Synthesis and Revised Structure of Garuganin III

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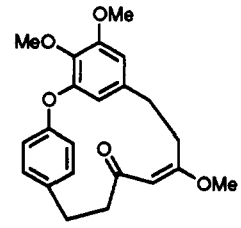
Macrocyclic β-methoxy enones **6** and **1–3**, i.e., garuganin III and its constitutional and stereoisomers, were synthesized using an isoxazole synthon for the introduction of the β-methoxy enone function. Ring closure was accomplished by an intramolecular Wittig reaction. Compound **6** rather than **1**, as suggested previously, was found to have an ^{1}H-NMR spectrum and a mp identical to those of garuganin III.

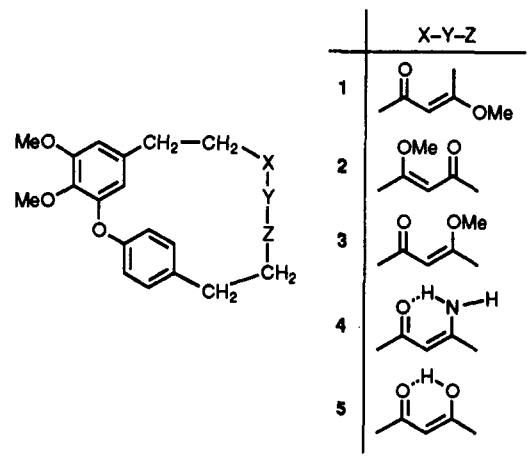
Garuganins are members of the large family of plant constituents called diarylheptanoids, which comprise both acyclic compounds such as curcumin[1] and macrocycles such as the acerogenins.[2] Garuganin III, for which the structure **1** was suggested by Mishra *et al.*,[3] and garuganin I (**7**)[4] and II (**10**)[5] were isolated from *Garuga pinnata*, an Indian medicinal plant. The closely related garugamblins-1 (**8**) and -2 (**9**) come from *Garuga gamblei*.[6] A remarkable feature of compounds **7–10** is the (*E*)-β-methoxy enone, which adds considerable strain to the ring system. On the basis of computations of electrostatic potential maps and preferred conformations for garruganin III and rifamycin SV, a potent commercial antibiotic, we believe that the two compounds have a similar mechanism of action.[7]

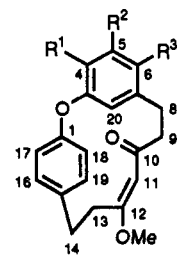
Our interest in the synthesis of macrocyclic diphenyl ethers[8] prompted us to tackle the synthesis of the diphenyl ether type diarylheptanoid garuganin III. Prior synthetic work on cyclic diarylheptanoics was scarce and limited to the syntheses of dimethylalnusone,[9] myricanol, and myricanone;[10] both of the latter two are biphenyl-type compounds.

In view of the notoriously low yields obtained and the drastic conditions required, it was impractical to employ the Ullmann diaryl ether synthesis as one of the concluding steps; therefore, the strategy of first preparing a suitably functionalized diaryl ether and then elaborating the C_7 chain was adopted. After unsuccessful attempts to effect ring closure by means of (i) the addition of a C_1 unit to a diaryl ether bis-propanoic acid, (ii) an intramolecular aldol condensation, and (iii) an intramolecular Würtz reaction were all frustrated, the following scheme finally proved to be successful: (i) The preparation of an unsymmetrically substituted diphenyl ether, (ii) the addition of a C_5 unit in the form of an isoxazole,[11] which



6 garuganin III





	R^1	R^2	R^3	
7:	OMe	H	OMe	garuganin I
8:	OMe	H	H	garugamblin-1
9:	$-OCH_2O-$		H	garugamblin-2

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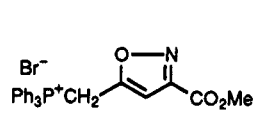
also served as a masked 1,3-dicarbonyl synthon, (iii) ring closure by an intramolecular Wittig reaction, and (iv) transformation of the isoxazole ring into a β-methoxy enone.

