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Antiviral Activity of Some β-Diketones. 4. Benzyl Diketones. In Vitro Activity against Both RNA and DNA Viruses

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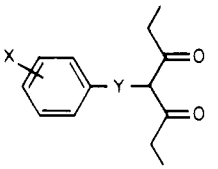
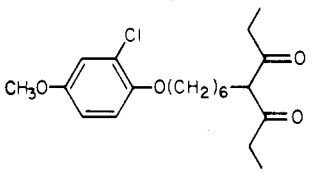
The synthesis and in vitro antiviral evaluation of a series of substituted benzyl β-diketones are described. The introduction of a styryl group onto the phenyl ring enhanced activity against herpesvirus type 2. The 4-methoxystyryl homologue 8 was evaluated extensively in vitro and was found to be effective against both RNA and DNA viruses. Compound 8 was evaluated in the mouse vagina against herpes simplex type 1 and produced a significant increase in survival rate as well as in survival time.

We have recently reported on the broad-spectrum in vitro antiviral activity of some β-diketones of the general structure I.[1,2] Several members in both of these series have



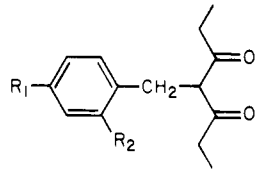
Ia, Y = $(CH_2)_n$
b, Y = $O(CH_2)_n$

exhibited activity against both DNA and RNA viruses, and one compound (II), designated as WIN 38,020, is currently



II

being considered for clinical trials against herpetic infections. This paper deals with the antiviral activity of a related series of compounds III where essentially the alkyl bridge in I has been replaced by a benzyl group.



III

Chemistry. The initial compound prepared in this series (**9**) was synthesized according to Scheme I. Ketone 1[3] was reduced with diborane in THF to give alcohol **2** in quantitative yield. The compound was not purified but treated directly with *p*-toluenesulfonic acid to give the stilbene **3**.[4] The ultraviolet absorption spectra of **3** exhibited peaks characteristic of *trans*-stilbenes (see the Experimental Section). Furthermore, GC analysis indicated the presence of only one component. Consequently, **3** was assigned the trans configuration. The reaction of **3** with cuprous cyanide gave **4** in excellent yield. The melting point of **4** was identical with that of the compound prepared by Dale[5] which was identified as the trans isomer. The nitrile **4** was hydrolyzed with ethanolic hydrogen chloride to give the ester **5** which was reduced with lithium aluminum hydride to alcohol **6**. Conversion of alcohol **6** with hydrogen bromide to **7** proceeded smoothly as did the alkylation of the lithium salt of heptanedione to produce **8**. Demethylation of **8** with boron tribromide gave **9** in 19% yield.

As our synthetic program progressed, an alternate and more direct synthetic approach was investigated and is shown in Scheme II. The phosphonate ester **10** was coupled with the appropriate aldehyde according to the procedure of Seus and Wilson[6] to give the *trans*-stilbenes **11**–**14** which were converted with NBS to bromides **15**–**17**.

The 2-chloro-4-methoxyphenyl homologue **23** was prepared by the procedure shown in Scheme III and was subsequently converted to **24**.

The reaction of 2-chloro-4-methoxyphenyldiazonium chloride with 4-methylcinnamic acid[7] gave **21** in 23.3% yield as a single component and was assigned the trans configuration on the basis of its UV spectra.

Compound **27** was prepared as described in Scheme IV.

The synthesis of compound **36** required several steps which are outlined in Scheme V. 4-Bromo-4′-methoxybenzophenone **28**[8] was converted to the nitrile **29** via treatment with cuprous cyanide in DMF. Hydrolysis of **29** with ethanolic hydrogen chloride provided ester **30** which was hydrogenated with 10% palladium on charcoal to the ester **31**. Acid **32**, obtained from **31** by hydrolysis with aqueous sodium hydroxide, was reduced with sodium in isoamyl alcohol producing a mixture of **33** and partially reduced material. This mixture was further reduced with 10% palladium on charcoal to give **33** as a cis–trans mixture. The next series of steps consisted of the reduction of **33** with diborane in THF followed by treatment of the resulting alcohol **34** with phosphorous tribromide and, finally, the reaction of bromide **35** with the lithium salt of 3,5-heptanedione to give **36** as a mixture of cis–trans isomers.

Compounds **43** and **44** were prepared according to the procedure outlined in Scheme VI and compounds **45**–**48**

