224 ($M^{\cdot+}$ 35), 206 (45), 193 (27), 178 (87), 165 (58), 164 (100), 163 (75), 149 (31), 148 (36), 121 (36), 105 (32), 91 (23), 90 (34), 79 (31), 77 (48), 76 (47), 51 (40), 39 (20); IR (neat) 3100 (br), 1730, 1600, 1590, 1475, 1440, 1265 cm^{-1}. Anal. Calcd for $C_{11}H_{12}O_5$: C, 58.93; H, 5.39. Found: C, 58.75; H, 5.49.

***tert*-Butyl 4-(8′-Methoxy-3′-isocoumarinyl)-3-oxobutanoate (9b).** *tert*-Butyl acetoacetate (4.82 g, 30.5 mmol) was converted to the dilithium salt by addition to LDA (61 mmol) in THF (30 mL) at 0 °C. After 10 min, 10 mmol of the sodium salt of ester **7b** [generated by addition of 2.28 g (10 mmol) of the compound in THF (40 mL) to a suspension of NaH (15 mmol) in THF (50 mL)] was added. The suspension was stirred at ambient temperature for 12 h, acidified at 0 °C to pH 5 with HOAc, and evaporated in vacuo. The residue was partitioned between Et_2O and aqueous $NaHCO_3$. The aqueous phase was acidified with dilute HCl and extracted with Et_2O followed by CH_2Cl_2. The combined extracts were evaporated; the residue was treated with Ac_2O (20 mL) for 3 h at 25 °C, followed by H_2O (20 mL) for 5 min at 50 °C. The solution was extracted with Et_2O; the organic solution was washed with aqueous $NaHCO_3$ to remove HOAc and then dried and evaporated in vacuo. Flash chromatography (50% EtOAc/hexane) of the residue gave a fraction that yielded 0.742 g (22%) of **9b** as a yellow solid: mp 89-92 °C after recrystallization from EtOH; ^1H NMR ($CDCl_3$) δ 1.47 (s, 9 H), 3.50 (s, 2 H), 3.72 (s, 2 H), 3.99 (s, 3 H), 6.33 (s, 1 H), 6.91 (d, 1 H, J = 7.2 Hz), 6.94 (d, 1 H, J = 7.2 Hz), 7.61 (t, 1 H, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$) δ 27.65, 46.55, 49.91, 55.98, 82.04, 106.31, 108.75, 110.10, 117.25, 135.67, 139.41, 150.08, 158.48, 161.29, 165.63, 197.10; EI-MS, m/z (relative intensity) 332 ($M^{\cdot+}$, 1), 276 (38), 258 (24), 216 (38), 190 (100), 161 (31), 59 (47), 57 (89), 43 (33), 41 (51), 39 (22); IR (KBr) 3965, 1730, 1710, 1600, 1570, 1480, 1330, 1250, 1150, 1010 cm^{-1}. Anal. Calcd for $C_{18}H_{20}O_6$: C, 65.05; H, 6.07. Found: C, 65.20; H, 6.19.

Anthrone Ester-Nitrile 32. Isocoumarin **9b** (0.332 g, 1 mmol) was added as a solid to a THF (25 mL) suspension of NaH (2 mmol) at -10 °C; the suspension was stirred at 25 °C until H_2 evolution ceased (15 min). The resulting light yellow suspension of monoanion was added slowly to 4 mmol of trianion **18** in THF at -78 °C. The mixture was stirred for 6 h at -78 °C and 12 h at 25 °C. The solvent was evaporated in vacuo, and the residue was partitioned between Et_2O and cold dilute HCl. The organic extract was evaporated in vacuo. Flash chromatography of the residue (50% EtOAc/hexane) gave a mixture of anthrone **32** and 3,5-dioxohexanenitrile. Crystallization (EtOH) gave 25.8 mg (6%) of **32** as a dark red solid: mp (vac) 248-252 °C dec; ^1H NMR ($CDCl_3$) a mixture of keto-enol tautomers δ 1.50 (s, 9 H), 3.82, 3.90, 4.04, 4.19, 4.28, 4.32 (6 s, 9 H), 6.75 (s, 1 H), 7.06 (m, 2 H), 7.55 (m, 1 H), 14.22 (s, 1 H); EI-MS, m/z (relative intensity) 421 ($M^{\cdot+}$, 2), 56 (47), 44 (52), 41 (100), 39 (36); IR (KBr) 3350, 3000 (br), 2240 (w), 1720, 1655, 1620, 1575, 1560, 1510, 1440, 1365, 1280, 1235, 1150, 1090, 960 cm^{-1}; UV (MeOH) λ_{max} nm (ϵ) 432 (3100), 408 (5200), 384 (8900), 366 (6200), 296 (13 200, sh), 266 (30 900), 253 (41 700), 230 (23 400). The parent ion in the mass spectrum was too weak for exact mass measurement.

1,3,10,11,12-Pentahydroxynaphthacene-2-carboxamide (Pretetramide, 1). Anthrone **32** (25.8 mg, 0.061 mmol) was combined with HI/H_2O (47%, 1 mL) and phenol (2 mL) and refluxed for 5 h. The solution was cooled; an orange solid (1.8 mg, which gave no mass spectrum) was removed by filtration. The filtrate was evaporated in vacuo and refluxed again with HI/H_2O (2 mL) and phenol (3 mL) for 12 h. The black solution was stored at ambient temperature for 10 h; pretetramide (**1**; 3.8 mg, 18%) was collected by filtration: mp (vac) 294-305 °C dec (lit.[30] 323-327 °C dec, lit.[28] 290-320 °C dec); EI-MS, m/z (relative intensity) 351 ($M^{\cdot+}$, 42), 335 (21), 334 (100), 308 (24); IR (Nujol) 3200 (br), 1660, 1630, 1595, 1575, 1410, 1348, 1290, 1170, 1080 cm^{-1}; UV [H_2SO_4/0.1% (w/w) H_3BO_3] λ_{max} nm (ϵ) 499 (10 500), 405 (14 500), 307 (28 200), 290 (27 500), 269 (23 400), 239 (21 900); HRMS calcd for $C_{19}H_{13}NO_6$ m/z 351.0743, found m/z 351.0752.

Acknowledgment. We wish to acknowledge preliminary experiments by Dr. A. D. Webb and to thank Drs. B. Sweetman and I. Blair for mass spectra and the US Public Health Service (Grant GM-12848) for generous support of this research.

(30) Murphy, J. A.; Staunton, J. *J. Chem. Soc., Chem. Commun.* **1979**, 1166.

Biomimetic Syntheses of Pretetramides. 3. Synthesis of 6-Methylpretetramides Using a Preassembled D Ring Template

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Abstract: A modification of the biomimetically engineered [5 + (2 × 2) + 1] route to pretetramide (**3**) described in the previous paper has been employed for the synthesis of 6-methylpretetramide (**1**). Tandem condensations of phthalide **6b** with *tert*-butyl acetoacetate dianion produced a bisadduct, which underwent aldol cyclizations during workup to give anthrone **7b**. Reduction of the anthrone using triethylsilane in trifluoroacetic acid with simultaneous *tert*-butyl ester cleavage gave the corresponding anthracene diacid, which due to its instability was methylated with dimethyl sulfate to give the trimethoxy dimethyl ester **8b**. Selective hydrolysis of the aliphatic ester group of **8b** gave ester-acid **15a**. Condensation of **15a** (as its sodium salt) with the dilithium salt of *N*-(trimethylsilyl)acetamide, followed by esterification with diazomethane gave β-keto amide **14a**. Cyclization of ring A and deprotection of the phenols to produce 6-methylpretetramide (**1**) were accomplished by using a refluxing mixture of hydriodic and acetic acids. 10-Dehydroxy-6-methylpretetramide (**12**) and 8-hydroxy-6-methylpretetramide (**4**) were synthesized by similar sequences.

6-Methylpretetramide (**1**) is a naphthacenecarboxamide the biosynthetic intermediacy of which was demonstrated by McCormick and co-workers in a blocked mutant of the organism that produces the antibiotic tetracycline (**2**).[1] 6-Methylpretetramide has been prepared by degradation of **2**[1,2] and by Barton et al. in a thwarted attempt to carry out a de novo synthesis of **2**.[3] In the first two papers of this series,[4,5] pretetramide (**3**) was prepared by biomimetic routes via what we term [3 + (2 × 2) + 1 + 2] and [5 + (2 × 2) + 1] strategies (Scheme Ia-b), the latter being based on elaboration of two ketide chains from the ester groups of dimethyl 3-methoxyhomophthalate. In the present paper the [5 + (2 × 2) + 1] route has been adapted to allow introduction of the methyl group found in 6-methylpretetramide.[6]

(1) McCormick, J. R. D.; Johnson, S.; Sjolander, N. O. *J. Am. Chem. Soc.* **1963**, *85*, 1692.

(2) (a) Hochstein, F. A.; Stephens, C. R.; Conover, L. H.; Regna, P. P.; Pasternack, R.; Gordon, P. N.; Pilgrim, F. L.; Brunings, K. J.; Woodward, R. B. *J. Am. Chem. Soc.* **1953**, *75*, 5455. (b) Green, A.; Wilkinson, R. G.; Boothe, J. H. *J. Am. Chem. Soc.* **1960**, *82*, 3946. (c) Green, A.; Boothe, J. H. *J. Am. Chem. Soc.* **1960**, *82*, 3950.

