rified by column chromatography (silica, 5% methanol in CH_2Cl_2, R_f 0.57) to yield the phenol derivative as white crystals (68 mg, 82%), mp 191–193 °C (ether–pentane). The tetrazolyl ether (41 mg, 0.1 mmol) was then dissolved in THF (5 mL) and hydrogenated over 10% palladium on charcoal (10 mg) at room temperature and atmospheric pressure for 48 h. Filtration of the catalyst and removal of the solvent under reduced pressure followed by preparative layer chromatography (silica, 10% ether in hexane, R_f 0.13, 3 developments) yielded *d*-estratrienone 1 as a white crystalline solid (15 mg, 60%), mp 135–136.5 °C, chromatographically and spectroscopically indentical with our synthetic sample and an authentic sample provided by Syntex.[13]

Acknowledgment. We thank Professor M. P. Cava and Dr. F. Li, Syntex Research Laboratories, for generous gifts of estrone and estra-1,3,5(10)-trien-17-one, respectively. The 360-MHz ^1H NMR spectra were recorded at the Middle Atlantic Regional NMR Facility (NIH No. RR542) at the University of Pennsylvania directed by Dr. G. McDonald. Financial support of this work was provided by Merck, Sharp, and Dohme, USA, Grunenthal Chemie, West Germany, and the University of Pennsylvania.

Registry No. *d*-1, 53-45-2; (±)-1, 69515-99-7; *epi*(*C*-9)-1, 72984-28-2; 2, 2471-91-2; 5, 72939-06-1; 5a, 72953-43-6; 6, 72939-07-2; 6a, 72939-08-3; 7, 72939-09-4; 7a, 72938-78-4; 8, 72938-79-5; 9, 72938-80-8; 10, 72938-81-9; 11a, 71721-30-7; 11b, 71721-31-8; 12a, 20480-66-4; 12b, 20480-67-5; 13a, 72938-82-0; 13b, 72938-83-1; (±)-*cis*-16, 72938-84-2; (±)-*trans*-16, 72938-85-3; (±)-*cis*-17, 72938-86-4; (±)-*trans*-17, 72938-87-5; (±)-*cis*-18, 72938-88-6; (±)-*trans*-18, 72938-89-7; (±)-*trans*-19, 72938-90-0; (±)-20a, 72938-91-1; (±)-20b, 72984-25-9; (±)-21a, 72938-92-2; (±)-21b, 72984-26-0; 22, 26435-99-4; 5-bromo-1-pentene, 1119-51-3; 6-iodo-1-hexene, 18922-04-8; 5-hexen-1-ol tosylate, 18922-06-0; 5-hexen-1-ol mesylate, 64818-36-6; ethyl iodide, 75-03-6; ethanol tosylate, 22381-54-0; (carbethoxymethylene)triphenylphosphorane, 1099-45-2; 2-methylcyclopentenone, 1120-73-6; vinyl bromide, 593-60-2; ethyl bromoacetate, 105-36-2; 5-chloro-1-phenyltetrazole, 14210-25-4.

Total Synthesis of the Major Metabolite of Methoxsalen

Pat N. Confalone* and Dianne L. Confalone[1]

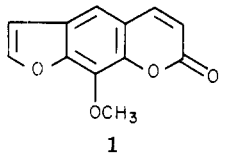
Chemical Research Department, Hoffmann-La Roche Inc., Nutley, New Jersey 07110

Received November 8, 1979

The total synthesis of the 6-coumarinylacetic acid (**15**), the major metabolic isolate of methoxsalen (**1**), starting from umbelliferone (**5**) is described. Several derivatives of a second metabolite, **4**, were also prepared from the common intermediate aldehyde **13**. This preparation involves a novel rearrangement of the bromoacetate **20** to the acetoxyphenol **21**. A mechanism for the displacement reactions of the metabolite **4** and its derivative **21** implicating the transient enone **24** is presented.