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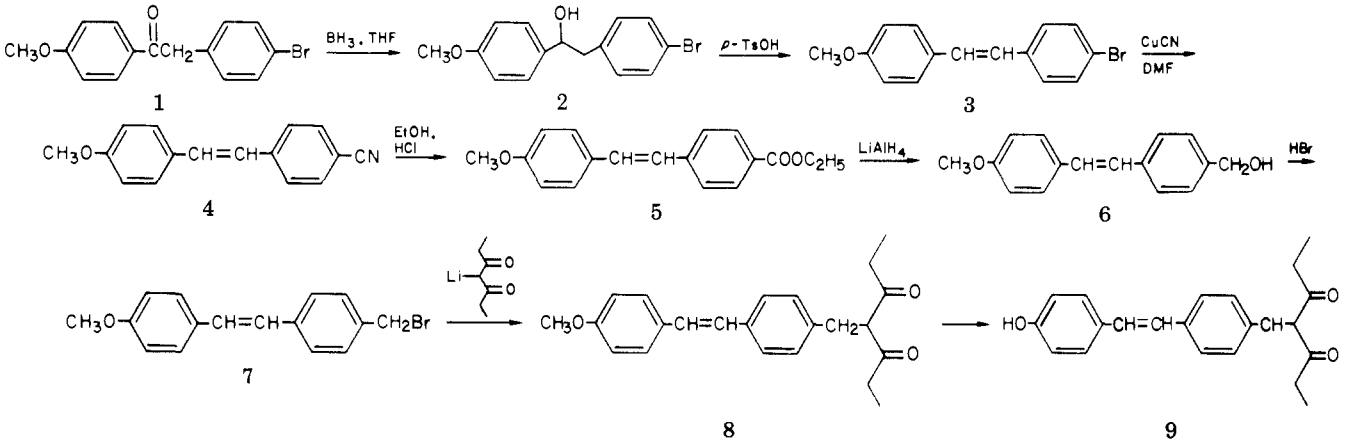
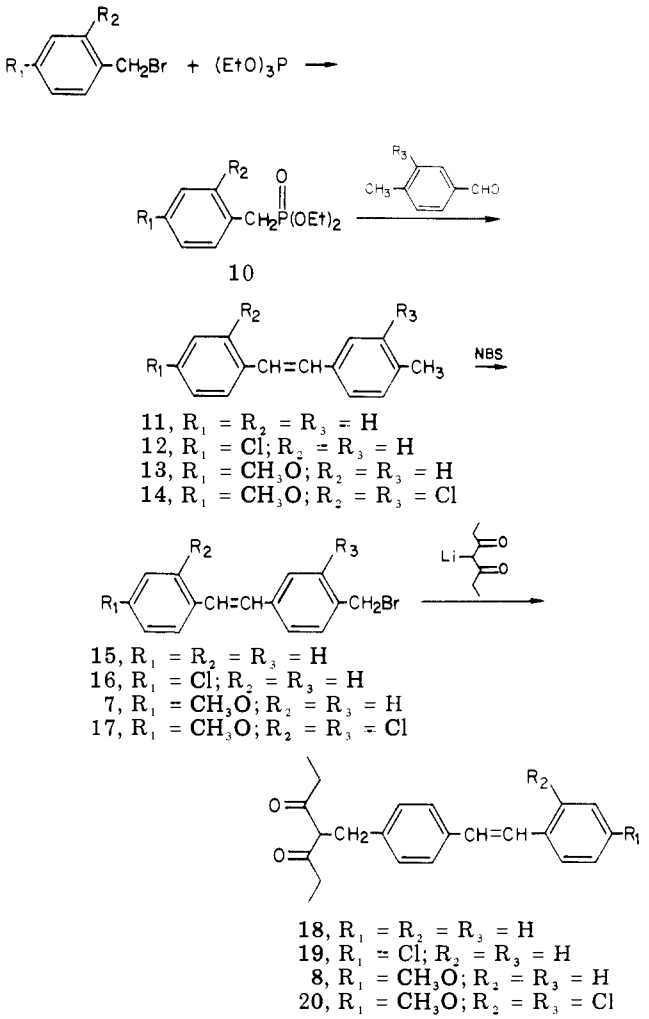
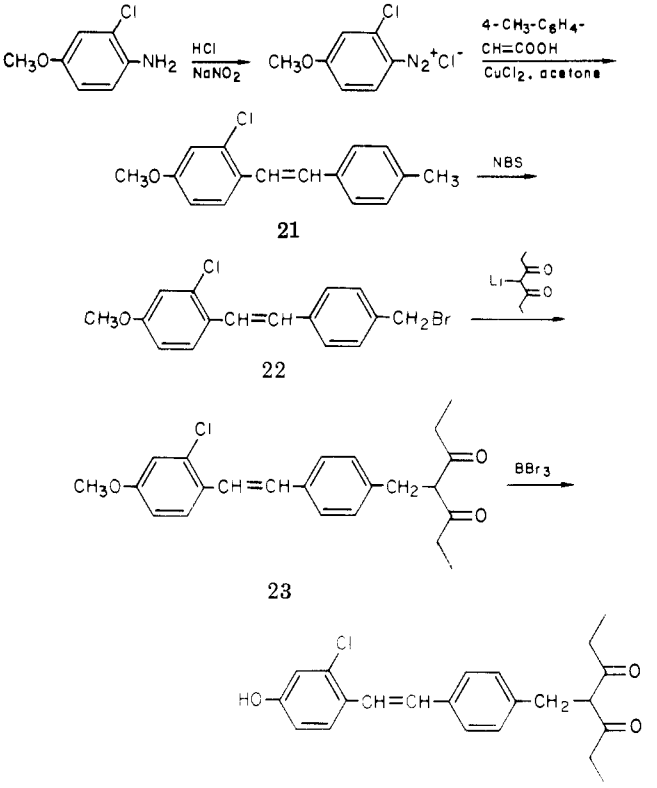
Scheme I



Scheme II



Scheme III



were prepared from the readily available bromides.

