preference for a pseudo-axial orientation of the C7 substituent is a result of avoidance of in-plane steric interference between the *p*-chlorophenyl and phenoxycarbonyl substituents. This crystal picture of 1,2-dihydropyridine (**2**) is consistent with the high stereoselectivity observed for dienophilic attack upon other 1,2-dihydropyridines (**1**) in solution.[3,7,8]

Experimental Section

1-(Phenoxycarbonyl)-2-(*p*-chlorophenyl)-4,5-dimethyl-1,2-dihydropyridine (**2**) was prepared by the established procedure.[13] Recrystallization from 2-propanol afforded white crystals, mp 113–114 °C (lit, 111–114 °C), circular dichroism (1.6 mg in 10 mL of absolute ethanol) $[\theta]_{300nm} = 8700$, $\Delta\epsilon = 2.636$. Crystals of **2** suitable for X-ray analysis were obtained by slow evaporation from methylene chloride. A suitable single crystal was mounted with epoxy on a glass fiber for diffraction work. Table I details the crystal data. Intensity data were collected at 293 K with an Enraf-Nonius CAD4 diffractometer using graphite single-crystal monochromated Mo Kα radiation ($\lambda = 0.71073$ Å; takeoff angle = 2.8°). A variable scan speed ω–2θ scan technique ($d\omega/d\theta = 2.0$), as suggested by peak shape analysis, was employed to collect 1728 unique intensity measurements in the range $2° \leq 2\theta \leq 50°$ ($^{+}h,^{+}k,^{+}l$). The minimum and maximum scan speeds (in ω) were 2.5° and 6.7° min^{-1}, respectively. Background measurements were obtained at each end of the scan range using a moving crystal–moving counter technique (scan time/background time = 2.0). Three standard reflections were measured every 3 h of X-ray exposure time. A plot of these standard intensities indicated no crystal decay during data collection. The data were corrected for Lorentz-polarization effects but not for absorption effects.

After rejection of systematically absent reflections and averaging of equivalent observations, 1628 measured intensities remained. Of these 1036 were deemed observed ($I \geq 3\sigma(I)$) and were used in the final least-squares treatments.

The structure was solved by direct methods using the program MULTAN.[20] Data were converted to normalized structure factor amplitudes and 216 E values ($E_{min} = 1.437$) were used for determining phases of reflections for the structural model development. An E-map calculated from the phase set with the highest combined figure of merit gave starting positions for all non-hydrogen atoms. Refinement of these positions along with isotropic thermal parameters afforded the values of the standard agreement factors: $R = \sum||F_o| - |F_c||/\sum|F_o| = 11.4\%$; $R_w = [\sum w(|F_o| - |F_c|)^2/\sum w(F_o)^2]^{1/2} = 11.1\%$, where the weights were initially defined as unity (isotropic refinement) and were eventually defined as $\omega = 1/\sigma(F_o)^2$ with $\sigma(F_o)^2 = [\sigma(I)^2 + (pF_o)^2]^{1/2}$ and $p = 0.05$ (final refinement). All least squares treatments were full matrix on F; the function minimized was $\omega(|F_o| - |F_c|)^2$. After refinement of all non-hydrogen atoms with anisotropic librational parameters a difference Fourier calculation next revealed positions for all hydrogen atoms. The hydrogen atoms were assigned isotropic thermal parameters (5.0, as suggested by a Wilson plot) and only their positions were allowed to vary in the final cycles of the refinement. The model used in the final cycle contained 24 atoms (anisotropic), 18 hydrogens, 270 variables and 1036 observations. Refinement converged to $R = 0.037$ and $R_w = 0.045$ with no non-hydrogen atom parameter shifting by more than 0.03 times its estimated standard deviation. The maximum corresponding shift for hydrogen atoms was 0.08 times it esd except H3C12 which shifted 0.18 times its esd in the final cycle. The goodness of fit was 1.157. An extinction coefficient was not refined. A final difference Fourier synthesis was featureless with no peaks of height greater than one-third of the height of a hydrogen atom. A plot of the function minimized vs. $(\sin\theta)\lambda^{-1}$ showed no significant trends. Values of the neutral atom scattering factors were taken from ref 21 as were the values of F' and F'' for anomalous dispersion, the effects of which were included in the refinement. Hydrogen atom scattering factors used were those of Stewart, Davidson, and Simpson.[22]

There are no unusually short intermolecular interactions; the intermolecular distances correspond to van der Waals interactions. The two phenyl systems are planar and show no unusual bonding features.

