Melcanthin A, B, and C, Three New *cis*-1(10),*cis*-4,5-Germacranolides from *Melampodium leucanthum* (Compositae, Heliantheae)

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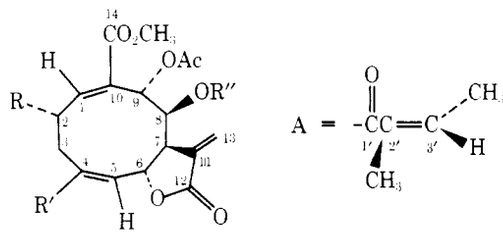
The isolation and structure elucidation of three new *cis*-1(10),*cis*-4,5-germacradienolides, melcanthin A, B, and C, from *Melampodium leucanthum* Torr. and Gray (Compositae, Heliantheae) are reported. The structures, configurations, and conformations of the new compounds were determined by chemical transformations, correlations, and spectral methods.

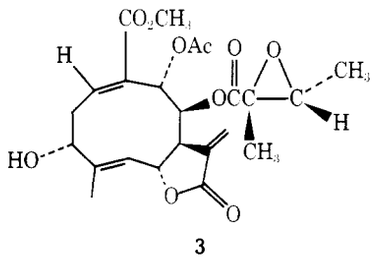
In spite of the nearly 300 known germacranolides of various skeletal types,[1] previous reports related to naturally occurring *cis*-1(10),*cis*-4,5-germacranolides have been limited to only three compounds.[2] Therefore, it was of particular interest to isolate from *Melampodium leucanthum*, a species which is known to produce melampolides[3] and germacranolide dilactones,[4] three new *cis*-1(10),*cis*-4,5-germacranolides.



A =

1a, R = H; R′ = CH_2OH; R″ = A
1b, R = H; R′ = CHO; R″ = A
2a, R = OH; R′ = CH_2OH; R″ = A
2b, R = OAc; R′ = CH_2OAc; R″ = A
2c, R = OH; R′ = CHO; R″ = A
3a, R = OH; R′ = CH_2OH; R″ = C(=O)$CH(CH_3)_2$

Typical representatives of the previously isolated skeletal types are the melampolide leucanthinin (**3**)[5] and the dilactone melampodin B (**4**).[4,6] Structural data for the three new *cis*-1(10),*cis*-4,5-germacradienes, which we named melcanthin A, B, and C, were obtained by chemical transformations and the use of physical methods, mainly NMR and MS of the new compounds and their derivatives.



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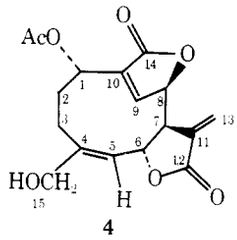