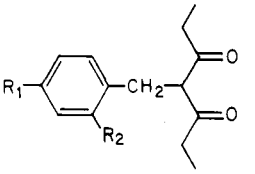
Biological Results. The compounds shown in Tables I and II were evaluated against herpesvirus type 2 according to the method previously described.[2a] The unsubstituted styryl homologue 18 as well as the 4-chlorophenyl compound 19 were devoid of activity at the levels tested. However, the 4-methoxy homologue 8 exhibited an MIC of 1.25 μg/mL. Replacement of the methoxy with a hydroxy (9) lowered activity as did the addition of a chloro group in the 2 position (23), although the levels of antiviral activity were still high. The introduction of a chlorine in the phenyl bridge, compound 20, destroyed activity. Reduction of the double bond in 8 produced a decrease in activity (compound 50).

The 4-methoxybenzyl homologue 44 was less active than the 4-methoxyphenethyl (50) and the 4-methoxyphenoxy compound 45. The remaining monophenyl homologues 46–49 were virtually inactive.

Two additional compounds (27 and 36) in Table II, with a cyclohexyl bridge, exhibited an MIC of 6 μg/mL.

Compound 8 was evaluated against a wide range of viruses (Table III) and exhibited in vitro activity against both DNA and RNA viruses when screened in the tissue culture test with rhinovirus being particularly susceptible. No activity was observed in the organ culture test against influenza A_2 Jap 170 at the levels tested. However, significant activity was demonstrated against equine rhinovirus. Because of its high in vitro activity against herpesvirus type 1, compound 8 was evaluated in vivo against herpes simplex virus type 1 (Sheely strain) in the mouse by intravaginal administration.[9,10] The results shown in Table IV indicate that mice treated with a suspension of 10% of compound 8 in 1% gum tragacanth

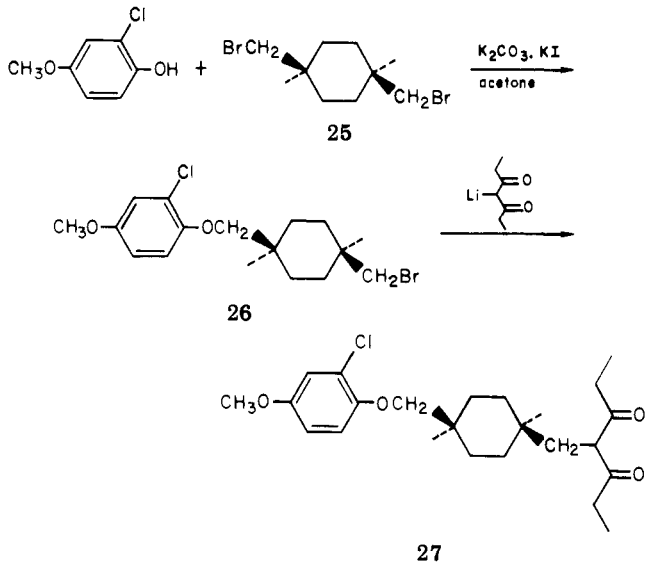
Table I. Chemical and Antiviral Properties of Aryl Diketones



compd	R_1	R_2	mp or bp (mm), °C	% yield[a]	recrystn solvent	formula	MIC, μg/mL (HSV-2)
8	4-$CH_3OC_6H_4CH$=CH-	H	113-115	67.8	Et_2O	$C_{23}H_{26}O_3$	2.5-1.25
9	4-HOC_6H_4CH=CH-	H	166-167	19.0	CH_3CN	$C_{22}H_{24}O_3$	3-1.5
18	C_6H_5CH=CH-	H	106-107	56.1	CH_3OH	$C_{22}H_{24}O_2$	inact
19	4-ClC_6H_4CH=CH-	H	132-133	39.6	CH_3CN	$C_{22}H_{23}ClO_2$	inact
20	2-Cl-4-$CH_3OC_6H_3CH$=CH-	Cl	89-90	75.5	CH_3OH-Et_2O	$C_{23}H_{24}Cl_2O_3$	inact
23	2-Cl-4-$CH_3OC_6H_3CH$=CH-	H	93-95	82.8	CH_3OH	$C_{23}H_{25}ClO_3$	3-1.5
24	2-Cl-4-HOC_6H_3CH=CH-	H	124-125	54.4[b]	CH_3OH	$C_{22}H_{23}ClO_3$	3-1.5
43	$C_6H_5CH_2$-	H	160 (0.04)	59.5		$C_{21}H_{24}O_2$	12-6
44	4-$CH_3OC_6H_4CH_2$-	H	197-199 (0.04)	64		$C_{22}H_{26}O_3$	12-6
45	4-$CH_3OC_6H_4O$-	H	182-186 (0.05)	57		$C_{21}H_{24}O_4$	6-3
46	CH_3O-	Cl	143-144 (0.03)	87		$C_{15}H_{19}ClO_3$	50
47	CH_3O-	H	116-117 (0.01)	25.6		$C_{15}H_{20}O_3$	inact
48	CH_3-	H	110-112 (0.02)	43		$C_{15}H_{20}O_2$	inact
49	HO-	H	95-96	37[e]	CH_3OH	$C_{14}H_{18}O_3$	inact
50	4-$CH_3OC_6H_4(CH_2)_2$-	H	190-196 (0.08)	31[c]		$C_{23}H_{28}O_3$	6-3
51	4-$HOC_6H_4CH_2$-	H	65-66	26[d]	hexane-Et_2O	$C_{21}H_{24}O_3$	6-3

[a] Based on immediate precursor. [b] Prepared by demethylation of **23**; see the Experimental Section. [c] Prepared by the reduction of **8** with 10% Pd/C. [d] Prepared by demethylation of **44**; see the Experimental Section. [e] Prepared by demethylation of **47**.