Acknowledgment. We thank the National Cancer Institute, DHEW, CA 24596, and Temple University for financial support.

Supplementary Material Available: Complete tables of bond distances, bond angles, torsional angles, calculated least squares planes, a figure showing packing of the molecules in the unit cell, additional tables listing all atomic positional and thermal parameters, root mean square amplitudes of thermal vibration, intermolecular distances and angles, and values of F_o and F_c (31 pages). Ordering information is given on any current masthead page.

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Artificial Receptor Recognizing Hydrophobic Carbonyl Compounds

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Hydrophobic recognition by cyclodextrin cavities in an aqueous solution is most effective for hydrophobic guests of appropriate sizes and shapes.[1] The large "recognition free energy change" ($-\Delta G$) associated with the best van der Waals contact and with maximum elimination of structured water along the guest surface,[2] is mainly responsible for this moderately sharp substrate specificity. An additional recognition element such as metal coordination enhances total $-\Delta G$ where the component recognition free energies (hydrophobic and metal coordination) are nearly additive (eq 1).[3] Therefore "artificial receptor" molecules

$$(-\Delta G)_T = (-\Delta G)_{\text{hydrophobic}} + (-\Delta G)_{\text{coordination}} \quad (1)$$

with a sophisticated capacity to recognize particular selected guests may be conveniently designed on the basis of the concept of multiple recognition.[4] This type of approach may lead to *artificial affinity column chromatography* based on appropriate molecular design. Prostaglandins like other transmitters and/or modulators, are known to bind to their corresponding native receptors via multiple recognition and therefore seem to be appropriate target substrates to be bound to a designed artificial receptor via multiple recognition.

We now wish to report that hydrophobic carbonyl compounds are selectively bound to the artificial receptor, *prim,prim*-bis((2-aminoethyl)sulfenyl)-β-cyclodextrin immobilized on polymer beads, via double recognition: hydrophobic binding by the cyclodextrin cavity and carbonyl binding via reversible amino alcohol formation.

The host compound **2** was prepared via A,D-cap **1** as shown in Scheme I. The host compound was then attached to acrylonitrile–methyl acrylate copolymer **3** (average

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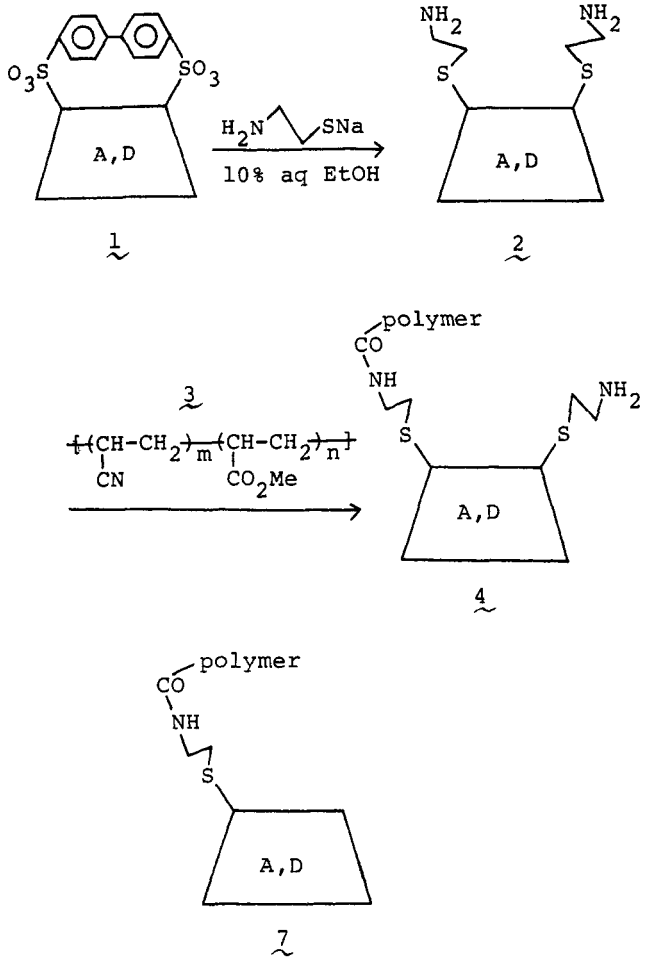
Scheme I



