46%), 195 (22), 182 (23), 168 (25), 129 (24), 127 (28), 114 (46), 105 (37), 87 (100). Anal. Calcd for $C_{10}H_{15}NO_4$: C, 56.33; H, 7.09. Found: C, 56.40; H, 6.94.

Acylation of 3 and 4 with Methyl Benzoate. Trianion 3 (8.0 mmol) was treated with methyl benzoate (0.54 g, 4.0 mmol) in THF for 1 h at 20 °C. Isolation gave an oil which was chromatographed on silica gel (hexane–EtOAc mixtures) to give 618 mg (59% yield) of ester 11 as a yellow solid, mp 72–74 °C (lit.[12] mp 73–76 °C).

Treatment of trianion 4 (3.11 mmol) with methyl benzoate (0.22 g, 1.6 mmol) in THF for 1 h at 20 °C gave triketo amide 12 in good yield but it could not be completely separated from recovered diketo amide 2 by chromatography on silica gel. Preparative-scale reverse-phase chromatography (3:1, $CHCl_3$–MeOH) on silica gel plates which had been pretreated with octadecyltrichlorosilane gave 286 mg (66% yield) of amide 12 as a yellow oil. The ^1H NMR spectrum indicated a complex mixture of enol–keto tautomers: IR (KBr) 1595, 1705, 2920, 3410 cm^{-1}; mass spectrum, *m/e* (relative intensity) 275 (M^+·, 8%), 230 (10), 211 (9), 191 (14), 161 (14), 149 (17), 147 (18), 129 (85), 121 (29), 105 (100), 87 (54). Anal. Calcd for $C_{15}H_{17}NO_4$: C, 65.44; H, 6.22. Found: C, 65.68; H, 6.52.

Condensation of 3 and 4 with Methyl Benzoylacetate. Trianion 3 (8.0 mmol) was treated with 4.0 mmol of the sodium salt of methyl benzoylacetate (prepared by treatment of the ester with excess NaH) in THF for 48 h at 50 °C. Workup yielded an oil which the ^1H NMR spectrum indicated to be approximately an equal mixture of tetraketo ester 13 and diketo ester 1. Complete separation of the two esters on silica gel was not possible because 13 underwent cyclization during the slow elution required for the separation. The cyclization products included resorcinol 14[9] and coumarin 15.[9]

Similar treatment of trianion 4 (6.5 mmol) with the sodium salt of methyl benzoylacetate (3.26 mmol) for 48 h at 45 °C gave pentaketo amide 16 which cyclized during isolation to resorcinol 17. EtOAc was required for extraction of sparingly soluble 17. The crude 17 (263 mg, 27% yield, mp 180–186 °C) was recrystallized from aqueous MeOH to give 186 mg of white crystals: mp 195–197 °C; ^1H NMR (Me_2SO-d_6) δ 2.69 (s, NMe), 2.78 (s, NMe), 3.70 (s, CH_2), 6.24 (d, J = 1 Hz, aromatic CH), 6.47 (d, J = 1 Hz, aromatic CH), 7.40 (s, C_6H_5), 10.10 (br s, OH), 10.85 (br s, OH); IR (KBr) 1600, 3100 cm^{-1}; mass spectrum, *m/e* (relative intensity) 299 (M^+·, 24%), 255 (30), 227 (42), 226 (100), 213 (52), 212 (31). Anal. Calcd for $C_{17}H_{17}NO_4$: C, 68.22; H, 5.72. Found: C, 67.91; H, 5.61.

Condensation of 3 with Methyl Acetoacetate. The condensation of trianion 3 (8.0 mmol) with the monosodium salt (4.0 mmol) of methyl acetoacetate (prepared from the ester and NaH) in THF at 60 °C for 44 h gave tetraketo ester 18 which cyclized during workup (EtOAc extraction) to give coumarin 19, isolated as a light yellow solid (190 mg, 25% yield) by chromatography on silica gel (hexane–EtOAc mixtures): mp 270 °C (lit.[10] mp 266–267 °C); ^1H NMR (Me_2SO-d_6) δ 2.64 (s, Me), 5.47 (s, 3-CH), 6.59 (s, aromatic CH's) (lit.[10] ^1H NMR δ 2.61, 5.46, 6.59).