(3) Barton, D. H. R.; Magnus, P. D.; Hase, T. *J. Chem. Soc. C* **1971**, 2215.

(4) Gilbreath, S. G.; Harris, C. M.; Harris, T. M. *J. Am. Chem. Soc.*, preceding paper (paper 1) in this issue.

(5) Harris, T. M.; Harris, C. M.; Oster, T. A. Brown, L. E., Jr.; Lee, J. Y.-C. *J. Am. Chem. Soc.*, preceding paper (paper 2) in this issue.

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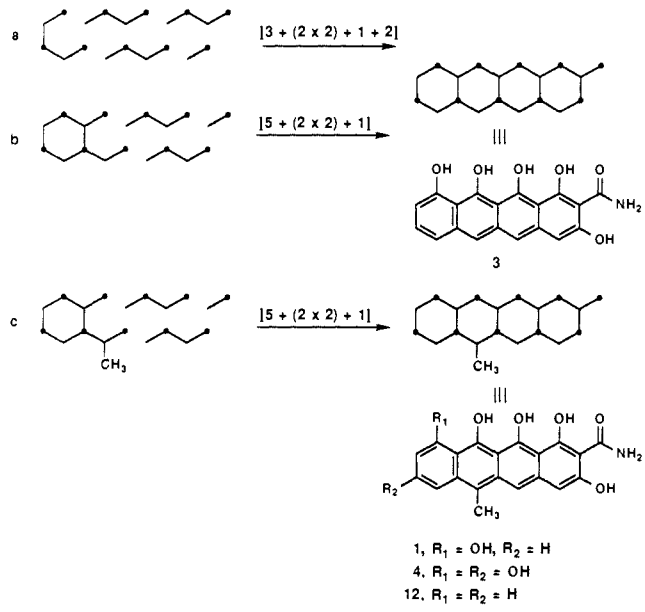
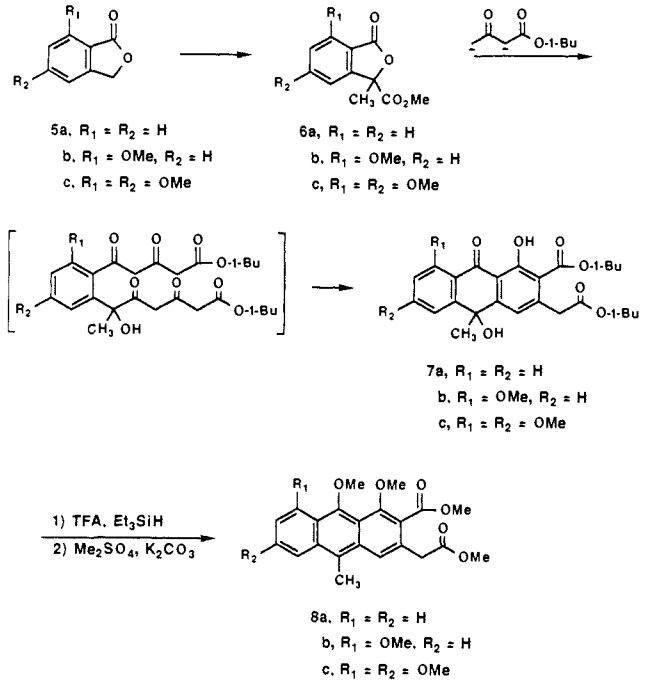
Scheme I



1, R_1 = OH, R_2 = H
4, R_1 = R_2 = OH
12, R_1 = R_2 = H

Scheme II



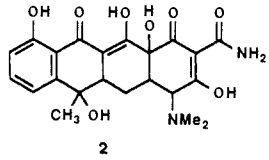
5a, R_1 = R_2 = H
b, R_1 = OMe, R_2 = H
c, R_1 = R_2 = OMe

6a, R_1 = R_2 = H
b, R_1 = OMe, R_2 = H
c, R_1 = R_2 = OMe

7a, R_1 = R_2 = H
b, R_1 = OMe, R_2 = H
c, R_1 = R_2 = OMe

8a, R_1 = R_2 = H
b, R_1 = OMe, R_2 = H
c, R_1 = R_2 = OMe

The new strategy has also been applied to a synthesis of 10-dehydroxy-6-methylpretetramide (**12**) and 8-hydroxy-6-methylpretetramide (**4**).



2

Results and Discussion

Phthalide esters **6** can be viewed as synthetic equivalents of the homophthalates employed in the previous paper. They are attractive intermediates for introduction of the methyl group found in the 6-methylpretetramides; use of **6** in subsequent condensations avoids the complications caused by the readily ionizable α protons

(6) A preliminary communication describing the synthesis of 6-methylpretetramide has been published: Mahalingam, S.; Kuzma, P. K.; Lee, J. Y.-C.; Harris, T. M. *J. Am. Chem. Soc.* **1985**, *107*, 7760.

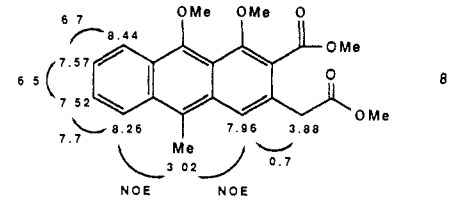
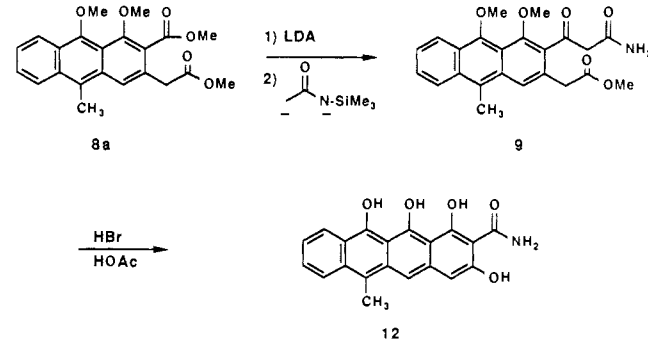


Figure 1. Coupling and nuclear Overhauser effects in anthracene **8a**.

Scheme III



of homophthalate esters.[7] Model studies were initiated with phthalide **6a**, which was prepared in 53% yield by treatment of phthalide (**5a**) with 2 equiv of lithium diisopropylamide followed by methyl chloroformate and then iodomethane in a one-pot reaction (Scheme II).

Tandem addition of the dilithium salt of *tert*-butyl acetoacetate (4 equiv) to the two ester groups of **6a** gave anthrone diester **7a** (Scheme II). The use of *tert*-butyl acetoacetate dianion as the nucleophile minimizes self condensation of the keto ester, which presents a serious problem with less hindered esters. Four equivalents of keto ester dianion are stoichiometrically required in this reaction, two for the condensations themselves and the other two for ionization of the newly formed acidic methylene groups.[8] The initial product of biscondensation, a bis(3,5-diketo ester) underwent two intramolecular aldol cyclizations during workup to give anthrone **7a** in an overall 66% yield.[9] A linear folding pattern to give **7a** was established spectroscopically; in particular, the infrared spectrum showed intramolecular hydrogen bonding to the anthrone carbonyl group (1620 cm^{-1}) and the ^1H NMR spectrum contained a hydrogen-bonded OH signal at 12.92 ppm. Other folding patterns are thereby excluded.

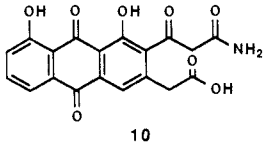
The next step in the synthesis was reduction to the anthracene by triethylsilane in trifluoroacetic acid. Although the anthrone **7a** is stable as a crystalline solid at room temperature, the corresponding 9-hydroxyanthracene and the tautomeric anthrone are highly vulnerable to air-oxidation. Consequently, the crude reduction product was immediately converted to the permethylated derivative by treatment with dimethyl sulfate and potassium carbonate. The two-step sequence gave anthracene diester **8a** in 63% yield. The acidic reaction conditions used to achieve anthrone reduction and dehydration also catalyzed hydrolysis of the *tert*-butyl esters, and the resulting carboxyl groups were converted to methyl esters during treatment with dimethyl sulfate. The structure of **8a** was established by careful analysis of the ^1H NMR spectrum, which showed (1) coupling between the methylene group at C-3 and H-4 and (2) nuclear Overhauser effects between the methyl group at C-10 and protons H-4 and H-5 as shown in Figure 1.

The dianion of *N*-(trimethylsilyl)acetamide[10] was employed to complete construction of the skeleton of 6-methylpretetramide;

(7) Kozikowski, A. P.; Schmiesing, R. *Synth. Commun.* **1978**, *8*, 363.
(8) (a) Huckin, S. N.; Weiler, L. *Tetrahedron Lett.* **1972**, 2405. (b) Huckin, S. N.; Weiler, L. *Can. J. Chem.* **1974**, *52*, 1343.
(9) (a) Harris, T. M.; Webb, A. D.; Harris, C. M.; Wittek, P. J.; Murray, T. P. *J. Am. Chem. Soc.* **1976**, *98*, 6065. (b) Harris, T. M.; Murray, T. P.; Harris, C. M.; Gumulka, M. *J. Chem. Soc., Chem. Commun.* **1974**, 362.
(10) Kuzma, P. C.; Brown, L. E.; Harris, T. M. *J. Org. Chem.* **1984**, *49*, 2015.

this acetamide synthon had worked well in the synthesis of pretetramide described in the previous paper in this series. The labile methylene position was ionized (using lithium diisopropylamide) prior to the condensation in order to block nucleophilic attack on the aliphatic ester group and thereby to direct reaction to the aromatic ester.[5] Condensation of **8a** monoanion with dilithio *N*-(trimethylsilyl)acetamide gave β-keto amide **9** in 22% yield (Scheme III). The structure of the adduct was established spectroscopically. Evidence that the condensation had proceeded via attack on the aromatic ester rather than the aliphatic one was obtained from the IR and ^{13}C NMR spectra, which indicated the presence of an aromatic keto group. The close correspondence of the spectra of **9** to its 6-demethyl counterpart in the accompanying paper[5] gives further credence to the structural assignment.