Diphenyl ether **10**[12] was prepared in high yield by allowing methyl 3-hydroxy-4,5-dimethoxybenzoate[13] to react with 4hfluorobenzaldehyde. Next, the aldehyde group of diphenyl ether **10** was protected by acetalization



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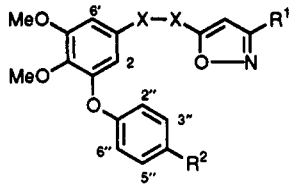
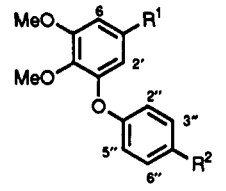
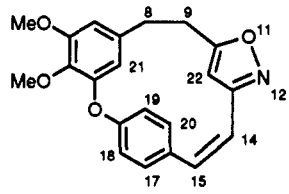




	R^1	R^2
10:	CO_2Me	CHO
11:	CO_2Me	$CH(OMe)_2$
12:	CH_2OH	$CH(OMe)_2$
13:	CHO	$CH(OMe)_2$

		R^1	R^2	X—X
	15:	CO_2Me	$CH(OMe)_2$	CH=CH
a →	**16:**	CO_2Me	$CH(OMe)_2$	CH_2CH_2
b →	**17:**	CH_2OH	$CH(OMe)_2$	CH_2CH_2
c →	**18:**	CH_2Br	CHO	CH_2CH_2
d →	**19:**	$CH_2P^+Ph_3Br^-$	CHO	CH_2CH_2

(a) H_2, Pd/C; (b) $LiAlH_4$; (c) $SOBr_2$; (d) PPh_3



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and the ester group of the resulting acetal **11** was transformed into an aldehyde (**13**) via reduction to alcohol **12** and reoxidation with active MnO_2 to **13**. Wittig reaction of **13** with isoxazole synthon **14**[14] gave olefin **15**, which was transformed in four steps (**15**→**16**→**17**→**18**→**19**) to a phosphonium salt with a free aldehyde group. Note that successful conversion of the alcohol **17** to the bromide **18** could only be achieved with thionyl bromide which also deprotected the aldehyde function. Addition of potassium *tert*-butoxide to a dilute solution of **19** in DMF produced cyclic olefin **20** in relatively high yield (67%). The cyclic structure of the product was indicated by, among other things, an 0.8-ppm upfield shift of one of the signals assigned to the trisubstituted aromatic ring (H-21 in **20**). This shift is characteristic of the "inside" proton in similar systems.[3-6] Hydrogenation over platinum oxide doped with Raney nickel[15] saturated the double bond and cleaved the isoxazole ring to give enamine **4**, which was readily hydrolyzed to diketone **5**. According to NMR, **5** exists exclusively in the hydrogen bonded (*Z*)-enol form. Diketone **5** was identified by its mp and high-field NMR spectrum, which were identical to those of the diketone obtained by hydrolysis of natural garuganin III.[3]

Treatment of diketone **5** with diazomethane in methanol–chloroform led to a mixture of four products (**1–3** and **6**) identified (see below) as the *Z* and *E* stereoisomers of the 10- and 12-keto regioisomers. The primary products of the methylation were the *Z* diastereomers **2** and **3** directly derived from the (*Z*)-enol form of diketone **5**. Diastereomers **2** and **3** isomerized spontaneously on standing in chloroform solution to *E* diastereomers **1** and **6**. Compounds **1** and **6** could be obtained pure by TLC. Compounds **2** and **3**, however, could not be separated from each other, but the mixtures could be analyzed by ^1H NMR at 400 MHz. Spontaneous isomerization of the kinetically favored (*Z*)-enol ethers to the more strained *E* forms was unexpected.