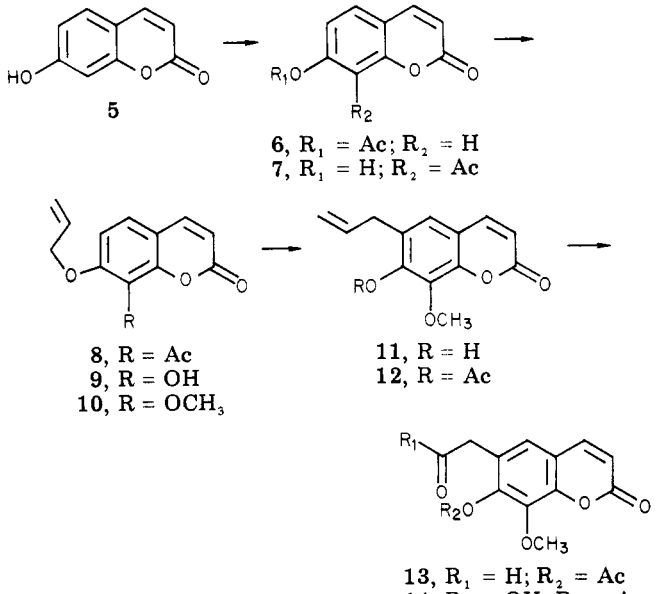
Extracts of the flowering plant *Ammi majus* Linn (family Umbelliferae),[2] a common annual herbaceous plant indigenous to the Nile Delta region, have been employed in the treatment of leukodermia in the form of an ocher powder known as "ameum" since the time of Charles the Great.[3] The active principle was isolated in 1947 by Fahmy and Abu-Shady[4] and was named "ammoidin". An elucidation of the structure was presented by Schönberg[5] in 1950 and shown to be identical with xanthotoxin, a furocoumarin previously reported by Thomas.[6] A number of total syntheses of this substance have since appeared.[7]

A renewed interest in this compound has been ignited by the disclosure that ammoidin (now primarily designated as methoxsalen (**1**) in the literature) is an effective photochemotherapeutic agent for the treatment of psoriasis.[8]



1

Scheme I



5

6, R_1 = Ac; R_2 = H
7, R_1 = H; R_2 = Ac

8, R = Ac
9, R = OH
10, R = OCH_3

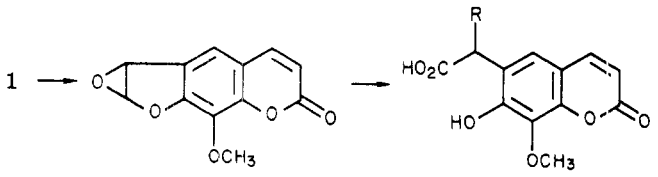
11, R = H
12, R = Ac

13, R_1 = H; R_2 = Ac
14, R_1 = OH; R_2 = Ac
15, R_1 = OH; R_2 = H
16, R_1 = OCH_3; R_2 = H

We have recently published[9] the isolation and structure determination of the major metabolites of methoxsalen (**1**) and wish to report herein the total synthesis of metabolite A (**3**) and a derivative of metabolite B (**4**). Metabolism

(1) Formerly, E. Dianne Lollar.
(2) Fahmy, I. R.; Abu-Shady, H. *Q. J. Pharm. Pharmacol.* **1947**, *20*, 281–91.
(3) "Die Heilpflanzen der verschieden Volker und Zeiten"; Dragendorff: Stuttgart, 1898; p 488.
(4) Fahmy, I. R.; Abu-Shady, H.; Schönberg, A.; Sina, A. *Nature (London)* **1947**, *160*, 468–9.
(5) Schönberg, A.; Sina, A. *J. Am. Chem. Soc.* **1950**, *72*, 4826–8.
(6) Thomas, H.; Preis, H. *Ber. Dtsch. Chem. Ges.* **1911**, *44*, 3325.
(7) Späth, E.; Vierhapper, F. *Ber. Dtsch. Chem. Ges.* **1937**, *70*, 248. Lagercrantz, C. *Acta Chem. Scand.* **1956**, *10*, 647. Rodighiero, G.; Antonello, C. *Ann. Chim. (Rome)* **1956**, *46*, 960. Seghadri, T. R.; Sood, M. S. *Indian J. Chem.* **1963**, *1*, 291. Chatterjee, D. K.; Sen, K. *Tetrahedron Lett.* **1969**, 5223–4. Liu, Y.-Y.; Thom, E.; Liebman, A. A. *J. Heterocycl. Chem.* **1979**, *16*, 799. Confalone, P. N.; Lollar, E. D.; Pizzolato, G.; Uskokovič, M. R. U.S. Patent 4 130 568.
(8) Wolff, K.; Fitzpatrick, T. B.; Parrish, J. A.; Gschnait, F.; Gilchrest, B.; Honigsmann, H.; Pathak, M. A.; Tannenbaum, L. *Arch. Dermatol.* **1976**, *112*, 943.
(9) Kolis, S. J.; Williams, T. H.; Postma, E. J.; Sasso, G. J.; Confalone, P. N.; Schwartz, M. A. *Drug Metab. Dispos.* **1979**, *7*, 220-5.