m/n = 5.6, viscosity, $[\eta]$ = 6.0 dL/g) prepared from 21.2 g of acrylonitrile and 3.4 g of methyl acrylate (mole ratio = 50:1) to form **4**. Small particles (80 mg) of **4** (250–8 μm) immersed in water (or followed by EtOH treatment) are packed into a *short* glass column (5 mm × 27 mm), through which 10–50 μL of a pH adjusted (pH 7, phosphate) aqueous solution (or aqueous ethanol solution) of a carbonyl compound **5** or its related compound was passed. The eluted solution was fractionated into 0.21 mL (0.09 mL for aqueous EtOH) fractions. Each fraction was quantitatively analyzed for the carbonyl compound by the use of electronic spectroscopy (**5b–e**, **6**), (dinitrophenyl)-hydrazine (**5f–h**), or $NaHSO_3$–I_2 (**5a**). Elution diagram (Figure 1) shows that compounds of similar structures are well separated even by a *very short* column. From the observed elution volume corresponding to the elution peak, the relative retention volume, $(V_i - V_0)/V_0$, was estimated by taking the average retention volume of independent measurements.

In Table I are shown the separation factors estimated for a series of aromatic compounds and cyclopentanones

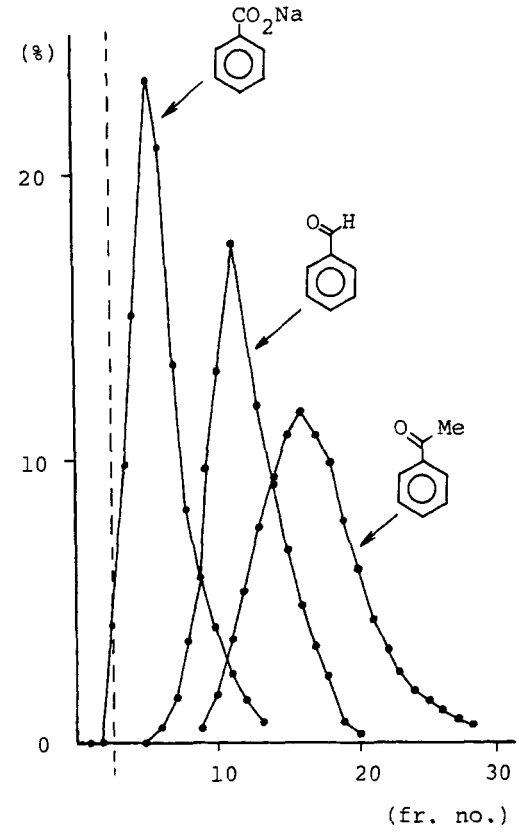


Figure 1. Elution diagram for aromatic molecules, pH 7.0 phosphate buffer. Each sample solution (30 μL, 1 × 10^{-2} M) was applied on the column. % = [amount of sample eluted/amount of sample applied] × 100. Fr. No.: number of fraction eluted from the column, one fraction = 0.21 mL. A dotted line shows void volume of this column (0.63 mL, 3 fractions).

Table I. Capacity Factor in Artificial Affinity Chromatography, 27 mm × 5 mm o.d.[a]

		H_2O		40% EtOH	
guest	no.	max fr[b]	$(V_i - V_0)/V_0$	max fr[c]	$(V_i - V_0)/V_0$
NaCl		3	0 (std)	7	0
$OHC(CH_2)_3CHO$	**5a**	4	0.3		
$C_6H_5CO_2Na$	**5b**	5	0.7		
$C_6H_5CH_2OH$	**6**	6	1.0	8.0	0.14
C_6H_5CHO	**5c**	11	2.6		
$C_6H_5COCH_3$	**5d**	16	4.3	8.3	0.19
plumbagin[d]	**5e**	too slow to elute		11	0.57
cyclopentanone	**5f**	4.5	0.5	7	0
2-butyl-cyclopentanone	**5g**			9.5	0.36
2-hexyl-cyclopentanone	**5h**			11.5	0.64

[a] Each sample (10–40 μL, 1–3 × 10^{-2} M) was applied on the column. [b] One fraction = 0.21 mL, pH 7.0 phosphate. [c] One fraction = 0.09 mL, without buffer. [d] 2-Methyl-5-hydroxy-1,4-naphthoquinone.

with or without an alkyl side chain. As seen in the cyclopentanone series more hydrophobic compounds have larger separation factors than do the corresponding less hydrophobic compounds: ca. 0, 0.36, and 0.64 for H, *n*-Bu, and *n*-Hex, respectively.