Condensation of 3 with 4-Methoxy-6-methyl-2-pyrone. Trianion 3 (8.5 mmol) was treated with the title pyrone[13] (0.59 g, 4.2 mmol) for 1 h at 20 °C. Workup of the reaction involved EtOAc extraction followed by chromatography of the crude product on silica gel (2:3, EtOAc–hexane) to give a red oil which crystallized in the presence of Et_2O. Recrystallization from $CHCl_3$–hexane gave 91 mg (8% yield) of hemiketal 25: mp 137 °C; ^1H NMR (acetone-d_6) δ 2.54 (s, Me), 2.73 (d, J = 16 Hz, one proton of diastereotopic CH_2), 2.81 (s, CH_2), 3.15 (d, J = 16 Hz, one proton of diastereotopic CH_2), 3.67 (s, OMe), 3.76 (s, OMe), 5.96 (br s, OH), 6.21 (d, J = 1 Hz, aromatic CH), 6.31 (d, J = 1 Hz, aromatic CH); IR (KBr) 1600, 1640, 1730, 3250 cm^{-1}; mass spectrum, *m/e* (relative intensity) 280 (M^+·, 27%), 262 (24), 207 (52), 165 (100), 164 (38). Anal. Calcd for $C_{14}H_{16}O_6$: C, 60.00; H, 5.75. Found: C, 60.22; H, 5.92.

Condensation of 4 with 4-Methoxy-6-phenyl-2-pyrone. Trianion 4 (3.7 mmol) was treated with the title pyrone[13] (0.37 g, 1.8 mmol) in THF for 80 min at 20 °C. Isolation, which included extraction with EtOAc and trituration with $CHCl_3$, yielded 221 mg (35% yield) of 28. Recrystallization from EtOAc gave white solid: mp 180–184 °C; ^1H NMR (Me_2SO-d_6) δ 2.96 (s, NMe), 3.04 (s, CH_2), 3.14 (s, NMe), 3.32 (s, CH_2), 3.85 (s, OMe), 6.43 (d, J = 1 Hz, aromatic CH), 6.56 (d, J = 1 Hz, aromatic CH), 7.42 (m, C_6H_5), 7.81 (s, OH); IR (KBr) 1585, 1600, 1680, 2940, 3200, 3450 cm^{-1}; mass spectrum, *m/e* (relative intensity) 355 (M^+·, 23%), 337 (36), 292 (74), 268 (81), 266 (52), 240 (100), 228 (65), 227 (91), 226 (35), 139 (28). Anal. Calcd for $C_{20}H_{21}NO_5$: C, 67.59; H, 5.96. Found: C, 67.52; H, 5.86.

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Registry No. 1, 29736-80-9; 2, 70155-27-0; 3, 54210-58-1; 4, 77255-91-5; 5, 77255-92-6; 6, 77255-93-7; 7, 77255-94-8; 8, 77255-95-9; 10, 70155-29-2; 11, 15148-46-6; 12, 70155-30-5; 13, 34723-78-9; 14, 77255-96-0; 15, 34684-64-5; 16, 77255-97-1; 17, 77255-98-2; 18, 77255-99-3; 19, 23664-28-0; 25, 77269-98-8; 28, 77256-00-9; 2,4-pentanedione, 123-54-6; methyl *N,N*-dimethylcarbamate, 7541-16-4; benzyl chloride, 100-44-7; benzophenone, 119-61-9; 2,4,6-heptanetrione, 626-53-9; methyl benzoate, 93-58-3; methyl benzoylacetate Na, 5381-09-9; methyl acetoacetate Na, 34284-28-1; 4-methoxy-6-methyl-2-pyrone, 672-89-9; 4-methoxy-6-phenyl-2-pyrone, 4225-45-0.

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Synthesis of Substituted Pyrroles by Intramolecular Condensation of a Wittig Reagent with the Carbonyl Group of a Tertiary Amide

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1,2,5-Trisubstituted pyrroles are obtained in 50–100% yields by addition of the conjugate bases of open-chain analogues of Reissert compounds to the vinyltriphenylphosphonium cation, with subsequent cyclization by an intramolecular Wittig reaction and base-catalyzed elimination of hydrogen cyanide.