To our surprise, the NMR spectrum of the (*E*)-12-keto isomer **6** was completely identical (apart from minor differences due to different field strength) with that reported for garuganin III.[3] Mishra et al. were probably influenced in their assignment of the structure of garuganin III by the structures of garuganins I and II, which were confirmed by X-ray crystallography.[16,5] The mp of synthetic **6** was also identical with that given for garuganin III.

Structures **1–3** and **6** were based on a careful analysis of 400-MHz proton spectra (see Table I). Based on known substituent effects, assignment of the signals of ring B in **2**, **3**, and **6** was trivial. In compound **1**, the hindered rotation of ring B destroyed the equivalence of 17- and 18-H as well as that of 16- and 19-H; therefore these signals appeared as individual multiplets. Assignments of the multiplets were based on NOE between 20- and 18-H. The substantial upfield shift experienced by 20-H is due to anisotropic effects inside the macrocyclic ring. Assignments of 6- and 20-H were confirmed by observation of long-range coupling between 6-H and 5-OMe and by NOE between 20-H and 17,18-H. Methoxy signals were distinguished by the above mentioned long-range coupling and NOE experiments (see below). Pairing of CH_2 signals was checked by decoupling, and assignments of the benzylic CH_2 signals to 8- and 14-H_2 were permitted by the observation of long-range interactions between 8-H_2 and its neighbors, i.e., 6- and 20-H, and interactions 14-H_2 and 16- and 19-H, respectively.

Structural assignments of the individual isomers were based on NOE experiments (see Table II). Irradiation of 11-H of *Z* isomers **2** and **3** resulted in enhancement of the signals for 9-H_2, 13-H_2, and 20-H, whereas in *E* isomers **1** and **6** the significant NOE between 11-H and the adjacent methoxy group was diagnostic.

The positions of the methoxy groups (at C-12 in **1** and at C-10 in **2**) in the *Z* isomers could be determined by the NOE between the methoxy protons and the protons of the adjoining ethylene chain (see Table II). Irradiation of H-11 in **6** produced an enhancement not only at the methoxy signal but also at the multiplets for 13-H_2 and 14-H_2. Since in **6**, H-11 can only interact with the protons of the $COCH_2CH_2$ moiety, the carbonyl group must be in position 12.

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Table I. ^{1}H NMR Data for Compounds 1–3 and 6 at 400 MHz

proton	(Z)-12-OMe-10-one (1)	(Z)-10-OMe-12-one (2)	(E)-12-OMe-10-one (3)	(E)-10-OMe-12-one (6)
4-OMe	3.963 s	3.995 s	3.978 s	3.966 s
5-OMe	3.842 s	3.850 s	3.836 s	3.826 s
6-H	6.33 d, J_m 2.0	6.28 d, J_m 2.0	6.27 d, J_m 2.0	6.27d, J_m 2.0
8-H_2	2.90 m	2.74 m	3.21 J_g 15, J_v 10, 2.5 2.26 J_v 6.5, 2	2.83 (2 H, br)
9-H_2	2.37 m	2.31 m,	2.51 J_g 17.5, J_v 6.5, 2.5 2.45 J_v 10, 2	2.95 (2 H, br)
10-OMe	–	3.810 s	–	3.438 s
11-H	4.72 s	4.81 s	5.31 s	5.18 s
12-OMe	3.976 s	–	3.688 s	–
13-H_2	2.46 t, J 7.0	2.57 t, J 7.0	4.00 J_g 13, J_v 12.2, 3.5 2.31 J_v 4.5, 3.3	2.75 t, J 7.0
14-H_2	2.98 t, J 7.0	3.00 t, J 7.0	2.97 J_g 12.8, J_v 12.2, 3.3 2.26 J_v 4.5, 3.5	3.07 t, J 7.0
16-H	7.13 d, J_o 8.4	7.25 d, J_o 8.4	7.35 dd, J_o 8, J_m 1.5	7.25 d, J_o 8.5
19-H			6.86 dd, J_o 8, J_m 1.5	
17-H	7.13 d, J_o 8.4	7.03 d, J_o 8.4	7.01 dd, J_o 8, J_m 2.0	6.93 d, J_o 8.5
18-H			6.84 dd, J_o 8, J_m 2.0	
20-H	5.10 d, J_m 2.0	5.56 d, J_m 2.0	4.91 d, J_m 2.0	4.93 d, J_m 2.0

[a] Measured at 20 °C. [b] Measured at 55 °C.

