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Biomimetic Syntheses of Pretetramides. 2. A Synthetic Route Based on a Preformed D Ring

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Abstract: A route to pretetramides has been developed on the basis of tandem condensations of homophthalate esters with the dianion of methyl acetoacetate to give aromatic bis(diketo esters), which cyclize spontaneously to anthracene diesters. A further condensation of one of the ester groups with acetamide synthons gives anthracene ester-keto amides, which can be cyclized to naphthacenecarboxamides. By this technique dimethyl 3-methoxyhomophthalate (**2b**) was condensed with the dilithium salt of methyl acetoacetate to give anthracene diester (**4b**). Protection of the hydroxyl groups followed by treatment with the dilithium salt of *N*-(trimethylsilyl)acetamide gave anthracene ester-keto amide **6**, which cyclized to pretetramide (**1**) on treatment with HBr in acetic acid. The procedure for synthesis of pretetramide was modified to permit separate addition of the ketide chains. By use of the aliphatic mono ester (**7b**) of 3-methoxyhomophthalic acid, chain extension was brought about at the aliphatic carboxyl group by condensation with the dilithium salt of *tert*-butyl acetoacetate. This product was cyclized to isocoumarin **9b** by treatment with acetic anhydride. Completion of the backbone was achieved in a single condensation by treatment of **9b** with trianion **18** of 3,5-dioxohexanenitrile (prepared from the nitrile or indirectly by cleavage of isoxazole **17** with LDA) to give anthrone **32**. A variety of other condensations of the trianion **18** were performed with electrophiles to demonstrate the utility of the reagent. The synthesis of pretetramide from anthrone **32** was completed by treatment with HI/phenol.

Pretetramide (**1**) is the fully aromatic tetracyclic precursor of the tetracycline antibiotics.[1] The first paper in this series[2] described a synthesis of pretetramide on the basis of tandem condensations of dianions of acetoacetic esters with glutarate derivatives to give a naphthalene diester after spontaneous cyclization. Further condensations with (a) *tert*-butyl lithioacetate and (b) the dianion of an isoxazole completed the carbon skeleton and after another spontaneous cyclization gave an anthracene-isoxazole, which could be transformed to pretetramide by treatment with a mixture of hydriodic acid and red phosphorus in acetic acid. The sequence circumvents the formidable problem of assembling a full decacarbonyl species prior to closure of the four rings; this segmented method for assembly of the polyketide intermediates is termed a [3 + (2 × 2) + 1 + 2] strategy (Scheme Ia).

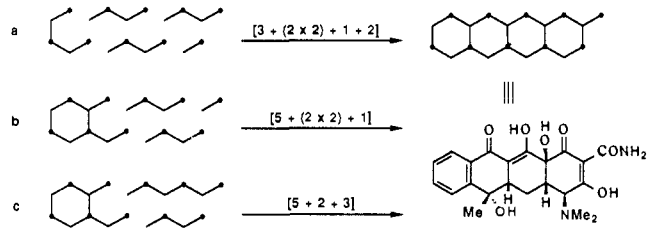
Alternative routes are described in this paper, which also skirt the preparation of large arrays of β carbonyl groups by employing homophthalate esters as pentacarbonyl equivalents; polyketide chains are extended from this central core by Claisen condensations with the two ester groups. The first of these routes is a [5 + (2 × 2) + 1] approach (Scheme Ib) in which tandem condensations of acetoacetate dianions with the two homophthalate ester groups yield a nonacarbonyl equivalent, which cyclizes to an anthracene. The skeleton is completed with an acetamide synthon followed by acid-catalyzed Claisen cyclization. The second synthesis, a [5 + 2 + 3] approach (Scheme Ic) involves addition of a diketide chain followed by a triketide chain to the homophthalate nucleus.

Results and Discussion

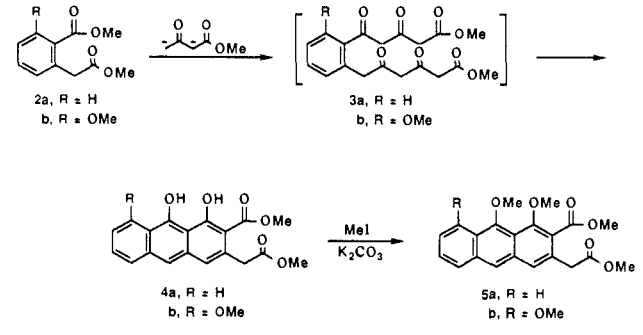
The 3-methoxy derivative of homophthalic acid is required as the central unit for the preparation of pretetramide by the [5 + (2 × 2) + 1] strategy; but pilot studies were carried out with homophthalic acid because of its commercial availability. Tandem chain extensions were achieved by Claisen condensation of dimethyl homophthalate (**2a**) with methyl acetoacetate dianion (see Scheme II). The dilithium salt was employed for the condensation to minimize the risk that the dianion, which is highly basic, would ionize the α-methylene group of homophthalate in preference to making nucleophilic attacks on the two ester groups. Prior studies of the condensation of aliphatic esters with the dianion of acetylacetone have demonstrated the advantage of lithium over sodium and potassium salts when dianions are being condensed with enolizable esters.[3] A substantial excess (7 equiv) of the dianion of methyl acetoacetate was employed to make allowance for the theoretical 4:1 stoichiometry of the reaction plus side reactions, which would expend dianion.[4] It was anticipated that the bis(diketo ester) adduct (**3a**) from the homophthalic ester would be unstable and would cyclize spontaneously by aldol processes to a naphthalene and probably on to an anthracene.[5]

