Tetrahedron Vol 49, No 22, pp 4893-4900, 1993
Printed in Great Britain

0040-4020/93 $6.00+ 00

The Synthesis of Garugamblin-1

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(*Received in UK* 3 *February* 1993)

Key Words: garugamblin-1; diarylheptanoids; synthesis; stereochemistry

Abstract: The *Z* isomer of the title compound (**21**) and its regioisomer (**22**) were synthesized using an isoxazole synthon (**17**) for the elaboration of the β-methoxy-enone function. **21** and **20** spontaneously isomerized to the *E* isomers i.e. to garugamblin-1 (**1**) and its regioisomer (**22**) resp.

Five closely related macrocyclic diarylheptanoids (**1-5**) were isolated from *Garuga* species, i.e. garugamblin-1 (**1**) and -2 (**2**) from *G. gamblei*[1], garuganin-I (**3**)[2], -III (**4**)[3], and -II (**5**)[4] from *G. pinnata*. These compounds belong to the broader family of 1,7-diarylheptanoids comprising both cyclic and acyclic representatives[5].

Now we report the synthesis of the simplest member of this group, i.e. of garugamblin-1 (**1**). This work was stimulated by the availability of a key intermediate (**6**) which had been repeatedly utilized in our syntheses of natural macrocyclic bis(bibenzyls)[6].

First aldehyde **6** was condensed with acetonyltriphenyl-phosphonium bromide[7] to give the enone **7**, which was hydrogenated to the butanone **8** over Raney nickel. Condensation with ethyl oxalate accompanied by transesterification afforded the diethylester of diketone **9**. At this point the 1,3-dicarbonyl function was masked by incorporation into an isoxazole ring (**10**)[8].

A more economic approach to the methyl ester analogue of **10** i.e. to **12** was to prepare an isoxazole synthon (**17**) from **15**, a drug intermediate[9] by bromination to **16**[10] and subsequent reaction with triphenylphosphine. Wittig reaction of **17** with aldehyde **6** gave the olefin **11** which was hydrogenated to the diester **12**.

Reduction of **12** with $LiAlH_4$ to the diol **13** followed by treatment with phosphorus tribromide led to the dibromide **14**. Ring closure was accomplished by the Wurtz-Boekelheide method, i.e. by treatment with the

radical anion generated from sodium and tetraphenylethene[11]. Cyclization proceeded in low yield and gave the enamine **18** by concomitant reductive ring cleavage of the isoxazole ring, a step which would have been carried out anyway. Evidence for ring closure was provided by the ^{1}H-NMR spectrum, in particular among by the large upfield shift (more than 1.0 ppm) of the H-20 signal. For example in **18** namely, this proton is located above the plane of the neighbouring aromatic ring. The molecular mass of the product, in turn, indicated cleavage of the isoxazole ring in **18**. Hydrolysis of the enaminoketone **18** to the diketone **19** (present as the (*Z*)-enol) was carried out in hot aqueous acetic acid. As shown by the appearance of one chelated and one non-chelated NH signal (1 H each) at 9.55 and 4.97 p.p.m. compound **18** is in the enamine form, while the signal at 15.22 p.p.m. and the complete lack of a $COCH_2CO$ methylene signal in the ^{1}H-NMR spectrum of the hydrolysis product indicated that latter is present in one of the (*Z*)-enol forms only (**19**), (see Tables 1 and 2). Assigment of the methylene signals was supported by NOE (see Experimental), that of the ^{13}C-NMR signals by 1D semiselective INEPT measurement[12] optimized for 7 Hz long-range coupling values.

Although it was reported[2], that the diketone precursor of garuganin I could not be methylated with diazomethane, we found that prolonged treatment of **19** with diazomethane in methanol gave a mixture of isomeric (*Z*)-enol ethers (**20** and **21**) of which the more polar was the desired regioisomer (**21**) i.e. the *Z* diastereomer of garugamblin-1 (**1**).

Our original concept was to convert **21** to garugamblin-1 (**1**) by photoisomerisation, but irradiation left **21** unchanged. However, on repeated recording again the spectrum of a sample of **21** dissolved in $CDCl_3$ after two weeks of standing we were surprised to find that it almost completely isomerized to garugamblin-1 **1**, as confirmed also by direct comparison (t.l.c., m.p., ^{1}H-NMR) with the natural product. A similar isomerization of **20** to **22** was also experienced. In fact all four isomers could also be isolated from the crude methylation mixture left standing in solution for several days.