Table II. Positive Nuclear Overhauser Effects

selective saturation	1	2	3	6
11-H	9-H_2, 13-H_2, 20-H, 19-H,	9-H_2, 13-H_2, 20-H		10-OMe, 13-H_2, 14-H_2, 19-H, 20-H
10-OMe		20-H, 18-H, 19-H, 9-H_2, 8-H_2,		11-H, 20-H, 18-H,
12-OMe	13-H_2, 14-H_2, 19-H		11-H	

The small amount of 1 available precluded detailed NOE studies, but proton chemical shifts for 1 were practically identical with those found for garugamblin-1[6] and also with the characteristic protons for garuganin I.[3,4] Consequently, the methoxy group in 1 is attached to C-12.

The occurrence of constitutional isomers of cyclic diarylheptanoids in the same plant is not unprecedented. For example acerogenin A[17] and B,[18] both constituents of *Acer nicoense*, differ only in the position of the alcoholic hydroxyl groups which are attached to C-10 and C-12, respectively.

Experimental Section

Chromatography was carried out on silica gel 60 (Merck), and solvent evaporations were done in vacuo. ^{1}H-NMR spectra were recorded, unless otherwise stated, in $CDCl_3$ with TMS as an internal standard at 400, 250, and 60 MHz. Nontrivial assignments were confirmed by double resonance and NOE experiments.

Methyl 3-(4-Formylphenoxy)-4,5-dimethoxybenzoate (10). To a solution of methyl 3,4-dimethoxy-5-hydroxybenzoate[12] (4.2 g, 19.7 mmol) and 4-fluorobenzaldehyde (2.4 g, 19.3 mmol) in dry DMF (30 mL) was added K_2CO_3 (2.4 g, 17.3 mmol). The mixture was heated at 155–160 °C for 4 h and poured into ice–water (150 mL) and the pale-yellow precipitate was filtered (6.0 g, 95%), mp 82–84 °C. Anal. Found: C, 64.40; H, 5.19. Calcd for $C_{17}H_{16}O_6$: C, 64.55; H, 5.10.

Methyl 3-[4-(Dimethoxymethyl)phenoxy]-4,5-dimethoxybenzoate (11). Aldehyde **10** (5.35 g, 16.8 mmol), *p*-toluenesulfonic acid (30 mg), dry MeOH (12 mL), and $HC(OMe)_2$ (9.5 mL, 87.5 mmol) were refluxed for 3 h. After the addition of Et_3N (0.1 mL) and evaporation of the solvents (under vacuum), **11** was obtained as an oil (5.88 g, 96%): ^{1}H NMR δ (60 MHz) 3.32 (s, 6 H, $CH(OCH_3)_3$), 3.80, 3.85, 3.89 (3s, 9 H, 3 × OCH_3), 5.26 (s, 1 H, ArCH), 6.83 (d, J = 8.5 Hz, 2 H, 2″,6″-H), 7.2–7.5 (m, 4 H, 2′,3″,5″,6′-H). Anal. Found: C, 62.96; H, 6.22. Calcd for $C_{19}H_{22}O_7$: C, 62.98; H, 6.12.