The condensation gave 30% of an air-sensitive product, m/z 340, consistent with the anthracene formulation. Prior studies of anthracenes formed from heptaketones provided strong pre-

Scheme I



Scheme II



(1) McCormick, J. R. D. In *Biogenesis of Antibiotic Substances*; Vanek, Z., Hostálek, Z., Eds.; Academic: New York, 1965; Chapter 8.

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

(3) Work, S. D.; Hauser, C. R. *J. Org. Chem.* **1963**, *28*, 725.

(4) The first paper in this series contains a discussion of the problems associated with this reaction; in that paper other strategies were utilized to achieve the condensations with the dianion of acetoacetate esters.[2]

(5) (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.

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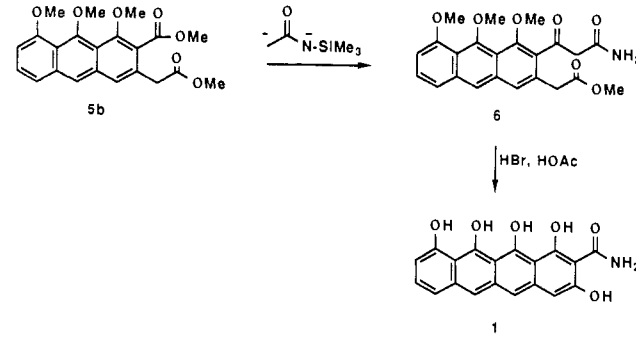
cedents for anthracene **4a**.[5,6] A zinc-dust distillation was carried out to confirm the structure before continuing with the synthesis. Pyrolysis of **4a** with zinc dust gave 2-methylanthracene, establishing that the adduct had indeed cyclized to give anthracene **4a**. The ^{1}H NMR spectrum was consistent with **4a** in that the phenolic protons were observed at 10.86 and 15.05 ppm, which are similar to those in 2-acyl-1,8-naphthalenediols;[7] the low-field signal can be assigned to the hydroxyl group which is hydrogen bonded to the carbonyl group. In the ^{1}H NMR spectrum of the supernatant from the crystallization of the compound could be seen small quantities of the anthrone tautomer, characterized by a strongly hydrogen-bonded hydroxyl group at 13.70 and the ring methylene group at 4.3 ppm, the latter being similar to that of anthrone itself. Methylation of **4a** under anaerobic conditions using dimethyl sulfate and K_2CO_3 gave dimethyl ether **5a** in good yield. The methylated compound, in contrast to **4a**, was stable to air.

With evidence that the proposed strategy would yield correct ring closures up to the anthracene stage, a synthesis of pretetramide was undertaken based on 3-methoxyhomophthalic acid. Treatment of dimethyl 3-methoxyhomophthalate (**2b**) with the dilithium salt of methyl acetoacetate gave the tandem acylation product (**3b**), which cyclized to anthracene **4b** in an overall 48% yield (Scheme II). The anthracene was reasonably stable in crystalline form and could be stored for short periods at ambient temperature in contact with air and for long periods at −5 °C under nitrogen; however, solutions of the compound deteriorated rapidly in contact with air. Oxidative degradation could be monitored qualitatively by TLC. To retard oxidation and to prepare for further chain extension, the phenols were methylated with dimethyl sulfate/K_2CO_3 under an inert atmosphere to give 1,8,9-trimethoxyanthracene **5b**.

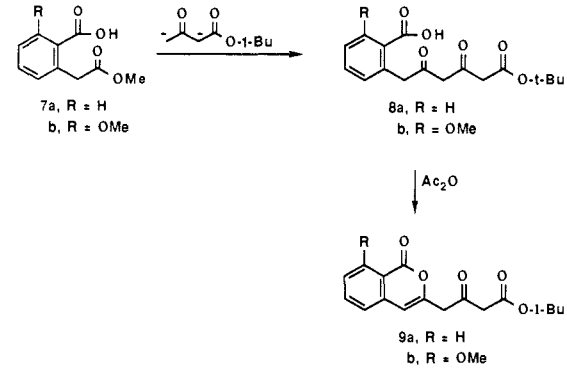
For completion of the synthesis the anion of acetamide or an equivalent synthon was required. However, acetamide itself does not form a useful anion. The monoanionic species is the amide anion rather than the enolate anion.[8] The α,N-dianion is unknown; attempts to form it by treatment of the monoanion with strong bases have led to the anion of acetonitrile.[9] The lithium salt of *N,O*-bis(trimethylsilyl)acetamide might potentially be useful as an acetamide synthon in the present situation; the anion reacts with ketones in excellent yield and the silyl group is lost spontaneously by contact with water during workup.[10] Its chief problem is that it is thermally unstable and unlikely to give good results if extended reaction periods or elevated temperatures are required. Acylations of the anion have been only marginally successful and the prospects for successful condensation with diester **5b** appeared poor because of the reduced reactivity of the aromatic ester due to steric hindrance by the ortho substituents and deactivation by the anion at the α methylene position, which would need to be employed to protect against attack on the aliphatic ester group. An attempt to condense the lithium salt of *N,O*-bis(trimethylsilyl)acetamide with **5b** confirmed this pessimism.