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Results and Discussion

Melcanthin A (1a), $C_{23}H_{28}O_9$, a gum which exhibited spectral absorptions typical of an α-methylene-γ-lactone (IR at 1755 cm^{-1} and NMR doublets at 5.79 and 6.35 ppm), showed IR absorptions at 3500, 1660, and 1640 cm^{-1}, indicating the presence of hydroxyl(s) and double bonds, respectively. The 100 MHz ^1H NMR spectrum of **1a** in $CDCl_3$ at ambient temperature exhibited broadened signals which sharpened considerably when the spectrum was obtained at 60 °C. This phenomenon was attributed to conformational changes of the germacradiene skeleton which will be discussed later. The assignments of the basic skeletal arrangement of melcanthin A were mainly deduced from ^1H NMR spectral data together with mass spectral fragmentation patterns. A three-proton singlet at 2.09 ppm together with MS peaks at *m/e* 406 (M − C_2H_2O) and *m/e* 388 (M − $C_2H_4O_2$) and a strong peak at *m/e* 43 (CH_3CO^+) indicated the presence of an acetate group in **1a.** Furthermore, the base peak at *m/e* 83 (C_5H_7O) and a peak at *m/e* 100 ($C_5H_8O_2$) suggested an ester moiety with five carbons. The NMR spectrum of **1a** showed a quartet of a quartet at 6.08 ppm (H-3′) and two three-proton methyl resonances: a doublet of a quartet at 1.94 ppm (C-3′ CH_3) and a narrow-spaced multiplet at 1.76 ppm (C-2′ CH_3), absorptions typical of the angeloyl moiety.[7] A singlet (3 H) at 3.69 ppm was assigned a carbomethoxy methyl in which the carboxyl group most likely represents C-14 of the sesquiterpene skeleton. Methyl esters of this type are typical for constituents of *M. leucanthum* which occur as α,β-unsaturated esters in which the β-hydrogens (H-1) are cis oriented to the carbomethoxy group as indicated by a downfield absorption near 7 ppm.[3,5] Therefore, a broadened triplet at 7.11 ppm strongly suggested a cis double bond between C-1 and C-10 in **1a.** Further proton resonances of **1a** were assigned by inspection and with the aid of double resonance experiments at 60 °C in $CDCl_3$. The presence of an allylic alcohol in **1a** was substantiated by MnO_2 oxidation of **1a** in ether, which afforded the aldehyde **1b.** Besides the aldehyde proton at 9.49 ppm, the expected downfield shift of H-5 from 5.65 ppm in **1a** to 6.45 ppm in **1b** was observed. The position of the aldehyde proton absorption near 9.5 ppm indicated a 4,5-cis double bond.[8] The use of chemical shifts of the aldehyde proton has been successfully applied in the configurational assignment of double bonds of other sesquiterpene lactones.[6,8]

The previously discussed groupings accounted for all oxygens in melcanthin A, and only two carbons and four hydrogens, which in the NMR spectrum appeared as an envelope between 2.15 and 2.87 ppm, needed to be assigned. They were best accounted for by two CH_2 moieties connecting C-1 and C-4, forming a *cis,cis*-germacranolide skeleton. This completed the basic arrangement of melcanthin A as shown in **1a** exclusive of the attachments of the lactone and ester functions and the stereochemistries of the various chiral centers, which will be discussed together with the arguments presented for melcanthin B.

Melcanthin B (2a), $C_{23}H_{28}O_{10}$, mp 83–84 °C, showed absorptions typical of an α-methylene-γ-lactone (IR band at 1765 cm^{-1} and NMR doublets in $CDCl_3$ at 5.88 and 6.35 ppm). Absorptions at 1660 and 1645 cm^{-1} suggested the presence of double bonds, and a strong band at 3450 cm^{-1} indicated hydroxyl(s). The 100 MHz ^1H NMR spectrum of **2a** in $CDCl_3$ showed strongly broadened, featureless signals at ambient temperature which sharpened considerably when the spec-

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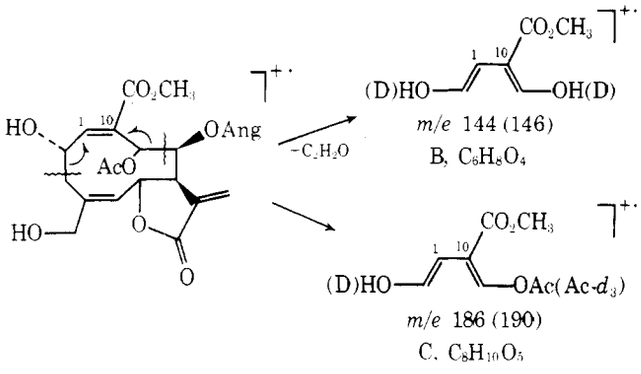
Scheme I. MS Fragments of Melcanthin B and Derivatives



trum was obtained at 60 °C. Inspection of the spectrum and selected double resonance experiments in $CDCl_3$ at 60 °C allowed complete assignments of the basic carbon skeleton of melcanthin B and its side chains. The additional oxygen atom in **2a** had to be present as a hydroxyl group at C-2 as indicated by the appearance of H-1 as a doublet at 7.13 ppm, coupled to a multiplet at 4.66 ppm (H-2), which upon acetylation shifted to 5.63 ppm.

