxyphenyl)-heptane-3,5-dione (**30**, 263 mg, 0.604 mmol, 71% yield, 2 steps) as a light yellow solid. Data for **30**: R_f 0.39 (2:1 hexanes:EtOAc); mp = 60−63 °C; IR (thin film) 3432 (br), 2934, 1594, 1511, 1489, 1356, 1202, 1106, 1010 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, enol tautomer) δ 15.41 (br s, 1 H), 7.42 (d, J = 8.2 Hz, 2 H), 7.08 (d, J = 8.2 Hz, 2 H), 6.45 (d, J = 1.7 Hz, 1 H), 6.31 (d, J = 1.7 Hz, 1 H), 5.74 (br s, 1 H), 5.44 (s, 1 H), 3.88 (s, 3 H), 3.85 (s, 3 H), 2.94−2.76 (m, 4 H), 2.63−2.53 (m, 4 H); ^{13}C NMR (101 MHz, $CDCl_3$, HSQC, DEPT, enol tautomer) δ *C* 192.9, 192.7, 152.3, 149.2, 139.6, 136.9, 133.9, 120.0; *C*H 131.6, 130.1, 107.7, 104.3, 99.7; CH_2 39.9, 39.7, 31.6, 30.8; CH_3 61.0, 55.8; HRMS (TOF MS ES+) calcd for $C_{21}H_{24}BrO_5$ [M + H] 435.0807, found 435.0791.

4,5-Dimethoxy-2-oxatricyclo[13.2.2.1^{3,7}]icosa-1(17),3,5,7-(20),15,18-henaene-10,12-dione (35). To a sealed tube were added **30** (21.8 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 to 130 °C. After 48 h, TLC indicated the complete consumption of the starting material. The reaction mixture was allowed to cool 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 (4 × 10 mL). The combined organic phases were dried with $MgSO_4$. Purification by flash column chromatography (hexanes:EtOAc = 8:1 to 5:1) gave **35** (9 mg, 0.0254 mmol, 51% yield) as a light yellow solid. Data for **35**: R_f 0.53 (2:1 hexanes:EtOAc); IR (thin film) 2932, 1589, 1507, 1454, 1432, 1215, 1096, 1003 cm^{-1}; ^1H NMR (700 MHz, $CDCl_3$) δ 15.16 (br s, 1 H), 7.19 (d, J = 8.4 Hz, 2 H), 7.01 (d, J = 8.4 Hz, 2 H), 6.35 (d, J = 1.8 Hz, 1 H), 5.29 (d, J = 1.8 Hz, 1 H), 4.97 (s, 1 H), 4.00 (s, 3 H), 3.88 (s, 3 H), 3.06 (t, J = 6.8 Hz, 2 H), 2.95 (m, 2 H), 2.48 (t, J = 6.8 Hz, 2 H), 2.39 (m, 2 H); ^{13}C NMR (176 MHz, $CDCl_3$, HSQC, DEPT) δ *C* 196.9, 188.7, 154.9, 154.8, 153.1, 136.6, 136.5, 136.1; *C*H 130.6, 123.1, 107.0, 105.6, 103.2; CH_2 39.4, 37.6, 32.2, 28.1; CH_3 61.2, 56.1; HRMS (TOF MS ES+) calcd for $C_{21}H_{23}O_5$ [M + H] 355.1545, found 355.1539.