Another characteristic of the present artificial receptor-affinity column is that aromatic compounds bearing a carbonyl group have a larger retention volume than those of similar hydrophobicity but without a carbonyl group (**5c**, **5d**, and **6**). A plant hormone **5e**, a naphthalene derivative bearing a carbonyl group, is eluted after a much larger retention volume and is thus successfully separated.

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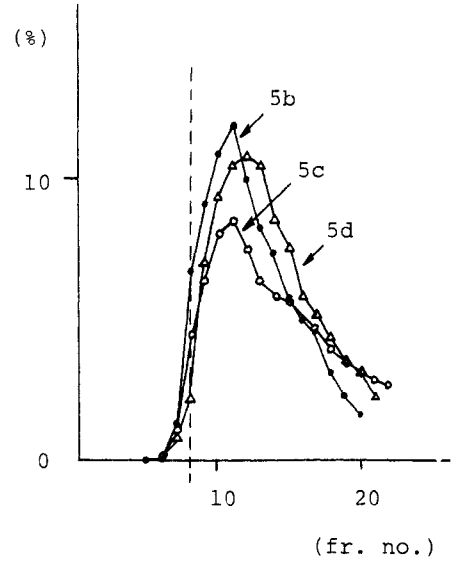

Figure 2. Elution diagram for **5b–d** by polymer **7** (80 mg, 24 mm × 13 mm o.d.), pH 7.0 phosphate buffer. One fraction = 0.23 mL.

The cyclodextrin attached to the same acrylonitrile–methyl acrylate polymer, which lacks the free (2-aminoethyl)sulfenyl side chains **7**, was also prepared form the copolymer **3** described above and (2-aminoethyl)-sulfenyl-β-cyclodextrin. The latter was prepared from β-cyclodextrin 6-tosylate.[3] From the observed elution volume, the relative retention volume was estimated as 0.37, 0.37, and 0.5 for **5b**, **5c**, and **5d**, respectively (see Figure 2 for the elution diagram), strongly indicating that these aromatic compounds are only much more poorly separated by the polymeric adsorbent **7**, compared to the present polymer **4**.

Parent cyclodextrins attached to an immobilized polymer via an aminoacyl linkage were applied to HPLC analysis,[5] revealing some successful separation between positional isomers such as *o*, *m*, and *p*-isomers of benzene derivatives[5c-g], or between compounds of similar structure including enantiomers[5g,h]. In this study, we have introduced the concept of double recognition into the field of cyclodextrin–polymer chromatography, providing excellent separation of hydrophobic carbonyl compounds in a preparative scale by use of a very short column. The present results show promise for effective separation of prostaglandins from compound of similar properties and structures, probably by the addition of one more recognition sites to the present artificial host.

Experimental Section

Bis((2-aminoethyl)sulfenyl)-β-cyclodextrin. Biphenylyl-4,4′-disulfonyl-A,D-capped-β-cyclodextrin (6.0 g, 4.25 mmol), 2-mercaptoethylamine hydrochloride (9.64 g, 85 mmol), sodium hydrosulfate (1.18 g, 6.8 mmol), and NaOH pellets (3.4 g, 85 mmol) were dissolved in 150 mL of a NaOH solution (pH 10, H_2O–EtOH = 9:1, v/v), which was degassed by bubbling O_2 free N_2 for 30 min. The solution was stirred at 60 °C for 3.5 h under Ar, and the pH of the mixture was adjusted to 8.0 by adding HCl. After concentration to ca. 60 mL by the use of a rotary evaporator, 10 mL of tetrachloroethylene was added to the mixture. White precipitates formed by stirring for 1 h at 0 °C were filtered off by suction filtration. The filtrate was concentrated to ca. 10 mL and then treated with 200 mL of EtOH. The precipitates were formed, which were collected by suction filtration. The solid was dissolved again in 10 mL of water, and then the solution was treated with 3 mL of tetrachloroethylene in a similar manner described above, giving 2.1 g (38%) of bis((2-aminoethyl)-sulfenyl)-β-cyclodextrin. Complete removal of tetrachloroethylene included in the cyclodextrin cavity was carried out by a reported procedure:[6] TLC R_f = 0.17 (SiO_2, *n*-PrOH–AcOEt–H_2O–NH_3 aqueous = 5:3:3:1, v/v); ν_{max} (KBr) 1565, 1490, 1220 cm^{-1}; ^1H NMR (D_2O) δ 2.9–3.3 (m, 12 H), 3.3–4.2 (m), 5.2 (br s, 7 H, C_1-H).