Information about the attachment of the acetoxy function at the medium ring in **2a** was obtained from mass spectral data of **2a,** its acetate, and acetate-d_3. Compound **2a** gave two significant peaks at *m/e* 144 and 186 which were tentatively assigned the ions B and C, shown in Scheme I. High-resolution mass spectra of the acetate **2b** verified the composition of fragments B and C. Furthermore, the mass spectrum of the acetate-d_3 of **2a** gave a parent peak at *m/e* 557 (acetate **2b,** M^+ at *m/e* 548) which indicated that under the acetylation conditions acetate exchange, but no exchange of the angeloyl group, had occurred. This is evidence for the attachment of the acetate group to C-9 in **2a** since facile substitutions at C-9 had been reported before for melampolides.[8] In agreement with the previous assignment for fragments B and C, the acetate-d_3 showed peaks at *m/e* 146 and 190, respectively. The differences in the masses of the fragments B and C (*m/e* 144 and 186 in the acetate and *m/e* 146 and 190 in the acetate-d_3, respectively) represented further support for the attachment of the acetate moieties to positions C-2 and C-9 in **2b.** The type of lactonization, either toward C-6 or C-8, and the position of the angeloyl side chain as well as the configurations of the chiral carbon centers in **2a** were derived mainly by the use of low-temperature ^1H NMR parameters of **2b.** At ambient temperatures, a number of NMR signals of **2b** appeared as unresolved, broad absorptions but sharpened dramatically when the samples were run at either +50 or −50 °C. Below 0 °C the proton signals sharpened strongly, showing maximal resolution at −50 °C. It was therefore assumed that at −50 °C the NMR spectrum of **2b** exhibited "frozen" conformation(s) signals.

The coupling constants of the absorptions due to the major conformer were used to obtain configurational and conformational information on **2b** and therefore on **2a.** It was assumed that on biogenetic grounds the side chain at C-7 in **2b** adopts a β configuration and the protons at C-5 and C-6 have an antiperiplanar orientation as indicated by the large coupling constant ($J_{5,6}$ = 10 Hz). A cis lactone with 7,6 or 7,8 lactonization would require a synperiplanar orientation of the C-6, C-7 protons or the C-7, C-8 protons, respectively. This generally results in *J* values that differ from the respective proton couplings observed for **2b.**[10] On these grounds the presence of a cis lactone in **2b** was considered unlikely. A possible 7,8-trans lactone was excluded by comparison of the predicted NMR coupling constants obtained from the dihedral angles of a stereomodel with the experimentally observed parameters. The presence of a 7,8-trans lactone in melcanthin B acetate would have dictated an angle near 150° between H-7 and H-8, giving a $J_{7,8} \geq 6$ Hz, contrary to the observed coupling ($J_{7,8}$ = 2.0 Hz). Furthermore, a nearly synperiplanar orientation of H-6 and H-7 expected in a 7,8-trans lactone should exhibit a larger coupling than the experimentally observed value ($J_{6,7}$ = 7.0 Hz).[10] The low-temperature coupling data of **2b** can be best interpreted with the presence of a 7,6-trans lactone, α orientations of H-7, H-8, and a β-oriented H-9, configurations that are common in germacranolides of known absolute configuration from *Melampodium.*[5,11,13] In a stereomodel of **2b,** the approximate dihedral angles between H-6,7, H-7,8, and H-8,9 are near 150, 90, and 130°, respectively, and they agree well with the observed *J* values ($J_{6,7}$ = 7.0 Hz, $J_{7,8}$ = 2.0 Hz, and $J_{8,9}$ = 4.0 Hz).

