Puberulin and Isopuberulin, Benzonorcaradiene and Benzocycloheptatriene Diterpenoids of Clerodanic Origin from *Salvia puberula*†

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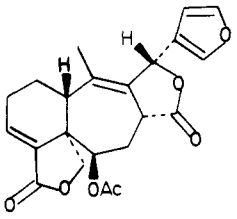
From the aerial parts of *Salvia puberula* Fern., two clerodane diterpenoids with novel benzonorcaradiene and benzocycloheptatriene structures were isolated. They were named puberulin and isopuberulin. A probable biogenetic relationship with salvigenolide from *S. fulgens* is proposed. The structures of puberulin and isopuberulin were established by spectroscopic means and X-ray diffraction analysis of isopuberulin. Puberulin is transformed into isopuberulin by a thermal reaction which could be the result of an electrocyclic reaction followed by 1,5-sigmatropic hydrogen shifts.

Recently we have undertaken a systematic chemotaxonomic study of the Mexican salvia species.[1] The *Salvia* spp. of Mexico and Central and South America have been classified in the Calosphace subgenus which was subdivided in 91 sections.[2] In this paper we describe the diterpenoid constituents of *Salvia puberula* Fern., which has been recently classified in the section Holwaya (Ramamoorthy).[3] This section is botanically related to section Fulgentes of which we have studied several species. From *S. lineata* (Fulgentes) neo-clerodane diterpenoids[4] structurally related to salviarin[5] were isolated. S. fulgens yielded[6] a rearranged neoclerodane diterpenoid, salvigenolide (**1**), which could be considered biogenetically related to the diterpenoids **2** and **3** isolated from *S. puberula*.



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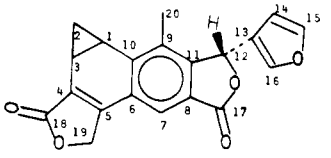

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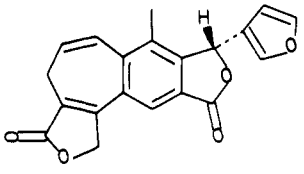

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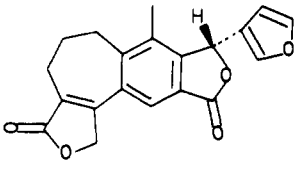

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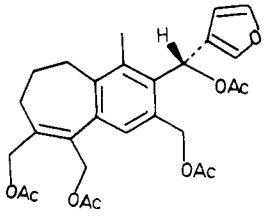

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Results and Discussion

Repeated column chromatography of the acetone extract of the aerial parts of *Salvia puberula* yielded product **2**, which was named puberulin, as an amorphous powder, mp 252 °C dec, whose MS supports molecular formula $C_{20}H_{14}O_5$. Its IR spectrum showed the presence of α,β-unsaturated γ-lactone (1756 and 1664 cm^{-1}) and β-substituted furan (1614, 1504, and 874 cm^{-1}). The UV spectrum (see Experimental Section) was consistent with a high degree of unsaturation in the molecule.

The ^1H NMR spectrum of **2** revealed the presence of a disubstituted cyclopropane ring. Analysis of the signals observed (Table I) and double resonance experiments led to the assignment of a quartet found at δ −0.04 (1 H, J = 5, 4 Hz; δ −0.55 in benzene-d_6) to the 2-endo proton; the

Table I. ^1H NMR Data for 2, 3, 4, and 5 [$CDCl_3$, 80 MHz][a]

H	2	3	4	5
1	2.55 td (9,5)	6.65 d (12)	2.95 t[b] (5)	
2	−0.04 q (5) endo	6.15 dt (12,6)	2.05 m[b]	
2′	1.91 td (9,5) exo			
3	2.4 td (9,5)	3.0 br d[b] (6)	2.7 tt[b] (5,3)	
7	7.6 s	7.8 s	7.65 s	7.2 s
12	6.35 s	6.45 s	6.4 s	7.05 br q (1)
14	6.15 dd (2,1)	6.15 dd (2,1)	6.1 dd (2,1)	6.25 dd (2,1)
15	7.4 t (2)	7.5 t (2)	7.4 t (2)	7.35 t (2)
16	7.5 br s	7.5 br s	7.5 br s	7.2 br s
17(2)				5.25 AB q (12)
18(2)				5.05 br s
19(2)	5.15 br s	5.15 t (1)	5.15 t (3)	4.9 br s
20(3)	2.3 s	2.25 s	2.2 s	2.4 s
$OCOCH_3$				2.0, 2.05, 2.15, 2.17 four s [3 H each]

[a] TMS as internal standard. Chemical shifts in δ (J values in parentheses, in Hz). [b] Two-proton intensity.