Syntheses of 2,3-dihydrofurans in 56–93% yields by intramolecular Wittig reactions involving the carbonyl group of esters have been reported.[1] Also, several examples of intramolecular Wittig reactions between esters and stabilized phosphoranes have been reported.[2-6] With the exception of formate esters, all of the latter esters contained strongly electron-withdrawing groups adjacent to

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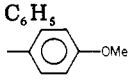
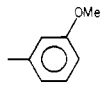
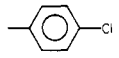
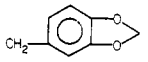
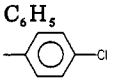
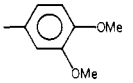
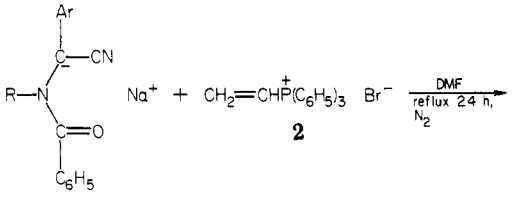
Table I. Synthesis of 1,2,5-Trisubstituted Pyrroles 4

			via Reissert analogue			by Paal-Knorr synthesis	
	R	Ar	% yield[a]	temp, °C/ time, h	mp (lit.), °C	% yield	conditions[b]
a	C_6H_5	C_6H_5	100	100/24	234-236 (228-234)[17-23,26]	93	c*
b		C_6H_5	97	100/20	227.5-229 (229)[22,27]	50	70 °C/0.5 h/HOAc
c		C_6H_5	97	100/22.5	163-164 (146)[27]	68	70 °C/1.0 h/HOAc
d		C_6H_5	89	100/23	226-227 (217-218)[22]	62	70 °C/0.5 h/HOAc
e		C_6H_5	61	120/24	122-123 (134)[22]	83	reflux/21 h*
f	CH_2Ph	C_6H_5	75	120/24.5	144-145 (144-145)[22,24]	86	reflux/1 day/HOAc
g		C_6H_5	89	120/23	125.5-126.5[d]	69	reflux/2 days/HOAc
h		C_6H_5	50	120/23[e]	104-105[d]	71	reflux/19 h/HOAc
i	n-C_6H_{13}	C_6H_5	67	reflux/24	oil[d,25]		f
j	C_6H_5		88	reflux/24	229.5-231.5[d]	g	
k	C_6H_5		65	reflux/20	158.5-159.5[d]	g	

[a] Isolated yield. [b] Asterisk indicates some of the amine hydrochloride present as catalyst. [c] Diketone dissolved in hot (155 °C) aniline (10 min). [d] New compound. [e] Refluxing 22.5 h also gave 50% yield. [f] None of the pyrrole could be produced via the diketone. [g] No attempt made to prepare compound by Paal-Knorr procedure.

the carbonyl group. We have found no reports in the literature of the successful reaction of Wittig reagents with the carbonyl group of *N,N*-disubstituted amides.

We have recently provided many examples of synthetic uses of open-chain analogues of Reissert compounds.[7,8] We now report the successful addition of conjugate bases (1) of these analogues to the vinyltriphenylphosphonium cation (2)[9] with subsequent ring closure of the adducts (3) to give 1,2,5-trisubstituted pyrroles (4) in 50–100% yields. Examples of the reaction are provided in Table I. In each case, the same pyrrole was prepared by reaction of the appropriate amine with 1,2-dibenzoylethane.[10] These results are also provided in Table I.



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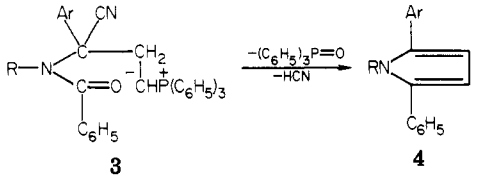

3 4

In 1963, Schweizer reported the first synthesis of a heterocyclic compound by use of an intramolecular Wittig reaction.[11] He has continued to develop this general approach up to the present time and has provided methods of preparation for many different heterocyclic ring systems, including 1-hydroxypyrroles and 1-aminopyrroles.[12] Thus, in the work reported herein, we have applied Schweizer's excellent procedure to the further development of synthetic applications of open-chain analogues of Reissert compounds.[7,8]

Whereas most of the previously reported[7,8] reactions of open-chain analogues of Reissert compounds are similar to those of conventional Reissert compounds,[13-15] the examples provided herein are an exception. Attempts to bring about reaction between the conjugate base of 2-benzoyl-1,2-dihydroisoquinaldonitrile and vinyltriphenylphosphonium bromide have led to the formation of a complex mixture of products, none in good yield.