Investigation of alternative acetamide synthons led to discovery of the *N*-(trimethylsilyl)acetamide dianion.[11] The dilithium salt of *N*-(trimethylsilyl)acetamide is readily formed by treatment of the amide with 2 equiv of LDA. The dianion is soluble in THF and thermally stable. Moreover, in that it is a dianion it is substantially more nucleophilic than the monoanion of the bissilylated acetamide. Efficient reaction has been observed with esters, including a model reaction with the dimethyl ester of homophthalic acid; in that case the condensation was carried out by using the enolate anion of the homophthalate ester, and reaction was observed exclusively with the aromatic ester.[11]

Scheme III



Scheme IV



The reaction of **5b** with dilithio-*N*-(trimethylsilyl)acetamide was carried out by first forming the anion of **5b** and then adding it to the trimethylsilylacetamide dianion (Scheme III). The reaction gave 51% of the desired adduct, amide–ester **6**; in addition, 17% of unaltered diester **5b** was recovered. The site of reaction was indicated by the IR spectrum, which showed that the compound contained an aliphatic ester (1738 cm^{-1}) and an aromatic ketone (1681 cm^{-1}). It is noteworthy that the ^{13}C NMR spectrum showed a ketonic carbonyl group at 203.1 ppm, unusually far downfield for an aromatic ketone but consistent with one flanked by substituents on both sides.[12]

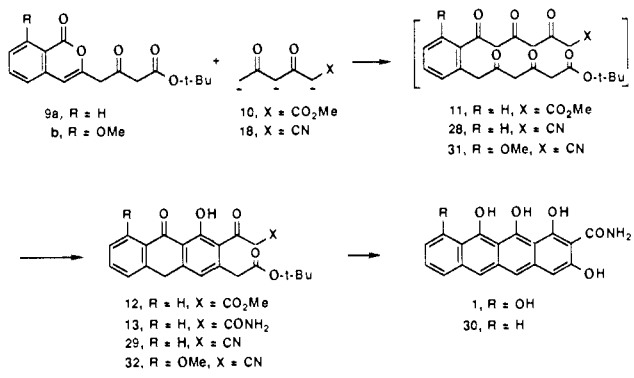
Acidic conditions were chosen for the final ring closure. A similar ring closure had been achieved by McCormick and Jensen;[13] protetrone quinone is isolated from a point-blocked mutant of a tetracycline-producing *Streptomyces* and, although not a precursor in the biosynthesis of pretetramide, could be converted to pretetramide chemically by treatment with HI, which not only closed the final ring but also reduced the quinone. In the present case HBr in acetic acid was employed; the reagent brought about closure of the final ring and demethylation of the three phenols to give in 86% yield pretetramide (**1**), the structure of which was established by spectral characterization and by comparison with an authentic sample.[14] The overall yield from dimethyl 3-methoxyhomophthalate (**2b**) is 11%.

The next approach to pretetramide involved creating a dicarbonyl extension to the aliphatic ester of homophthalate and then a tricarbonyl extension to the aromatic ester, i.e., a [5 + 2 + 3] strategy (see Scheme Ic). Such a strategy would mimic the biological process more closely than the [5 + (2 × 2) + 1] scheme in that it would result in a monocyclic species containing all of the carbon atoms needed to form the other three rings. On the practical side, it would permit more versatility in subsequent synthesis of substituted pretetramides.

The [5 + 2 + 3] strategy requires being able to make a clear distinction between the two carboxyl groups in their condensations with the appropriate enolate anions to assemble the two side chains.

(6) (a) Harris, T. M.; Wittek, P. J. *J. Am. Chem. Soc.* **1975**, *97*, 3270. (b) Webb, A. D.; Harris, T. M. *Tetrahedron Lett.* **1977**, 2069.
(7) Dreyer, D. L.; Arai, I.; Bachman, C. D.; Anderson, W. R., Jr.; Smith, R. G.; Daves, G. D., Jr. *J. Am. Chem. Soc.* **1975**, *97*, 4985.
(8) Wolfe, J. F.; Trimitsis, G. B. *J. Org. Chem.* **1968**, *33*, 894.
(9) Creger, P. L. *J. Org. Chem.* **1972**, *37*, 1907.
(10) (a) Evans, D. A.; Wong, R. Y. *J. Org. Chem.* **1977**, *42*, 350. (b) Morwick, T. *Tetrahedron Lett.* **1980**, *21*, 3227.
(11) Kuzma, P. C.; Brown, L. E.; Harris, T. M. *J. Org. Chem.* **1984**, *49*, 2015.
(12) Wehrli, F. W.; Wirthlin, T. *Interpretation of Carbon-13 NMR Spectra*; Heyden: Philadelphia, 1978; Chapter 2.
(13) McCormick, J. R. D.; Jensen, E. R. *J. Am. Chem. Soc.* **1968**, *90*, 7126.
(14) We are grateful to Dr. J. R. D. McCormick for an authentic sample of pretetramide.