Acid-catalyzed Claisen closure of the final ring has proven to be an effective method for completion of the naphthacene nucleus of pretetramides with simultaneous demethylation of the phenolic ethers.[4,5] McCormick et al. had used HI to effect the closure of ring A and to reduce the quinone moiety of protetrones **10** and **11** to give pretetramide (**2**) and 6-methylpretetramide (**3**), re-



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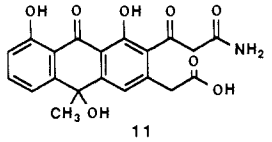

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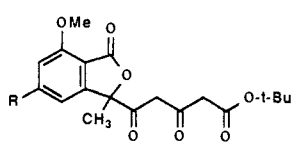
spectively; the protetrones had been isolated from blocked mutants of tetracycline-producing organisms.[11] Acid-catalyzed closure of ring A and phenol deprotection were accomplished with a mixture of refluxing acetic and hydrobromic acids to produce crystalline 10-dehydroxy-6-methylpretetramide (**12**) in 82% yield. Because of the meager solubility of **12** in organic and aqueous solvents, NMR spectra could not be obtained. The product was identified on the basis of the close similarity of its ultraviolet spectrum with that reported for 6-methylpretetramide.[2a,3]

The success of the model synthesis of 10-dehydroxypretetramide inspired confidence that the same sequence could be applied to obtain 6-methylpretetramide itself. Toward this goal phthalide **6b** was synthesized from 7-methoxyphthalide (**5b**) (Scheme II).[12] Carbomethoxylation and methylation of 7-methoxyphthalide proceeded as in the model synthesis to give phthalide ester **6b** in 70% yield.

Phthalide **6b** was subjected to tandem attack by the dianion of *tert*-butyl acetoacetate to give anthrone **7b** in 57% yield. A major byproduct of the reaction was tentatively identified as monoadduct **13a** arising from nucleophilic attack of *tert*-butyl acetoacetate dianion on the aliphatic ester group. Anthrone **7b** was reduced with triethylsilane and methylated with dimethyl sulfate to give trimethoxyanthracene **8b** in 66% yield.

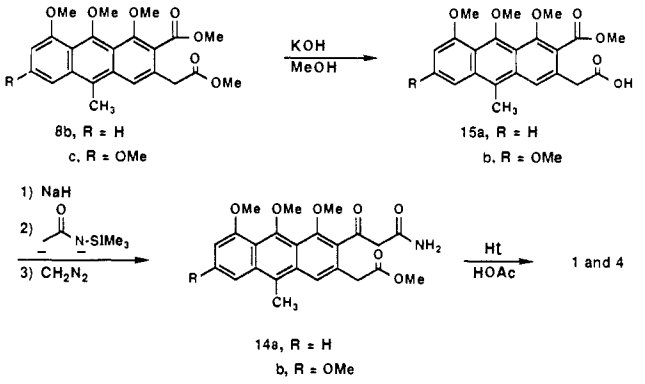


13a, R = H

b, R = OMe

The anion of **8b** was treated with the dianion of *N*-(trimethylsilyl)acetamide to form **14a**; however, the reaction failed

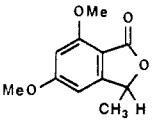
Scheme IV



to produce useful quantities of the adduct. A complex mixture of products resulted, probably stemming from nucleophilic attack occurring in part at the *aliphatic* ester group. The apparent cause of the problem is the increased electron density of **8b** relative to **8a** due to the additional methoxyl group. As an alternative approach, the aliphatic ester group of **8b** was converted to the carboxylate anion prior to the condensation (Scheme IV), thus eliminating the requirement for preionization of the methylene group. It should be noted that ionization of the methylene group in anthracenes **8** will deactivate the aromatic ester group to nucleophilic attack as well as the aliphatic one but to a lesser extent. Limited alkaline hydrolysis of **8b**[13] with methanolic KOH gave ester acid **15a** in 85% yield.

The sodium salt of **15a** was then treated with *N*-(trimethylsilyl)acetamide dianion to give the corresponding β-keto amide, which was more conveniently isolated as methyl ester **14a** than as the free acid; the ester was formed by brief treatment with diazomethane (Scheme IV). The yield for conversion of **15a** to **14a** was 25%. The final ring closure was effected with a refluxing mixture of hydriodic and acetic acids; 6-methylpretetramide (**1**) was obtained in 50% yield as a brick red solid, the physical and spectroscopic properties of which closely matched those reported for the compound.[2a,3]

The synthesis of 8-hydroxy-6-methylpretetramide (**4**) parallels that described for 6-methylpretetramide (Schemes II and IV). 5,7-Dimethoxyphthalide (**5c**) was prepared from commercially available 3,5-dimethoxybenzyl alcohol in 69% yield by a modification of Trost's method.[12] Conversion of phthalide **5c** to the 3-methyl-3-carbomethoxy analogue by "one-pot" methylation and acylation with methyl chloroformate occurred in 60% yield; a byproduct, identified as the unacylated methyl derivative (**16**),



16

was also isolated. Attempts to carboxylate **16** to give **5c** were unsuccessful. Tandem addition of *tert*-butyl acetoacetate dianion to **6c** proceeded smoothly to give anthrone **7c** in 63% yield. A significant amount (25%) of monoadduct **13b** was also isolated. *tert*-Butyl acetoacetate dianion failed to convert **13b** to the bis-(adduct) even under vigorous reaction conditions; the sodium salt of **13b** (preformed with excess sodium hydride) also failed to acylate the dilithium salt of *tert*-butyl acetoacetate.[14]

Reduction and aromatization of anthrone **7c** were effected using triethylsilane and trifluoroacetic acid; methylation gave anthracene **8c** in 22% overall yield. This methylation is sensitive to experimental conditions. Vigorous mechanical stirring throughout the reaction and the use of only *freshly distilled* dimethyl sulfate are critical. Anthracene **8c** was relatively stable as a solid, but was

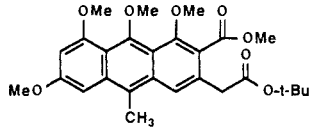
(11) (a) McCormick, J. R. D.; Jensen, E. R. *J. Am. Chem. Soc.* **1968**, *90*, 7126. (b) McCormick, J. R. D.; Jensen, E. R.; Arnold, N. H.; Corey, H. S.; Joachim, U. H.; Johnson, S.; Miller, P. A.; Sjolander, N. O. *J. Am. Chem. Soc.* **1968**, *90*, 7127.

(12) (a) Trost, B. M.; Rivers, G. T.; Gold, J. M. *J. Org. Chem.* **1980**, *45*, 1835. (b) We are grateful to C. A. Townsend for this suggestion.

(13) Chatterjea, J. N.; Bhakta, C.; Vakula, T. R. *J. Ind. Chem. Soc.* **1972**, *49*, 1161.

(14) Murray, T. P.; Harris, T. M. *J. Am. Chem. Soc.* **1972**, *94*, 8253.

susceptible to oxidation when not crystalline. A byproduct (16%) from the reaction sequence was identified as mixed *tert*-butyl methyl diester **17**, in which cleavage of the aliphatic *tert*-butyl group had failed to occur. Further treatment of the mixed ester with trifluoroacetic acid gave ester acid **15b** (58%), identical with material made by limited hydrolysis of dimethyl ester **8c** with methanolic KOH.



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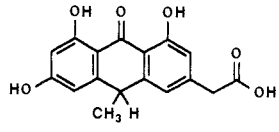
Neither dimethyl ester **8c** nor *tert*-butyl methyl diester **17** reacted with the dilithium salt of *N*-(trimethylsilyl)acetamide to give isolable quantities of the corresponding β-keto amide. Ester–acid **15b** was converted to its carboxylate sodium salt and treated with excess *N*-(trimethylsilyl)acetamide dianion. Amide–ester **14b** was isolated from the product mixture in 26% yield, after brief treatment with diazomethane. In addition, 24% of dimethyl ester **8c**, the methylation product of unreacted ester acid **15b**, was obtained. Treatment of amide–ester **14b** with refluxing hydriodic and acetic acids gave 53% of 8-hydroxy-6-methylpretetramide (**4**). A major byproduct (33% yield) was identified as anthrone **18** in which the keto amide chain and the *O*-methyl groups have been lost.



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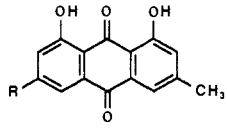
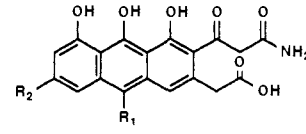
In summary, 10-dehydroxy-6-methylpretetramide (**12**), 6-methylpretetramide (**1**), and 8-hydroxy-6-methylpretetramide (**4**) have been synthesized from phthalides by a biogenetically modeled route in yields of 4.0, 3.3, and 2.1%, respectively. Only **1** has been synthesized previously; to the extent that yields can be ascertained from the literature reports,[2a,3] the yield of the present procedure for 6-methylpretetramide compares favorably with the earlier de novo and degradative routes.