(11*E*)-4,15,12-Trimethoxy-2-oxatricyclo[13.2.2.1^{3,7}]icosa-1-(17),3,5,7(20),11,15,18-heptaen-10-one (44) and Garuganin III (9). To a solution of **35** (21.3 mg, 0.06 mmol in a mixed solvent of CH_3CN and MeOH (6 mL, 0.01 M, 10:1 v/v) was added $TMSCHN_2$ (0.3 mL, 0.6 mmol, 2 M in hexanes). After stirring at rt for 4 h, the solvent was removed under reduced pressure. Purification by flash column chromatography (hexanes:EtOAc = 5:1 to 3:1) gave **37d** (10.6 mg, 0.0288 mmol, 48% yield, white solid, more polar) and **38d** (10.6 mg, 0.0288 mmol, 48% yield, white solid, less polar) in 1:1 ratio. Treating **37d** and **38d** with dry acidic $CDCl_3$ ("old" $CDCl_3$ dried by 3 Å MS) at rt (approximately 5 min) gave **44** and garuganin III (**9**), respectively in >99% yield. Data for garuganin III (**9**): R_f 0.25 (2:1 hexanes:EtOAc); IR (thin film) 2925, 1667, 1589, 1568, 1506, 1451, 1271, 1214, 1093 cm^{-1}; ^1H NMR (700 MHz, $CDCl_3$) δ 7.32−7.26 (m, 2 H), 6.97 (d, J = 8.6 Hz, 2 H), 6.30 (d, J = 1.7 Hz, 1 H), 5.22 (s, 1 H), 4.92 (d, J = 1.7 Hz, 1 H), 4.00 (s, 3 H), 3.86 (s, 3 H), 3.47 (s, 3 H), 3.11 (t, J = 7.0 Hz, 2 H), 3.08−2.40 (m, 6 H); ^{13}C NMR (176 MHz, $CDCl_3$, HSQC, DEPT) δ *C* 198.8, 173.8, 155.2, 154.5, 153.1, 137.4, 136.1, 135.3; *C*H 131.2, 123.4, 106.0, 105.0, 102.1; CH_2 44.3, 31.1, 28.5, 26.9; CH_3 61.2, 56.0, 55.7; HRMS (TOF MS ES+) calcd for $C_{22}H_{25}O_5$ [M + H] 369.1702, found 369.1686.

Data for **44**: R_f 0.41 (2:1 hexanes:EtOAc); IR (thin film) 2935, 1682, 1589, 1506, 1432, 1261, 1210, 1147, 1096, 1007 cm^{-1}; ^1H NMR (700 MHz, $CDCl_3$) δ 7.38 (dd, J = 8.2, 1.4 Hz, 1 H), 7.04 (dd, J = 8.2, 1.9 Hz, 1 H), 6.90−6.84 (m, 2 H), 6.30 (d, J = 1.8 Hz, 1 H), 5.33 (s, 1 H), 4.94 (d, J = 1.8 Hz, 1 H), 4.02 (td, J = 12.9, 3.4 Hz, 1 H), 4.00 (s, 3 H), 3.86 (s, 3 H), 3.71 (s, 3 H), 3.24 (dd, J = 14.7, 11.4 Hz, 1 H), 2.99 (dt, J = 12.8, 4.0 Hz, 1 H), 2.91 (td, J = 12.9, 3.1 Hz, 1 H), 2.57−2.51 (m, 1 H), 2.48 (dd, J = 17.5, 11.0 Hz, 1 H), 2.34 (dt, J = 12.8, 3.8 Hz, 1 H), 2.28 (dd, J = 15.6, 6.7 Hz, 1 H); ^{13}C NMR (176 MHz, $CDCl_3$, HSQC, DEPT) δ *C* 196.8, 173.0, 155.6, 155.5, 152.8, 138.1, 137.4, 135.7; *C*H 130.8, 130.2, 124.4, 122.2, 108.9, 105.5, 101.2; CH_2 45.0, 33.9, 33.0, 27.5; CH_3 61.2, 56.2, 55.2; HRMS (TOF MS ES+) calcd for $C_{22}H_{25}O_5$ [M + H] 369.1702, found 369.1692.