Scheme V

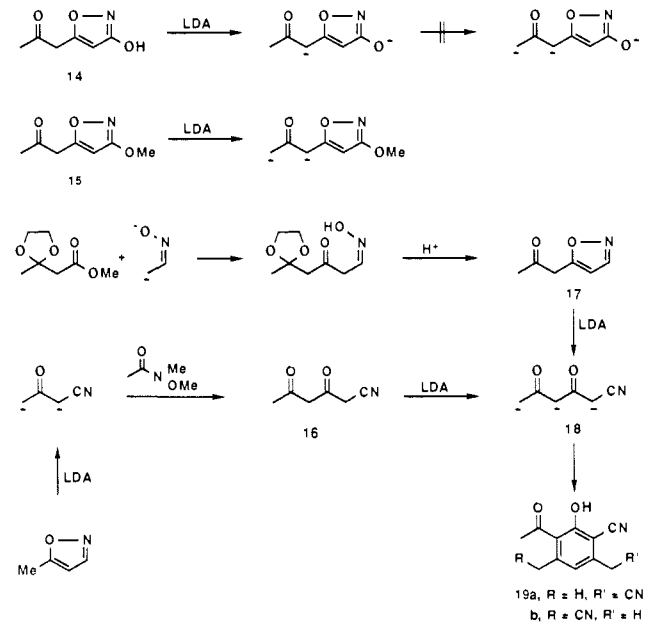


In the previous paper a similar aromatic diacid was converted to the anhydride; the aliphatic carboxyl group of the anhydride was the preferred site of attack by an enolate anion, but the reaction was not completely regiospecific. In the present case differential reactivity of the two carboxyl groups with nucleophiles was achieved by conversion of the homophthalic acid to its monoester. Initial studies were made again with homophthalate. Limited methylation of homophthalic acid by Fischer esterification[15] gave aliphatic ester **7a** in 69% yield. Condensation of **7a** with 4 equiv of the dilithium salt of *tert*-butyl acetoacetate gave the aliphatic adduct (**8a**), which on treatment with acetic anhydride cyclized to isocoumarin **9a** in an overall yield of 24% (Scheme IV). The dianion of *tert*-butyl acetoacetate is more satisfactory for this condensation than that of the methyl ester used in the reactions of diesters **2ab** because the sterically hindered *tert*-butyl ester is resistant to self-condensation, thus reducing the amount of keto ester dianion required for the reaction.[5b,16,17] Furthermore, the *tert*-butyl ester would also solve another problem; it would later block an unwanted nucleophilic attack by the diketo amide synthon on the side-chain ester group of **9a**.

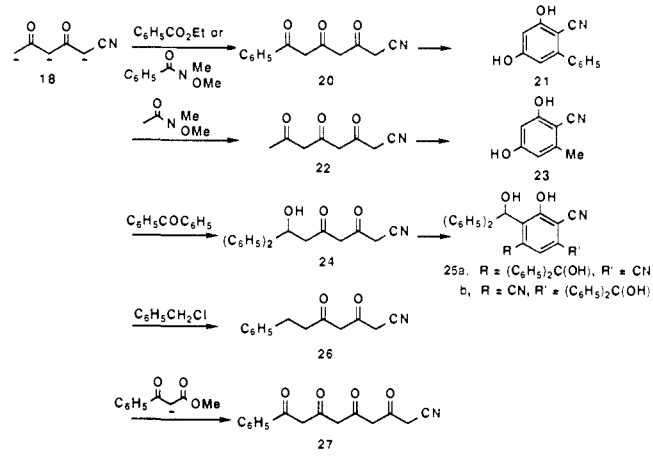
It had been hoped that the trianion (**10**) of methyl dioxohexanoate could serve as the diketo amide synthon for attack on the aromatic carboxyl group and that the ester group could be converted to a carboxamide at a later stage. The diketo ester trianion had previously been characterized in this laboratory.[18] Treatment of **9a**, as its enolate anion, with trianion **10** gave adduct **11**, which cyclized spontaneously to a tricyclic product, assigned as anthrone **12** by analogy with the previous study (Scheme V). Problems arose in the completion of the synthesis; the final ring failed to close when **12** was treated with HI or with HBr in acetic acid.[13] In addition, an attempted conversion of **12** to carboxamide **13** with dimethylaluminum amide[19] failed, although model compounds such as methyl salicylate readily underwent this transformation.

The primary goal of the model study with **7a** had been to evaluate the prospects for obtaining selective extension of the aliphatic side chain of homophthalate by two carbonyl groups and the aromatic one by three, and this goal had been achieved. However, the unanticipated difficulty in conversion of the ester to the carboxamide suggested that a different triketide should be used. Preferably, the synthon should be equivalent to 3,5-dioxohexanamide rather than to the diketo acid in order to avoid the need for functional group conversion. The direct approach of employing a polyanionic species derived from 3,5-dioxohexanamide was unlikely to be successful, since even acetamide cannot be satisfactorily converted to an enolate anion.[8] *N,N*-Dimethyl-3,5-dioxohexanamide readily forms a trianion and the trianion is nucleophilic;[18] however, problems were anticipated with later removal of the methyl groups.