Copolymer of Acrylonitrile–Methyl Acrylate. Acrylonitrile (26.5 g, 0.5 mol) and methyl acrylate (0.86 g, 10 mmol) were added to 370 mL of degassed water by bubbling N_2 for 30 min. All procedures were carried out under N_2 or Ar. The mixture was stirred for 10 min at ca. 40 °C, and then a solution of potassium persulfate (0.375 g) dissolved in 10 mL of water was added to the mixture. After 1 min, a solution of sodium bisulfite (0.185 g) was added, and then the mixture was stirred for further 3 h at ca. 40 °C, giving white precipitates, which were collected by suction filtration, washed with water, and dried in vacuo: ν_{max} (KBr) 2900, 2230 (ν_{CN}), 1720 (ν_{CO}), 1610, 1440, 1350, 1250, 1160 cm^{-1}. Viscosity of the copolymer solution in *N,N*-dimethylformamide was measured by using an Ostwald viscometer. Three independent measurements were carried out at each of the three polymer concentrations, c = 0.0507, 0.087, and 0.154 g/dL, and the average of the specific viscosity, η_{SP}, was obtained to be 0.34 ± 0.01, 0.67 ± 0.01, and 1.28 ± 0.01, respectively. The intrinsic viscosity, $[\eta]$, was determined as 6.1 ± 0.6 (dL/g) from the intercept by extrapolating the concentration c to zero in the plots of η_{SP}/c vs. c which fell on a fairly good straight line.

Synthesis of a Receptor Polymer. Acrylonitrile–methyl acrylate copolymer (0.6 g) prepared as described above and 0.13 g (1.3 mmol) of triethylamine were added to 50 mL of pyridine–water (1:1, v/v) solution of 2.0 g (1.55 mmol) of bis((2-aminoethyl)sulfenyl)-β-cyclodextrin. The mixture was heated at 100 °C with occasional stirring for 80 h under Ar. After cooling to room temperature, 100 mL of water was added. The solids formed were collected by suction filtration, washed with 50 mL of water, 50 mL of EtOH, and finally 50 mL of H_2O, and then dried in vacuo, giving 0.8 g of the receptor polymer. Unreacted bis((β-aminoethyl)sulfenyl)-β-cyclodextrin (1.0 g) was recovered by concentration of the filtrate. Receptor polymer: ν_{max} (KBr) 3400 (br), 2930, 2250, 1665, 1560, 1455, 1160, 1080, 1040 cm^{-1}.

Synthesis of a Monofunctional β-Cyclodextrin-Immobilized Polymer (7). A suspension of 0.54 g of the acrylonitrile–methyl acrylate copolymer, 1.1 g of ((2-aminoethyl)-sulfenyl)-β-cyclodextrin, 0.12 g of triethylamine in 44 mL of pyridine–water (1:1, v/v) was heated at 100 °C for 58 h under N_2. After cooling to room temperature, the mixture was filtered, and the polymer was washed with 50 mL of water, 50 mL of ethanol, and 50 mL of ether, successively. The product **7**, which was dried in vacuo overnight, weighted 0.767 g. **7**: ν_{max} (KBr) 3400, 2920, 2240, 1650, 1570, 1440, 1150, 1030 cm^{-1}.