Methyl 3-[4-(Dimethoxymethyl)phenoxy]-4,5-dimethoxybenzyl Alcohol (12). To an ice-cooled suspension of $LiAlH_4$ (2.0 g, 42 mmol) in dry THF (100 mL) was added ester **11** (5.6 g, 15.4 mmol) under argon in THF (40 mL) over 30 min. After stirring at rt for 1 h, excess reagent was decomposed by the careful addition of water. The precipitate formed was dissolved by the addition of 1 M NaOH, and the solution was extracted with Et_2O. The combined extracts were dried and evaporated to give to benzyl alcohol **12** as a colorless oil (4.4 g, 85%): ^{1}H NMR δ (60 MHz) 3.33 (s, 6 H, $CH(OCH_3)_3$), 3.78, 3.87 (2s, 6 H, 2 × OCH_3), 4.57 (s, 2 H, $-CH_2O-$), 5.33 (s, 1 H, ArCH), 6.56 (d, J = 2 Hz, 1 H, 2′-H), 6.76 (d, J = 2.0 Hz, 1 H, 6′-H), 6.90 (d, J = 8.5 Hz, 2 H, 2″,6″-H), 7.36 (d, J = 8.5 Hz, 2 H, 3″,5″-H). Anal. Found: C, 64.49; H, 6.58. Calcd for $C_{18}H_{22}O_6$: C, 64.66; H, 6.63.

3-[4-(Dimethoxymethyl)phenoxy]-4,5-dimethoxybenzaldehyde (13). To a solution of **12** (4.0 g, 11.9 mmol) in dry CH_2Cl_2 (250 mL), activated MnO_2 (26.0 g, 0.3 mol) was added, and the mixture was stirred for 1.5 h. Filtration and evaporation gave **13** as an oil (3.7 g, 93%): ^{1}H NMR δ (60 MHz) 3.33 (s, 6 H, $CH(OCH_3)_2$), 3.88, 3.93 (2s, 6 H, OCH_3), 5.33 (s, 1 H, ArCH), 6.91 (d, J = 8.5 Hz, 2 H, 2″,6″-H), 7.11 (d, J = 2.0 Hz, 1 H, 2′-H), 7.24 (d, J = 2.0 Hz, 1 H, 6′-H), 7.40 (d, J = 8.5 Hz, 2 H, 3″,5″-H), 9.73 (s, 1 H, CHO). Anal. Found: C, 64.96; H, 6.17. Calcd for $C_{18}H_{20}O_6$: C, 65.05; H, 6.07.

3-(Methoxycarbonyl)-5-{2-[4,5-dimethoxy-3-[4-(dimethoxymethyl)phenoxy]phenyl]-1-ethenyl}isoxazole (15). To a solution of KOtBu (0.44 g, 3.8 mmol) in dry DMF (15 mL) was added phosphonium salt **14** (2.0 g, 4.0 mmol) under argon. The mixture was stirred for 30 min until dissolution was complete. Aldehyde **13** (1.8 g, 3.1 mmol) in DMF (5 mL) was then added to the orange-yellow solution. The mixture was stirred for 1 h, quenched with saturated NaCl solution (200 mL), and extracted with Et_2O (3 × 50 mL). The combined extracts were washed with saturated sodium chloride, dried, and evaporated. The residue was chromatographed (hexane–EtOAc 3:1) to give **15** as a pale-yellow solid (1.62 g, 63%), mp 128–140 °C): ^{1}H NMR δ (100 MHz) 3.31, 3.33 (2s, 6 H, $CH(OCH_3)_2$), 3.86 (s, 3 H, (*E*)-OCH_3), 3.87 (s, 3 H, (*Z*)-OCH_3), 3.94 (s, 3 H, (*Z*)-OCH_3), 3.97 (s, 3 H, (*E*)-OCH_3), 5.35 (s, 1 H, (*E*)-ArCH), 5.37 (s, 1 H, (*Z*)-ArCH), 6.3–7.5 (m, 9 H, 4-H, ArH, CH=CH). Anal. Found: C, 63.37; H, 5.49; N, 3.01. Calcd for $C_{24}H_{25}NO_8$: C, 63.29; H, 5.53; N, 3.08.