1-(3-Bromo-5-methoxyphenyl)-7-(4-hydroxyphenyl)-heptane-3,5-dione (31). To a slurry of NaH (540 mg, 13.5 mmol) in THF (15 mL, 0.3 M) was added ethyl 2-(diethoxyphosphoryl)-acetate (2.68 mL, 13.5 mmol) over a period of 10 min at 0 °C. After stirring at 0 °C for 30 min, a solution of 3-bromo-5-methoxybenzaldehyde[26] (1.935 g, 9 mmol) in THF (15 mL) was added. The mixture was warmed to rt and stirred at rt for 30 min. The reaction was quenched with saturated aqueous NH_4Cl (50 mL). The organic phase was then separated, and the aqueous phase was extracted with EtOAc (3 × 50 mL). The combined organic phases were dried with $MgSO_4$. Purification by flash column chromatography (hexanes:EtOAc = 10:1 to 5:1) gave (*E*)-ethyl 3-(3-bromo-5-methoxyphenyl)acrylate (**S22**, 2.541 g, 8.91 mmol, 99% yield) as a colorless solid. Data for **S22**: R_f 0.41 (5:1 hexanes:EtOAc); mp = 43−45 °C; IR (thin film) 2981, 1713, 1641, 1565, 1456, 1422, 1270, 1178, 1050 cm^{-1}; ^1H NMR (700 MHz, $CDCl_3$) δ 7.56 (d, J = 16.0 Hz, 1 H), 7.27 (t, J = 1.3 Hz, 1 H), 7.07 (t, J = 2.0 Hz, 1 H), 6.96 (t, J = 1.7 Hz, 1 H), 6.42 (d, J = 16.0 Hz, 1 H), 4.28 (q, J = 7.1 Hz, 2 H), 3.83 (s, 3 H), 1.35 (t, J = 7.1 Hz, 3 H); ^{13}C NMR (176 MHz, $CDCl_3$, HSQC) δ *C* 166.5, 160.5, 137.2; *C*H 142.9, 123.3, 120.0, 118.7, 112.5; CH_2 60.7; CH_3 55.6, 14.3; HRMS (TOF MS ES+) calcd for $C_{12}H_{14}BrO_3$ [M + H] 285.0126, found 285.0138.

To a solution of **S22** (2.024 g, 7.1 mmol) in THF (36 mL, 0.1 M) were added H_2O (36 mL), NaOAc (2.33 g, 28.4 mmol) and a solution of $TsNHNH_2$ (3.967 g, 21.3 mmol) in THF (35 mL) over a period of 1 h at 80 °C. After 24 h, TLC indicated the complete consumption of the starting material. The mixture was allowed to cool to rt. The organic phase was then separated, and the aqueous phase was extracted with EtOAc (3 × 50 mL). The combined organic phases were dried with $MgSO_4$. Purification by flash column chromatography (hexanes:EtOAc = 10:1 to 8:1) gave ethyl 3-(3-bromo-5-methoxyphenyl)propanoate (**S23**, 2.04 g, 7.1 mmol, >99% yield) as a colorless oil. Data for **S23**: R_f 0.55 (3:1 hexanes:EtOAc); IR (thin film) 2939, 1724, 1598, 1568, 1459, 1430, 1153, 1055 cm^{-1}; ^1H NMR (700 MHz, $CDCl_3$) δ 6.97 (t, J = 1.5 Hz, 1 H), 6.92 (d, J = 2.0 Hz, 1 H), 6.70 (m, 1 H), 4.16 (q, J = 7.1 Hz, 2 H), 3.80 (s, 3 H), 2.91 (t, J = 7.7 Hz, 2 H), 2.62 (t, J = 7.7 Hz, 2 H), 1.27 (t, J = 7.1 Hz, 3 H); ^{13}C NMR (176 MHz, $CDCl_3$, HSQC, DEPT) δ *C* 172.6, 160.4, 143.8, 122.7; *C*H 123.8, 114.9, 113.4; CH_2 60.6, 35.5, 30.7; CH_3 55.4, 14.2; HRMS (EI+) calcd for $C_{12}H_{15}BrO_3$ [M] 286.0205, found 286.0201.