Structural assignment of the enol ethers was based on ^{1}H and ^{13}C-NMR spectroscopy. Spectra of the *Z* compounds **20** and **21** showed characteristic differences as compared with that of **1**. Thus due to shielding by the *p*-disubstituted benzene ring the signals of the enolic protons in **20** and **21** suffered an upfield shift of 0.47 and 0.55 p.p.m. respectively. Detailed assignment of the CH_2 signals in **21** and determination of the position of the enol function was enabled by recording a phase sensitive 2D NOESY spectrum.[13] Steric proximity of protons indicated by arrows in the formula was deduced from cross peaks. In particular NOE between H-11 and C(13)H_2 proved the *Z* configuration of the compound, while that between the OCH_3 signal at 3.98 p.p.m. and C(13)H_2 positioned the methoxy on C-12. An interesting feature of the ^{1}H spectra of **19**, **20** and **21** is that signals for one of the ethylene bridges appear as a pair of triplets, while those for the other one as two multiplets. Inspection of a Dreiding model suggested that in **20** and **21** the CH_2CH_2 bridges are rather mobile. As a consequence chemical shifts for geminal protons in the latter become averaged. In the spectrum of **19** and **21** these triplets could be unambigously assigned to C(13)H_2 and C(14)H_2. In the more rigid *E* isomers i.e. in **1** and **22** all CH_2 signals appear at different chemical shifts.

A common feature of the spectra of the *Z* isomers **20** and **21** is the downfield shift of the signals for 20-H, indicating C(10)=O and 20-H are not so close to each other as in **1** and therefore the diamagnetic anisotropic effect of the carbonyl group is not present in these compounds.

Additional support for the proposed structures came from ^{13}C-NMR data. E.g. lack of the γ-steric effect between C(13) and C(10)=O in **21** manifested itself as an upfield shift by 4.5 p.p.m. of the C(13) signal relative to that in **1**.

Table 1. ^{1}H Chemical Shifts of Compounds **1, 18-22** in ppm (400 MHz, $CDCl_3$).

	1[a]	**18**	**19**	**20**	**21**	**22**
5-H	6.73	6.79	6.78	6.80	6.80	6.82
6-H	6.59	6.67	6.66	6.61	6.69	6.64
8-H	2.28; 3.20	2.95	2.90	2.74	2.91	2.85[b,c]
9-H	2.33; 2.52	2.35	2.33	2.30	2.35	2.96[b,c]
11-H	5.30	4.44	4.93	4.81	4.73	5.19
13-H	2.30; 4.02	2.31	2.45	2.58	2.46	2.75[b,d]
14-H	2.8-3.0	2.92	3.02	3.01	2.98	3.09[b]
16,19-H	6.83; 7.05	7.15	7.17	7.26	7.14	7.27
17,18-H	6.83; 7.05	7.00	6.98	7.04	7.03	6.97
20-H	5.27	5.68	5.60	5.93	5.46	5.27
4-MeO	3.92	3.93	3.92	3.95	3.93	3.93
OMe	3.68			3.80	3.98	3.43
	4.97(NH) 15.22(OH) 9.55(NH)					

[a]Identical within experimental error with literature values[1b] measured at 250 MHz.

[b]Measured at 40 °C, coalescence at r.t.

[c]Interchangeable assignments.

[d]Assigment was supported by N.O.E. at 16,19-H on irradiation of 14-H_2.

Table 2. ^{13}C-NMR Shifts for Compounds **1, 19-21** in ppm.

	1[a]	**19**	**20**	**21**		**1**[a]	**19**	**20**	**21**	
C-1	155.3	154.5	154.6	154.6	C-12	173.0	189.2	198.1	169.6	
C-3	151.8	151.0	150.9	150.9	C-13	33.9	39.5	45.9	38.4	
C-4	146.4	146.6	147.3	146.2	C-14	32.9	32.2	33.7	32.8	
C-5	111.3	111.7	111.7	111.8	C-15	138.1	136.7	137.7	136.6	
C-6	120.6	121.2	111.7	121.2	C-16,19	130.4	130.6	130.7	130.5	
C-7	135.0	133.8	134.3	134.1	C-17,18	122.2	123.2	123.6	123.5	
C-8	26.7	27.5	28.3	27.5	C-20		115.6	113.6	114.0	113.6
C-9	45.4	38.0	35.5	41.5	4-OMe	56.2	56.2	56.2	56.2	
C-10	196.9	196.7	170.9	195.5	OMe	55.1		60.9	59.5	
C-11	101.2	103.1	107.4	106.9						

[a]Literature values[1b] quoted to support assignments.