Our interest in 8-hydroxypretetramides stems from the question of when reduction at C-8 occurs.[11b,15] Does the reduction occur while the polyketide chain exists as a linear enzyme-bound complex or at an intermediate stage of cyclization or after formation of the pretetramide? The first process would involve reduction of a ketone to an alcohol followed by dehydrative elimination of the resultant hydroxyl group. Many aromatic polyketide-derived natural products that lack an oxygen atom at the analogous "corner" position are believed to arise in this manner, one well-studied example being 6-methylsalicyclic acid.[16] The alternative possibility, loss of the hydroxyl group after aromatization, has been established for the biosynthesis of chrysophanol (**19a**) from emodin (**19b**).[17]



19a, R = H
b, R = OH

The stage at which the hydroxyl is lost in the tetracycline pathway is unknown beyond the fact that it lies prior to 6-methylpretetramide. Conceivably, the process involves dehydroxylation of 8-hydroxy-6-methylpretetramide (**3**); the present synthesis of **3**, which could readily be adapted to incorporation of isotopic labels, paves the way for the appropriate metabolic studies to test this question. Loss of the hydroxyl group could well occur at the tricyclic stage. McCormick's protetrones **10** and **11** failed to be transformed to tetracyclines by tetracycline-producing organisms, possibly because they are oxidation products of the putative true protetrone intermediates **20a,b**.[11] The present synthesis of 8-hydroxy-6-methylpretetramide passes through protetrone **14b**, which is the methyl ester, tetramethyl ether of **20c**. Modifications of the syntheses reported in this paper may make it possible to synthesize protetrone **20c** as well as **20a** and **20b** by using more labile protective groups such that their removal can be effected without simultaneous closure of the final ring. It is interesting to note that loss of the 8-hydroxyl group is not mandatory for biosynthesis of the naphthacene ring system; recent reports have described isolation of several 8-methoxytetracyclines.[18]



20a, $R_1 = R_2 = H$
b, R_1 = Me, $R_2 = H$
c, R_1 = Me, R_2 = OH

Experimental Section

General Procedure. The general procedures described in paper one of this series were employed.[4] Additionally, diazomethane was generated from Diazald (Aldrich) by using the procedure printed on the container. Dichloromethane when used as a reaction solvent was first distilled from calcium hydride. *tert*-Butyl acetoacetate (Aldrich) was distilled at reduced pressure and was stirred under vacuum for at least 30 min prior to use. ^1H and ^{13}C NMR spectra were recorded at 90 and 22.5 MHz, respectively, unless otherwise indicated.

Preparation of 3-Carbomethoxy-3-methylphthalides 6. Treatment of phthalide **5** (3.3 mmol) with 2 equiv of LDA (6.6 mmol) in 100 mL of THF at −78 °C under N_2 gave the yellow anion, which after 15 min was treated with 1 equiv of freshly distilled methyl chloroformate (0.32 g, 3.30 mmol). After an additional 1 h, iodomethane (1.87 g, 13.19 mmol) was added, and the mixture was heated at 35–40 °C for 8 h. The mixture was filtered, and the filtrate was evaporated in vacuo. The residue was partitioned between CH_2Cl_2 and cold dilute HCl. The aqueous layer was further extracted with EtOAc. The CH_2Cl_2 and EtOAc extracts were combined and evaporated to give **6** as an oil, which was purified by chromatography on silica gel.

Phthalide **5a** (6.7 g, 50 mmol) was converted to **6a** according to the general procedure. The crude product was purified by short-column chromatography (Et_2O) and then recrystallized from Et_2O/hexane/$CHCl_3$ to give 5.50 g (53% yield) of **6a**: mp 57–58 °C (lit.[19] mp 57–58 °C); ^1H NMR ($CDCl_3$) δ 1.93 (s, 3 H, CH_3), 3.83 (s, 3 H, OCH_3), 7.50–8.10 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 23.6 (CH_3), 53.2 (OCH_3), 84.8 (C-3), 122.1 (CH), 125.1 (C), 125.8 (CH), 130.0 (CH), 134.5 (CH) 168.9 (COOR), 169.6 (COOR).

7-Methoxyphthalide **5b**[12] (5.42 g, 33.0 mmol) was converted to phthalide **6b** by the general procedure. The product was purified by short-column chromatography (40% EtOAc/hexane) to yield a yellow oil, which was triturated with ether to give 5.48 g (70% yield) of **6b** a a white solid: mp 64–65 °C; ^1H NMR ($CDCl_3$) δ 1.87 (s, 3 H, CH_3), 3.73 (s, 3 H, ester OCH_3), 4.01 (s, 3 H, ether OCH_3), 7.01 (d, 1 H, J = 9 Hz), 7.14 (d, 1 H, J = 10 Hz), 7.67 (t, 1 H, J = 9 Hz); ^{13}C NMR ($CDCl_3$) δ 23.5 (CH_3), 53.1 (ester OCH_3), 56.04 (ether OCH_3), 83.6

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(C-3), 111.8 (CH), 113.6 (CH), 136.7 (CH), 137.4 (C), 151.6 (C), 158.5 (C-7), 167.1 (ArCOOR), 169.6 (COOMe); EI-MS, *m/z* (relative intensity) 236 ($M^{\cdot+}$, 5), 177 (100); IR (KBr) 2945, 1770, 1730, 1600, 1480, 1435, 1375, 1330, 1290, 1260, 1220, 1130, 1040, 1005 cm^{-1}. Anal. Calcd for $C_{12}H_{12}O_5$: C, 61.01; H, 5.12. Found: C, 61.18; H, 5.15.

3,5-Dimethoxybenzyl alcohol was converted to 5,7-dimethoxyphthalide (**5c**) in 69% yield by the procedure employed by Trost et al.[12a] for preparation of **5b**, except benzene[12b] was used as the solvent; phthalide **5c** was identical in all respects with material prepared by the method of Noire and Franck.[20] Conversion of **5c** (0.64 g, 3.30 mmol) to phthalide **6c** gave a pale yellow oil, which was purified by flash column chromatography[21] (40% EtOAc/hexane) followed by trituration with Et_2O to give 0.53 g (60%) of **6c** as a white solid: mp 126–127 °C; ^1H NMR ($CDCl_3$) δ 1.84 (s, 3 H, CH_3), 3.73 (s, 3 H, ester OCH_3), 3.90 (s, 3 H, ether OCH_3), 3.95 (s, 3 H, OCH_3), 6.45 (d, 1 H, J = 2 Hz), 6.57 (d, 1 H, J = 2 Hz); ^{13}C NMR (acetone-d_6) δ 23.7 (CH_3), 53.5 (ester OCH_3), 56.5 (ether OCH_3), 56.7 (ether OCH_3), 83.8 (C-3), 99.4(CH), 100.4 (CH), 106.1 (C), 154.8 (C), 160.6 (COR), 166.5 (COR), 168.1 (ArCOOR), 170.5 (COOMe); EI-MS, *m/z* (relative intensity) 266 ($M^{\cdot+}$, 7), 207 (100); IR (KBr) 1780, 1760, 1620, 1600, 1460, 1335, 1270, 1250, 1225, 1210, 1160, 1125, 1050, 1020 cm^{-1}. Anal. Calcd for $C_{13}H_{14}O_6$: C, 58.63; H, 5.30. Found: C, 58.52; H, 5.42.

3-Methyl-5,7-dimethoxyphthalide (**16**) was obtained as a byproduct of this reaction: a pale yellow oil; ^1H NMR ($CDCl_3$) δ 1.57 (d, 3 H, J = 6.6 Hz, CH_3), 3.93 (s, 3 H, OCH_3), 3.96 (s, 3 H, OCH_3), 5.39 (q, 1 H, J = 6.6 Hz, CH), 6.50 (d, 1 H, J = 2 Hz), 6.60 (d, 1 H, J = 2 Hz). Phthalide **16** failed to give **6c** on treatment with LDA followed by methyl chloroformate.

Preparation of Anthrones 7. *tert*-Butyl acetoacetate (2.08 g, 13.2 mmol) was converted to the dilithium salt by treatment with LDA (26.3 mmol) in THF (100 mL) for 30 min at 0 °C under N_2. Phthalide **6** (2.63 mmol) was added; the mixture was refluxed for 48 h, cooled to 0 °C, and quenched with excess HOAc. The solvent was evaporated in vacuo. The residue was partioned between CH_2Cl_2 and cold dilute HCl; the organic extract was evaporated in vacuo to give an oil, which was purified by chromatography on silica gel.