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To a solution of **S23** (2.01 g, 7 mmol) in CH_2Cl_2 (70 mL, 0.1 M) at −78 °C was added DIBAL-H (7 mL, 8.4 mmol, 1.2 M in toluene) over a period of 1 h. After the addition was complete, TLC indicated complete consumption of the starting material. The reaction was quenched with saturated aqueous Rochelle's salt (100 mL) at −78 °C. The mixture was warmed to rt. The organic phase was separated, and the inorganic phase was extracted with EtOAc (3 × 10 mL). The combined organic phases were dried with $MgSO_4$. Purification by flash column chromatography (hexanes:EtOAc = 5:1) gave 3-(3-bromo-5-methoxyphenyl)propanal (**S24**, 1.38 g, 5.68 mmol, 81% yield) as a light yellow oil. Data for **S24**: R_f 0.41 (3:1 hexanes:EtOAc); IR (thin film) 2981, 1713, 1641, 1565, 1456, 1422, 1270, 1178, 1050 cm^{-1}; ^1H NMR (700 MHz, $CDCl_3$) δ 9.83 (t, J = 1.2 Hz, 1 H), 6.95 (t, J = 1.5 Hz, 1 H), 6.92 (t, J = 2.0 Hz, 1 H), 6.69 (m, 1 H), 3.79 (s, 3 H), 2.91 (t, J = 7.5 Hz, 2 H), 2.81−2.77 (m, 2 H); ^{13}C NMR (176 MHz, $CDCl_3$, HSQC, DEPT) δ *C* 160.4, 143.6, 122.9; *C*H 200.9, 123.7, 114.8, 113.5; CH_2 44.9, 27.8; CH_3 55.5; HRMS (EI+) calcd for $C_{10}H_{11}BrO_2$ [M] 241.9942, found 241.9940.

To a solution of diisopropylamine (481 mg, 4.75 mmol) in THF (20 mL, 0.1 M) was slowly added *n*-BuLi (2.97 mL, 4.75 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-(benzyloxy)phenyl)butan-2-one[27] (1.16 g, 4.56 mmol) in THF (9 mL) was added over a period of 1 h. After stirring at −78 °C for 30 min, a solution of **S24** (924 mg, 3.8 mmol) in THF (9 mL) was added over a period of 1 h. After stirring for 2 h, the reaction was quenched with saturated aqueous NH_4Cl (30 mL). The organic phase was separated, and the aqueous phase was extracted with EtOAc (3 × 30 mL). The combined organic phases were dried with $MgSO_4$. Purification by flash column chromatography (hexanes:EtOAc = 5:1 to 3:1) gave 1-(4-(benzyloxy)phenyl)-7-(3-bromo-5-methoxyphenyl)-5-hydroxyheptan-3-one (**S25**, 1.377 g, 2.77 mmol, 73% yield) as a light yellow solid. Data for **S25**: R_f 0.25 (2:1 hexanes:EtOAc); mp = 80−82 °C; IR (thin film) 3371 (br), 2929, 1705, 1605, 1566, 1512, 1454, 1237, 1154, 817 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.49−7.30 (m, 5 H), 7.10 (d, J = 8.6 Hz, 2 H), 6.95 (br s, 1 H), 6.94−6.87 (m, 3 H), 6.69 (br s, 1 H), 5.06 (s, 2 H), 4.03 (m, 1 H), 3.79 (s, 3 H), 3.09 (d, J = 3.1 Hz, 1 H), 2.92−2.46 (m, 8 H), 1.84−1.59 (m, 2 H); ^{13}C NMR (101 MHz, $CDCl_3$, HSQC, DEPT) δ *C* 211.2, 160.4, 157.3, 145.1, 137.1, 132.9, 122.7; *C*H 129.2, 128.6, 127.9, 127.4, 123.9, 115.0, 114.5, 113.5, 66.6; CH_2 70.1, 49.2, 45.2, 37.6, 31.5, 28.7; CH_3 55.4; HRMS (TOF MS ES+) calcd for $C_{27}H_{30}BrO_4$ [M + H] 497.1327, found 497.1310.

To a solution of **S25** (497 mg, 1 mmol) in EtOAc (10 mL, 0.1 M) at rt was added IBX (840 mg, 3 mmol). The reaction mixture was heated to reflux until complete consumption of the starting material was observed (TLC, approximately 4−8 h). The reaction mixture was allowed to cool to rt, filtered through a short pad of silica gel, and concentrated to give crude **S26**, which was used directly without further purification.