EXPERIMENTAL

Chromatography was carried out on silica gel (Kieselgel 60 Merck). NMR spectra were recorded, if not otherwise stated, in $CDCl_3$ at room temperature with TMS as internal standard on one of the following instruments: Perkin-Elmer A60, JEOL FX-100 and Bruker AM-400.

(*E*)-1-[4-Methoxy-3-(4-methoxycarbonylphenoxy)-phenyl]-buten-1-3-one (**7**): To a solution of acetonyl-triphenylphosphonium bromide (0.80 g, 2.0 mmol) in methanol (25 ml) first a solution of aldehyde **6** (0.50 g, 1.75 mmol) in methanol (20 ml) and then 1N sodium methoxide (2.0 ml) was added under nitrogen. After stirring for 24 h the filtered solution was evaporated and the residue chromatographed with benzene as eluantand the product recrystallized from methanol to give **7** (0.25 g, 44%), m.p. 94-95 °C. - ^{1}H-NMR (60 MHz): δ= 2.32 (s, 3 H, COMe), 3.82 and 3.88 (2xs, 6 H, OMe), 6.53 (d, J = 16 Hz, 1 H, 2-H), 6.88 (d, J = 8 Hz, 2 H, 2",6"-H), 7.03 (d, J = 7.5 Hz, 5'-H), 7.2-7.6 (m, 2 H, 2',6'-H), 7.98 (d, J = 8 Hz, 2 H, 3",5"-H).

$C_{19}H_{18}O_5$ (326.4) Calcd. C 69.92 H 5.60
Found C 69.73 H 5.72

6-[4-Methoxy-3-(4-methoxycarbonylphenoxy)]-butan-2-one (**8**): Enone **7** (1.63 g, 5.0 mmol) was hydrogenated in acetone (60 ml) over Raney-nickel. The usual work-up gave **8** as a colourless oil (1.32 g, 80%). - ^{1}H-NMR (60 MHz): δ= 2.08 (s, 3 H, COMe), 2.75 (mc, 4 H, CH_2CH_2), 3.70 and 3.80 (2xs, 6 H, OMe), 6.7-7.3 (m, 5 H, aromatic H), 7.90 (d, J = 8 Hz, 2 H, 3"-, 5"-H).

$C_{19}H_{20}O_5$ (328.4) Calcd. C 69.50 H 6.14
Found C 69.44 H 5.60

Ethyl 6-[4-methoxy-3-(4-ethoxycarbonylphenoxy)]-2,4-dioxohexanoate (**9**): A solution of ketone **8** (0.66 g, 2.0 mmol) in dry benzene (10 ml) was added dropwise to a slurry of sodium hydride (70 mg, 80% in mineral oil) under argon at 0 °C followed by diethyl oxalate (0.30 ml, 2.2 mmol) diluted with benzene (3.0 ml). After stirring at r.t. for 6 h the yellow reaction mixture was acidified with ice cold 5% hydrochloric acid. The organic phase was separated, washed with water, dried, evaporated and the residue chromatographed (eluant toluene-ethyl acetate 2:1) to give 9 (0.40 g, 45%) as an oil. - ^{1}H-NMR (100 MHz): δ= 1.36 and 1.38 (2xt, J = 6 Hz, 6 H, Me), 2.85 (m, 4 H, CH_2CH_2), 3.73 (s, 3 H, OMe), 3.86 (s, 0.5 H, $COCH_2CO$), 4.32 and 4.33 (2xq, J = 5 Hz, 4 H, OCH_2), 6.30 (s, 0.75 H, O-C=CH), 6.90-7.05 (m, 5 H, aromatic-H), 7.95 (d, J = 8 Hz, 2 H, 3",5"-H).

$C_{23}H_{26}O_7$ (414.5) Calcd. C 66.65 H 6.32
Found C 66.88 H 6.55

3-Ethoxycarbonyl-5-[2-[4-methoxy-3-(4-ethoxycarbonylphenoxy)]-ethyl]-isoxazole (**10**): Diester **9** (1.77 g, 4.0 mmol) and $NH_2OH.HCl$ (1.16 g) was boiled in ethanol (75 ml) for 3 h. Evaporation, treatment of the residue with water, extraction with ethyl acetate and chromatography (eluant toluene-2-butanone 10:1) gave **10** (1.1 g, 65%) as colourless crystals, m.p. 103-104 °C (from MeOH). - ^{1}H-NMR (100 MHz): δ= 1.33 and 1.36 (2xt, J = 5 Hz, 6 H, Me), 3.04 (mc, 4 H, CH_2CH_2),3.76 (s, 3 H, OMe), 4.34 and 4.41 (2xq, J = 5 Hz, 4 H, OCH_2), 6.32 (s, 1 H, 4-H), 6.8-7.0 (m, 5 H, aromatic-H), 7.36 (d, J = 8 Hz, 2 H, 3",5"-H).