Scheme VI



Scheme VII



Three other diketo amide synthons were investigated: hydroxyisoxazole **14**,[20] methoxyisoxazole **15**, and 3,5-dioxohexanenitrile (**16**), all to be converted to the appropriate anionic species before attempting the condensation (Scheme VI). The two isoxazoles, **14** as the trianion and **15** as the dianion, seemed ideally suited for the condensation with **9a**, because isoxazoles, being easily cleaved by hydrogenolysis, can serve as masked β-keto amides.[20,21] However, attempts to form the trianion of **14** with LDA and other strong bases met with failure, giving an unreactive precipitate, believed to be the O,α-dianion. Methoxyisoxazole **15** was readily converted to the dianion by treatment with 2 equiv of LDA; however, the dianion had low nucleophilicity and failed to react with methyl benzoylacetate or with **9a** (as their enolate anions).

The fourth diketo amide synthon, 3,5-dioxohexanenitrile (**16**), presented a potential problem because β-keto nitriles are well known to be unstable, undergoing facile aldol-type condensations.[22]

(15) Fieser, L. F.; Pechet, M. M. *J. Am. Chem. Soc.* **1946**, *68*, 2577.
(16) (a) Weiler, L. *J. Am. Chem. Soc.* **1970**, *92*, 6702. (b) Huckin, S. N.; Weiler, L. *Can. J. Chem.* **1974**, *52*, 2157. (c) Kaiser, E. M.; Petty, J. D.; Knutson, P. L. A. *Synthesis* **1977**, 509 and references contained therein.
(17) Huckin, S. N.; Weiler, L. *Can. J. Chem.* **1974**, *52*, 1343.
(18) Hubbard, J. S.; Harris, T. M. *J. Org. Chem.* **1981**, *46*, 2566.
(19) Basha, A.; Lipton, M.; Weinreb, S. M. *Tetrahedron Lett.* **1977**, 4171.
(20) Oster, T. A.; Harris, T. M. *J. Org. Chem.* **1983**, *48*, 4307.
(21) See (a) Wakefield, B. J.; Wright, D. J. In *Advances in Heterocyclic Chemistry*; Katritzky, A. R., Boulton, A. J., Eds.; Academic: New York, 1979; Vol. 25, pp 147–204. (b) Kochetkov, N. K.; Sokolov, S. D. In *Advances in Heterocyclic Chemistry*; Katritzky, A. R., Boulton, A. J., Lagowski, J. M., Eds.; Academic: New York, 1963; Vol. 2, pp 365–422. (c) Quilico, A.; Speroni, G. In *Five and Six-Membered Compounds with Nitrogen and Oxygen*; Wiley, R. H., Ed.; Wiley Interscience: New York, 1962; Part I. (d) Rylander, P. N. In *Catalytic Hydrogenation in Organic Syntheses*; Academic: New York, 1979; pp 294–298.
(22) Vinick, F. J.; Pan, Y.; Gschwend, H. W. *Tetrahedron Lett.* **1978**, 4221.

However, their enolate anions are stable. The enolate anions can be prepared from isoxazoles that are free of substituents at the 3-position by treatment with base.[21a-c,22] Keto isoxazole **17**, required for formation of trianion **18**, was prepared by acylation of the dianion[23] of acetaldehyde oxime with ketal-protected methyl acetoacetate followed by acid-catalyzed isoxazole formation and then deprotection of the ketone (Scheme VI). Treatment of **17** with 3 equiv of LDA gave the trianion **18** as an orange solution in THF.

A second route to trianion **18** involved direct ionization of diketo nitrile **16** with LDA. The dianion of 3-oxobutanenitrile, formed by treatment of 5-methylisoxazole with 2 equiv of LDA,[22] was acylated by *N*-methyl-*N*-methoxyacetamide[24,25] to give **16** (Scheme VI). Despite significant losses during isolation, a 46% yield of **16** was obtained. The compound was a liquid and unstable at room temperature but could be stored without decomposition as a crystalline solid at 4 °C. At pH 5.0, **16** dimerized rapidly to give an aromatic product identified as **19a** or **19b**. Trianion **18** was condensed with a variety of electrophiles to show its synthetic utility before employing it in the pretetramide synthesis; these reactions are shown in Scheme VII. Efforts were not made in every case to optimize the yields, a major problem being that the keto nitrile products, like the starting material, are unstable and readily undergo aldol-type dimerization to give phenolic products. Nevertheless, it was clear that the trianion was of sufficient nucleophilicity to be of potential value in the present study.

Condensation of trianion **18** with isocoumarin **9a** (as its enolate anion) gave adduct **28**, which cyclized in situ to anthracene **29**; the compound was unstable by virtue of the fact that it is both an air-sensitive anthrone and a β-keto nitrile subject to aldol condensations. Substantial losses undoubtedly occurred during isolation and purification; **29** was obtained in 13% yield after chromatography and recrystallization. The *tert*-butyl group was cleaved, the final ring closed, and the nitrile hydrolyzed to the amide with refluxing hydriodic acid/phenol to give dehydroxypretetramide **30** in 21% yield.