To a stirred solution of **S26** (approximately 1 mmol, from previous step) in CH_2Cl_2 (20 mL, 0.05 M) were added pentamethylbenzene (445 mg, 3 mmol) and BCl_3 (4 mL, 4 mmol, 1 M in DCM) over a period of 10 min at −78 °C. After the addition was complete, TLC indicated complete consumption of the starting material. The reaction was quenched with MeOH (2 mL) at −78 °C. The resultant mixture was allowed to warm 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 (3 × 20 mL). The combined organic phases were dried with $MgSO_4$. Purification by flash column chromatography (hexanes:EtOAc = 6:1 to 4:1) gave 1-(3-Bromo-5-methoxyphenyl)-7-(4-hydroxyphenyl)heptane-3,5-dione (**31**, 291 mg, 0.72 mmol, 72% yield, 2 steps) as a light yellow solid. Data for **31**: R_f 0.49 (2:1 hexanes:EtOAc); mp = 54−57 °C; IR (thin film) 3402 (br), 2936, 1724, 1699, 1600, 1569, 1515, 1456, 1266, 1054, 828 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, enol tautomer) δ 15.39 (br s, 1 H), 7.05 (d, J = 8.3 Hz, 2 H), 6.95 (br s, 1 H), 6.92 (t, J = 1.9 Hz, 1 H), 6.77 (d, J = 8.3 Hz, 2 H), 6.67 (br s, 1 H), 5.44 (s, 1 H), 5.26 (br s, 1 H), 3.79 (s, 3 H), 2.92−2.72 (m, 4 H), 2.62−2.51 (m, 4 H); ^{13}C NMR (101 MHz, $CDCl_3$, HSQC, DEPT, enol tautomer) δ *C* 193.02, 193.0, 160.4, 154.1, 143.8, 132.6, 122.8; *C*H 129.4, 123.8, 115.4, 114.9, 113.4, 99.8; CH_2 40.2, 39.6, 31.1, 30.8; CH_3 55.5; HRMS (TOF MS ES+) calcd for $C_{20}H_{22}BrO_4$ [M + H] 405.0701, found 405.0709.

5-Methoxy-2-oxatricyclo[13.2.2.1^{3,7}]isoca-1(17),3,5,7-(20),15,18-hexaene-10,12-dione (36). To a sealed tube were added **31** (40.5 mg, 0.1 mmol), CuO (19.9 mg, 0.25 mmol) and K_2CO_3 (27.6 mg, 0.2 mmol). The tube was evacuated and backfilled with Ar, followed by the addition of pyridine (20 mL, 0.005 M). The tube was then sealed and heated to 130 °C. After 72 h, the reaction mixture was allowed to cool to rt. After evaporation of the solvent, aqueous HCl (2 mL, 1 M) and H_2O (10 mL) were added. The mixture was extracted with EtOAc (4 × 20 mL). The combined organic phases were dried with $MgSO_4$. Purification by flash column chromatography (hexanes:EtOAc = 8:1 to 6:1) gave **36** (13 mg, 0.04 mmol, 40% yield) as a light yellow solid. Data for **36**: R_f 0.63 (2:1 hexanes:EtOAc); IR (thin film) 2939, 1599, 1505, 1461, 1434, 1342, 1294, 1218, 1137, 1059 cm^{-1}; ^1H NMR (700 MHz, $CDCl_3$) δ 15.20 (br s, 1 H), 7.20 (d, J = 8.4 Hz, 2 H), 6.99 (d, J = 8.4 Hz, 2 H), 6.60 (t, J = 2.2 Hz, 1 H), 6.34 (m, 1 H), 5.21 (m, 1 H), 4.97 (s, 1 H), 3.82 (s, 3 H), 3.06 (t, J = 6.8 Hz, 2 H), 2.96 (m, 2 H), 2.48 (t, J = 6.8 Hz, 2 H), 2.38 (m, 2 H); ^{13}C NMR (176 MHz, $CDCl_3$, HSQC) δ *C* 197.0, 188.8, 162.9, 160.6, 154.6, 143.3, 136.7; *C*H 130.6, 123.1, 107.8, 105.7, 103.2, 100.3; CH_2 39.4, 37.7, 32.2, 28.4; CH_3 55.4; HRMS (TOF MS ES+) calcd for $C_{20}H_{21}O_4$ [M + H] 325.1440, found 325.1456.