$C_{24}H_{25}NO_7$ (439.5) Calcd. C 65.59 H 5.73 N 3.19
Found C 65.80 H 5.79 N 3.33

3-Methoxycarbonyl-5-[2-[4-methoxy-3-(4-methoxycarbonylphenoxy)]-ethyl]-isoxazole (12): Isoxazole **11** (1.56 g, 4.0 mmol) was hydrogenated in ethyl acetate (200 ml) over palladium-on-carbon. The usual work-up gave **12** (1.4 g, 90%). - ^{1}H-NMR (60 MHz): δ= 3.00 (mc, 4 H, CH_2CH_2), 3.73, 3.85 and 3.92 (3xs, 9 H, OMe), 6.30 (s, 1 H, 4-H), 6.7-7.0 (m, 5 H, aromatic-H), 7.95 (d, J = 8 Hz, 2 H, 3",5"-H).

$C_{22}H_{21}NO_7$ (411.4) Calcd. C 64.22 H 5.15 N 3.40
Found C 64.01 H 5.42 N 3.48

3-Methoxycarbonyl-5-isoxazolylmethyl-triphenylphosphonium bromide (17): A solution of methyl 5-methylisoxazole-3-carboxylate **15** (5.0 g, 0.039 mol), N-bromosuccinimide (12.5 g, 0.107 mol) and benzoyl peroxide (0.28 g) in carbon tetrachloride (50 ml) was boiled under reflux for 1 h while irradiated by a Cole & Palmer high intensity lamp. After cooling and filtering off succinimide the solution was evaporated to give the bromomethyl compound **13** contaminated with the dibromomethyl and 4-bromo compound. This was dissolved in acetonitrile (50 ml), triphenylphosphine (8.3 g, 0.0315 mol) added and the mixture refluxed for 90 min. Evaporation and trituration of the residue with benzene gave **17** (9.5 g, 54%), m.p. 158-160 °C. - ^{1}H-NMR (60 MHz): δ= 3.84 (s, 3 H, OMe), 6.20 (d, J = 15 Hz, 2 H, CH_2), 7.08, d, J = 4 Hz, 1 H, 4-H), 7.5-8.1 (m, 15 H, C_6H).

$C_{24}H_{21}BrNO_3P$ (482.3) Calcd. C 59.76 H 4.39 N 3.90
Found C 59.65 H 4.44 N 3.75

(*E*)- and (*Z*)-3-Methoxycarbonyl-5-[2-[4-methoxy-3-(4-methoxycarbonylphenoxy)]-1-ethenyl]-isoxazole (11): Freshly sublimed potassium-t-butoxide (0.24 g, 2.1 mmol) was dissolved under argon in dry dimethyl sulphoxide (25 ml) and to this phosphonium salt **17** (1.0 g, 2.0 mmol) was added. After stirring for 15 min a solution of aldehyde **6** (0.29 g, 1.0 mmol) in dimethyl sulphoxide (5 ml) was added with a syringe to the deep yellow solution. After 24 h brine was added and the product extracted with ethyl acetate. Evaporation and chromatography (eluant toluene-2-butanone 10:1) gave **11** (0.34 g, 80%), m.p. 173-174 °C (from MeOH). - ^{1}H-NMR: δ= 3.83, 3.88, 3.95 and 3.97 (4xs, 9 H, OMe), 6.48 (s, 1 H, 4-H), 6.6-7.3 (m, 7 H, CH=CH, aromatic-H), 7.95 (d, J = 8 Hz, 2 H, 3",5"-H).