0022-3263/80/1945-1470$01.00/0

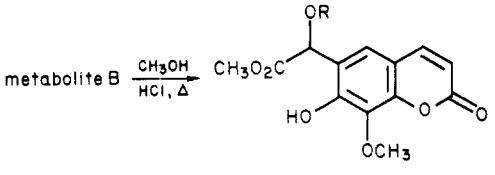


2

3, R = H, metabolite A
4, R = OH, metabolite B

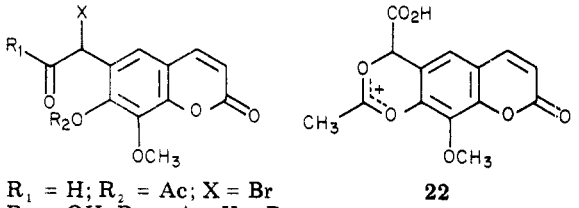
of the psoralen system present in 1 occurs primarily at the furan moiety and leads to the 6-coumarinylacetic acid metabolites A and B. The earliest common intermediate is presumably the reactive epoxide **2**.[10] The synthesis of metabolite A is presented in Scheme I. Commercially available umbelliferone (**5**) was acetylated to the corresponding acetate **6** which underwent a smooth Fries rearrangement[11] to the phenolic ketone **7**. Allylation afforded the *O*-allyl derivative **8**, which was treated with basic hydrogen peroxide to yield the phenol **9**. O-Methylation to the anisole **10** was followed by a Claisen rearrangement to produce the 6-allylumbelliferone derivative **11**.[12] This material was acetylated to the allyl acetate **12** which was oxidatively cleaved to the oily aldehyde **13** by osmium tetraoxide (catalyst) and sodium metaperiodate. This aldehyde proved to be a common intermediate in the synthesis of both metabolite A and the metabolite B derivative. Oxidation of the aldehyde **13** by Jones reagent afforded the acetoxy acid **14** which was deacetylated with 1 N HCl in dioxane at 100 °C to yield the phenolic acid **15**, identical in all respects with metabolite A (**3**) isolated from methoxsalen metabolism. The derived methyl ester **16** of both samples was likewise shown to be identical.

When metabolite B (**4**) was treated with methanolic hydrogen chloride for 1 h, the simple methyl ester **17** was



17, R = H
18, R = CH_3

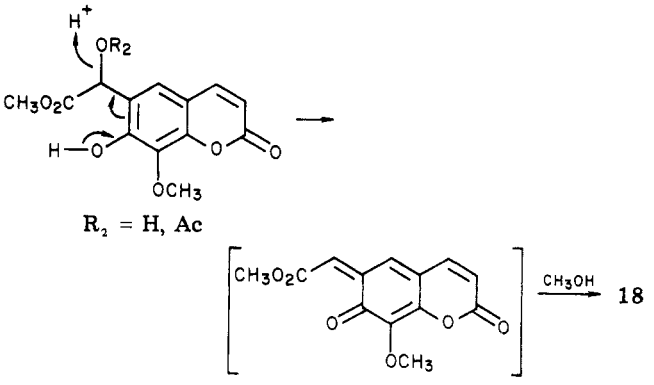
produced.[9] Prolonged reaction afforded the α-methoxy derivative **18**. In order to confirm these results obtained on the natural metabolite, we decided to synthesize an authentic sample of the α-methoxy methyl ester **18**. The readily available aldehyde **13** was smoothly brominated at the benzylic position by direct treatment with elemental bromine to yield the bromo aldehyde **19**. Jones oxidation



19, R_1 = H; R_2 = Ac; X = Br
20, R_1 = OH; R_2 = Ac; X = Br
21, R_1 = OH; R_2 = H; X = OAc

22

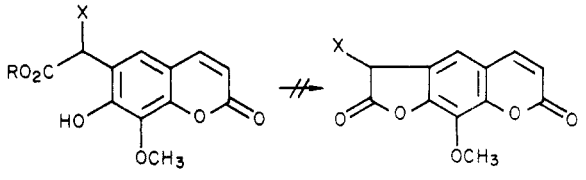
afforded the α-bromo acid **20**, which was found to undergo a useful rearrangement upon acid hydrolysis. Treatment of **20** with 1 N hydrochloric acid in tetrahydrofuran at 65 °C led smoothly to the α-acetoxy phenolic acid **21**. This result implicates an internal solvolysis of the bromide by the proximate acetate group through an intermediate tricyclic cation related to **22**. Interestingly, product **21**, an acetylated derivative of metabolite B, is extremely stable to further hydrolysis to the metabolite. Treatment of **21** with methanolic hydrogen chloride yielded the desired α-methoxy methyl ester **18**, identical in all respects to the sample derived from natural metabolite B. The ready substitution of the α-acetoxy group with methoxy as well as the conversion of metabolite B to the derivative **18** is presumably the result of the acid-catalyzed production of the reactive enone **23**. This species would be expected to readily add methanol to afford the observed products.