Separation of Carbonyl Compounds or Related Compounds. Small particles (80 mg) of the receptor polymer (100–3000 mesh) were packed into a short glass column (5 mm × 27 mm) and 10–50 μL of a phosphate buffered (pH 7) or a pH-adjusted (by HOAc) aqueous solution (or aqueous ethanol solution) of a carbonyl compound or its related compound was passed through the column. The elution system was composed of a pump (FMI Lab pump RRP), a pressure damper (FMI #PD-60 LF), and an injector. The eluted solution was fractionated into 100 μL each, which was quantitatively analyzed by the use of electronic spectrum with or without treatment with dinitrophenylhydrazine, or by colorimetry for the determination of glutaraldehyde after color development by treatment with NaH-SO_3–I_2–starch.

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Registry No. 2, 101652-40-8; $C_6H_5CO_2Na$, 532-32-1; $C_6H_5CH_2OH$, 100-51-6; C_6H_5CHO, 100-52-7; $C_6H_5COCH_3$, 98-86-2; plumbagin, 481-42-5; cyclopentanone, 120-92-3; 2-butylcyclopentanone, 934-42-9; 2-hexylcyclopentanone, 13074-65-2.

Synthesis of 5,8-Dimethoxy-1-naphthoic Acid and 1,4-Dimethoxy-7,12-dimethylbenz[*a*]anthracene[1]

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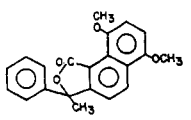
This work was undertaken as part of a program to synthesize possible metabolites of 7,12-dimethylbenz[*a*]-anthracene. Our first goal, to develop a good synthesis of 5,8-dimethoxy-1-naphthoic acid, **5**, was achieved as shown in Scheme I.

The Diels–Alder reaction of ethyl 2,4-pentadienoate,[3] **1**, with benzoquinone yielded ethyl 5,8-diketo-1,4,5,8-tetrahydro-1-naphthoate, **2**, which was immediately methylated[4] to ethyl 1,4-dihydro-5,8-dimethoxy-1-naphthoate, **3**, from which ethyl 5,8-dimethoxy-1-naphthoate, **4**, was obtained in a 53% overall yield from **2** by heating with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ).

The acid, **5**, obtained by hydrolysis of **4** was converted via its acid chloride into *N,N*-diethyl-5,8-dimethoxy-1-naphthamide,[5] **6**. On lithiation followed by reaction with acetophenone and acid hydrolysis there was obtained 5,8-dimethoxy-2-(α-hydroxy-α-methylbenzyl)-1-naphthoic acid lactone, **7**, which was reduced to 5,8-dimethoxy-2-(α-methylbenzyl)-1-naphthoic acid, **8**.



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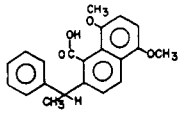

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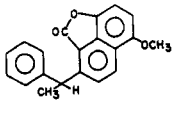

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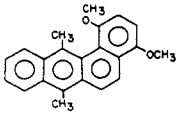

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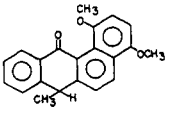

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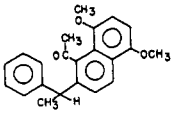
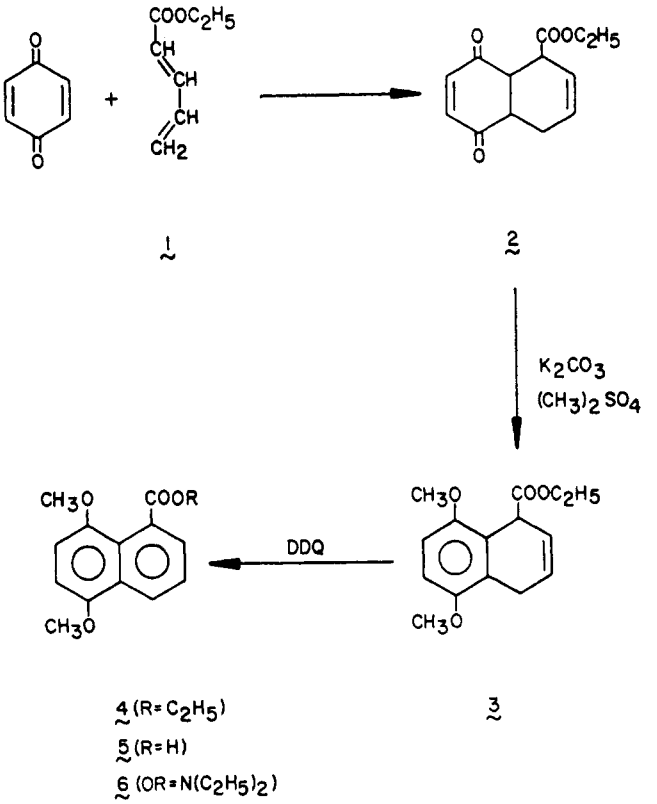