3-(Methoxycarbonyl)-5-{2-[4,5-dimethoxy-3-(4-(dimethoxymethyl)phenoxy]phenyl]-1-ethyl}isoxazole (16). Ethene **15** (1.4 g, 3.1 mmol) in EtOAc (200 mL) was hydrogenated over 5% Pd–C (200 mg). The usual workup gave ethane **16** as a white

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solid (mp 69–71 °C) in almost quantitative yield: ^{1}H NMR δ (60 MHz) 3.02 (mc, 4H, CH_2CH_2), 3.33 (s, 6 H, $CH(OCH_3)_2$), 3.77, 3.84, 3.94 (3s, 9 H, 3 × OCH_3), 5.26 (s, 1 H, ArCH), 6.33 (s, 1 H, 4-H), 6.41 (d, J = 2.0 Hz, 1 H, 2′-H), 6.49 (d, J = 2.0 Hz, 1 H, 6′-H), 6.91 (d, J = 8.5 Hz, 2 H, 2″,6″-H), 7.36 (d, J = 8.5 Hz, 2 H, 3″,5″-H). Anal. Found: C, 63.19; H, 5.70; N, 2.95. Calcd for $C_{24}H_{27}NO_8$: C, 63.01; H, 5.95; N, 3.06.

5-{2-[4,5-Dimethoxy-3-[4-(dimethoxymethyl)phenoxy]-phenyl]-1-ethyl}-3-(hydroxymethyl)isoxazole (17). To an ice-cooled suspension of $LiAlH_4$ (0.4 g, 10.5 mmol) in dry THF (100 mL) under argon was added ester **16** (1.5 g, 3.2 mmol) in dry THF (10 mL) over 30 min with stirring. After 1 h, the excess reagent was decomposed by careful addition of water. The precipitate formed was dissolved by the addition of 1 M NaOH, and the solution was extracted with Et_2O. The combined extracts were dried and evaporated to give **17** as a colorless oil (1.1 g, 85%): ^{1}H NMR δ (100 MHz) 3.00 (mc, 4 H, CH_2CH_2), 3.30 (s, 6 H, $CH(OCH_3)_2$), 3.78, 3.86 (2s, 6 H, 2 × OCH_3), 4.66 (s, 2 H, CH_2O), 5.36 (s, 1 H, ArCH), 5.96 (s, 1 H, 4-H), 6.38 (d, J = 2.0 Hz, 1 H, 2′-H), 6.52 (d, J = 2.0 Hz, 1 H, 6′-H), 6.88 (d, J = 8.0 Hz, 2 H, 2″,6″-H), 7.36 (d, J = 8.0 Hz, 2 H, 3″,5″-H). Anal. Found: C, 64.38; H, 6.29; N, 3.42. Calcd for $C_{23}H_{27}NO_7$: C, 64.32; H, 6.34; N, 3.26.

3-(Bromomethyl)-5-{2-[4,5-dimethoxy-3-(4-formylphenoxy)phenyl]-1-ethyl}isoxazole (18). To an ice-cooled solution of **17** (0.7 g, 1.5 mmol) in 50 mL of dry benzene was added $SOBr_2$ (1.17 mL, 1.5 mmol). After stirring for 3 h, the reaction mixture was poured into ice–water (100 mL). The benzene layer was dried and evaporated to give **18** as an oil (0.54 g, 86%): ^{1}H NMR δ (400 MHz) 2.97 (mc, 2 H, 2-CH_2), 3.04 (mc, 2 H, 1-CH_2), 3.76 (s, 3 H, 4′-OCH_3), 3.87 (s, 3 H, 5′-OCH_3), 4.36 (s, 2 H, CH_2Br), 6.04 (s, 1 H, 4-H), 6.52 (d, J = 2.0 Hz, 1 H, 2′-H), 6.59 (d, J = 2.0 Hz, 1 H, 6′-H), 7.00 (d, J = 9.0 Hz, 2 H, 2″,6″-H), 7.83 (d, J = 9.0 Hz, 2 H, 3″,5″-H), 9.91 (s, 1 H, CHO). Anal. Found: C, 56.46; H, 4.43; N, 3.04. Calcd for $C_{21}H_{20}BrNO_5$: C, 56.52; H, 4.52; N, 3.14.