R_2 = H, Ac

23

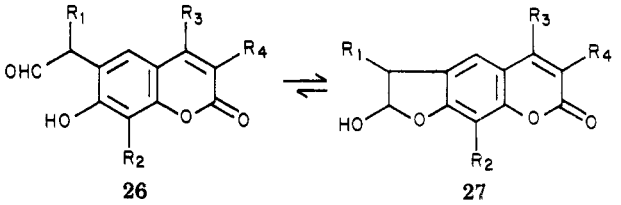
These various ortho phenolic phenylacetic acids and esters of general structure **24** did not exhibit any tendency whatsoever to cyclize to the lactonic derivatives **25**. This



24, R = H, CH_3; X = H, OH, OCH_3, OAc

25

was surprising in view of our recent observation[13] that the corresponding aldehydes **26** exist predominantly in the hemiacetal form **27**.



26

27

In summary, we have confirmed by total synthesis the structures of the two major metabolites A and B of the clinically important antipsoriatic drug methoxsalen (**1**). In this effort we have also discovered some further examples of the novel rearrangements that can occur when the synthetic chemist is dealing with ortho substituents on an aromatic nucleus.

Experimental Section

Melting points were determined on a Rinco Model M-50 melting point apparatus and are uncorrected. IR spectra were obtained by using a Beckmann IR-9 spectrophotometer. A Cary 14 recording spectrophotometer was used for UV absorption spectra. NMR spectra were determined with Varian T-60 and HA-100

(10) Mitchell, J. B.; Nelson, W. L.; Potter, W. Z.; Sasame, H. A.; Jollow, D. J. *J. Pharmacol. Exp. Ther.* **1976**, *199*, 41.
(11) Shah, D. N.; Shah, N. M. *J. Chem. Soc.* **1954**, 1681–5.
(12) This compound was previously reported by T. R. Seshadri and M. S. Sood (*Indian J. Chem.* **1963**, *1*, 291). See the Experimental Section for modifications of this process.
(13) Confalone, P. N.; Lollar, E. D.; Pizzolato, G.; Uskokovič, M. R. U.S. Patent 4 130 568.

spectrometers using tetramethylsilane as the internal reference. Mass spectra were recorded on a CEC 21-110B mass spectrometer at 70 eV using a direct insertion probe. Thin-layer chromatography was carried out by using Merck F-254 silica gel plates.

7-Acetoxycoumarin (6). To a slurry of 200 g (1.24 mol) of 7-hydroxycoumarin (**5**) in 300 mL of methylene chloride was added in one portion a solution of 232 mL (2.48 mol) of acetic anhydride in 100 mL of pyridine. The product separated rapidly, and after 15 min, the volatiles were removed by evaporation and thorough drying in vacuo. The yield of the acetate **6** of sufficient purity to be used directly in the next step was 253 g (100%). An analytical sample was obtained by recrystallization from absolute ethanol to afford white needles: mp 139–140 °C; IR (KBr) 1750 (acetate), 1740 (coumarin), 1610, 1200 cm^{-1}; NMR ($CDCl_3$) δ 7.8–6.4 (m, 5 H, Ar), 2.32 (s, 3 H, Ac); UV max (CH_3OH) 280 nm (ϵ 10 900), 310 (9080).

Anal. Calcd for $C_{11}H_8O_4$ (mol wt 204.18): C, 64.71; H, 3.95. Found: C, 64.71; H, 3.85.

8-Acetyl-7-hydroxycoumarin (7). An intimate mixture of 110 g (0.538 mol) of finely pulverized 7-acetoxycoumarin (**6**) and 215 g (1.61 mol) of anhydrous aluminum trichloride was heated at 150 °C for 1 h. The reaction was quenched at that temperature with an excess of ice/water and crude **7** was collected by filtration. The product was recrystallized from acetonitrile to afford 70.0 g (64%) of pure Fries product **7**. An analytical sample was obtained by recrystallization from absolute ethanol to afford white crystals: mp 167–168 °C; IR (KBr) 1735 (coumarin), 1720 (ketone) cm^{-1}; NMR ($CDCl_3$) δ 7.8–6.2 (m, 4 H, Ar), 2.46 (s, 3 H, Ac); UV max (CH_3OH) 209 nm (ϵ 22 500), 233 (9400), 242 (9400), 267 (8700), 316 (11 580), 340 (sh, 9700).

Anal. Calcd for $C_{11}H_8O_4$ (mol wt 204.18): C, 64.71; H, 3.95. Found: C, 64.54; H, 4.06.

8-Acetyl-7-(allyloxy)coumarin (8). To a solution of 157 g (0.77 mol) of the ketone **7** in 2.5 L of acetone were added 75 mL (0.92 mol) of allyl chloride (mechanical stirring), 126 g (1.52 mol) of potassium carbonate (anhydrous), and 11.8 g (0.077 mol) of sodium iodide. The mixture was heated at reflux for 24 h and allowed to cool to room temperature. The solid was filtered and washed well with acetone. The filtrate was evaporated to dryness to yield approximately 170 g (100%) of crude allyloxy compound **8**, which was recrystallized from absolute ethanol to afford 138 g (81%) of pure **8**: mp 87–88 °C; IR (KBr) 1745 (coumarin), 1710 ketone, 1650 (vinyl), 1250 cm^{-1}; NMR, ($CDCl_3$) δ 7.8–6.8 (m, 3 H, Ar), 6.0–5.2 (m, 3 H, vinyl), 4.8 (d, 2 H, CH_2), 2.60 (s, 3 H, Ac); UV max (CH_3OH) 254 nm (ϵ 4210), 300 (infl, 12 500), 320 (15 800; mass spectrum, m/e 244 (M^+), 226, 215, 201, 189 (base), 173.