12

In an attempt to cyclize **8** to 7,12-dihydro-1,4-dimethoxy-7-methyl-12-benz[*a*]anthracenone, **10**, or its enol acetate by heating with acetic anhydride–$ZnCl_2$ reagent there was obtained mainly the lactone of 8-hydroxy-5-methoxy-2-(α-methylbenzyl)-1-naphthoic acid, **9**. Cyclization of **8** to **10** was accomplished in 90% yield by a 1-h treatment with anhydrous HF.[6] Reaction of **10** with methyllithium yielded 1,4-dimethoxy-7,12-dimethylbenz-[*a*]anthracene, **11**. On treatment of the acid chloride of **8** with lithium dimethylcuprate,[7] 1-aceto-5,8-dimethoxy-2-(α-methylbenzyl)naphthalene, **12**, was obtained. However, attempts to cyclize **12** by heating with PPA or trifluoroacetic acid yielded 5,8-dimethoxy-2-(α-methylbenzyl)naphthalene, **13**, the product resulting from loss of the acetyl group.

Scheme I



Experimental Section[6]

Ethyl 1,4-Dihydro-5,8-dimethoxynaphthoate, 3. A solution of 27.0 g (0.25 mol) of *p*-benzoquinone and 31.5 g (0.25 mol) of ethyl 2,4-pentadienoate, **1**, in 500 mL of benzene was refluxed for 2 days. After rotary evaporation of the benzene the residue was washed with 50–100 mL of hexane (discarded) and taken into CH_2Cl_2. After being washed with saturated salt solution, the solvent was removed. As the crude Diels–Alder product was sensitive it was dissolved in 1 L of deaerated acetone (N_2) containing 138 g of K_2CO_3 and treated with 69 g (0.55 mol) of dimethyl sulfate at reflux for 1 day.[4] Most of the acetone was removed and water added. The resulting solid was collected, washed with a little pentane, and dried. The solid was then extracted with 600–700 mL of hot hexane. Cooling yielded 37.4 g (57%) of **3**: mp 91–92 °C; IR (KBr) 1728 cm^{-1} (CO); NMR ($CDCl_3$) 1.23 (t, 3, CH_3), 3.22–3.48 (m, 2, CH_2), 3.74 (s, 3, OCH_3), 3.79 (s, 3, OCH_3), 4.14 (q, 2, OCH_2), 4.37–4.55 (m, 1, CH), 5.91–6.06 (m, 2, CH=CH), 6.69 (s, 2-ArH); MS, M^+ 262.1213, calcd for $C_{15}H_{18}O_4$ 262.3083. Anal.[8] Calcd for $C_{15}H_{18}O_4$: C, 68.7; H, 6.9. Found: C, 68.6; H, 6.7.

A small part of the crude adduct was crystallized from hexane to yield pale yellow prisms of ethyl 5,8-diketo-1,4,4a,5,8,8a-hexahydro-1-naphthoate: mp 90–91 °C; IR 1720, 1685 cm^{-1}; NMR 1.28 (t, 3, CH_3), 2.12–2.42 (m, 2, CH_2), 3.08–3.43 (m, 2, 4a,8aH), 4.02 (t, 1, 1 H), 4.25 (q, 2-OCH_2), 5.12–5.87 (m, 1, =CH), 6.15–6.35

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(8) Microanalyses by the Galbraith Laboratories, Knoxville, TN. The term "worked up as usual" means that an ether–benzene solution of the product was washed with dilute acid and/or alkali and then saturated brine and filtered through anhydrous $MgSO_4$. The solvent was then removed on a rotary evaporator. All melting points are uncorrected. All NMR are done in $CDCl_3$. Mass spectra by Mr. R. Weisenberger.

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