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Table II. ^{13}C NMR Data for Compounds 3 and 4 ($CDCl_3$, 20 MHz)[a]

C	3	4
1	127.0 (d)	28.0 (t)*
2	133.0 (d)	25.0 (t)
3	22.2 (t)	29.5 (t)*
4	147.5 (s)	150.0 (s)
5	153.5 (s)	152.5 (s)
6	131.8 (s)	132.0 (s)
7	121.4 (d)	122.0 (d)
8	124.9 (s)	125.0 (s)
9	128.2 (s)	130.0 (s)
10	142.0 (s)	149.0 (s)
11	133.5 (s)	133.0 (s)
12	75.3 (d)	76.0 (d)
13	121.1 (s)	122.0 (s)
14	108.9 (d)	109.0 (d)
15	144.5 (d)	145.0 (d)
16	142.3 (d)	143.0 (d)
17	169.0 (s)	170.0 (s)
18	174.0 (s)	175.0 (s)
19	69.5 (t)	71.0 (t)
20	16.0 (q)	16.0 (q)

[a] Chemical shifts are in ppm with respect to TMS. SFORD multiplicities are in parentheses. * indicates these values could be interchangeable.

chemical shift found for this proton can be explained as a result of the diamagnetic effect exerted by the aromatic B ring. The 2-exo proton was observed as a triple doublet at δ 1.91 (1 H, J = 9, 5 H); H-1 and H-3 were responsible for partially superimposed triple doublets at δ 2.55 (1 H, J = 9, 5 Hz) and 2.40 (1 H, J = 9, 5 Hz), respectively. Irradiation at δ −0.04 transformed these three triple doublets to triplets (J = 9 Hz). The chemical shifts of these protons are consistent with a substituted benzonorcaradiene structure as shown in **2**.[7] A singlet (3 H) at δ 2.3 was ascribed to the methyl group. The β-substituted furan protons gave characteristic signals at δ 6.15 (1 H, H-14, dd, J = 2, 1 Hz), 7.4 (1 H, H-15, t, J = 2 Hz) and 7.5 (1 H, H-16, br s). A sharp singlet at δ 7.6 (1 H) was assigned to H-7 and a singlet at δ 6.35 (1 H) to H-12. The presence of an abundant fragment at m/e 95 (30) in the mass spectrum of puberulin (see Experimental Section) supports[8] the existence of the γ-lactone group and a furan moiety bound to C-12. A broad singlet (2 H) at δ 5.15 was assigned to the C-19 methylene; the large paramagnetic shift shown by these protons as compared with the chemical shifts usually observed for them[6] must be due to their benzylic nature. Based on the evidence described, puberulin can be represented by structure **2**.

The second diterpenoid isolated from *S. puberula* was a crystalline product, mp 206–211 °C. Its MS was consistent with molecular formula $C_{20}H_{14}O_5$. The fragmentation pattern differed from that of puberulin only in the relative abundances of the fragments, so it was considered an isomer of puberulin and was named isopuberulin. Structure **3** was assigned to it on the following evidence. Its IR spectrum differed from that of puberulin (**2**) only in the fingerprint region.