Although the Paal–Knorr synthesis of 1,2,5-trisubstituted pyrroles from 1,4-diketones and primary amines is a classical and widely used one, it is our opinion that the new method of synthesis reported herein is superior in some instances. In addition to the obvious example (given in Table I) in which 1-*n*-hexyl-2,5-diphenylpyrrole was prepared in 67% yield by the Reissert analogue approach but could not be obtained at all by the Paal–Knorr method, the preparations of certain of the 1,2,5-triarylpyrroles from the Reissert analogues are also superior to the Paal–Knorr approach. For example, 1-(*p*-methoxyphenyl)-2,5-diphenylpyrrole (**4b**) is obtained in an overall yield of about 70% in the three-step process from the commercially available starting materials (*p*-anisidine, mandelonitrile, benzoyl chloride, and vinyltriphenylphosphonium bromide), involving α-(*p*-methoxyanilino)-

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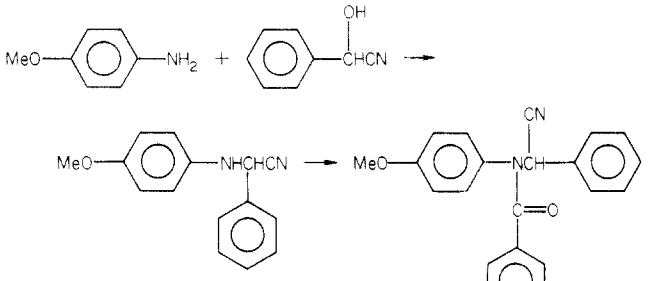
Table II. Properties of 1,2,5-Trisubstituted Pyrroles 4[a]

4	isolation method	recryst solvent	NMR (δ from Me_4Si)[b]
a	A	$CHCl_3$ or HOAc	6.52 (s, 2 H), 7.1-7.3 (m, 15 H)
b	A	C_6H_6	3.75 (s, 3 H), 6.47 (s, 2 H), 6.8-7.4 (m, 14 H)
c	A	C_6H_{12} or HOAc	3.55 (s, 3 H), 6.51 (s, 2 H), 6.6-7.3 (m, 14 H)
d	A	HOAc	6.56 (s, 2 H), 6.9-7.4 (m, 14 H)
e	B	aq EtOH	0.6-2.0 (br m, 10 H), 4.05 (br s, 1 H), 6.21 (s, 2 H), 7.25-7.75 (m, 10 H)
f	B	aq EtOH	5.30 (s, 2 H), 6.45 (s, 2 H), 6.6-7.5 (m, 15 H)
g	B	aq EtOH	5.14 (s, 2 H), 5.59 (d, J = 6 Hz, 1 H), 6.12 (dd, J = 4 Hz, 1 H), 6.35 (s, 2 H), 7.15-7.6 (m, 11 H)
h	B	aq EtOH	5.17 (s, 2 H), 5.86 (s, 2 H), 6.39 (s, 2 H), 6.0-6.65 (m, 3 H), 7.2-7.5 (m, 10 H)
i	B		0.6-1.7 (m, 11 H), 4.08 (t, 2 H, J = 7 Hz), 6.30 (s, 2 H), 7.25-7.6 (m, 10 H)
j	A	HOAc or aq EtOH	6.52 (m, 2 H), 7.0-7.4 (m, 14 H)
k	A	aq EtOH	3.15 (s, 3 H), 3.49 (s, 3 H), 6.13 (s, 2 H), 6.35-7.0 (m, 13 H)

[a] In view of the many discrepancies between found and reported melting points (Table I), all of the solid pyrroles were analyzed. Satisfactory analytical data (±0.3% for C, H, and N) were reported for all compounds. [b] All IR spectra were consistent with structures.