Scheme IV



had higher survival rates over the placebo-treated controls. After 14 days, 60% of the animals survived in the group treated with 10% of **8**, 50% in the group treated with 5% of **8**, and 40% in placebo-treated controls. A delay in deaths was observed for both groups of animals treated with 5 and 10% of compound **8** where the average survival time was >11.4 and >11.3 days, respectively, while the average survival time for the placebo-treated controls was >10.7 days.

The carryover of activity from an in vitro to in vivo system is governed by many factors, one of which is the ability of the drug to penetrate. Although compound **8** did produce a positive effect when applied intravaginally to the mouse, the effect was not as dramatic in the test as one would have expected in view of the high in vitro activity demonstrated by the compound. The use of other vehicles to deliver the drug in a more efficient manner is currently under investigation.

Experimental Section

Melting points were run according to the USP procedure and are uncorrected. Where analyses are indicated only by symbols of the elements, analytical results are within ±0.4% of the theoretical values. Analyses were performed by Instranal Laboratories, Rensselaer, N.Y. NMR spectra were determined on a Varian A-60 spectrophotometer and the mass spectra on a

Scheme V

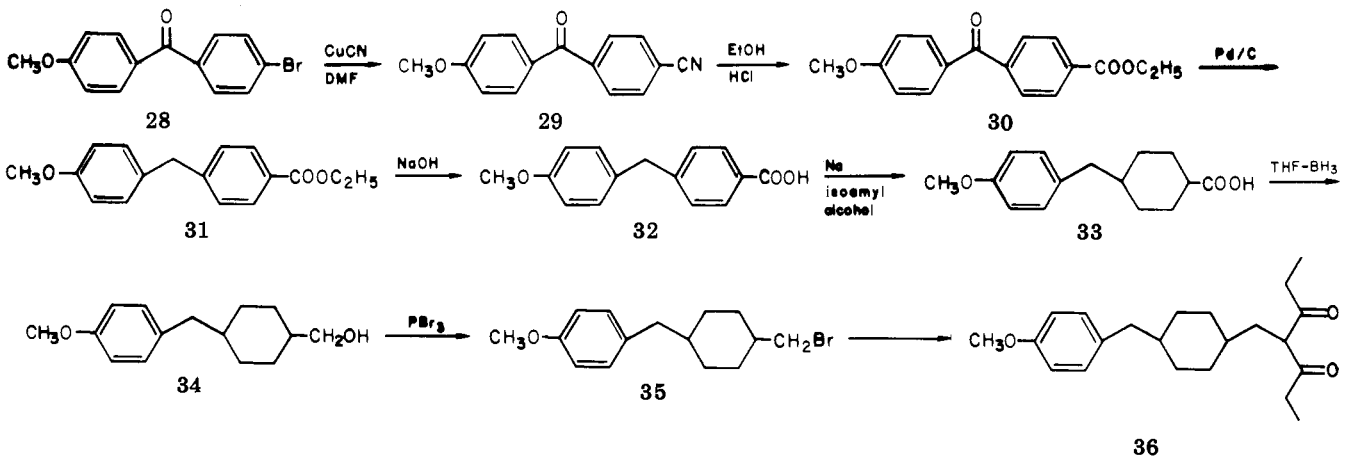
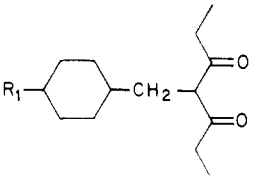


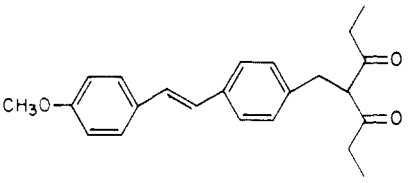
Table II



compd	R	mp or bp (mm), °C	% yield[a]	recrystn solvent	formula	MIC, μg/mL (HSV-2)
27	2-Cl-4-$CH_3OC_6H_3OCH_2$-	60-62	24	cyclohexane-C_2H_5OH	$C_{22}H_{31}ClO_4$	12-6
36	4-$CH_3OC_6H_4CH_2$-	182-186 (0.02)	37		$C_{22}H_{32}O_3$	12-6

[a] Based on immediate precursor.