Reported Structure of Garuganin IV (8) and (10*E*)-5,10-Dimethoxy-2-oxatricyclo[13.2.2.1^{3,7}]isoca-1(17),3,5,7-(20),10,15,18-heptaen-12-one (45). To a solution of **36** (26 mg, 0.08 mmol) in a mixed solvent of CH_3CN and MeOH (8 mL, 0.01 M 10:1 v/v) was added $TMSCHN_2$ (0.4 mL, 0.8 mmol, 2 M in hexanes). After stirring at rt for 4 h, the solvent was removed under reduced pressure. Purification by flash column chromatography (hexanes:EtOAc = 5:1 to 3:1) gave **37e** (13.3 mg, 0.0393 mmol, 49% yield, white solid, more polar) and **38e** (13 mg, 0.0384 mmol, 48% yield, white solid, less polar) in 1:1 ratio. Treating **37e** and **38e** with dry acidic $CDCl_3$ ("old" $CDCl_3$ dried by 3 Å MS) at rt (approximately 5 min) gave garuganin IV (**8**) and **45**, respectively in >99% yield. Data for garuganin IV (**8**): white solid, R_f 0.57 (2:1 hexanes:EtOAc); IR (thin film) 2932, 1682, 1591, 1503, 1462, 1434, 1212, 1136, 1098 cm^{-1}; ^1H NMR (700 MHz, $CDCl_3$) δ 7.38 (d, J = 8.3 Hz, 1 H), 7.04 (dd, J = 8.3, 1.8 Hz, 1 H), 6.90−6.83 (m, 2 H), 6.56 (t, J = 2.2 Hz, 1 H), 6.28 (br s, 1 H), 5.33 (s, 1 H), 4.86 (br s, 1 H), 4.03 (td, J = 12.9, 3.4 Hz, 1 H), 3.80 (s, 3 H), 3.71 (s, 3 H), 3.26 (dd, J = 14.5, 11.7 Hz, 1 H), 2.99 (dt, J = 12.6, 3.9 Hz, 1 H), 2.92 (td, J = 12.9, 3.0 Hz, 1 H), 2.57−2.50 (m, 1 H), 2.47 (dd, J = 17.8, 11.2 Hz, 1 H), 2.34 (dt, J = 12.9, 3.8 Hz, 1 H), 2.30 (dd, J = 15.2, 7.0 Hz, 1 H); ^{13}C NMR (176 MHz, $CDCl_3$, HSQC, DEPT) δ *C* 196.9, 173.0, 163.6, 160.4, 155.4, 144.2, 138.2; *C*H 130.7, 130.3, 124.4, 122.2, 107.6, 107.4, 101.3, 99.5; CH_2 45.0, 33.9, 32.9, 27.6; CH_3 55.4, 55.2; HRMS (TOF MS ES+) calcd for $C_{21}H_{23}O_4$ [M + H] 339.1596, found 339.1584.

Data for **45**: white solid, R_f 0.31 (2:1 hexanes:EtOAc); IR (thin film) 2917, 1668, 1589, 1567, 1505, 1458, 1440, 1267, 1215, 1133 cm^{-1}; ^1H NMR (700 MHz, $CDCl_3$) δ 7.32−7.26 (m, 2 H), 6.96 (d, J = 8.6 Hz, 2 H), 6.55 (t, J = 2.3 Hz, 1 H), 6.30 (m, 1 H), 5.21 (s, 1 H), 4.87 (m, 1 H), 3.80 (s, 3 H), 3.46 (s, 3 H), 3.11 (t, J = 7.0 Hz, 2 H), 3.08−2.40 (m, 6 H); ^{13}C NMR (176 MHz, $CDCl_3$, HSQC, DEPT) δ *C* 198.7, 173.9, 163.2, 160.4, 154.4, 142.8, 137.5; *C*H 131.1, 123.5, 107.1, 104.7, 102.0, 99.6; CH_2 44.3, 31.2, 28.3, 27.1; CH_3 55.6, 55.3; HRMS (TOF MS ES+) calcd for $C_{21}H_{23}O_4$ [M + H] 339.1596, found 339.1601.