Phthalide **6a** (2.00 g, 9.71 mmol) was converted to **7a** by the general procedure. Purification by short-column chromatography (10% EtOAc/hexane) gave 2.92 g (66%) of **7a** as yellow needles: mp 138–139 °C; ^1H NMR ($CDCl_3$) δ 1.42 (s, 9 H, *t*-Bu CH_3's), 1.54 (s, 3 H, CH_3), 1.60 (s, 9 H, *t*-Bu CH_3's), 3.60 (s, 2 H, CH_2), 7.28–8.18 (m, 5 H), 12.92 (s, 1 H, phenol OH); ^{13}C NMR ($CDCl_3$) δ 28.0 (3 CH_3), 28.2 (3 CH_3), 37.8 (CH_3), 40.5 (CH_2), 70.0 (C-10), 81.5 (*t*-Bu quaternary C), 82.7 (*t*-Bu quaternary C), 112.7 (C), 118.4 (CH), 123.5 (C), 125.7 (CH), 126.7 (CH), 127.9 (CH), 128.5 (C), 134.5 (CH), 140.6 (C), 149.1 (C), 151.1 (C), 159.9 (C-1), 165.8 (ArCOOR), 169.2 ($ArCH_2COOR$), 187.7 (C-9 C=O); EI-MS, *m/z* (relative intensity) 454 ($M^{\cdot+}$, 30), 342 (53), 325 (65), 324 (50), 309 (50), 307 (33), 291 (32), 280 (100), 265 (30); IR (KBr) 3390, 2980, 2945, 1735 (br), 1620, 1600, 1570, 1480, 1460, 1410, 1360, 1260, 1140 cm^{-1}; UV (MeOH) λ_{max} nm (ϵ) 355 (5600), 291 (12900), 269 (9800). Anal. Calcd for $C_{26}H_{30}O_7$: C, 68.70; H, 6.65. Found: C, 68.66; H, 6.75.

Phthalide **6b** (1.00 g, 4.24 mmol) was converted to **7b** by the general procedure. Purification by short-column chromatography (15% EtOAc/hexane) and recrystallization (EtOAc/hexane) gave 1.17 g (57% yield) of **7b** as yellow needles: mp 197–198 °C; ^1H NMR ($CDCl_3$) δ 1.50 (s, 9 H, *t*-Bu CH_3's), 1.52 (s, 3 H, CH_3), 1.68 (s, 9 H, *t*-Bu CH_3's), 3.68 (s, 2 H, CH_2), 3.98 (s, 3 H, OCH_3), 6.94 (d, 1 H, J = 8 Hz), 7.30 (s, 1 H), 7.36 (d, 1 H, J = 8 Hz), 7.52 (t, 1 H, J = 8 Hz), 13.26 (s, phenol OH); ^{13}C NMR ($CDCl_3$) δ 28.0 (*t*-Bu CH_3's), 28.2 (*t*-Bu CH_3's), 38.2 (CH_3), 40.4 (CH_2), 56.1 (OCH_3), 70.2 (C-10), 81.4 (*t*-Bu quaternary C), 82.4 (*t*-Bu quaternary C), 111.1 (CH), 113.8 (C), 117.2 (C), 117.3 (CH), 117.4 (CH), 123.6 (C), 135.6 (CH), 139.3 (C), 149.5 (C), 151.6 (C), 159.6 (C), 160.5 (C), 165.9 (ArCOOR), 169.4 ($ArCH_2COOR$), 187.4 (C-9 C=O); EI-MS, *m/z* (relative intensity) 484 ($M^{\cdot+}$, 8), 355 (28), 354 (34), 312 (28), 310 (35), 178 (100), 177 (72), 164 (29); IR (KBr) 3490, 2980, 1720, 1620, 1590, 1490, 1440, 1400, 1360, 1300, 1260, 1200, 1140, 1060 cm^{-1}; UV (MeOH) λ_{max} nm (ϵ) 356 (10200), 291 (12600), 268 (13200). Anal. Calcd for $C_{27}H_{32}O_8$: C, 66.91; H, 6.66. Found: C, 67.08; H, 6.72.

A faster eluting fraction was also isolated and identified as monoadduct **13a**, a yellow solid: ^1H NMR (400 MHz, $CDCl_3$) enol form δ 1.43 (s, 9 H, *t*-Bu CH_3's), 1.82 (s, 3 H, CH_3), 3.22 (s, 2 H, CH_2), 3.99 (s, 3 H, OCH_3), 6.01 (s, 1 H, vinyl CH), 6.85 (d, 1 H, J = 8 Hz), 7.22 (d, 1 H, J = 8 Hz), 7.62 (t, 1 H, J = 8 Hz), 14.9 (br s, 1 H, enol); ^{13}C NMR (100 MHz, $CDCl_3$) enol form δ 23.97 (CH_3), 27.82 (*t*-Bu CH_3's), 45.14 (CH_2), 56.05 (CH_3), 82.27 (C), 85.36 (C), 95.73 (CH), 111.57 (C), 111.94 (CH), 114.39 (CH), 136.92 (C), 152.28 (C), 158.52 (C), 166.07 (C), 167.15 (C), 185.73 (C), 192.82 (C); IR (KBr) 2990, 1765, 1730, 1611, 1600, 1490, 1370, 1290, 1230, 1148, 1050, 1030 cm^{-1}; FAB$^+$ MS, *m/z* (relative intensity) 363 (MH^+, 4), 308 (19), 307 (100), 289 (17), 262 (13), 203 (20), 178 (35), 177 (52).

Phthalide **6c** (0.70 g, 2.63 mmol) was converted to **7c** in the manner described in the general procedure. Trituration of the crude product with EtOAc gave 0.73 g of **7c**. Flash column chromatography of the mother liquors (20% EtOAc/hexane) gave an additional 0.12 g (63% total) of **7c**: mp 214–215 °C; ^1H NMR ($CDCl_3$) δ 1.43 (s, 9 H, *t*-Bu CH_3's), 1.55 (s, 3 H, CH_3), 1.59 (s, 9 H, *t*-Bu CH_3's), 3.04 (s, 1 H, OH), 3.59 (s, 2 H, CH_2), 3.91 (s, 3, OCH_3), 3.92 (s, 3, OCH_3), 6.42 (d, 1 H, J = 2.3 Hz), 7.04 (d, 1 H, J = 2.3 Hz), 7.21 (s, 1 H), 13.38 (s, 1 H, OH); ^{13}C NMR ($CDCl_3$) δ 28.02 (*t*-Bu CH_3's), 28.18 (*t*-Bu CH_3's), 38.39 (CH_3), 40.37 (CH_2), 55.67 (OCH_3), 56.22 (OCH_3), 70.93 (C-10), 81.30 (*t*-Bu quaternary C), 82.43 (*t*-Bu quaternary C), 98.33 (CH), 102.14 (CH), 111.89 (C), 113.78 (C), 116.93 (CH), 123.73 (C), 139.14 (C), 149.24 (C), 154.79 (C), 159.88 (C), 163.10 (C), 165.43 (C), 166.07 (C), 169.31 (C), 186.45 (CO); EI-MS, *m/z* (relative intensity) 514 ($M^{\cdot+}$, 32), 402 (27), 385 (59), 384 (100), 369 (21), 367 (21), 351 (21), 341 (50), 304 (27); IR (KBr) 3415, 2980, 1730, 1720, 1620, 1600, 1450, 1365, 1320, 1250, 1210, 1150, 1125, 1050 cm^{-1}; UV (MeOH) λ_{max} nm (ϵ) 356 (17400), 304 (9800), 274 (13800), 253 (15800). Anal. Calcd for $C_{28}H_{34}O_9$: C, 65.34; H, 6.66. Found: C, 65.17; H, 6.81.

A faster eluting fraction (a yellow oil, ~25%) was tentatively identified as monoadduct **13b**: ^1H NMR ($CDCl_3$) mixture of keto–enol tautomers δ 1.42 (s), 1.46 (s), 1.81 (s), 3.24 (s), 3.72 (br s), 3.87 (s), 3.90 (s), 5.95 (s), 6.23 (s), 6.42 (d, J = 2 Hz), 6.60 (d, J = 2 Hz); ^{13}C NMR ($CDCl_3$) mixture of keto–enol tautomers δ 23.83, 27.84, 28.03, 31.11, 44.98, 51.00, 55.63, 55.82, 80.76, 81.98, 92.60, 95.91, 98.37, 99.64, 100.00, 100.35, 112.75, 135.02, 148.56, 157.53, 163.89, 164.98, 165.63, 165.93, 166.36, 167.61, 185.19, 190.93, 193.42.

Preparation of Anthracenes 8. Anthrone **7** (2.2 mmol) was treated with 1.5 equiv of triethylsilane (0.45 g, 3.89 mmol) and 2.6 equiv of trifluoroacetic acid (0.67 g, 5.83 mmol) in 50 mL of refluxing CH_2Cl_2 for 10 h. Solvent was evaporated, and the residue was treated with *freshly distilled* dimethyl sulfate (4.2 equiv, 1.18 g, 9.33 mmol) and K_2CO_3 (5.7 equiv, 1.72 g, 12.5 mmol) in refluxing acetone (50 mL) with vigorous mechanical stirring for 7 h. The mixture was filtered, concentrated in vacuo, cooled to 0 °C, treated with Et_3N (5.7 equiv, 1.52 g, 12.5 mmol), and stirred for 1 h at 20 °C. The reaction mixture was partitioned between Et_2O and cold dilute HCl. The organic extract was concentrated in vacuo, and crude **8** was purified by column chromatography on silica gel.