The synthesis was then repeated with 3-methoxyhomophthalic acid. Condensation of the dilithium salt of *tert*-butyl acetoacetate with monomethyl ester **7b** yielded adduct **8b**, which was treated with Ac_2O to give isocoumarin **9b** in 22% yield (Scheme IV). The isocoumarin was condensed with diketo nitrile trianion **18**; the adduct (**31**) cyclized to give anthrone **32** (Scheme V). Only a 6% yield of the anthrone was obtained, probably because of low reactivity of the isocoumarin carboxyl group due to the flanking methoxyl group. Treatment of **32** with HI/phenol brought about the required transformation, including removal of the methyl group to give pretetramide (**1**) in 18% yield. The overall yield of the sequence from 3-methoxyhomophthalic acid is less than 1%.

The two syntheses of **1** mimic the biosynthesis to the extent that the rings are formed in the same sequence and by the same types of reactions as in the natural process. The overall yield of the second synthesis is inferior to that of the first, but the pathway more closely approaches the putative biosynthetic pathway in that the polyketide chain is fully assembled before the last three rings are closed.

Experimental Section

General Procedures. The general procedures described in paper one of this series were employed.[2] Additionally, some ^1H NMR spectra were recorded with a JEOL MH-100 spectrometer and high-resolution (EI) mass spectra were obtained at Florida State University, Tallahassee, FL.

Methyl 2-Carbomethoxy-1,9-dihydroxyanthracene-3-acetate (4a). Dimethyl homophthalate (**2a**)[26] was prepared by treatment of the diacid with CH_2N_2. Methyl acetoacetate (16.24 g, 140 mmol) in THF was added slowly to a solution of 300 mmol of lithium diisopropylamide in 500 mL of THF at −78 °C under N_2 followed by dimethyl homophthalate (4.16 g, 20 mmol). The reaction was allowed to warm to 0 °C over 4 h and then quenched with excess HOAc. The solvent was evaporated in vacuo. The residue was partioned between $CHCl_3$ and dilute HCl. The organic extract was evaporated to dryness. The residue was triturated with Et_2O to give an orange solid, which was recrystallized from $CHCl_3$/EtOH to give 1.83 g (30%) of **4a**: mp 177.5–180 °C; ^1H NMR ($CDCl_3$) δ 3.77 (s, 3 H, OCH_3), 3.95 (s, 5 H, OCH_3 and CH_2), 7.15 (s, 1 H), 7.40–7.80 (m, 3 H), 7.90 (d, 1 H), 8.55 (d, 1 H), 10.86 (s, 1 H, OH), 15.05 (s, 1 H, OH); EI-MS, *m/z* (relative intensity) 340 ($M^{\cdot+}$, 48), 308 (57), 280 (38), 276 (100); IR (Nujol) 1735, 1630, 1620, 1560, 1330, 1285, 1200, 1190, 1170, 1090 cm^{-1}; UV (EtOH) λ_{max} nm (ε) 391 (17 500), 376 (10 000), 267 (3500) 227 (16 700), 212 (20 000). Anal. Calcd for $C_{19}H_{16}O_6$: C, 67.05; H, 4.74. Found: C, 66.94; H, 4.85.

Zinc-Dust Reduction of 4a. A mixture of **4a** (20 mg) and Zn dust (500 mg) was packed in a 1.5 × 15 cm test tube and covered with an additional 1–2 g of Zn dust. The top of the tube was wrapped with a wet paper towel to provide cooling. The tube was heated at a red heat for 5 s. Distilled material around the top of the tube was purified by chromatography on silica gel (hexane). The UV and MS data indicated it was a mixture of anthracene and methylanthracene. Identical results were obtained in a similar zinc-dust distillation of 2-methylanthraquinone.

Methyl 2-Carbomethoxy-1,9-dimethoxyanthracene-3-acetate (5a). Compound **4a** (2.4 g, 7 mmol) was refluxed with dimethyl sulfate (13.2 g, 105 mmol) and K_2CO_3 (19.3 g, 140 mmol) in acetone (300 mL) for 3 h. Solids were filtered off, the filtrate was concentrated, and Et_2O was added. Et_3N was added at 0 °C to destroy excess dimethyl sulfate. The mixture was partitioned between Et_2O and water. The organic layer was concentrated to dryness. The residue was recrystallized from MeOH to give 2.0 g (80%) of **5a** as pale yellow crystals: mp 98–99 °C; ^1H NMR ($CDCl_3$) δ 3.70 (s, 3 H, OCH_3), 3.77 (s, 2 H, CH_2), 3.95 (s, 3 H, OCH_3), 4.00 (s, 3 H, OCH_3), 4.02 (s, 3 H, OCH_3), 7.40–7.50 (m, 2 H), 7.60 (s, 1 H), 7.80–8.00 (m, 1 H), 8.10 (s, 1 H), 8.20–8.40 (m, 1 H); ^{13}C NMR (22.5 MHz, $CDCl_3$) δ 39.2 (CH_2), 52.0 ($COOCH_3$), 52.2 ($COOCH_3$), 63.8 (2 OCH_3, resolved with Eu(fod)$_3$), 117.9, 122.6, 122.8, 125.8, 126.6, 127.9, 133.4, 134.1, 152.7, 154.3, 168.2 ($ArCOOCH_3$), 171.2 (CH_2CO-OCH_3); EI-MS, *m/z* (relative intensity) 368 ($M^{\cdot+}$, 100), 336 (20), 293 (18); IR (Nujol) 1730, 1700, 1340, 1325, 1270, 1195, 1170, 1095, 1065 cm^{-1}; UV (EtOH) λ_{max} nm (ε) 377 (7000), 262 (123 000), 223 (15 500). Anal. Calcd for $C_{21}H_{20}O_6$: C, 68.47; H, 5.47. Found: C, 68.43; H, 5.57.