Garugamblin I (11). To a solution of **12** (1.5 mg, 4.63 μmole) in dry MeOH (0.46 mL, 0.01 M) was added TsOH (0.1 mg, 0.58 μmole) in a conical vial and heated to 60 °C. After 3 d, the reaction was quenched with pH = 7 buffer (1 mL), extracted with DCM (3 × 2 mL) and concentrated. Analysis of the crude material by NMR indicated that it was a mixture of unreacted starting material and garugamblin I (**11**) (50% yield).

Garuganin I (7). To a solution of **32** (2.0 mg, 5.65 μmole) in dry MeOH (0.57 mL, 0.01 M) was added TsOH (0.1 mg, 0.58 μmole) in a conical vial and heated to 60 °C. After 3 d, the reaction was quenched with pH = 7 buffer (1 mL), extracted with DCM (3 × 2

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mL) and concentrated. Analysis of the crude material by NMR indicated that it was a mixture of unreacted starting material and garuganin I (**7**) (17% yield).

Reported Structure of Garuganin IV (8). To a solution of **37** (1.8 mg, 5.55 μmole) in dry MeOH (0.56 mL, 0.01 M) was added TsOH (0.1 mg, 0.58 μmole) in a conical vial and heated to 60 °C. After 3 d, the reaction was quenched with pH = 7 buffer (1 mL), extracted with DCM (3 × 2 mL) and concentrated. Analysis of the crude material by NMR indicated that it was a mixture of unreacted starting material and reported structure of garuganin IV (**8**) (14% yield).

Garugamblin II (13). To a solution of **34** (1.5 mg, 4.44 μmole) in dry MeOH (0.44 mL, 0.01 M) was added TsOH (0.1 mg, 0.58 μmole) in a conical vial and heated to 60 °C. After 3 d, the reaction was quenched with pH = 7 buffer (1 mL), extracted with DCM (3 × 2 mL) and concentrated. Analysis of the crude material by NMR indicated that it was a mixture of unreacted starting material and garugamblin II (**13**) (12% yield).

(11*E*)-4,15,12-Trimethoxy-2-oxatricyclo[13.2.2.1^{3,7}]icosa-1-(17),3,5,7(20),11,15,18-heptaen-10-one (44). To a solution of **30** (2.2 mg, 6.21 μmole) in dry MeOH (0.62 mL, 0.01 M) was added TsOH (0.1 mg, 0.58 μmole) in a conical vial and heated to 60 °C. After 3 d, the reaction was quenched with pH = 7 buffer (1 mL), extracted with DCM (3 × 2 mL) and concentrated. Analysis of the crude material by NMR indicated that it was a mixture of unreacted starting material and (11*E*)-4,15,12-trimethoxy-2-oxatricyclo-[13.2.2.13,7]icosa-1(17),3,5,7(20),11,15,18-heptaen-10-one (**44**) (16% yield).

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Depiction of ^{1}H and ^{13}C NMR spectra of all new compounds, VT NMR spectra, simulated spectra for line shape analysis, and SIR data. 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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(13) Furthermore, natural garuganin IV was hydrolyzed to the corresponding diketone, which does not have the same NMR shifts as synthetic **37** prepared in this report. See ref 5g.

(14) Molecules of structure type **D** and **E** were prepared from structure type **A** as described above and in the Experimental Section. They showed chemical shift equivalent geminal methylene protons in their ^{1}H NMR. However, they were converted to structure types **B** and **C**, respectively, without full characterization.

(15) Some line broadening of the geminal methylene protons can be seen in **41** and **14**. This is the result of a coalescence temperature near rt. See the Supporting Information for collated VT NMR spectra at multiple temperatures.

(16) Note that the chemical shift equivalence could, in principle, be the unlikely result of accidental equivalence of all geminal methylene and symmetry-related phenyl protons.

(17) For all garuganin and garugamblin molecules, symmetry related phenyl protons (i.e., H_{15} and H_{19}) were used to determine the coalescence temperature (T_C) as indicated by * in Figure 3. See also the spectra in the Supporting Information.

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