Table III. 4-[[4-[2-(4-Methoxyphenyl)ethenyl]phenyl]methyl]-3,5-heptenedione

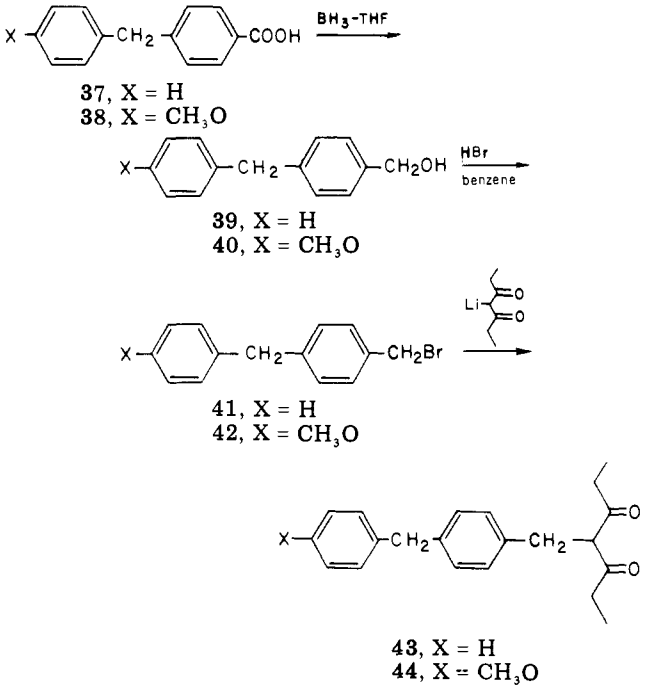


8

in vitro

tissue culture			organ culture			
virus	type	MIC, μg/mL	virus	tissue	concn, μg/mL	% redn in virus yield
human rhino type 2	RNA	0.7-0.2	influenza	ferret	25	0
type 17	RNA	3-0.3	A_2 Jap 170	trachea	50	0
equine rhino	RNA	0.5-0.06	equine	monkey	25	1.7 log
parainfluenza type 3	RNA	6-3	rhino	trachea	50	2.0 log
resp syncytial	RNA	3-1.5				
herpes simplex type 1	DNA	1.5-0.7				
type 2	DNA	2.5-1.25				

Scheme VI



37, X = H
38, X = CH_3O
39, X = H
40, X = CH_3O
41, X = H
42, X = CH_3O
43, X = H
44, X = CH_3O

Jeolco double-focusing high-resolution mass spectrometer by S. Clemans.

In Vivo Antiherpetic Evaluation. The in vivo evaluation of compound 8 against herpes simplex virus type 1 (Sheely strain) was performed in the mouse by intravaginal administration.

Table IV. Effect of Compound 8 Intravaginally Administered on the Survival of Mice Infected with Herpes Simplex Type 1

daily dose[a] b.i.d., %	% survival	av survival time, days
10	60	>11.4
5	50	>11.3
placebo	40	>10.7

[a] Medication applied 4 h postinfection.

Thirty Blue Spruce mice weighing 11–13 g were infected intravaginally with approximately 100 000 $TCID_{50}$ of virus per mouse. Compound 8 was prepared as a 10 and 5% suspension in 1% gum tragacanth and 5% Tween 80 in water. Four hours after infection, groups of ten mice were treated with each concentration of compound 8 and placebo vehicle. The treatment consisted of inserting into the vagina a cotton tampon (approximately 3 mm diameter) saturated with a suspension of compound in the placebo vehicle. Cotton tampons were left inserted for 24 h and a second treatment was given 6 h later by adding 0.02 mL of the drug suspension or placebo into the inserted tampon. Freshly impregnated cotton tampons were inserted every 24 h and a second treatment followed 6 h later. The treatment was carried out for 7 days. Surviving animals were kept for 14 days postinfection and deaths recorded daily.

(*E*)-4-**Bromo-4'-methoxystilbene** (3). A suspension of 127 g (0.46 mol) of 2-(4-bromophenyl)-4-methoxyacetophenone (1) in 200 mL of THF was cooled to 0 °C and 170 mL of 1 M BH_3–THF (0.17 mol) was added dropwise over a 15-min period. The mixture was stirred for an additional 4 h at 0 °C and then 200 mL of 2 N HCl was added dropwise. The organic layer was separated, washed with a saturated $NaHCO_3$ solution, and dried. Removal of the solvent gave 135 g of an oil which was dissolved

in 750 mL of benzene. *p*-Toluenesulfonic acid (100 mg) was added and the solution refluxed using a water separator for 4 h. After the separation of H_2O had ceased, the solution was cooled to 20 °C and filtered to give 82 g of material which was recrystallized from ethyl acetate: mp 177–179 °C; UV λ_{max} (95% C_2H_5OH) 231 nm (ε 13 200), 293 (shoulder) (13 600), 308 (27 200), 325 (29 800). Anal. ($C_{15}H_{13}BrO$) C, H, Br.

(*E*)-4-Cyano-4′-methoxystilbene (4). A mixture of 82 g (0.285 mol) of bromide **3** and 36 g (0.40 mol) of CuCN in 55 mL of DMF was heated to reflux for 1.5 h and then poured into a warm solution of 230 mL of H_2O, 39 mL of concentrated HCl, and 155 g of $FeCl_3$–H_2O. The mixture was allowed to come to room temperature and then 1 L of $CHCl_3$ was added. The mixture was filtered through filtercell and the layers were separated. The $CHCl_3$ layer was washed with H_2O and dried. Removal of the solvent gave 67 g (quantitative) of **4**, mp 135–140 °C (lit.[5] 143–143.5 °C).

Ethyl 4-[2-(4-Methoxyphenyl)ethenyl]benzoate (5). A solution of 67 g (0.285 mol) of **4** in 1 L of ethanolic HCl (5 N) was heated to reflux for 8 h. An additional 100 mL of 10 N ethanolic HCl was added and the solution heated under reflux for an additional 18 h; 2 L of H_2O was added and the resulting solid was collected and dried. The material was recrystallized from C_2H_5OH and produced 73 g (91%), mp 141–142 °C. Anal. ($C_{18}H_{18}O_3$) C, H.