The configuration at C-2 in **2a** was tentatively derived from the coupling data between H-1, H-2 and the two H-3 in **2b.** The stereomodel of **2b** with an α-oriented 2-acetoxy group showed the following dihedral angles: H-1,2 = ~150°, H-2,3α = ~90°, and H-2,3β = ~130°, values that correlated well with the observed couplings of **2b** ($J_{2,3\beta}$ = 4.0 Hz, $J_{2,3\alpha}$ = 1 Hz). On the basis of the above chemical transformations and correlations, we tentatively assign the configurational structure **2a** for melcanthin B and a conformation for the medium ring skeleton as shown in Figure 1. A conformation with both C-14 and C-15 below the plane of the medium ring had previously been predicted for a *cis*-1(10),*cis*-4,5-germacranolide on the basis of least transannular hydrogen interactions.[9]

Melcanthin C (3a), $C_{22}H_{28}O_{10}$, a minor constituent, exhibited NMR and mass spectral patterns very similar to melcanthin B. In the NMR spectrum, signals due to the medium ring skeleton of **3a** were very similar to those of **2a;** the major difference was that the absorptions due to the angeloyl moiety (A) were missing and instead signals typical for the isobutyrate group appeared. The mass spectrum of **3a** with peaks at *m/e* 364 ($M - C_3H_7COOH$) and 71 ($C_3H_7CO^+$) verified the NMR assignments. The lack of material prevented more detailed investigations on melcanthin C. However, the similarity of the NMR parameters of H-5 to H-9 in **1a, 2a,** and **3a** and the CD spectral data suggested the same configurations at these chiral centers and also similar conformations as shown in Figure 1.

The question regarding other conformational isomers in the new *cis,cis*-germacradienolides requires comment. In contrast to the 7,6-lactonized germacrolides,[12] melampolides,[13] and heliangolides,[9] which generally have rigid or preferred conformations, 7,6-lactonized *cis*-1(10),*cis*-4,5-germacradienolides have a considerably more flexible medium ring skeleton.[2] In the cyclodecadienes **1a, 2a,** and **3a,** several major conformations could in principle be adopted, but the number of conformers could not be determined from the low-temperature NMR data of **2b** since the signals of the major conformer constituted >90% of all absorptions. Four singlets of similar intensity at 3.68 and 3.77 ppm (most likely due to carbomethoxy methyls) and at 2.22 and 2.13 ppm (acetates) could be

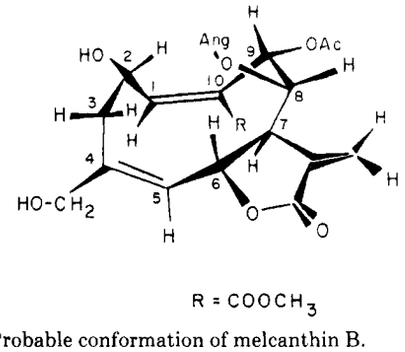


Figure 1. Probable conformation of melcanthin B.

observed in the low-temperature spectrum of **2b**, but not in the spectrum at +60 °C. This suggested the existence of one major (>90%) and at least two minor conformations in **2b**. The strong broadening of the NMR signals assigned to H-3b, H-6, H-9, H-13b, and the carbomethoxy methyl in **2b** at +50 °C in $CDCl_3$ with sharp signals for all other proton absorptions suggests considerable conformational flexibility most likely involving changes of the whole medium ring.

Finally, it is worthy mentioning that the three newly isolated *cis,cis*-germacranolides were isolated from a species which is known to produce melampolides represented by leucanthinin (**3**)[5] and the dilactone melampodin B (**4**).[4,6] The three new melcanthins contain structural features of both of the two types of sesquiterpene lactones and represent "biogenetic hybrids" of the two systems. These findings raise the question whether the biogenesis of the different types of cyclodecadienes follows two separate pathways in the formation of the medium ring or double bond isomerizations take place at a later stage, that is, after the germacradiene ring has been formed. The above described results also demonstrate that caution should govern structural correlations among germacranolides simply on the basis of occurrence in the same species.