5-{2-[4,5-Dimethoxy-3-(4-formylphenoxy)phenyl]-1-ethyl}-3-[(triphenylphosphonio)methyl]isoxazole (19). Bromide **18** (0.4 g, 0.86 mmol) was refluxed in dry MeCN (10 mL) with Ph_3P (0.25 g, 0.95 mmol) for 3 h. After evaporation, the residue was stirred with a small amount of benzene, and the white participate was boiled with hexane (3 × 20 mL) to remove the excess Ph_3P. Trituration with Et_2O gave **19** (0.54 g, 89%) as an amorphous solid: ^{1}H NMR δ (400 MHz) 2.82–2.96 (m, 4H, CH_2CH_2), 3.73 and 3.87 (2s, 6H, OCH_3), 5.57 (d, J = 15 Hz, 2H, P^+CH_2), 6.43 (d, J = 2.0 Hz, 1H, 2′-H), 6.63 (d, J = 2.0 Hz, 1H, 6′-H), 6.64 (s, 1H, CH=), 6.99 (d, J = 8.5 Hz, 2H, 2″,6″-H), 7.83 (d, J = 8.5 Hz, 2H, 3″,5″-H), 7.63–7.89 (m, 15H, aromatic-H), 9.89 (s, 1H, CHO). Anal. Found: C, 66.04; H, 5.07; N, 1.72. Calcd for $C_{39}H_{35}BrNPO_5$: C, 66.11; H, 4.98; N, 1.98.

4,5-Dimethoxy-2,11-dioxa-12-azatetracyclo[14.2.2.1.^{2,7}1^{10,13}]-docosa-3,5,7(21),10(22),12,14,16,18,19-nonaene (20). To an ice-cooled solution of **19** (0.41 g, 0.58 mmol) in dry DMF (290 mL) under argon was added KOtBu (78 mg, 0.71 mmol). After stirring at rt for 1 h, the mixture was concentrated under high vacuum and the residue was chromatographed on silica gel (benzene–ethyl acetate 8:1) to give **20** as a white solid (109 mg, 67%, mp 144–146 °C): δ (400 MHz) 2.74 (m, 2 H, 8-H_2), 2.82 (m, 2 H, 9-H_2), 3.86 (s, 3 H, 5-OCH_3), 4.02 (s, 3 H, 4-OCH_3), 4.86 (s, 1 H, 22-H), 5.71 (d, J = 2.0 Hz, 1 H, 21-H), 6.36 (d, J = 2.0 Hz, 1 H, 6-H), 6.69 (d, J = 11.0 Hz, 1 H, 14-H), 7.05 (d, J = 8.5 Hz, 2 H, 18,19-H), 7.18 (d, J = 8.5 Hz, 2 H, 17,20-H), 7.37 (d, J = 11.0 Hz, 1 H, 15-H). Anal. Found: C, 72.24; H, 5.41; N, 3.94. Calcd for $C_{21}H_{19}NO_4$: C, 72.19; H, 5.48; N, 4.01.