phenylacetonitrile (**5**) and its *N*-benzoyl derivative, **6**, as intermediates. On the other hand, 1,2-dibenzoylethane is obtained in 85% yield by reduction of the commercially available *trans*-1,2-dibenzoylethylene with stannous chloride, and the yield of **4b** by the Paal–Knorr method (Table I) is 50%. Thus, the overall yield of **4b** by this approach is but 43%



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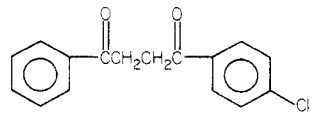
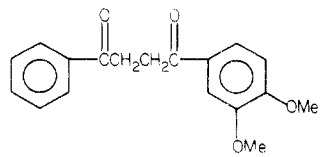
6

It should also be noted that the preparation of 1,5-diphenyl-2-(*p*-chlorophenyl)pyrrole (**4j**) or 1,5-diphenyl-2-(3,4-dimethoxyphenyl)pyrrole (**4k**) by the Paal–Knorr synthesis would require a relatively difficult prior preparation of the unsymmetrical 1,4-diketones **7** and **8**, respectively. However, the Reissert analogue approach requires only the use of *p*-chlorobenzoyl chloride or 3,4-dimethoxybenzoyl chloride, respectively, in place of benzoyl chloride in reaction with α-anilinophenylacetonitrile, **9**, or else the prior preparation of the cyanohydrins of *p*-chlorobenzaldehyde or 3,4-dimethoxybenzaldehyde, respectively. Actually, we made use of the latter procedure in the synthesis of **4j** and **4k** (Table I).



7



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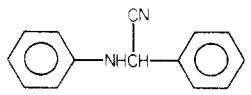

9

It has been our experience that the time required for the synthesis of the pyrroles, **4**, is about the same by either route.

The carbonyl group of an amide is notoriously less reactive in nucleophilic addition reactions than the carbonyl group of an aldehyde, ketone, acid chloride, or ester. In spite of this, we have, for the first time, been able to utilize the carbonyl group of a tertiary amide in an intramolecular Wittig reaction leading to the production of substituted pyrroles in generally high yields.

Experimental Section

Vinyltriphenylphosphonium Bromide. This salt (which is commercially available[16]) was synthesized by the method of Schweizer and Bach.[9]

Synthesis of 1,2,5-Trisubstituted Pyrroles from Reissert Analogues. To 0.53 g (0.011 mol) of sodium hydride (50% by weight in oil dispersion), maintained in a nitrogen atmosphere, was added with stirring over a 10-min period a solution of 0.010 mol of the open-chain Reissert analogue in anhydrous dimethylformamide. After hydrogen evolution had ceased, a solution of 4.24 g (0.0115 mol) of vinyltriphenylphosphonium bromide in anhydrous dimethylformamide was added, and the mixture was heated at 100 °C (or at the temperature and for the period of time specified in Table I) for 24 h, the nitrogen atmosphere being maintained. If a precipitate appeared when the flask was cooled, the mixture was refrigerated at −25 °C and the solid collected by filtration (method A). If no precipitate formed, the mixture was poured into ice-cold water and extracted with ether, and the dried (anhydrous magnesium sulfate) ether solution concentrated to dryness (method B). The products obtained by either method were recrystallized from an appropriate solvent (Table II). The physical properties of the products are given in Table II.

1,2-Dibenzoylethane. This compound was prepared by reduction of *trans*-1,2-dibenzoylethylene by the method of Bailey and Lutz.[10]

Paal–Knorr Synthesis of Pyrroles, 4. Procedures reported in the literature[17-27] were followed. The results are provided in Table I.