Experimental Section[14]

Melcanthin A (1a) and Melcanthin B (2a). Collection of *M. leucanthum* was made in Val Verde County, Tex., 8.3 miles north of the Pecos River on June 14, 1974 (Stuessy-Meacham No. 3522). Dried leaves (134 g) were extracted with $CHCl_3$ and worked up as described before, providing 0.4 g of crude syrup which was chromatographed over 50 g of silica gel using *n*-propyl acetate as eluent, with 15-mL fractions being collected. Fractions 5–8 gave 35 mg of **1a** as a gum: UV λ_{max} (MeOH) 226 nm (ϵ 4.6 × 10^3); CD (c 2.5 × 10^{-4}, MeOH) $[\theta]_{220}$ −10 × 10^4, $[\theta]_{243}$ +3 × 10^3; IR ν_{max} (neat) 3500, 1755, 1735, 1720, 1660, 1640 cm^{-1}. The high-resolution mass spectrum (70 eV) showed significant peaks at the following *m/e* (relative intensity) compositions: 448.1733 (0.3, $C_{23}H_{28}O_9$), 406.1640 (0.1, $C_{21}H_{26}O_8$), 388.1493 (0.3, $C_{21}H_{24}O_7$), 306.1092 (0.2, $C_{16}H_{18}O_6$), 288.0997 (1.4, $C_{16}H_{16}O_5$), 260.1048 (1.6, $C_{15}H_{16}O_4$), 257.0814 (1.9, $C_{15}H_{13}O_4$), 229.0864 (2.3, $C_{14}H_{13}O_3$), 228.0787 (2.3, $C_{14}H_{12}O_3$), 211.0759 (1.3, $C_{16}H_{11}O_2$), 183.0820 (1.1, $C_{13}H_{11}O$), 143.0867 (1.4, $C_{11}H_{11}$), 117.0725 (2.4, C_9H_9), 100.0536 (4.0, $C_5H_8O_2$), 91.0559 (10.5, C_7H_7), 83.0519 (100.0, C_5H_7O).

Anal. Calcd for $C_{23}H_{28}O_9$: M_r 448.1733. Found: M_r (MS) 448.1733.

Fractions 42–68 of the above chromatographic run provided 140 mg of crude **2a** which was recrystallized from $CHCl_3$–isopropyl ether to yield 120 mg of pure **2a**: mp 83–84 °C; UV λ_{max} (MeOH) 222 nm (ϵ 1.8 × 10^4); CD (c 5.6 × 10^{-5}, MeOH) $[\theta]_{218}$ −74 × 10^3, $[\theta]_{244}$ +4 × 10^3; IR ν_{max} (neat) 3450, 1765, 1740, 1730, 1660, 1645 cm^{-1}. The low-resolution mass spectrum (20 eV) showed significant peaks at *m/e* (relative intensity) 464 (2.0, M^+), 404 (3.9, M − 60), 364 (1.0, M − 100), 304 (7.4, M − 100 − 60), 186 (18.4, C), 144 (13.5, B), 139 (8.8), 100 (6.9), 83 (100), and 55 (9.7).

Acetylation of 40 mg of **2a** gave 42 mg of acetate **2b** as a gum: UV λ_{max} (MeOH) 218 nm (ϵ 8.4 × 10^3); CD (c 4.7 × 10^{-5}, MeOH) $[\theta]_{220}$ −48 × 10^3, $[\theta]_{242}$ +3.0 × 10^3; IR ν_{max} (neat) 1765, 1755, 1740, 1730, 1660, 1645 cm^{-1}. The low-resolution mass spectra (70 eV) of the acetate and the acetate-d_3 of **2a** showed the following significant peaks [*m/e* acetate/*m/e* acetate-d_3 (relative intensity)]: 548/557 (1.8), 488/494 (3.2), 448/457 (3.2), 285/285 (7.0), 186/190 (3.2), 144/146 (4.1), 83/83 (100), 55/55 (31), 43/46 (64). The high-resolution data of selected peaks of the acetate **2b** are *m/e* (composition) 548.1915 ($C_{27}H_{32}O_{12}$), 186.0529 ($C_8H_{10}O_5$), 144.0422 ($C_6H_8O_4$), and 139.0395 ($C_7H_7O_3$).