Anal. Calcd for $C_{14}H_{12}O_4$ (mol wt 244.25): C, 68.86; H, 4.95. Found: C, 68.98; H, 4.98.

7-(Allyloxy)-8-hydroxycoumarin (9). A suspension of 138 g (0.62 mol) of the allyloxy compound **8** in 780 mL of 2 N sodium hydroxide was heated at reflux for 45 min. The reaction was cooled to 0 °C and 174 mL of 30% hydrogen peroxide was added dropwise with stirring. The reaction was allowed to proceed an additional 2 h. The mixture was acidified to pH 1 by the dropwise addition at 0 °C of 400 mL of 2 N hydrochloric acid. The phenol **9** separated and was collected to yield 129 g (95%) of product, mp 136–139 °C. An analytical sample was obtained by recrystallization from ethyl acetate/pentane to afford pure **9**: mp 138–139 °C; IR (KBr) 1720 (coumarin), 1650 (vinyl), 1100 cm^{-1}; NMR ($CDCl_3$) δ 7.7–6.3 (m, 4 H, Ar), 6.3–5.2 (m, 3 H, vinyl), 4.68 (d, 2 H, CH_2); UV max (CH_3OH) 204 nm (ϵ 38 000), 277 (infl, 8000), 270 (8800), 318 (13 500); mass spectrum, m/e 218 (M^+), 177 (base), 149, 121, 93, 65.

Anal. Calcd for $C_{12}H_{10}O_4$ (mol wt 218.21): C, 66.05; H, 4.62. Found: C, 66.21; H, 4.59.

7-(Allyloxy)-8-methoxycoumarin (10). To a solution of 23.1 g (0.106 mol) of the phenol **9** in 540 mL of acetone was added 12.8 mL of dimethyl sulfate and 20.7 g of anhydrous potassium carbonate. The reaction was heated under reflux overnight, cooled to 25 °C, and filtered. The solid was washed well with acetone, and the filtrate was evaporated to yield 24.3 g (99%) of crude O-methyl compound **10**. The product was filtered over 250 g of silica, eluting with ethyl acetate/hexane (1:1), to afford 22.24 g (91%) of pure **10** as a pale yellow solid. An analytical sample was obtained by recrystallization from ethyl acetate/pentane: mp 74–75 °C; IR (KBr) 1720 (coumarin), 1620 (vinyl), 1300, 1100 cm^{-1}; NMR ($CDCl_3$) δ 7.7–6.3 (m, 4 H, Ar), 6.1–5.4 (m, 3 H, vinyl), 4.7 (d, 2 H, CH_2), 3.98 (s, 3 H, OCH_3); UV max (CH_3OH) 245 nm (sh, ϵ 4500), 255 (5050), 316 (15 100); mass spectrum, m/e 232 (M^+), 191, 174, 163 (base).

Anal. Calcd for $C_{13}H_{12}O_4$ (mol wt 232.4): C, 67.24; H, 5.21. Found: C, 67.43; H, 5.20.

6-Allyl-7-hydroxy-8-methoxycoumarin (11). A charge of 300 g (1.29 mol) of the *O*-methyl compound **10** was added to 600 mL of silicone oil preheated to 205 °C. The reaction was stirred rapidly, and the temperature was maintained for 3 h at 200 °C. The mixture was cooled to 25 °C, and the solid was filtered and then dissolved in 850 mL of ethyl acetate by warming to 50 °C. Hexane was added to the point of turbidity, and the solution was filtered over 60 g of silica, eluting with 250 mL of ethyl acetate/hexane (1:1). The eluate was stripped, and the residue was triturated with ether. The insoluble solid was dried to afford 149 g of pure Claisen product **11**. The mother liquors yielded an additional 49.5 g to afford a total of 198.5 g (66%) of pure product. Additional runs at higher scale yielded 70% on the average. For analysis, a sample was recrystallized from ethanol to yield pure **11**: mp 125–126 °C; IR (KBr) 1720 (coumarin), 1615 (vinyl), 1400, 1200 cm^{-1}; NMR ($CDCl_3$) δ 7.8–6.3 (m, 3 H, Ar), 6.2–5.1 (m, 3 H, vinyl), 5.1 (br s, 1 H, OH), 4.14 (s, 3 H, OCH_3), 3.6 (br d, 2 H, CH_2); UV max (CH_3OH) 205 nm (ϵ 16 500), 328 (14 300), 349 (infl, 8900); mass spectrum, m/e 232 (M^+, base), 217, 204, 189, 171, 161.