Anthrone **7a** (0.500 g, 1.10 mmol) was converted to **8a** by the general procedure. Purification by short-column chromatography (10% EtOAc/hexane) and recrystallization (Et_2O/hexane) gave 0.266 g (63%) of **8a** as yellow needles: mp 106–107 °C; TLC (20% EtOAc/hexane) R_f 0.30, bright yellow fluorescence under long wavelength UV light; ^1H NMR (300 MHz, $CDCl_3$, see also Figure 1) δ 3.02 (s, 3 H, CH_3), 3.73 (s, 3 H, OCH_3), 3.88 (d, 2 H, J = 0.7 Hz, CH_2), 3.99 (s, 3 H, OCH_3), 4.00 (s, 3 H, OCH_3), 4.02 (s, 3 H, OCH_3), 7.52 (m, 1 H), 7.57 (m, 1 H), 7.96 (t, 1 H, J = 0.7 Hz, H-4), 8.26 (d with additional long-range coupling, 1 H, J = 7.7 Hz), 8.44 (d with additional long-range coupling, 1 H, J = 6.7 Hz); ^{13}C NMR ($CDCl_3$) δ 14.1 (CH_3), 39.5 (CH_2), 51.8 (ester OCH_3), 52.0 (ester OCH_3), 63.49 (ether OCH_3), 63.6 (ether OCH_3), 117.4 (C), 123.0 (CH), 123.1 (CH), 123.9 (C), 124.4 (CH), 125.1 (CH), 125.90 (C), 125.93 (C), 126.3 (CH), 127.4 (C), 131.7 (C), 132.0 (C), 151.0 (COR), 154.5 (COR), 168.1 (ArCOOR), 171.2 ($ArCH_2COOR$); EI-MS, *m/z* (relative intensity) 382 ($M^{\cdot+}$, 100), 351 (32), 339 (34), 324 (37), 307 (39), 290 (38), 279 (39), 262 (49); IR (KBr) 2960, 1730, 1620, 1455, 1380, 1280, 1150, 1095, 1065, 1020 cm^{-1}; UV (MeOH) λ_{max} nm (ϵ) 373 (6200), 266 (117500), 225 (14800). Anal. Calcd for $C_{22}H_{22}O_6$: C, 69.10; H, 5.80. Found: C, 69.23; H, 5.96.

Anthrone **7b** was converted to **8b** by the general procedure. Purification by short-column chromatography (10% Et_2O/hexane) and recrystallization (Et_2O/hexane) gave 0.298 g (66% yield) of **8b** as yellow needles: mp 124–125 °C; TLC (20% EtOAc/hexane) R_f 0.25, bright yellow under long λ UV light; ^1H NMR ($CDCl_3$) δ 3.02 (s, 3 H, CH_3), 3.78 (s, 3 H, OCH_3), 3.90 (s, 2 H, CH_2), 3.98 (s, 3 H, OCH_3), 4.05, (s, 6 H, 2 OCH_3), 4.12 (s, 3 H, OCH_3), 6.90 (d, 1 H, J = 8 Hz), 7.50 (t, 1 H, J = 8 Hz), 7.90 (d, 1 H, J = 8 Hz), 8.02 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 15.4 (CH_3), 39.7 (CH_2), 52.0 (ester OCH_3), 52.1 (ester OCH_3), 56.4 (ether OCH_3), 63.9 (ether OCH_3), 64.0 (ether OCH_3), 104.2 (CH), 117.3 (CH), 118.6 (C), 119.3 (C), 122.9 (CH), 124.4 (C), 125.5 (C), 126.2 (CH), 128.1 (C), 132.8 (C), 134.2 (C), 153.0 (COR), 155.4 (COR), 157.4 (COR), 168.5 (ArCOOR), 171.3 ($ArCH_2COOR$); EI-MS, *m/z* (relative intensity) 412 ($M^{\cdot+}$, 34), 337 (8), 319 (14), 178 (58), 177 (100); IR (KBr) 2960, 1745, 1725, 1610, 1550, 1440, 1415, 1360, 1320, 1310, 1255, 1230, 1190, 1145, 1110, 1025 cm^{-1}; UV

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(MeOH) λ_{max} nm (ϵ) 420 (4600), 400 (6800), 378 (8500), 363 (4600), 269 (85100), 252 (sh 38900), 231 (17000). Anal. Calcd for $C_{23}H_{24}O_7$: C, 66.97; H, 5.87. Found: 66.94; H, 6.01.

Anthrone **7c** (1.1 g, 2.2 mmol) was converted to **8c** by the general procedure. Purification by flash column chromatography (10% EtOAc/hexane → 30%) gave **8c** (0.21 g, 22%) as an oil, which could be crystallized by isothermal evaporation of an Et_2O solution at room temperature: mp 137–138 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 2.90 (s, 3 H, CH_3), 3.72 (s, 3 H, OCH_3), 3.84 (s, 2 H, CH_2), 3.90, 3.96, 3.97, 3.98, 4.04 (s, 3 H, OCH_3, 5×), 6.53 (s, 1 H, J = 2 Hz, aromatic), 6.95 (d, 1 H, J = 2 Hz, aromatic), 7.87 (s, 1 H, aromatic); ^{13}C NMR ($CDCl_3$) δ 15.5 (CH_3), 39.8 (CH_2), 51.9 (ester OCH_3), 52.0 (ester OCH_3), 55.1 (ether OCH_3), 56.4 (ether OCH_3), 63.8 (ether OCH_3), 63.9 (ether OCH_3), 94.1 (CH), 98.9 (CH), 116.2 (C), 117.3 (C), 122.5 (C), 123.2 (C), 123.5 (C), 128.4 (CH), 133.5 (C), 134.9 (C), 153.3 (COR), 155.8 (COR), 158.2 (COR), 159.9 (COR), 168.6 (ArCOOR), 171.4 ($ArCH_2COOR$); EI-MS, m/z (relative intensity) 442 ($M^{\cdot+}$, 100); IR (CH_2Cl_2) 2930, 1735, 1600, 1540, 1430, 1270, 1210, 1160 cm^{-1}; UV (MeOH) λ_{max} nm (ϵ) 427 (5400), 404 (6900), 376 (8200), 353 (5040), 335 (2960), 274 (87000), 244 (25000); HRMS calcd for $C_{24}H_{26}O_8$ m/z 442.1628, found m/z 442.1659. Anal. Calcd for $C_{24}H_{26}O_8$: C, 65.15; H, 5.92. Found: C, 65.40; H, 6.03.

From an earlier eluting fraction in the purification of **8c**, mixed ester **17** was isolated; trituration with cold Et_2O gave **17** as a yellow solid (0.17 g, 16%), which was recrystallized with Et_2O/hexane (−4 °C): mp 107–108 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 1.70 (s, 9 H, *t*-Bu CH_3's), 3.12 (s, 3 H, aryl CH_3), 3.98 (s, 2 H, CH_2), 4.13 (s, 3 H, OCH_3), 4.19 (s, 3 H, OCH_3), 4.199 (s, 3 H, OCH_3), 4.202 (s, 3 H, OCH_3), 4.26 (s, 3 H, OCH_3), 6.74 (d, 1 H, J = 2.2 Hz), 7.17 (d, 1 H, J = 2.2 Hz), 8.08 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 15.99 (C-10 CH_3), 28.02 (*t*-Bu CH_3's), 41.13 (CH_2), 52.17 (ester OCH_3), 55.16 (ether OCH_3), 56.45 (ether OCH_3), 63.93 (ether OCH_3), 63.99 (ether OCH_3), 81.09 (*t*-Bu quaternary C), 93.98 (CH), 98.80 (CH), 116.03 (C), 117.22 (C), 122.35 (CH), 123.25 (C), 123.78 (C), 129.12 (C), 133.55 (C), 134.78 (C), 153.20 (COR), 155.62 (COR), 158.09 (COR), 158.89 (COR), 168.75 (ArCOOR), 170.39 ($ArCH_2COOR$); EI-MS, m/z (relative intensity) 484 ($M^{\cdot+}$, 54), 428 (100); IR (KBr) 3440 (br), 2982, 2938, 2835, 1731, 1724, 1610, 1565, 1449, 1407, 1362, 1310, 1252, 1204, 1145, 1063, 1038 cm^{-1}; UV (CH_3CN) λ_{max} nm (ϵ) 430 (2920), 405 (4300), 374 (5700), 354 (3800), 274 (65000), 237 (31000). Anal. Calcd for $C_{27}H_{32}O_8$: C, 66.93; H, 6.66. Found: C, 67.11; H, 6.87.

Preparation of Anthracene Ester–Acids 15ab from Dimethyl Esters 8bc. A mixture of methyl ester **8b** (0.28 g, 0.70 mmol) and KOH (0.040 g, 0.70 mmol) in methanol (10 mL) and H_2O (5 mL) was heated at reflux; the reaction was complete after 8 h. The solvent was evaporated, and the residue was partitioned between cold dilute HCl and EtOAc. The EtOAc extract was evaporated to leave ester acid **15a** (0.224 g, 85%) after the residue was washed with Et_2O: mp 169–171 °C; ^1H NMR ($CDCl_3$) δ 2.95 (s, 3 H, CH_3), 3.86 (s, 2 H, CH_2), 3.91 (s, 3 H, OCH_3), 3.97 (s, 6 H, 2 OCH_3), 4.06 (s, 3 H, OCH_3), 6.82 (d, 1 H, J = 7 Hz), 7.42 (dd, 1 H, J = 9 Hz, J = 7 Hz), 7.81 (d, 1 H, J = 9 Hz), 7.95 (s, 1 H), 8.84 (br s, 1 H, COOH); ^{13}C NMR ($CDCl_3$) δ 15.4 (CH_3), 39.82 (CH_2), 52.42 (ester OCH_3), 56.39 (ether OCH_3), 63.98 (ether OCH_3), 64.04 (ether OCH_3), 104.16 (CH), 117.32 (CH), 118.63 (C), 119.36 (C), 123.29 (CH), 123.97 (C), 125.76 (C), 126.40 (CH), 127.46 (C), 132.79 (C), 134.26 (C), 152.98 (COR), 155.86 (COR), 157.43 (COR), 168.99 (COOR), 176.15 (COOH); EI-MS, m/z (relative intensity) 398 ($M^{\cdot+}$, 100); IR (KBr) 3245 (br), 2912, 1722, 1707, 1616, 1552, 1362, 1240 cm^{-1}; UV (MeOH) λ_{max} nm (ϵ) 377 (4400), 267 (88000), 245 (sh, 24000), 225 (11000); HRMS calcd for $C_{22}H_{22}O_7$ m/z 398.1366, found m/z 398.1353.