(*E*)-4-[2-(4-Methoxyphenyl)ethenyl]benzenemethanol (6). To a slurry of 12 g (0.317 mol) of $LiAlH_4$ in 300 mL of THF was added 67 g (0.235 mol) of **5** in 600 mL of THF at such a rate to maintain gentle reflux. After the addition was complete, the mixture was heated under reflux for an additional 1 h and then filtered through a steam-heated Büchner funnel. The solid was washed several times with hot THF. The filtrate was concentrated in vacuo leaving a solid residue which was recrystallized from EtOAc to give 55 g (96%), mp 200–202 °C. Anal. ($C_{16}H_{16}O_2$) C, H.

Diethyl (2-Chloro-4-methoxyphenyl)methylphosphonate (10, R_1 = CH_3O; R_2 = Cl). A mixture of 1-bromomethyl-2-chloro-4-methoxybenzene[11] (67.0 g, 0.286 mol) and 50 g (0.3 mol) of triethyl phosphite was heated with stirring and CH_3CH_2Br was evolved rapidly. Heating was continued for 1 h at 120–130 °C and the material distilled to give 69.9 g (84%) of the desired material, bp 140–144 °C (0.3 mm). Anal. ($C_{12}H_{18}ClO_4P$) C, H, Cl.

(*E*)-2,3′-Dichloro-4-methoxy-4′-methylstilbene (14). A 50% dispersion of NaH in oil (7.4 g, 0.154 mol) was suspended in 180 mL of dry DMF. Absolute CH_3OH (6.5 mL) was added all at once. When hydrogen evolution had ceased, 45.1 g (0.154 mol) of **10** was added and the solution was cooled to 5 °C. A solution of 3-chloro-4-methylbenzaldehyde[12] (23.7 g, 0.154 mol) in 20 mL of dry DMF was added in small portions with stirring below 35 °C. Considerable foaming occurred. The mixture was stirred at 28 °C for an additional 15 min after the addition was complete and then poured into 1 L of H_2O. An oil separated which solidified rapidly. The solid was collected and taken up in CH_2Cl_2, and the organic layer was extracted with H_2O and dried. Removal of the solvent produced an oil which solidified on cooling and which was recrystallized from EtOH. **14** (27.8 g, 61.5%) was obtained: mp 77–79 °C; UV λ_{max} (95% EtOH) 212.5 nm (ε 24 859), 257.5 (16 127), 310 (29 898), 321 (shoulder) (27 949). Anal. ($C_{16}H_{14}Cl_2$) C, H.

(*E*)-4′-Bromomethyl-2,3′-dichloro-4-methoxystilbene (17). A mixture of (*E*)-2,3′-dichloro-4-methoxy-4′-methoxystilbene (**14**) (27.8 g, 0.0948 mol), *N*-bromosuccinimide (17.8 g, 0.1 mol), benzoyl peroxide (0.5 g), and 250 mL of CCl_4 was refluxed with stirring for 6 h and filtered, and the filtrate was concentrated in vacuo to a solid. The solid was recrystallized from cyclohexane to give 23.0 g (65.3%) of **17**: mp 106–108 °C; UV λ_{max} (95% EtOH) 228.5 nm (ε 15 554), 318.5 (shoulder) (30 631), 327 (31 904). Anal. ($C_{16}H_{13}BrCl_2O$) C, H.

(*E*)-4-[[4-[2-(2-Chloro-4-methoxyphenyl)ethenyl]-2-chlorophenyl]methyl]-3,5-heptanedione (20). Lithium hydride (0.8 g, 0.1 mol) was suspended in 75 mL of dry DMF and a solution of 3,5-heptanedione (15.9 g, 0.124 mol) in 30 mL of dry DMF was added with stirring over a period of 1 h. After all of the LiH had dissolved, 23.0 g (0.0617 mol) of **17** was added all at once and the resulting solution was stirred at 80 °C for 3 h and then poured into 1 L of H_2O. The mixture was acidified with dilute HCl and extracted three times with CH_2Cl_2 and the extract was washed twice with H_2O. The organic layer was dried and the solvent removed in vacuo leaving an oil which solidified when triturated with CH_3OH. The solid was recrystallized from CH_3OH–Et_2O to give 19.5 g (75.5%) of **20**, mp 89–90 °C. Anal. ($C_{23}H_{24}Cl_2O_3$) C, H, Cl.

(*E*)-2-Chloro-4-methoxy-4′-methylstilbene (21). A mixture of 2-chloro-4-methoxyaniline (62.5 g, 0.4 mol), 20 mL of H_2O, and 120 mL of concentrated HCl was heated to boiling and cooled to 5 °C in ice, then 500 g of ice was added, and the mixture was stirred vigorously while a solution of $NaNO_2$ (28 g, 0.405 mol) in 50 mL of H_2O was added dropwise. After 1.5 h almost all of the aniline HCl had dissolved. The solution was filtered and $NaOAc·3H_2O$ (88 g, 0.788 mol) was added. A suspension of 4-methylcinnamic acid (59.8 g, 0.369 mol) in 1200 mL of CH_3COCH_3 was added, followed by $CuCl_2·2H_2O$ (20 g, 0.119 mol). Vigorous gas evolution occurred and solid began to separate. After stirring for 6 h, the mixture was allowed to stand overnight and then diluted to 4 L with H_2O. The solid was collected and the filtrate extracted with CH_2Cl_2. The extracts were concentrated to a semisolid which was combined with the solid originally collected and stirred with dilute NH_4OH. After filtration, the solid was stirred with dilute HCl, H_2O, and, finally, with 100 mL of CH_3OH. After filtration, the solid was recrystallized from CH_3CN to give 22.3 g (23.3%) of the desired material: mp 153–154 °C; UV λ_{max} (95% EtOH) 293 nm (ε 29 272), 300 (shoulder) (26 974), 320 (shoulder) (16 056), 331 (shoulder) (11 881). Anal. ($C_{16}H_{15}ClO$) C, H.