Anal. Calcd for $C_{13}H_{12}O_4$ (mol wt 232.24): C, 67.24; H, 5.21. Found: C, 67.47; H, 5.28.

7-Acetoxy-6-allyl-8-methoxycoumarin (12). A solution of 10.0 g (0.0431 mol) of 6-allyl-7-hydroxy-8-methoxycoumarin (**11**) in 50 mL of chloroform was treated with 7 mL of acetic anhydride and 14 mL of pyridine and was stirred overnight at 25 °C. The volatiles were removed to afford crude acetoxy product **12** in quantitative yield. The material could be recrystallized from absolute ethanol to yield 9.87 g (84%) of pure **12**: mp 102–103 °C; IR (KBr) 1765 (acetate), 1730 (coumarin), 1640 (vinyl) cm^{-1}; NMR ($CDCl_3$) δ 7.6–6.3 (m, 3 H, Ar), 6.2–5.1 (m, 3 H, vinyl), 4.00 (s, 3 H, OCH_3), 3.3 (br d, 2 H, CH_2), 2.34 (s, 3 H, Ac); UV max (CH_3OH) 204 nm (ϵ 42 800),224 (sh, 20 000), 287 (12 800), 325 (sh, 4300); mass spectrum, m/e 274 (M^+), 232 (base), 217, 206, 199, 189.

Anal. Calcd for $C_{15}H_{14}O_5$ (mol wt 274.27): C, 65.69; H, 5.15. Found: C, 65.67; H, 4.92.

7-Acetoxy-6-(formylmethyl)-8-methoxycoumarin (13). A solution of 9.87 g (0.036 mol) of the allyl acetate **12** in 180 mL of ethyl acetate was treated with 180 mL of water, 28.82 g of KIO_4 (0.123 mol), and 20 mL of 10% osmium tetraoxide (aqueous, corresponding to 10 mg of OsO_4/mL of solution). The mixture was stirred vigorously for 7.5 h. The organic phase was separated, and the aqueous layer was further extracted two times with ethyl acetate. The organic extracts were dried and evaporated to afford 9.9 g (100%) of pure oily aldehyde **13**: IR (CH_2Cl_2) 2730 (CHO), 1765 (acetate), 1730 (coumarin, CHO) cm^{-1}; NMR ($CDCl_3$) υ 9.7 (t, 1 H, CHO), 7.9–6.4 (m, 3 H, Ar), 4.2 (s, 3H, OCH_3), 3.8 (d, 2 H, CH_2), 2.5 (s, 3 H, Ac); UV max (CH_3OH) 223 nm (sh, ϵ 16 500), 249 (4290), 287 (11 580), 325 (sh, 4140); mass spectrum, m/e 276 (M^+), 258, 234, 216, 205, 43 (base). The material is of sufficient purity for use in the next step.

7-Acetoxy-6-(carboxymethyl)-8-methoxycoumarin (14). A solution of 9.9 g (0.036 mol) of the aldehyde **13** dissolved in 200 mL of acetone was treated dropwise with 95 mL of Jones reagent. After 20 min, the reaction was partitioned between methylene chloride and water (emulsion). The organic phases were percolated over Celite after drying. The filtrate was evaporated to yield 10.0 g (100%) of crude acid **14** as a light gray solid. The product was recrystallized from absolute ethanol for analysis to give an off-white solid: mp 169–170 °C; IR (KBr) 2700, 2580 (acid), 1768 (acetate), 1730 (coumarin), 1708 (acid) cm^{-1}; NMR (Me_2SO) δ 7.8–6.2 (m, 3 H, Ar), 3.98 (s, 3 H, OCH_3), 3.53 (s, 2 H, CH_2), 2.35 (s, 3 H, Ac); UV max (CH_3OH) 223 nm (sh, ϵ 15 200), 247 (4000), 287 (11 750), 330 (sh, 3000); mass spectrum, m/e 292 (M^+), 278, 250, 232, 204 (base), 148.

Anal. Calcd for $C_{14}H_{12}O_7$ (mol wt 292.24): C, 57.54; H, 4.14. Found: C, 57.28; H, 4.12.

6-(Carboxymethyl)-7-hydroxy-8-methoxycoumarin (15 ≡ 3). A solution of 1.90 g (6.51 mmol) of the acetyloxy acid **14** in 20 mL of dioxane was treated with 20 mL of 1 N hydrochloride

and heated at 100 °C overnight. The reaction was cooled and partitioned between methylene chloride and 1 N HCl. The aqueous extract was extracted three times with methylene chloride/methanol (4:1).