4,5-Dimethoxy-12-amino-2-oxatricyclo[12.2.2.1.^{3,7}]eicosa-3,5(20),11,15,17,18-heptaen-10-one (4). A solution of **20** (100 mg, 0.28 mmol) in MeOH (50 mL) was reduced under atmospheric pressure at rt over PtO_2 catalyst prereduced with a small amount of Raney nickel in MeOH (20 mL). After the hydrogenation was complete, the solution was filtered through Celite, and the filtrate was evaporated to give enamino ketone **4** as a white solid (80 mg, 79%, mp 228–229 °C): δ (400 MHz) 2.30 (mc, 2 H, 9-H_2), 2.34 (t, J = 7 Hz, 2 H, 13-H_2), 2.92 (mc, 2 H, 8-H_2), 2.94 (t, J = 7 Hz, 14-H_2), 3.84, 3.96 (2s, 6 H, 2 × OCH_3), 4.43 (s, 1 H, 11-H), 5.04 (br s, 1 H, NH), 5.34 (d, J = 2.1 Hz, 1 H, 20-H), 6.34 (d, J = 2.1 Hz, 1 H, 6-H), 6.99 (d, J = 8.5 Hz, 2 H, 17,18-H), 7.13 (d, J = 8.5 Hz, 2 H, 16,19-H), 9.50 (s, 1 H, H-bonded NH). Anal. Found: C, 71.15; H, 6.42; N, 4.03. Calcd for $C_{21}H_{23}NO_4$: C, 71.37; H, 6.56; N, 3.96.

4,5-Dimethoxy-2-oxatricyclo[12.2.2.1.^{3,7}]eicosa-3,5,7-(20),15,17,18-hexaene-10,12-dione (5). Compound **4** (30 mg, 0.08 mmol) was treated with 90% aqueous AcOH acid for 24 h. Evaporation gave **5** as a colorless solid in almost quantitative yield: mp 149–150 °C (lit.[3] mp 149–150 °C); ^{1}H NMR δ (400 MHz), 2.37 (mc, 2 H, 9-H_2), 2.46 (t, J = 7 Hz, 2 H, 13-H_2), 2.93 (mc, 2 H, 8-H_2), 3.03 (t, J = 7 Hz, 2 H, 14-H_2), 3.85 (s, 3 H, 5-CH_3), 3.97 (s, 3 H, 4-OCH_3), 4.95 (s, 1 H, 11-H), 5.26 (d, J = 2 Hz, 1 H, 20-H), 6.32 (d, J = 2 Hz, 1 H, 6-H), 6.98 (d, J = 8.5 Hz, 2 H, 17,18-H), 7.17 (d, J = 8.5 Hz, 2 H, 16,19-H), 15.1 (br, 1 H, OH). Anal. Found: C, 71.25; H, 6.32. Calcd for $C_{21}H_{22}O_5$: C, 71.17; H, 6.26.

(*E*)-4,5,10-Trimethoxy-2-oxatricyclo[12.2.2.1.^{3,7}]eicosa-3,5,7-(20),11,15,17,18-heptaen-12-one (Garuganin III) (6). To a solution of diketone **5** (72 mg) in $CHCl_3$–MeOH (1:1, 10 mL) was added a solution of CH_2N_2 (generated from 1 g of *N*-nitroso-*N*-methylurea) in $CHCl_3$ (5 mL). After 24 h, the solvent was evaporated, and the product was separated by TLC (C_6H_6–EtOAc 2:1) to give **6** (11 mg), mp 175–177 °C (from MeOH), as the fastest moving component (lit.[3] mp 176–177 °C); ^{1}H NMR δ (100 MHz) 2.74 (m, 2 H), 2.84 (m, 4 H), 3.10 (t, J = 6.5 Hz, 2 H), 3.45. 3.84, 3.94 (3s, 9 H), 4.90 (d, J = 1.5 Hz, 1 H), 5.20 (s, 1 H), 6.28 (d, J = 1.5 Hz, 1 H), 6.95 (dd, J = 8 and 2 Hz, 2 H), 7.27 (dd, J = 8 and 2 Hz, 2 H). The main component of the more-polar fraction was **3** along with about 30% of **1**. When the methylation was terminated after 2 h, the fastest moving fraction consisting mainly of **2** in admixture with some **6**, and the more-polar fraction was almost pure **1** (for NMR data, see Tables I and II).

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