(*E*)-4-[[4-[2-(2-Chloro-4-hydroxyphenyl)ethenyl]-phenyl]methyl]-3,5-heptanedione (24). A solution of 16.8 g (0.0436 mol) of (*E*)-4-[[4-[2-(2-chloro-4-methoxyphenyl)-ethenyl]phenyl]methyl]-3,5-heptanedione (**23**) in 400 mL of CH_2Cl_2 was cooled to −78 °C, and a solution of 32.8 g (0.13 mol) of BBr_3 in 30 mL of CH_2Cl_2 was added dropwise with stirring over a 15-min period. The mixture was allowed to come to room temperature during 2 h and stirred for an additional 1 h. The solution was poured into 1500 mL of H_2O and stirred vigorously for 1 h. The H_2O was decanted, 1500 mL of H_2O and 50 mL of CH_3OH were added, and, after stirring for 0.5 h, the layers were separated. The CH_2Cl_2 layer was concentrated in vacuo to a solid which was recrystallized from CH_3OH giving 8.8 g (54.4%) of the desired product, mp 124–125 °C. Anal. ($C_{22}H_{23}ClO_3$) C, H, Cl.

4-[4-(4-Hydroxyphenylmethyl)phenylmethyl]heptane-3,5-dione (51). A solution of 26 g (0.077 mol) of **44** in 160 mL of CH_2Cl_2 was stirred at −65 °C while BBr_3 (29 g, 0.12 mol in CH_2Cl_2, 160 mL) was added dropwise.[13] At the end of the addition, the cooling bath was removed and stirring at ambient temperature was continued for 3 h. Ice water (500 mL) was then added and the mixture was stirred 0.5 h. The CH_2Cl_2 layer was separated, washed with saturated Na_2CO_3, dried ($MgSO_4$), and concentrated in vacuo to give an oil. This oil was partitioned between Et_2O (300 mL) and H_2O (300 mL) and shook until only two phases remained. The Et_2O layer was separated, washed with saturated $NaHCO_3$, dried ($MgSO_4$), and concentrated to give an oil (22 g). This oil was placed on a SiO_2 (1 kg) column packed wet with EtOAc–hexane (1:4) and eluted with the same solvent in 500-mL fractions. Fractions 7–15 were combined and concentrated to give an oil (17.5 g). This material was crystallized from hexane–Et_2O to give the desired product (6.5 g, 26%), mp 65–66 °C.

(*E*)-1-Bromomethyl-4-(2-chloro-4-methoxyphenoxymethyl)cyclohexane (26). A mixture of 162 g (0.6 mol) of *trans*-bis(1,4-bromomethyl)cyclohexane (**25**),[14] 23.8 g (0.15 mol) of 2-chloro-4-methoxyphenol,[15] 62.1 g (0.45 mol) of K_2CO_3, and 3 g (0.018 mol) of KI in 1000 mL of $CH_3COCH_2CH_3$ was heated to reflux for 24 h. The mixture was filtered and the filtrate concentrated to dryness in vacuo. The residue was partitioned between H_2O and CH_2Cl_2, and the organic layer was separated and dried. After removal of the solvent, the residual solid was recrystallized from Et_2O to give 33.8 g (60.5%) of **26**, mp 75–78 °C. Anal. ($C_{15}H_{20}BrClO_2$) C, H, Br.

4-(4-Methoxybenzoyl)benzonitrile (29). A mixture of 4-bromo-4′-methoxydiphenyl ketone (**28**) (48 g, 0.165 mol), CuCN (18 g, 0.20 mol), and DMF (30 mL) was stirred and heated under reflux for 3 h and then poured into a solution of $FeCl_3·6H_2O$ (80 g) in H_2O (120 mL) containing concentrated HCl (20 mL). This mixture was then heated at 60–70 °C for 0.25 h and cooled, and

EtOAc (800 mL) was added. The resulting mixture was filtered and the EtOAc layer was separated, washed with H_2O (3 × 500 mL), dried ($MgSO_4$), and concentrated to dryness to give the desired product (33.5 g, 85%), mp 131–132 °C. Anal. ($C_{15}H_{11}NO_2$) C, H.

Ethyl 4-(4-Methoxybenzoyl)benzoate (30). A mixture of 5 g (0.021 mol) of **29** and 30 mL of 5 N ethanolic HCl was heated under reflux for 5 h and concentrated in vacuo. The residue was partitioned between 2 N HCl and EtOAc, and the EtOAc layer was separated, dried ($MgSO_4$), and concentrated to dryness to give an oil (6 g). Crystallization of this oil from EtOH gave the desired product (3.1 g, 52%), mp 82–84 °C. Anal. ($C_{17}H_{16}O_4$) C, H.