The ^1H NMR spectrum of isopuberulin did not show the cyclopropane protons present in puberulin; instead the signals due to vinylic protons were observed at δ 6.65 (1 H, d, J = 12 Hz) and 6.15 (1 H, dt, J = 12,6 Hz) and were ascribed to H-1 and H-2. The C-3 methylene appeared as a broad doublet (2 H, J = 6 Hz) at δ 3.0. Irradiation

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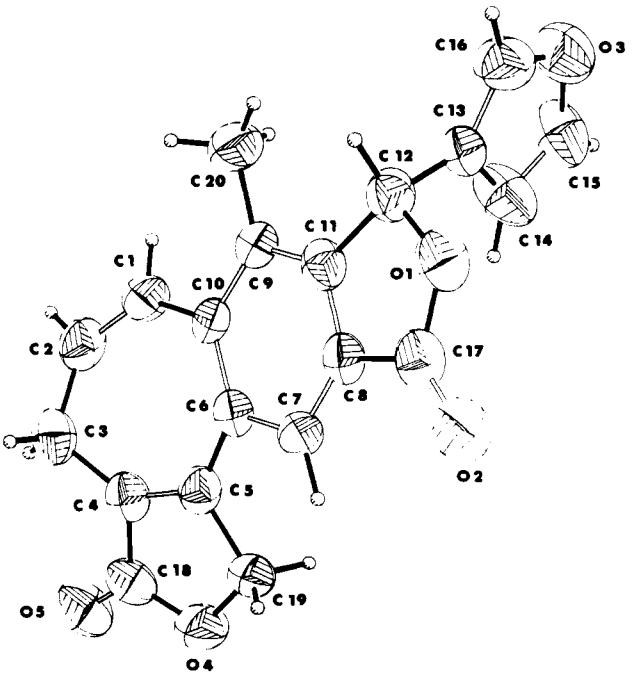


Figure 1. The molecular conformation of isopuberulin compound, showing atom numbering. The thermal ellipsoids are drawn at the 50% probability level.

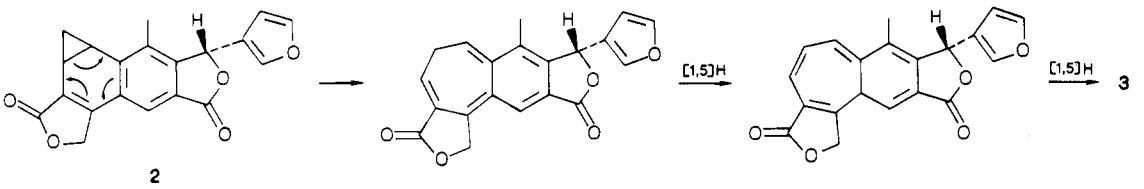
Table III. Atomic Coordinates (×10⁴) for Isopuberulin

atom	x	y	z
O(1)	4252 (4)	−1145 (2)	7332 (1)
O(2)	4789 (4)	660 (3)	7840 (1)
O(3)	−390 (5)	−3494 (3)	7086 (2)
O(4)	2461 (5)	5153 (2)	5439 (2)
O(5)	2505 (5)	5583 (3)	4267 (2)
C(1)	2477 (6)	872 (4)	4390 (2)
C(2)	2734 (6)	1746 (4)	3909 (2)
C(3)	3493 (6)	2977 (4)	3985 (2)
C(4)	3098 (5)	3545 (4)	4690 (2)
C(5)	3071 (5)	3078 (3)	5350 (2)
C(6)	3287 (5)	1811 (3)	5598 (2)
C(7)	3734 (5)	1658 (3)	6327 (2)
C(8)	3814 (5)	498 (4)	6596 (2)
C(9)	2945 (5)	−398 (3)	5466 (2)
C(10)	2929 (5)	781 (3)	5159 (2)
C(11)	3401 (5)	−497 (3)	6189 (2)
C(12)	3489 (6)	−1617 (4)	6661 (2)
C(13)	1714 (6)	−2167 (4)	6822 (2)
C(14)	100 (6)	−1545 (4)	6923 (3)
C(15)	−1128 (7)	−2380 (5)	7062 (3)
C(16)	1350 (7)	−3334 (4)	6942 (3)
C(17)	4329 (5)	93 (4)	7322 (2)
C(18)	2669 (6)	4854 (4)	4739 (2)
C(19)	2686 (6)	4081 (3)	5874 (2)
C(20)	2568 (7)	−1521 (3)	5029 (2)