Registry No. **1a**, 77270-03-2; **1b**, 77270-04-3; **1c**, 77270-05-4; **1d**,

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Synthesis of Dihydro Diols as Potential Proximate Carcinogens of Benzofluoranthenes[1,2]

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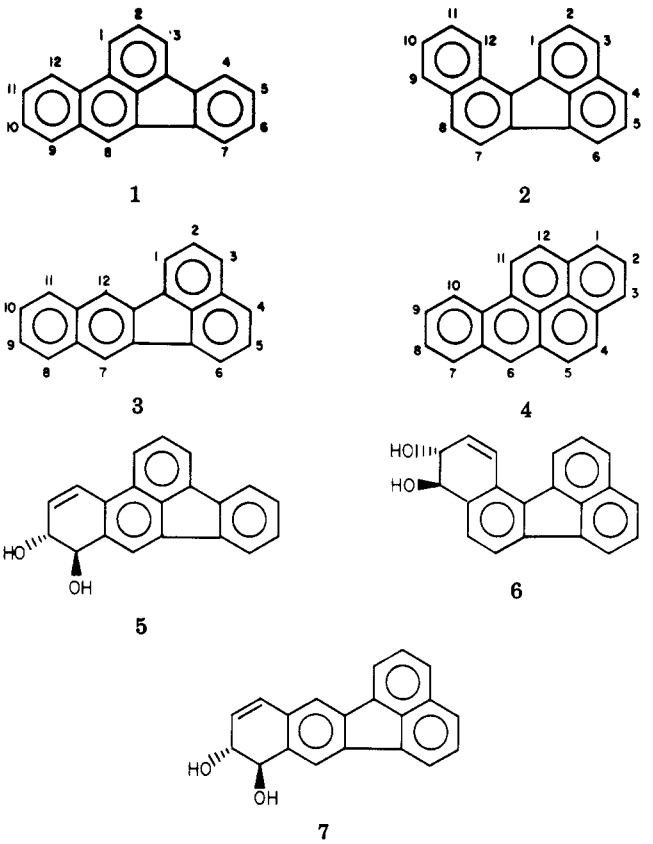
Dihydro diols which are potential proximate carcinogens of the environmental agents benzo[*b*]fluoranthene (**1**), benzo[*j*]fluoranthene (**2**), and benzo[*k*]fluoranthene (**3**) were synthesized. The dihydro diols synthesized were *trans*-9,10-dihydro-9,10-dihydroxybenzo[*b*]fluoranthene (**5**), *trans*-9,10-dihydro-9,10-dihydroxybenzo[*j*]-fluoranthene (**6**), and *trans*-8,9-dihydro-8,9-dihydroxybenzo[*k*]fluoranthene (**7**). In each case, the precursor to the dihydro diol was the corresponding ketone, e.g., 9-oxo-9,10,11,12-tetrahydrobenzo[*b*]fluoranthene (**21**) for **5**. The ketones were converted to the dihydro diols by reduction, dehydration, Prevost reaction, allylic bromination, dehydrobromination, and hydrolysis. The trans stereochemistry of the products from the Prevost reactions was established by comparison to the analogous derivatives prepared by osmium tetraoxide oxidation and by NMR. The UV spectra of the dihydrodiols **5**–**7** are presented.

Benzo[*b*]fluoranthene (**1**), benzo[*j*]fluoranthene (**2**), and benzo[*k*]fluoranthene (**3**) (see Chart I) are environmental carcinogens. Benzofluoranthenes have been detected in automobile engine exhaust, polluted urban air, cigarette smoke, soil, drinking water, marine sediments, and broiled and smoked foods.[3] Both **1** and **2** are tumor initiators and complete carcinogens on mouse skin, while **3** is marginally active.[4-6] However, **1** and **3** induce sarcomas when injected in mice.[7]

Despite the importance of the benzofluoranthenes as environmental carcinogens, no reports had been published on their metabolic activation prior to 1980. The metabolic activation of several other polynuclear aromatic hydrocarbons proceeds by formation of angular-ring dihydro diol epoxides in which one carbon of the epoxide is in the bay region of the molecule.[8] For example, the proximate and ultimate carcinogens of benzo[*a*]pyrene (**4**) are *trans*-7,8-dihydro-7,8-dihydroxybenzo[*a*]pyrene and an isomer of the corresponding 7,8-dihydro diol 9,10-epoxide.[9-12] Similar

Chart I



dihydro diol epoxides are involved in the activation of chrysene, benz[*a*]anthracene, and their methylated homologues as well as other polynuclear aromatic hydrocarbons.[13-20] These results suggested that *trans*-9,10-di-

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