$C_{22}H_{19}NO_7$ (409.4) Calcd. C 64.54 H 4.68 N 3.42
Found C 64.41 H 4.73 N 3.73

3-Hydroxymethyl-5-[2-[4-methoxy-3-(4-hydroxymethylphenoxy)]-1-ethenyl]-isoxazole (16): A solution of diester **12** (1.23 g, 3.0 mmol) in dry tetrahydrofuran (50 ml) was added to a slurry of lithium aluminum hydride (0.5 g) in tetrahydrofuran (5 ml) at -5 °C. After decomposition of excess hydride with water and dilute hydrochloric acid, the mixture was evaporated, the residue extracted with ethyl acetate, the extract evaporated and the residue chromatographed (eluant toluene-ethyl acetate 2:1) to give **13** as an oil (0.95 g, 89%).- ^{1}H-NMR (60 MHz): δ= 2.98 (s, 4 H, CH_2CH_2), 3.82 (s, 3 H, OMe), 4.60 (s, 4 H, CH_2O), 5.90 (s, 1 H, 4-H), 6.6-7.0 (m, 5 H, aromatic-H), 7.28 (d, J = 8 Hz, 2 H, 3",5"-H).

$C_{20}H_{19}NO_5$ (353.4) Calcd. C 67.97 H 5.42 N 3.96
Found C 67.70 H 5.84 N 3.63

3-Bromomethyl-5-[2-[4-methoxy-3-(4-bromomethylphenoxy)]-ethyl]-isoxazole (14): To a solution of diol **13** (1.07 g, 3.0 mmol) in dry benzene (100 ml) phosphorus tribromide (0.87 g, 3.2 mmol) was added. After 24 h the solution was washed until neutral with water, dried and evaporated to give **14** as an oil (0.84 g, 58%). - ^{1}H-NMR (60 MHz): δ= 2.85 (s, 4 H, CH_2CH_2), 3.78 (s, 3 H, OMe), 4.33 and 4.47 (2xs, 4 H, CH_2Br), 5.98 (s, 1 H, 4-H), 6.7-7.0 (m, 5 H, aromatic-H), 7.32 (d, J = 8 Hz, 2 H, 3",5"-H).

$C_{20}H_{19}Br_2NO_3$ (481.2) Calcd. C 49.92 H 3.98 N 2.91
Found C 49.55 H 4.15 N 2.65

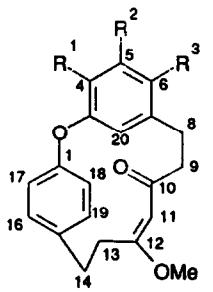
(Z)-12-Amino-4-methoxy-2-oxatricyclo[13.2.2.1^{3,7}]eicosa-3,5,7(20),11,15,17,18-heptaen-10-one (18): Into a flask containing a piece of sodium (about 0.5 g) and tetraphenylethene (0.20 g) tetrahydrofuran freshly distilled from sodium/benzophenone was introduced under argon through a short column filled with powdered 4A molecular sieve. The surface of the sodium was scratched with a spatula introduced through a septum. On striring the deep purple color of the radical anion appeared soon. Then a solution of the dibromide **14** (0.70 g, 1.45 mmol) and tetraphenylethene (0.20 g) was added dropwise at such a rate that the solution remained deep red. After completion of the addition stirring was continued for another hour followed by acidification, evaporation and chromatography of the residue (eluant toluene-ethyl acetate 2:1) to give **18** (90 mg, 16%) m.p. 220-221 °C (from MeOH), present as the enaminoketone. - ^{1}H-NMR (250 MHz): δ= 2.31, 2.35, 2.92 and 2.95 (4xtm, 8 H, CH_2), 3.93 (s, 3 H, OMe), 4.44 (s, 1 H, 11-H), 5.68 (d, J = 1.8 Hz, 1 H, 20-H), 6.67 (dd, J = 8.1 and 1.8 Hz, 1 H, 6-H), 6.73 (d, J = 8.1 Hz, 1 H, 5-H), 7.00 (d, J = 8.5 Hz, 2 H, 17,18-H), 7.15 (d, J = 8.5 Hz, 2 H, 17,18-H), 9.55 (br. s, nH). ^{13}C-NMR (62.5 MHz)δ= 14.1 (Me), 22.7, 27.8, 29.3, 31.9, 33.4, 38.6, 40.2, 56.2 (OMe), 99.7, 111.6, 113.6, 121.2, 123.3, 130.4. - MS (70 ev): *m/z* (%): 323 (100) /M^+/.