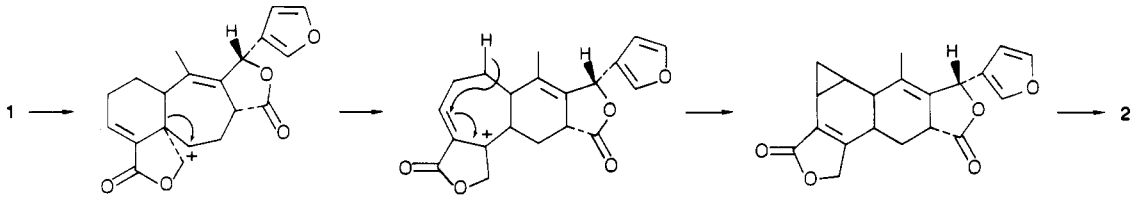
at δ 3.0 transformed the double triplet attributed to H-2 into a doublet (J = 6 Hz), and also sharpened the signal at δ 5.15 (2 H, t, J = 1 Hz) ascribed to the C-19 methylene, showing the homoallylic coupling between the two methylene groups. The rest of the spectrum was identical with that of puberulin (**2**) (Table I).

The ^{13}C NMR spectrum of isopuberulin **3** (Table II) confirmed its highly unsaturated character. There were only two triplets, at δ 22.2 and 69.5, which were assigned to C-3 and C-19, respectively. Three doublets at δ 127, 133, and 121.4 were ascribed to the vinylic 1 and 2 and the aromatic 7 carbon atoms. A doublet at δ 75.3 was unambiguously assigned to C-12; the quartet at δ 16.0 was ascribed to the C-20 methyl carbon atom. The rest of the signals were the three doublets of the β-substituted furan ring and ten singlets (Table II). The assignments were

Scheme I



Scheme II



made by calculation of the theoretical chemical shifts expected for the substituted aromatic ring.[9]

The structure of isopuberulin (3) was confirmed by X-ray diffraction analysis of a single crystal. The molecular structure of isopuberulin determined from the X-ray data is illustrated in Figure 1. Final positional parameters for non-H atoms are listed in Table III. The seven-membered ring does not adopt any of the symmetric conformations. The γ-lactone ring C(4)–C(5)–C(19)–O(4)–C(18) is almost planar. However the other γ-lactone ring C(8)–C(11)–C(12)–O(1)–C(17)–C(8) adopts a conformation intermediate between a half-chair and a β-envelope conformation. The dihedral angles between the seven- and six-membered rings and the γ-lactone rings containing the O(4) and O(1) atoms are 20.7° and 4.1°, respectively. The benzene and furan rings are planar within the limit of experimental error. The dihedral angle between the furan ring and γ-lactone containing the O(1) atom is 98.2°.

Catalytic hydrogenation of isopuberulin (3) gave the dihydroderivative 4, which was also obtained on catalytic hydrogenation of puberulin (2). Lithium aluminum hydride reduction of 4 followed by acetylation gave the tetraacetate 5, whose ^{1}H NMR spectrum (Table I) showed the methylenes bound to acetoxy groups as two broad singlets at δ 5.05 and 4.9 (2 H each) and an AB quartet at δ 5.25 (2 H, J = 12 Hz); H-12 appeared as a narrow quartet at δ 7.05 (1 H, J = 1 Hz) due to its coupling with the furan protons.

Puberulin (2) was slowly transformed into isopuberulin (3) in boiling methanolic solution and even in methylene chloride solution. This transformation can occur by a disrotatory electrocyclic reaction followed by two suprafacial 1,5-sigmatropic hydrogen shifts as shown in Scheme I. This type of transformation is well documented.[7,10-14]

2 is sufficiently stable at room temperature to show clear signals for the cyclopropane protons in the ^{1}H NMR spectrum (vide supra). An acid-catalyzed opening of the cyclopropane in 2 cannot be ruled out.

Purberulin (2) can be biogenetically derived from salvigenolide (1) as outlined in Scheme II, by the loss of the C-6 acetoxy group followed by a 6 → 7 expansion of the A ring, formation of the norcarene system and dehydrogenation to 2.

This biogenetic relation between puberulin (2) and salvigenolide (1) provides a chemical basis for the botanical relationship established between the Holwaya and Fulgentes sections. Puberulin and isopuberulin are, to our knowledge, the first natural product of clerodanic origin described with benzonorcaradiene–benzocycloheptatriene structures.

Experimental Section

For general experimental procedures see ref 4. Plant material was collected in the state of San Luis Potosí, México, in July 1985 and a voucher specimen was deposited at the Herbarium of the Instituto de Biología [Ramamoorthy et al., 4858(MEXU)].