The only other materials isolated were starting diester **8b** and the corresponding diacid, which could be converted to **8b** by brief exposure to ethereal CH_2N_2. On the basis of the recovered starting material and diacid, which could be converted to starting material, the conversion of diester **8b** to ester acid **15a** is quantitative.

Dimethyl ester **8c** (0.123 g, 0.28 mmol) was converted to the ester acid **15b** by the same procedure. After filtration and washing with Et_2O, acid ester **15b** (0.084 g, 71%) was isolated as a chartreuse solid, mp 203–205 °C. Evaporation of the Et_2O filtrate gave additional 0.035 g of **15b** (100% total): ^1H NMR (400 MHz, acetone-d_6) δ 2.90 (s, 3 H, CH_3), 3.82 (s, 3 H, OCH_3), 3.85 (s, 2 H, CH_2), 3.89 (s, 3 H, OCH_3), 3.90 (s, 3 H, OCH_3), 3.99 (s, 3 H, OCH_3), 4.04 (s, 3 H, OCH_3), 6.58 (d, 1 H, J = 2.2 Hz), 7.06 (d, 1 H, J = 2.2 Hz), 8.04 (s, 1 H), 8.27 (br s, 1 H, COOH); ^{13}C NMR ($CDCl_3$) δ 15.57 (CH_3), 39.89 (CH_2), 52.27 (ester OCH_3), 55.17 (ether OCH_3), 56.44 (ether OCH_3), 63.86 (2 ether OCH_3), 94.28 (CH), 97.61 (C), 99.18 (CH), 117.36 (C), 122.72 (CH), 123.16 (C), 123.29 (C), 127.90 (C), 133.50 (C), 135.10 (C), 153.41 (COR), 156.28 (COR), 158.31 (COR), 158.97 (COR), 169.10 (ArCOOR), 175.08 (COOH); EI-MS, m/z (relative intensity) 428 ($M^{\cdot+}$, 100), 413 (18); IR (KBr) 3390 (br), 2950, 1740, 1725, 1635, 1470, 1380, 1238, 1182, 1067 cm^{-1}; UV (MeOH) λ_{max} nm (ϵ) 425 (4800), 403 (6370), 378 (7400), 355 (5100), 335 (3300), 274 (82000), 245 (sh 23000), 235 (sh 20000); HRMS calcd for $C_{23}H_{24}O_8$ m/z 428.1471, found m/z 428.1480.

Trifluoroacetic Acid Mediated Conversion of *tert*-Butyl Methyl Ester 17 to Ester–Acid 15b. Mixed ester **17** (0.623 g, 1.28 mmol) was dissolved in CH_2Cl_2 (7 mL) and cooled to 0 °C, and TFA (Aldrich, 7 mL) was added. The resulting burgundy solution was stirred at 0 °C for 3 h, after which solvent evaporation in vacuo left an olive foam. Chromatotron separation (80% EtOAc/hexane) produced **15b** as an olive foam (0.322 g, 58%), which must be used quickly, before residual TFA causes acid-catalyzed cleavage of the aryl ester. The spectral data for **15b** produced in this manner are identical with those for **15b** obtained by the alternative base-catalyzed synthesis from dimethyl ester **8c**.

Protetrone 9. Anthracene **8a** (0.310 g, 0.813 mmol) was converted to its monoanion by addition to 0.812 mmol of LDA in THF (75 mL) at −78 °C under N_2. The anion was added to 3.25 mmol of the dilithium salt of *N*-(trimethylsilyl)acetamide, prepared by treatment of 0.426 g (3.25 mmol) of the amide with 6.5 mmol of *n*-butyllithium in THF for 30 min at 0 °C under N_2. After 8 h at 0 °C and 8 h at 25 °C, excess HOAc was added to quench the reaction, and the solvent was removed in vacuo. The residue was partitioned between CH_2Cl_2 and cold dilute HCl. The organic extract was evaporated, and the residue was purified by short-column chromatography (40% EtOAc/hexane) to give 74.2 mg (22%) of **9** as a yellow oil: ^1H NMR ($CDCl_3$) δ 2.97 (s, 3 H, CH_3), 3.70 (s, 3 H, OCH_3), 3.90 (s, 3 H, OCH_3), 3.99 (s, 2 H, $ArCH_2COOR$), 4.02 (s, 3 H, OCH_3), 4.14 (s, 2 H, $COCH_2CO$), 6.18 (m, 2 H, NH_2), 7.48–7.60 (m, 2 H), 7.87 (s, 1 H), 8.18–8.28 (m, 1 H), 8.38–8.49 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 14.3 (CH_3), 38.8 ($ArCH_2COOR$), 51.0 ($COCH_2CO$), 52.1 (ester OCH_3), 63.8 (2 ether OCH_3), 117.3 (C), 123.3 (CH), 123.9 (CH), 124.6 (CH), 125.5 (CH), 126.1 (C), 126.2 (C), 127.3 (C), 126.8 (CH), 129.9 (C), 132.1 (C), 132.3 (C), 151.4 (COR), 155.9 (COR), 169.0 ($CONH_2$), 172.2 (COOR), 203.0 (C=O); EI-MS, m/z (relative intensity) 409 ($M^{\cdot+}$, 100), 392 (31), 377 (25) 323 (35); IR (KBr) 3430, 3350, 2935, 1730, 1670, 1620, 1560, 1435, 1365, 1320, 1250, 1160 cm^{-1}; UV (MeOH) λ_{max} nm (ϵ) 410 (2770), 375 (3800), 356 (2800), 267 nm (42700); HRMS calcd for $C_{23}H_{23}NO_6$ m/z 409.1535, found m/z 409.1525.

Preparation of Protetrones 14ab. The dilithium salt of *N*-(trimethylsilyl)acetamide (4 equiv, Aldrich, 0.122 g, 0.934 mmol, distilled, stored in desiccator) was generated (8 equiv of *n*-BuLi, 1.87 mmol) in THF (15 mL) at 0 °C. In a separate flask, anthracene ester–acid **15** (0.233 mmol) in THF (5 mL) was added at 0 °C to 2 equiv of sodium hydride (Aldrich, 0.019 g, 60% oil dispersion, washed 2 × 10 mL pentane) in THF (10 mL). After 30 min at room temperature, the amber solution was transferred by syringe to the principal reaction vessel (0 °C) containing *N*-(trimethylsilyl)acetamide dianion. A burgundy color resulted; the solution was stirred for 36 h at room temperature. After the mixture was cooled to 0 °C, HOAc (0.14 g, 2.33 mmol) was added, and solvent was evaporated under vacuum, leaving an oil, which was partitioned between EtOAc and 5% aqueous $NaHCO_3$. The aqueous phase was acidified (pH 2) with dilute HCl and extracted with EtOAc. The organic extract was treated with ethereal CH_2N_2 (7 mmol); excess CH_2N_2 was destroyed after 10 min with HOAc. Solvent was evaporated in vacuo, and the residue was purified (Chromatotron, 50% EtOAc/hexane → 80%) to give protetrone **14**.

Protetrone 14a. Condensation of the dianion of *N*-(trimethylsilyl)-acetamide with the sodium salt generated from **15a** (0.224 g, 0.564 mmol) was performed according to the general procedure. Protetrone **14a** was obtained (0.062 g, 25%) as a glass: ^1H NMR ($CDCl_3$) δ 2.96 (s, 3 H, CH_3), 3.71 (s, 3 H, OCH_3), 3.88 (br s, 5 H, $ArCH_2COOR$, OCH_3), 3.92 (s, 3 H, OCH_3), 4.10 (s, 2 H, $COCH_2CO$), 5.52 (br s, 1 H, NH), 6.84 (d, 1 H, J = 8 Hz), 7.02 (br s, 1 H, NH), 7.44 (t, 1 H, J = 8 Hz), 7.82 (d, 1 H, J = 8 Hz), 7.88 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 15.33 (CH_3), 38.84 (CH_2COOR), 51.21 ($COCH_2CONH_2$), 52.15 (ester OCH_3), 56.49 (ether OCH_3), 63.95 (ether OCH_3), 64.10 (ether OCH_3), 104.54 (CH), 117.34 (CH), 118.40 (C), 119.10 (C), 123.58 (CH), 125.86 (C), 126.68 (CH), 127.98 (C), 130.20 (C), 132.77 (C), 134.69 (C), 153.28 (COR), 156.86 (COR), 157.65 (COR), 168.78 ($CONH_2$), 172.11 (COOR), 203.42 (C=O); EI-MS, m/z (relative intensity) 439 ($M^{\cdot+}$, 18), 422 (12), 396 (100), 354 (45), 321 (16), 97 (30); HRMS calcd for $C_{23}H_{24}O_6$ (M − HNCO) m/z 396.1573, found m/z 396.1541.