$C_{20}H_{21}NO_3$ (323.4) Calcd. C 74.28 H 6.55 N 4.33
Found C 74.35 H 6.50 N 4.51

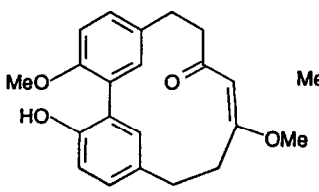
4-Methoxy-2-oxatricyclo[13.2.2.1^{3,7}]eicosa-3,5,7(20),15,17,18-hexaen-10,12-dione (19): Enaminoketone **18** (97 mg, 0.30 mmol) was stirred in 90% aqueous acetic acid (45 ml). Dissolution and hydrolysis was complete in 24 h. Evaporation gave **19** (95 mg, 98%), m.p. 103-105 °C (from MeOH) present in the enol form. ^{1}H-^{1}H NOEs: [irradiated proton : % enchancement (at)]: 6-H : 4.0 % (5-H), 3.4 % (8-H_2); 8-H_2 : 6.8 % (6-H), 3.4 % (9-H_2), 1.5 % (20-H); 14-H_2 : 4.4 % (13-H_2), 10.5 % (16, 19-H_2).

$C_{20}H_{20}O_4$ (324.4) Calcd. C 74.06 H 6.21
Found C 73.96 H 6.01

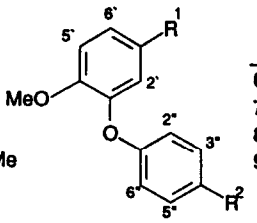
Methylation of 19: To a solution of diketone **19** (100 mg) in chloroform-methanol (1:1) a solution of diazomethane in chloroform generated from *N*-nitroso-*N*-methylurea (1.0 g) was added and after 24 h this treatment was repeated. After evaporation the products were subjected to layer chromatography (eluant: toluene ethyl acetate 2:1) to give (in decreasing order of R_f values) **1** m.p. 204-205 °C (lit.[1] 205-206 °C), **22** (colorless resin), **20** m.p. 165-167 °C (from MeOH), and **21** (33 mg), m.p. 131-133 °C (from MeOH).



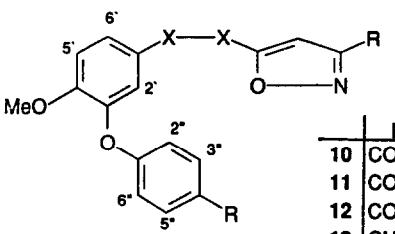
	R^1	R^2	R^3	
1	OMe	H	H	Garugamblin-1
2	OCH_2O		H	Garugamblin-2
3	OMe	H	OMe	Garuganin I
4	OMe	OMe	H	Garuganin III



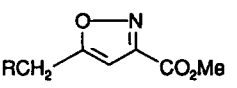
5 (Garuganin II)



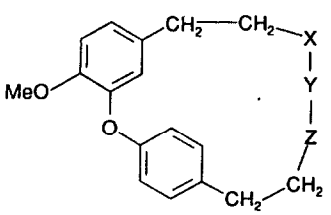
	R^1	R^2
6	CHO	CO_2Me
7	CH=CHCOMe	CO_2Me
8	$(CH_2)_2COMe$	CO_2Me
9	$(CH_2)_2COCH_2COCO_2Et$	CO_2Et

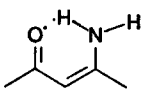
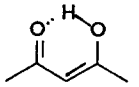
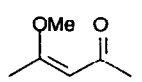
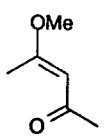


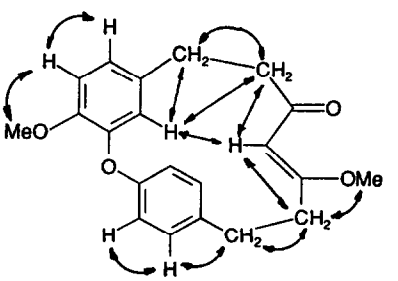
	R	X----X
10	CO_2Et	CH_2CH_2
11	CO_2Me	CH=CH
12	CO_2Me	CH_2CH_2
13	CH_2OH	CH_2CH_2
14	CH_2Br	CH_2CH_2



	R
15	H
16	Br
17	$P^+Ph_3.Br^-$



	X -- Y -- Z
18	
19	
20	
22	



21

20:	$C_{21}H_{22}O_4$ (338.4)	Calcd. C 74.53 H 6.55
		Found C 74.70 H 6.72
21:	$C_{21}H_{22}O_4$ (338.4)	Calcd. C 74.53 H 6.55
		Found C 74.66 H 6.41

Financial help by the Hungarian National Scientific Research Fund (OTKA grants no. 5.632 and 5.349) is gratefully acknowledged. Gy. M. K. thanks for a József Varga Foundation fellowship. A sample of natural garugamblin-1 was kindly provided by Prof. H. G. Krishnamurthy (New Delhi).

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