Isolation of Constituents of *Salvia puberula* Fern. Dried and powdered aerial parts of *S. puberula* (850 g) were extracted with Me_2CO for 1 week at room temperature. The solvent was removed in vacuo to yield 60 g of gummy extract, which was subjected to column chromatography over Si-gel (1.8 kg deactivated with 10% water). Mixtures of petroleum ether–EtOAc and EtOAc–MeOH of increasing polarity were used as eluents.

From the fractions eluted with petroleum ether–EtOAc (19:1) was isolated 426 mg (0.050% dry weight) of β-sitosterol, identified by comparison with an authentic sample.

Extensive purification by column chromatography of the fraction eluted with petroleum ether–EtOAc (4:1) led to the isolation of three compounds. The most abundant one (5.2 g, 0.62% dry weight) was a white powder identified as oleanolic acid by comparison of its methyl ester derivative with an authentic sample.

The least polar compound was a crystalline solid, named isopuberulin (3) (0.885 g, 0.104% dry weight): mp 206–211 °C; IR($CHCl_3$) ν_{max} (cm^{-1}) 1750, 1660, 1610, 1070, 870; UV λ_{max} [nm (ε)] 206 (25 300), 258 (43 860); ^{1}H NMR, see Table I; ^{13}C NMR, see Table II; MS, m/z (relative intensity) 336 (3.6), 335 (19.7), 334 (100), 339 (3), 305 (30), 240 (10), 239 (70), 202 (10), 179 (15), 152 (15), 139 (10), 95 (15). $C_{20}H_{14}O_5$ requires M^+ at m/z 334.

The most polar compound was an amorphous powder, named puberulin (2) (750 mg, 0.0882% dry weight): mp 252 °C dec; IR ($CHCl_3$) ν_{max} (cm^{-1}) 1756, 1664, 1614, 1504, 1027, 874; UV λ_{max} [nm (ε)] 200 (11 780), 250 (19 239), 295 (5186), 330 (shoulder 2074); ^{1}H NMR, see Table I; MS, m/z (relative intensity) 335 (20), 334 (89.7), 319 (10), 305 (43), 240 (15), 239 (100), 210 (20), 202 (20), 189 (20), 152 (20), 95 (30). $C_{20}H_{14}O_5$ requires M^+ at m/z 334.

Catalytic Hydrogenation of 3. Compound 3 (130 mg) in EtOAc (10 mL) was hydrogenated with Pd/C (26 mg, 10%) as catalyst, for 4.5 h. After the usual workup, 4 (122 mg) was obtained as a crystalline solid: mp 171–173 °C (CH_2Cl_2–isopropyl ether); IR ($CHCl_3$) ν_{max} (cm^{-1}) 3027, 1768, 1750, 1640, 1600, 1580, 1291, 1090, 948, 870. UV λ_{max} [nm (ε)] 278 (20 200), 245 (44800); ^{1}H NMR, see Table I; ^{13}C NMR, see Table II; MS, m/z (relative intensity) 336 (56.9), 307 (10), 241 (100), 141 (10), 139 (10), 115

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(20), 95 (25.8). $C_{20}H_{16}O_5$ requires M^+ at m/z 336.

Conversion of 4 to 5. Compound **4** (92 mg) in THF (10 mL) was added to a suspension of $LiAlH_4$ (130 mg) in THF. The mixture was stirred at 0 °C under Ar for 21 h. After the usual workup 88 mg of crude product was obtained, which was acetylated without purification, with Ac_2O (1 mL) in C_5H_5N (1 mL) for 14 h at room temperature. After the usual workup, 82 mg of crude product was obtained. It was purified by flash chromatography to yield 42 mg of **5** as an oily product: IR ($CHCl_3$) ν_{max} (cm^{-1}) 1735, 1377, 1241, 1025, 958; ^1H NMR, see Table I; MS m/z (relative intensity) 514 (0.4), 513 (1.6), 512 (3.8), 452 (20), 410 (20), 350 (40), 308 (20), 291 (20), 290 (20), 95 (10), 81 (20), 43 (100). $C_{28}H_{32}O_9$ requires M^+ at m/z 512.