Table I. ^1H NMR Parameters[a] of Melcanthin A (1a), Melcanthin B (2a), Acetate 2b, and Melcanthin C (3a)

signal	1a	1b[f]	2a	2b[b,f]	2b	2c[f]	3a
H-1	7.11 dd (8.0, 8.0)	7.05 m	7.13 d (7.0)	7.03 d (6.0)	7.01 d (7.0)	7.30 m	7.16 d (7.0)
H-2	2.15–2.87[e]	2.5, 2.9	4.66 m	5.62 br dd (6.0, 6.0)	5.63 br ddd (2.5, 7.0, ~7.0)	4.58 m	4.72 m
H-3			(a) 2.45 br d (15.0) (b) 2.78 br dd (4.0, 15.0)	2.47 br d (16.0) 2.77 dd (6.0, 16.0)	(a) 2.55 dd (2.5, 14.5) (b) 2.95 br dd (~7.0, 14.5)	(a) 2.66 dd (2.15, 15) (b) 2.90 br d (15)	(a) 2.54 d (15.0) (b) 2.83 dd (5.0, 15.0)
H-5	5.65 br d (10.0)	6.45 br d (9)	5.73 br d (9.0)	5.80 d (10.0)	5.80 br d (9.0)	6.80 d (9.0)	5.73 d (9.0)
H-6	5.44 dd (5.0, 10.0)	5.78 br	5.19 br dd (6.5, 9.0)	5.11 dd (10.0, 7.0)	5.25 m	5.39 dd (9.0, 9.0)	5.21 dd (10.0, 7.0)
H-7	3.16 m	3.27 m	3.28 m	3.24 m	3.29 m	3.33 m	3.18 m
H-8	5.89 dd (2.5, 4.5)	5.94 dd (2.5, 5.0)	5.93 dd (2.0, 3.5)	5.90 dd (2.0, 4.0)	5.94 dd (2.0, 3.5)	6.15[e]	5.91 m
H-9	6.09 d (4.5)	6.21 br (5.0)	5.69 d (3.5)	5.55 d (4.0)	~5.8[e]	5.52 d (6.0)	5.71 d (4.5)
H-13a	5.79 d (2.5)	5.88 br	5.88 d (2.5)	5.92 d (2.5)	5.86 d (2.5)	6.13 d (3.0)	5.83 d (2.5)
H-13b	6.35 d (3.0)	6.46 d (2.5)	6.35 d (3.0)	6.33 d (3.0)	6.38 d (3.0)	6.53 d (3.0)	6.36 d (3.5)
H-3′/H-2′	6.08 qq (1.2, 7.0)	6.21 br q (7.0)	6.09 qq (1.2, 7.0)	6.12 qq (1.5, 7.0)	6.09 qq (1.5, 7.0)	6.06 br q (6.0)	2.41 hept[g] (7.0)
H-15	4.12 d[c] (1.0)	9.49 s	4.27 br[c]	(a) 4.60 br d (15.0) (b) 4.70 br d (15.0)	(a) 4.60 dd (1.0, 13.0) (b) 4.77 dd (1.5, 13.0)	9.65 br s	4.30 br[c]
C-2′ Me	1.76 p (1.2)	1.80 br s	1.74 m	1.66 br s	1.76 m	1.77 br s	(a) 1.05 d (7.0) (b) 1.08 d (7.0)
C-3′ Me	1.94 dq (1.2, 7.0)	1.97 br d (7.0)	1.94 dq (1.2, 7.0)	1.89 br d (7.0)	1.95 dq (1.5, 7.0)	1.97 br d (6.0)	
COOMe	3.69	3.74	3.62	3.51	3.56	3.66	3.69
acetates	2.09	2.14	2.05	2.06, 2.04[d]	2.00, 1.97[d]	2.08	2.10

[a] Spectra were run at 60 °C in $CDCl_3$ at 100 MHz, and Me_4Si was used as an internal standard. Values are recorded in parts per million relative to Me_4Si. Singlets are unmarked and multiplets are designated as follows: d, doublet; t, triplet; q, quartet; p, pentet; m, multiplet whose center is given; br, broad. Figures in parentheses are coupling constants or line separations in hertz. [b] Run in CD_2Cl_2 at −50 °C. [c] Intensity of two protons. [d] Intensity of six protons. [e] Obscured by other signals. [f] Run at 270 MHz. [g] H-2′.