Dimethyl 3-Methoxyhomophthalate (2b). 3-Hydroxyhomophthalic acid (K&K Laboratories Division, ICN Pharmaceuticals, Plainview, NJ) was esterified with $(CH_3)_2SO_4$ and K_2CO_3 in refluxing acetone to give 94% of **2b**.[27]

Methyl 2-(Methoxycarbonyl)-1,9-dihydroxy-8-methoxyanthracene-3-acetate (4b). Note: *This compound is air-sensitive, rapidly darkening particularly when not in crystalline form; an N_2 atmosphere was employed throughout the entire preparation, including workup and crystallization.* Methyl acetoacetate (2.34 g, 20 mmol) was added to lithium diisopropylamide (43 mmol) in 100 mL of THF at −78 °C followed after 15 min by dimethyl 3-methoxyhomophthalate (**2b**; 0.60 g, 2.5 mmol). After 1 h at −78 °C and 4 h at 0 °C, the reaction was quenched with acetic acid (5.66 g, 94 mmol). After evaporation of solvent, the residue was partitioned between $CHCl_3$ and cold dilute HCl. The organic extract was concentrated to dryness in vacuo. Recrystallization of the residue from $CHCl_3$/EtOH gave 0.45 g (48%) of **4b**: mp 168 °C; TLC ($CHCl_3$) R_f 0.19, very bright yellow under long wavelength UV light; ^1H NMR ($CDCl_3$) indicated a mixture of anthrone and anthranol tautomers δ 3.71 (s, 3 H), 3.73 (s, 3 H), 4.06 (s, 2 H), 4.25 (s, 1.5 H), 6.75–7.58 (m, aromatic protons) 11.25 (br s, OH), 13.48 (br s, OH), 13.80 (br s, OH); EI-MS, *m/z* (relative intensity) 370 ($M^{\cdot+}$, 93), 339 (32), 338 (74), 310 (51), 307 (30), 306 (73), 295 (32), 278 (38), 249 (92), 207 (36), 182 (32), 180 (30), 179 (100), 178 (44), 175 (31), 150 (25), 102 (31), 101 (100), 74 (38); UV (EtOH) λ_{max} nm (ε) 389 (17 400), 376 (12 600), 351 (7900), 280 (38 000), 231 (17 000), 212 (24 000). Anal. Calcd for $C_{20}H_{18}O_7$: C, 64.86; H, 4.90. Found: C, 64.65; H, 5.01.

Methyl 2-(Methoxycarbonyl)-1,8,9-trimethoxyanthracene-3-acetate (5b). Anthranol **4b** (1.01 g, 2.7 mmol) was methylated with dimethyl sulfate/K_2CO_3 as above to give after recrystallization (hot EtOH) 0.61 g (56%) of **5b** as shiny yellow needles: mp 161.5–162 °C; TLC ($CHCl_3$) R_f 0.60 (bright yellow spot under long wavelength UV); ^1H NMR ($CDCl_3$) δ 3.69 (s, 3 H, aliphatic $COOCH_3$), 3.77 (s, 2 H, CH_2), 3.91 (s, 3 H, aromatic $COOCH_3$), 3.96 (s, 6 H, 2 OCH_3), 4.00 (s, 3 H, OCH_3), 6.68 (d, 1 H, J = 7 Hz, 5-CH), 7.25 (t, 1 H, J = 7 Hz, 6-CH), 7.40 (d, 1 H, J = 7 Hz, 7-CH), 7.51 (s, 1 H, 4-CH), 7.95 (s, 1 H, 10-CH); ^{13}C NMR (22.5 MHz, $CDCl_3$) δ 39.8 (C-12), 51.6 ($COOCH_3$), 51.8 (CO-OCH_3), 55.9 (C-8 OCH_3), 63.7 (C-1 OCH_3 and C-9 OCH_3), 104.2 (C-7), 118.7 (C-10a), 119.2 (C-8a), 120.6 (C-5), 122.4 (C-10), 124.7 (C-2), 125.8 (C-4), 126.1 (C-6), 128.3 (C-9a), 134.0 (C-4a), 135.4 (C-3),

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154.0 (C-1), 154.7 (C-9), 156.5 (C-8), 168.0 (C-11 CO), 170.8 (C-13 CO); EI-MS, m/z (relative intensity) 398 ($M^{\cdot+}$, 100), 366 (17), 323 (17); IR ($CDCl_3$) 1725 (br), 1710, 1620, 1555, 1435, 1355, 1325, 1270, 1100 cm^{-1}; UV (EtOH) λ_{max} nm (ϵ) 374 (6800), 358 (2700), 267 (75 900), 258 (32 400), 223 (14 100). Anal. Calcd for $C_{22}H_{22}O_7$: C, 66.32; H, 5.57. Found: C, 66.15; H, 5.77.