Protetrone 14b. The dilithium salt of *N*-(trimethylsilyl)acetamide was condensed with the sodium salt generated from anthracene acid ester **15b** (0.100 g, 0.233 mmol) by this procedure. The resulting crude burgundy oil and solid mixture was purified (Chromatotron, 50% EtOAc/hexane → 80%) to give **14b** (R_f 0.2, 80% EtOAc/hexane, orange under long wavelength UV light) as a pale yellow oil (0.028 g, 26%) as well as

dimethyl ester **8c** (0.025 g, 24%), which can be quantitatively recycled to ester-acid **15b**. On the basis of this recovery, the conversion of **15b** to the protected protetrone **14b** is 34%: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.89 (s, 3 H, CH_3), 3.70 (s, 5 H, OCH_3, $ArCH_2COOR$), 3.89 (s, 3 H, OCH_3), 3.93 (s, 3 H, OCH_3), 3.99 (s, 3 H, OCH_3), 4.05 (s, 3 H, OCH_3), 4.12 (s, 2 H, $COCH_2CO$), 5.63 (br s, 1 H, NH), 6.55 (d, 1 H, J = 2.2 Hz), 6.95 (d, 1 H, J = 2.2 Hz), 7.19 (br s, 1 H, NH), 7.60 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 15.48 (CH_3), 38.83 ($ArCH_2COOR$), 51.02 (ester OCH_3), 52.19 ($ArCOCH_2CO$), 55.18 (ether OCH_3), 56.44 (ether OCH_3), 64.03 (ether OCH_3), 64.12 (ether OCH_3), 94.02 (CH), 98.98 (CH), 116.20 (C), 116.89 (C), 123.21 (CH), 123.30 (C), 128.13 (C), 129.22 (C), 133.26 (C), 135.34 (C), 153.39 (COOR), 157.22 (COR), 158.41 (COR), 158.88 (COR), 169.01 ($CONH_2$), 172.24 (COOR), 203.43 (C=O); EI-MS, m/z (relative intensity) 469 ($M^{\cdot+}$, 52), 451 (57), 424 (33), 423 (100), 411 (24), 393 (31), 383 (67), 367 (28), 354 (28); IR (KBr) 3355 (br), 2948, 1745, 1710, 1668, 1608, 1428, 1323, 1209, 1163, 1038 cm^{-1}; UV (CH_3CN) λ_{max} nm (ϵ) 430 (1180), 386 (1930), 331 (5780), 274 (16 200), 239 (19 400); HRMS calcd for $C_{25}H_{27}NO_8$ m/z 469.1737, found m/z 469.1735.

10-Dehydroxy-6-methylpretetramide (12). A slurry of anthracene **9** (8.4 mg, 0.021 mmol) in acetic acid (10 mL) was treated with aqueous HBr (10 mL, 49%, freshly distilled from red phosphorus) for 7 h at 40 °C under N_2. The mixture was then stored at 4 °C. Crystals deposited and were collected and washed with H_2O, MeOH, CH_2Cl_2, $CHCl_3$, Et_2O, and EtOAc to yield naphthacene **12** (5.9 mg, 82%): mp (vac) 200-300 °C dec; too insoluble to obtain NMR spectra; EI-MS, m/z (relative intensity) 349 ($M^{\cdot+}$, 55), 332 (100), 318 (91), 306 (82), 292 (73), 291 (86), 263 (23), 262 (23), 189 (50), 176 (32); IR (KBr) 3470, 3410, 1655, 1595 cm^{-1}; UV (1:9 AcOH/EtOH) λ_{max} nm (ϵ) 435 (4800), 350 (5200), 315 (6800), 265 (11 200); HRMS calcd for $C_{20}H_{15}NO_5$ m/z 349.0950, found m/z 349.0955.

6-Methylpretetramide (1). Protetrone **14a** (0.025 g, 0.057 mmol) was refluxed for 3 h in 2 mL of a 50% mixture of acetic and hydriodic acids (47% aqueous, distilled from red P, 123-124 °C, stabilized with 1.5% H_3PO_2). After cooling to room temperature, the reaction mixture was poured over 10 g of crushed ice and filtered. The brick red solid was washed with H_2O, acetone, EtOAc, and Et_2O to give 6-methylpretetramide (**1**; 10 mg, 50%): mp (vac) 220-240 °C dec (lit.[2a] mp 200-300 °C dec); EI-MS, m/z (relative intensity) 365 ($M^{\cdot+}$ 42), 348 (100); UV [98% H_2SO_4/0.1% (w/w) H_3BO_3] λ_{max} nm (ϵ) 505 (9600), 403 (11 200), 343 (sh, 3900), 328 (4600), 293 (7200), 275 (8200), 263 (8800) [lit.[3] 512 (15 100), 398 (17 650), 339 (16 200), 295 (22 900), 276 (23 900), 262 (24 700), 233 (20 200)]; HRMS calcd for $C_{20}H_{15}NO_6$ m/z 365.0876, found m/z 365.0893.

8-Hydroxy-6-methylpretetramide (4). A solution of protetrone **14b** (0.014 g, 0.030 mmol) in acetic acid (0.4 mL) under an argon atmosphere was treated with hydriodic acid (0.4 mL, 47% aqueous, distilled from red P, 123-124 °C, stabilized with 1.5% H_3PO_2) at reflux for 3 h. The orange suspension was poured over crushed ice (15 g), and the precipitate was collected by suction filtration and washed with H_2O (6 mL), cold acetone (0.5 mL), cold EtOAc (2 mL), and Et_2O (2 mL) to yield 8-hydroxy-6-methylpretetramide (**4**) as a brick-orange solid (0.006 g, 53%): mp (vac) 330-338 °C dec; ^{1}H NMR insufficiently soluble in DMSO-d_6/1% $Mg(OCOCD_3)_2$ to obtain a satisfactory spectrum at 400 MHz; EI-MS, m/z (relative intensity) 381 ($M^{\cdot+}$, 10), 364 (26), 339 (31), 338 (100), 324 (39), 323 (95), 309 (24), 295 (21); IR (KBr) 3434 (br), 1726 (w), 1709 (w), 1689 (w), 1655, 1638, 1627, 1609, 1600, 1411, 1400, 1390, 1381, 1350, 1290, 1170 cm^{-1}; UV (CH_3CN) λ_{max} nm (ϵ) 438 (14 700), 326 (17 000), 296 (20 100), 280 (20 500), 259 (19 500); HRMS calcd for $C_{20}H_{15}NO_7$ m/z 381.0849, found m/z 381.0852.

Extraction of the aqueous filtrate with EtOAc yielded anthrone **18** as an orange solid (3.0 mg, 33%): 300-MHz ^{1}H NMR (acetonitrile-d_3) δ 1.50 (d, 3 H, CH_3, J = 7 Hz), 3.63 (s, 2 H, CH_2), 4.21 (q, 1 H, C-10 CH, J = 7 Hz), 6.27 (d, 1 H, J = 2 Hz), 6.48 (d, 1 H, J = 2 Hz), 6.75 (d, 1 H, J = 1.8 Hz), 6.90 (d, 1 H, J = 1.8 Hz), 8.03 (s, 1 H, isolated phenol OH), 12.29 (s, 1 H, H-bonded phenol OH), 12.42 (s, 1 H, H-bonded phenol OH); EI-MS, m/z (relative intensity) 314 ($M^{\cdot+}$, 100), 299 (90), 271 (25), 270 (20), 268 (50), 204 (60); IR (KBr) 3260 (br), 2580, 1700, 1655, 1602, 1457, 1418, 1363, 1282, 1258, 1220, 1162 cm^{-1}; UV (CH_3CN) λ_{max} nm (ϵ) 429 (2120), 362 (4540), 270 (5130), 244 (7660), 226 (9820), 198 (20 150); HRMS calcd for $C_{17}H_{14}O_6$ m/z 314.0790, found m/z 314.0786.

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Stereocontrolled Construction of an Ingenol Prototype Having a Complete Array of Oxygenated and Unsaturated Centers

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Abstract: The keto tetrol **3**, a close prototype of ingenol, has been synthesized in highly stereoselective fashion. Starting with β-diketone **9**, the allylic alcohol **13** was first crafted. The stage was thereby set for Sharpless oxidation and introduction of the ring A double bond. Subsequent regiospecific opening of epoxy alcohol **16** with titanium isopropoxide in the presence of ammonium benzoate followed by acetonide formation delivered **21**. Once the benzoyloxy group in this intermediate was transformed into a carbonyl, conversion to **34** was readily accomplished. Selenoxide elimination and adjustment of the oxidation level at two centers followed by removal of the acetonide functionalities delivered **3**. This target molecule can be cleanly acylated at its 3- and 3,5-positions with palmitoyl chloride.

Euphorbia, the largest genus (ca. 1600 species) of the family *Euphorbiaceae* (290 genera),[3] occur as succulent or nonsucculent plants in most parts of the world. Although the lattices of most of these species are widely known to be highly irritating, various parts have nonetheless seen extensive use in folk medicine against all kinds of diseases.[4] The types that grow as weeds have often been held responsible for the poisoning of livestock.[5] Of special medicinal relevance are the various esters of phorbol (**1**) and ingenol (**2**) that are contained therein.[6] Detailed investigations

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