The organic extracts were dried and evaporated to yield 1.61 g (99%) of relatively pure metabolite **15** ≡ **3**. For analysis, a sample was recrystallized from ethyl acetate to yield white crystals: mp 215 °C dec; IR (KBr) 3365 (OH), 2700–2560 (acid), 1720 (coumarin, acid), 1130 cm^{-1}; NMR (Me_2SO) δ 7.8–6.2 (m, 3 H, Ar), 3.94 (s, 3 H, OCH_3), 3.6 (s, 2 H, CH_2); UV max (CH_3OH) 225 nm (sh, ε 15000), 247 (3750), 257 (3800), 329 (14100); mass spectrum, *m/e* 250 (M^+), 232, 204 (base), 190, 161.

Anal. Calcd for $C_{12}H_{10}O_6$ (mol wt 250.21): C, 57.61; H, 4.03. Found: C, 57.53; H, 4.02.

This synthetic material was shown to be identical with the natural metabolite.

6-[(Carbomethoxy)methyl]-7-hydroxy-8-methoxycoumarin (16). A sample of 0.411 g (1.643 mmol) of the synthetic metabolite **15** in 15 mL of dry methanol was treated with 3 drops of concentrated sulfuric acid and heated under reflux for 1.5 h. The reaction was cooled and partitioned between water and methylene chloride. The aqueous phase was further extracted two times with methylene chloride/methanol (4:1). The organic extracts were dried and evaporated to afford 0.266 g (61%) of the methyl ester **16**, which was recrystallized from ethyl acetate to yield white needles: mp 138–139 °C; IR (KBr) 3290 (OH), 1740 (ester), 1720 (coumarin), 1605, 1150 cm^{-1}; NMR ($CDCl_3$) δ 7.8–6.2 (m, 3 H, Ar), 6.9 (br s, 1 H, OH), 4.08 (s, 3 H, OCH_3), 3.71 (s, 3 H, CO_2CH_3), 3.69 (s, 2 H, CH_2); UV max (CH_3OH) 204 nm (ε 44200), 225 (sh, 15200), 257 (4200), 327 (13600); mass spectrum, *m/e* 264 (M^+), 232, 205 (base), 204, 190, 176, 148, 133.

Anal. Calcd for $C_{13}H_{12}O_6$ (mol wt 246.23): C, 59.09; H, 4.58. Found: C, 59.08; H, 4.62.

6-(α-Bromoformylmethyl)-7-acetoxy-8-methoxycoumarin (19). A solution of 1.38 g (0.05 mol) of the aldehyde **13** in 25 mL of dry methylene chloride was treated dropwise over 5 min with 0.26 mL of bromine in 50 mL of the same solvent. The reaction was allowed to proceed for 1 h at 25 °C. The solvent was evaporated to afford 1.78 g (100%) of pure α-bromo aldehyde **19** as a light yellow oil of sufficient purity to be used directly in the next step: IR ($CHCl_3$) 2850 (CHO), 1765 (AcO), 1740 (CHO), 1190, 1120 cm^{-1}; NMR ($CDCl_3$) δ 9.5 (d, 1 H, CHO), 7.64 (d, 1 H, C(4) H), 7.31 (s, 1 H, C(5) H), 6.39 (d, 1 H, C(3) H), 5.37 (d, 1 H, CHBr), 4.06 (s, 3 H, OCH_3), 2.38 (s, 3 H, Ac); UV max (CH_3OH), 223 nm (sh, ε 14500), 238 (sh, (13000), 290 (10800), 322 (sh, 5500); mass spectrum, *m/e* 354/356 (M^+), 312/314, 294/296, 233 (base), 216.

6-(α-Bromocarboxymethyl)-7-acetoxy-8-methoxycoumarin (20). A solution of 1.78 g (0.05 mol) of the α-bromo aldehyde **19** in 50 mL of acetone at 0 °C was treated dropwise with 1.25 mL of Jones reagent over 1 min. After 0.5 h at 0 °C, the reaction was partitioned between methylene chloride and water. The organic phase was dried and evaporated to yield 1.812 g (98%) of the α-bromo acid **20** as a colorless oil of sufficient purity for use directly in the next step: IR ($CHCl_3$) 3500 (OH), 2700–2550 (CO_2H), 1740–1715 (br, acid, acetate, coumarin), 1400, 1190, 1160 cm^{-1}; NMR ($CDCl_3$) δ 7.69 (d, 1 H, C(4) H), 7.59 (s, 1 H, C(5) H), 6.43 (d, 1 H, C(3) H), 5.53 (5, 1 H, CHBr), 4.06 (s, 3 H, OCH_3), 2.40 (s, 3 H, Ac); UV max (CH_3OH) 242 nm (ε 11950), 288 (9000), 325 (sh, 3200), 365 (sh, 580); mass spectrum, *m/e* 328/330 (M^+ – CH_2CO), 310/312 (M^+ – HOAc), 249, 231 (base).