Ethyl 4-[(4-Methoxyphenyl)methyl]benzoate (31). To a solution of ethyl 4-(4-methoxybenzoyl)benzoate (**30**) (2.8 g, 0.010 mol) in ethanol (200 mL) was added 10% Pd/C (0.5 g). The mixture was hydrogenated on a Parr apparatus under 45 psi of H_2 for 3 h at ambient temperature and 2 h at 50–60 °C. The mixture was cooled, the catalyst was removed, and the solution was concentrated to dryness to give an oil which slowly crystallized (2.5 g, 92%). Recrystallization from cold pentane gave an analytical sample, mp 44–45 °C. Anal. ($C_{17}H_{18}O_3$) C, H.

4-[(4-Methoxyphenyl)methyl]benzoic Acid (32). A mixture of ethyl 4-[(4-methoxyphenyl)methyl]benzoate (**31**) (22 g, 0.081 mol), 2 N NaOH (aqueous, 100 mL), and EtOH (50 mL) was heated with stirring under reflux 0.5 h. After the mixture was cooled, water (200 mL) was added and the resulting solution was washed with Et_2O and made acidic with 2 N HCl (aqueous, 110 mL) to give a solid as the desired product (17.7 g, 90%), mp 147–149 °C. The analytical sample was recrystallized from EtOH–H_2O, mp 152–153 °C. Anal. ($C_{15}H_{14}O_3$) C, H.

4-[(4-Methoxyphenyl)methyl]cyclohexane-1-carboxylic Acid (33). A solution of 17.7 g (0.073 mol) of **32** in isoamyl alcohol (325 mL) was heated under reflux with stirring in a 2-L flask while sodium (39 g, 1.7 mol) was added over a 0.5-h period. The mixture was then heated under reflux 3 h and cooled, and H_2O (500 mL) was added. The isoamyl alcohol was steam distilled out of the reaction mixture, concentrated HCl (180 mL) was added to the aqueous residue, and the resulting mixture was extracted with Et_2O. The Et_2O extract was dried ($MgSO_4$) and concentrated to dryness to give an oil which partially crystallized (16 g). Mass spectral analysis showed the desired M^+ 248 along with about 40% M^+ 246, indicating the presence of some partially reduced material. Therefore, some of the product (5 g) was dissolved in EtOH (200 mL) to which 10% Pd/C (0.5 g) was added, and this mixture was hydrogenated on a Parr apparatus at ambient temperature under 45 psi of H_2 for 1 h. The catalyst was removed and the solution was concentrated to dryness to give an oil which became semisolid (5 g). Anal. ($C_{15}H_{20}O_3$) C, H.

The VPC analysis of the methyl ester (prepared from MeOH and H_2SO_4) of this semisolid on an OV_1 column at 230 °C showed two compounds to be present in a 1:3 ratio, presumably the cis and trans isomers.

4-[[(4-Methoxyphenyl)methyl]cyclohexyl]methanol (34). A solution of **33** (34 g, 0.13 mol) in THF (77 mL) was stirred in an ice bath while 1 M BH_3 in THF (180 mL, 0.180 mol) was added slowly during 0.5 h. The mixture was stirred at ambient temperature for 1 h and then 2 N HCl (aqueous, 50 mL) was added cautiously. Concentration of the reaction mixture to dryness gave a semisolid which was partitioned between H_2O and Et_2O. The Et_2O layer was separated, washed with 2 N NaOH (aqueous, 2 × 50 mL), dried ($MgSO_4$), and concentrated to dryness to give an oil (27 g) which was vacuum distilled to give the product (25.4 g, 83%), bp 132–136 °C (0.03 mm). A small portion was crystallized from cyclohexane to give an analytical sample, mp 68–70 °C. Anal. ($C_{15}H_{22}O_2$) C, H.

4-[4-[(4-Methoxyphenyl)methyl]cyclohexylmethyl]heptane-3,5-dione (36). A solution of **34** (23.4 g, 0.10 mol) in benzene (75 mL) was stirred and cooled in an ice bath at −5 to 5 °C while PBr_3 (10 g, 0.37 mol) was added dropwise in 0.5 h. Stirring at −5 to +5 °C was continued 1.5 h and at ambient temperature for 3 days. Ether (100 mL) and H_2O (50 mL) were added; then 2 N NaOH (aqueous, 50 mL) was slowly added with cooling. The organic layer was separated, washed with 2 N NaOH (aqueous), dried ($MgSO_4$), concentrated to dryness, and distilled to give the desired bromide (17.5 g), bp 126–128 °C (0.03 mm). The bromide (17.5 g, 0.065 mol) was combined with sodium iodide (11 g, 0.073 mol) and acetone (100 mL) and heated under reflux 2 h. The reaction mixture was concentrated to dryness, taken up in H_2O, and extracted with Et_2O. The Et_2O extract was dried ($MgSO_4$) and concentrated to dryness to give the iodide (19.8 g) as an oil.

This iodide (19.8 g, 0.058 mol) was combined with lithium heptane-3,5-dione (13 g, 0.097 mol) and DMF (150 mL) and stirred at 80 °C for 2 days. The mixture was concentrated to dryness, Et_2O (300 mL) was added, and the mixture was filtered. The filtrate was washed with H_2O (2 × 300 mL) and dried. Removal of the solvent gave an oil (19 g). Vacuum distillation yielded the pure desired product (12.7 g, 37%), bp 82–86 °C (0.02 mm). Anal. ($C_{22}H_{32}O_3$) C, H.

References and Notes

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