Anal. Calcd for $C_{27}H_{32}O_{12}$: M_r 548.1894. Found: M_r (MS) 548.1915.

Aldehydes 1b and 2c. A sample of 3 mg of each of **1a** and **2a** was dissolved in 3 mL of ether and shaken at room temperature for 1 h with about 100 mg of activated MnO_2. After filtration and evaporation, the NMR spectra of the residual gums, **1b** and **2c**, were obtained at 270 MHz without further purification (Table I). The spectra indicated complete conversion of **1a** and **2a** into **1b** and **2c**, respectively.

Melcanthin C (3a). A second collection of *M. leucanthum*, Stuessy No. 3829, made in Grant County, N. Mex., 1.4 mile west of Silver City on Highway 260 on September 9, 1975, provided, by the above extraction procedure, 13 g of crude syrup which was chromatographed over 300 g of silica gel using *n*-propyl acetate as eluent, with 20-mL fractions being collected. Rechromatography of fractions 71–79 over 20 g of silica gel using $CHCl_3$–*n*-propyl acetate (3:2) as eluent yielded in fractions 63–75 90 mg of melcanthin C as a gum: CD (*c* 2.43×10^{-4}, MeOH) $[\theta]_{214}$ -1.64×10^4, $[\theta]_{239}$ $+1.13 \times 10^3$, $[\theta]_{261}$ -5.75×10^2; IR ν_{max} ($CHCl_3$) 3500, 1760, 1740, 1720, 1230, 1130 cm^{-1}. The low-resolution mass spectrum (70 eV) showed significant peaks at *m/e* (relative intensity) 452 (0.2, M^+), 392 (0.3, M − 60), 364 (0.7, M − 88), 304 (4.0, M − 60 −88), 71 (62.0), and 43 (100.0).

Anal. Calcd for $C_{22}H_{28}O_{10}$: M_r 452.168. Found: M_r (MS) 452.167.

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Registry No.—**1a**, 68024-34-0; **1b**, 68024-35-1; **2a**, 68024-36-2; **2b**, 68024-37-3; **2c**, 68024-38-4; **3a**, 68024-39-5.

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Mechanism of the Rearrangement of 5,6-Disubstituted-dibenzo[*a*,*e*]cyclooctatetraenes to the 5,11-Isomers[1]

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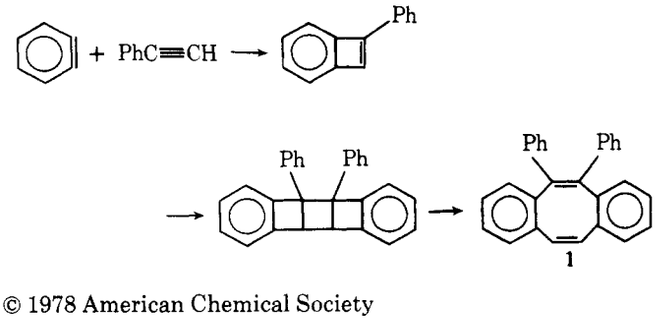
The previously reported rearrangement of 5,6-disubstituted-dibenzo[*a*,*e*]cyclooctatetraenes to the 5,11-isomers has been shown to proceed via biradical intermediates. The biradicals derived from the 5,6-diphenyl and 5,11-diphenyl representatives were trapped by reaction with benzenethiol, and the structures of the resulting reduction products were established by chemical and spectroscopic data and by comparison with known compounds. The rate of reaction of **1** with butanethiol was similar to its rate of rearrangement, indicating that the two processes required a common intermediate, the biradical **4**.

Benzyne, generated under the appropriate conditions, undergoes reaction with acetylene derivatives to give dibenzocyclooctatetraenes.[2] The reaction is illustrated by the formation of 5,6-diphenyldibenzo[*a*,*e*]cyclooctatetraene (**1**), a compound of central interest to the present paper.

Investigation of the thermal behavior of **1** and related compounds such as the 5,6-dicarbomethoxy analogue led to the discovery of a novel rearrangement.[3] When heated, the starting materials are smoothly rearranged to the 5,11-isomers; e.g., **1** yields **2**.



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