6-(α-Acetoxycarboxymethyl)-7-hydroxy-8-methoxycoumarin (21). A solution of 1.08 g (2.91 mmol) of the α-bromo acid **20** in 20 mL of tetrahydrofuran was treated with 20 mL of N hydrochloric acid. The reaction was heated at 70 °C for 7.5 h, cooled, and partitioned between methylene chloride and water. The organic phases were dried and evaporated to yield 0.844 g (94%) of the α-acetoxy acid **21** as a colorless oil. The compound was chromatographed over silica (EtOAc/HOAc, 9:1) to afford 0.597 g (67%) of pure product **21** isolated at R_f 0.55: IR (KBr) 3340–3100 (OH), 2680–2500 (CO_2H), 1740 (br, acetate, acid, coumarin), 1190, 1160 cm^{-1}; NMR (Me_2SO) δ 8.02 (d, 1 H, C(4) H), 7.61 (s, 1 H, C(5) H), 6.40 (d, 2 H, C(3) H), 5.65 (s, 1 H, CHOAc), 3.94 (s, 3 H, OCH_3), 2.26 (s, 3 H, Ac); UV (CH_3OH) 206 nm (ε 26100), 230 (sh, 13800), 289 (9900), 325 (sh, 4400); mass spectrum, *m/e* 290 (M^+ – H_2O), 266, 232 (base).

6-[(Methoxycarbonyl)methylene]-7-oxo-8-methoxycoumarin (23). A solution of 40 mg (0.130 mmol) of the α-acetoxy acid **21** in 5 mL of dry methanolic hydrogen chloride was heated under reflux for 5 h. The reaction was cooled and evaporated to yield 39 mg (100%) of the α-methoxy ester **23**. A sample was chromatographed over silica (EtOAc/hexane, 1:1) to yield pure **23** at R_f = 0.5: obtained as a white solid; mp 105–106 °C (EtOAc/pentane); IR (KBr) 3500 (OH), 1735–1718 (ester, coumarin) cm^{-1}; NMR (Me_2SO) δ 10.4 (br s, 1 H, OH), 7.97 (d, 1 H, C(4) H), 7.33 (s, 1 H, C(5) H), 6.25 (d, 1 H, C(3) H), 5.14 (s, 1 H, $CHOCH_3$), 3.83 (s, 3 H, OCH_3), 3.62 (s, 3 H, CO_2CH_3), 3.32 (s, 3 H, $CHOCH_3$); UV max (CH_3OH) 205 nm (ε 47980), 228 (sh, 19900), 295 (6480), 323 (17960), 380 (sh, 1030); mass spectrum, *m/e* 294 (M^+), 262 (M^+ – CH_3OH), 235 (base), 230, 220, 202.

Acknowledgment. We wish to thank the staff of the Physical Chemistry Department of Hoffmann-La Roche, Inc., for the determination of physical spectra and analytical data.

Registry No. 5, 93-35-6; **6**, 10387-49-2; **7**, 6748-68-1; **8**, 72939-36-7; **9**, 72939-37-8; **10**, 72939-38-9; **11**, 66510-31-4; **12**, 5307-54-0; **13**, 66510-36-9; **14**, 72939-39-0; **15**, 71942-06-8; **16**, 71942-08-0; **18**, 71942-11-5; **19**, 71942-09-1; **20**, 72939-40-3; **21**, 72939-41-4; allyl chloride, 107-05-1.

Synthesis of 4-Acyl-2-(acylamino)-Δ^2-1,3,4-thiadiazolines and 4-Acyl-2-amino-Δ^2-1,3,4-thiadiazolines by Acylation of Thiosemicarbazones[1]

Seiju Kubota,* Yasufumi Ueda, Kazuichi Fujikane, Kouhei Toyooka, and Masayuki Shibuya

Faculty of Pharmaceutical Sciences, University of Tokushima, Shomachi, Tokushima, Japan 770

Received October 11, 1979

Acylation of aldehyde and ketone thiosemicarbazones (**2**) with acid anhydrides or acid chlorides gave 4-acyl-2-(acylamino)-Δ^2-1,3,4-thiadiazolines (**3**) in good yields. Treatment of **3** with hydrazine hydrate furnished the 2-amino derivatives (**4**). The 4-methylthiosemicarbazone of benzaldehyde underwent a similar cyclization with acetic anhydride to furnish the corresponding 2-(acetylmethylamino)thiadiazoline.

Acetylation of aldehyde thiosemicarbazones (**2**) followed by peracid oxidation has been reported as a route to 1,3,4-thiadiazoles.[2,3] The intermediate acylation products were considered to be the N^4,*S*-diacyl derivatives **1**. In a

0022-3263/80/1945-1473$01.00/0