X-ray Analysis of Isopuberulin. Colorless crystals of isopuberulin were grown by slow evaporation from methylene chloride/methanol. Intensities were collected on a single crystal (0.36 × 0.36 × 0.44 mm) on a Nicolet R3m automated diffractometer using graphite-monochromatized Mo Kα radiation (λ 0.7107 Å). Lattice constants were as follows: a = 7.557 (2) Å, b = 11.021 (4) Å, c = 18.573 (7) Å; space group $P2_12_12_1$, V = 1547 (1) Å^3, $F(000)$ = 696, T = 293 K, D_{calcd} = 1.43 g cm^{-3}, Z = 4, and μ(Mo Kα) = 0.97 cm^{-1}. Of the 1582 reflections within the 2θ range of 3-50° collected, 1191 had values of $|Fo|^2$ that were greater than three times their estimated standard deviations, and these were used in the final refinement. The crystal structure was solved by direct methods as incorporated by Sheldrick (1981) into the SHELXTL[15] system. The program SOLV was employed with 186 phases with $|E| > 1.6$ and 12 reflections in the starting set. The trial structure was refined by a blocked cascade least-squares procedures with anisotropic temperature factors for the non-H atoms and with a fixed isotropic temperature factor, U = 0.06 Å^2, for the H atoms. The final R factor was 0.047 and Rw = 0.045 and S = 1.22 (see supplementary material).

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Registry No. **2**, 115321-31-8; **3**, 115321-32-9; **4**, 115321-33-0; **5**, 115338-19-7; β-sitosterol, 83-46-5; oleanolic acid, 508-02-1.

Supplementary Material Available: Tables of thermal parameters, bond distances, and bond angles (4 pages); tables of observed and calculated structure factors (8 pages). Ordering information is given on any current masthead page.

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A New Coumarin Synthesis and Its Utilization for the Synthesis of Polycyclic Coumarin Compounds with Anticarcinogenic Properties

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A novel synthesis of coumarins based on the ortho-directed metalation of methoxymethyl phenolic ethers with alkyllithium reagents is described. The method entails reaction of the ortho-lithiated intermediates with dimethylformamide to yield the corresponding ortho-aldehydes. Reaction of the latter with lithio-*N*,*N*-dimethylacetamide affords the addition products which on heating in refluxing acetic acid undergo smooth conversion directly to coumarins. This synthetic approach affords good overall yields and appears general in its applicability. A wide range of coumarins containing substituents in the 6- and 7-positions as well as the polycyclic coumarin analogues of phenanthrene, benz[*a*]anthracene, and benzo[*a*]pyrene and their methyl-substituted derivatives were synthesized by appropriate modification of this method. Preliminary assays of biological activity indicate that the benzo[*a*]pyrene coumarin analogue **11b** is a potent inhibitor of tumor induction when administered prior to the carcinogen 7,12-dimethylbenz[*a*]anthracene, and **11b** is itself devoid of tumorigenic activity. The polycyclic coumarins hold promise as agents for the chemoprevention of cancer.

Coumarins constitute an important class of naturally occurring compounds many of which exhibit useful pharmacological activity. Several polycyclic coumarin derivatives have also been shown to be potent inhibitors of tumor induction by carcinogenic polycyclic aromatic hydrocarbons.[1-3] However, investigations of anticarcinogenic activity have been primarily confined to coumarin derivatives available from plant sources, the majority of which are highly oxygenated. Systematic investigations of structural modifications of molecules of this type in relation to anticarcinogenic activity have not been reported.

As the initial phase in a program to examine the structure-activity relationships of anticarcinogenic coumarin compounds, we undertook the synthesis of a series of polycyclic coumarins. For this purpose, we required an efficient method that would be adaptable to the synthesis of both simple coumarins as well as polycyclic coumarin analogues of potent carcinogenic hydrocarbons, such as benzo[*a*]pyrene and 7,12-dimethylbenz[*a*]anthracene, having three to five rings. Interest in the latter compounds was dictated by evidence that suggested that polycyclic coumarins with these dimensions may be more effective than their smaller analogues in blocking tumor induction. Although various synthetic routes to coumarins are known,[4-6] these methods were generally unsatisfactory for

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