Methyl 2-Malonamoyl-1,8,9-trimethoxyanthracene-3-acetate (6). Diester **5b** (0.698 g, 1.75 mmol) was added to 3.5 mmol of lithium diisopropylamide in 75 mL of THF at −78 °C to give a 1:1 mixture of its bright red monoanion and lithium diisopropylamide. This solution was then added to a solution of the dianion of *N*-(trimethylsilyl)acetamide, prepared by treatment of *N*-(trimethylsilyl)acetamide (0.023 g, 1.75 mmol) with 3.50 mmol of *n*-butyllithium for 30 min at 0 °C. After 4 h at 0 °C, the reaction was quenched with acetic acid (0.92 g, 15.4 mmol), the solvent was evaporated, and the residue was partitioned between $CHCl_3$ and H_2O. The organic extract was evaporated. Chromatography on deactivated silica gel (Et_2O) gave unaltered starting material (0.12 g, 17%) followed by amide-ester **6** (0.38 g, 51%; 61% based on recovered starting material) as a yellow solid. No suitable solvent for recrystallization was found: ^1H NMR ($CDCl_3$) δ 3.76 (s, 5 H, $ArCH_2CO$ and CH_2COOCH_3), 3.95 (s, 3 H, $ArOCH_3$), 4.03 (s, 3 H, $ArOCH_3$), 4.12 (s, 3 H, $ArOCH_3$), 4.16 (s, 2 H, $COCH_2CO$), 6.92 (d, 1 H, J = 6 Hz, 7-CH), 7.16 (s, 1 H, 4-CH), 7.57 (t, 1 H, J = 6 Hz, 6-CH), 7.61 (d, 1 H, J = 6 Hz, 5-CH), 8.18 (s, 1 H, 10-CH); ^{13}C NMR (22.5 MHz, $CDCl_3$) δ 38.2, 50.9, 52.1, 56.2, 64.0, 64.2, 104.6, 118.6, 119.6, 120.8, 122.5, 126.7 (2×), 128.3, 130.6, 134.3, 136.0, 154.5, 156.1, 156.9, 166.1, 172.0, 203.1; EI-MS, m/z (relative intensity) 425 ($M^{\cdot+}$, 100), 408 (27), 393 (18), 376 (24), 340 (22), 339 (30); IR ($CDCl_3$) 1730, 1681, 1556, 1454, 1356, 1100 cm^{-1}; UV (MeOH) λ_{max} nm (ϵ) 376 (9800), 358 (6300), 268 (75 900), 248 (50 100); HRMS calcd for $C_{23}H_{23}NO_7$ m/z 425.1473, found m/z 425.1460.

Conversion of 6 to Pretetramide (1). A solution of amide ester **6** (21 mg, 0.049 mmol) in a mixture of 10 mL of 49% aqueous HBr (freshly distilled from red phosphorus) and acetic acid (10 mL) was refluxed for 7 h under N_2 and then stored at 4 °C for 10 h to induce crystallization of product. The crystals were separated and washed with H_2O, MeOH, and CH_2Cl_2 to yield pretetramide (**1**; 14 mg, 86%): mp (vac) ~250 °C dec; UV [98% H_2SO_4/0.1% (w/w) H_3BO_3] λ_{max} nm (ϵ) 234 (28 800), 267 (30 200), 288 (32 400), 342 (24 000), 400 (17 400), 490 nm (13 500). Chromatography on silica gel ($CHCl_3$/MeOH/DMF) gave 65% of purified **1** essentially identical with an authentic sample: mp (vac) 290–295 °C dec; authentic sample[14] mp (vac) 310–315 °C dec (lit.[13,28] mp 290–320 °C); EI-MS, m/z (relative intensity) 351 ($M^{\cdot+}$, 46), 334 (100); IR (Nujol) 3460, 1625, 1590, 1345, 1285 cm^{-1}; UV [98% H_2SO_4/0.1% (w/w) H_3BO_3] λ_{max} nm (ϵ) 503 (13 500), 400 (12 900), 343 (15 100), 287 (30 900), 267 (26 300), 236 (21 900); authentic sample 494 (19 100), 398 (15 800), 342 (17 000), 284 (37 200), 267 (31 600), 236 (26 300).

***tert*-Butyl 4-(3′-Isocoumarinyl)-3-oxobutanoate (9a).** *tert*-Butyl acetoacetate (15.82 g, 100 mmol) was added to LDA (220 mmol) in THF (150 mL) at −10 °C. The resulting light orange solution of dianion was cooled to −78 °C; methyl 2-carboxyphenylacetate[15] (**7a**; 4.85 g, 25 mmol) was added in THF (25 mL). The mixture was stirred at −78 °C for 3 h followed by ambient temperature for 1.5 h; the orange-red solution was cooled to −10 °C, neutralized slowly with HOAc (50 mL), and evaporated to dryness in vacuo. The residue was taken up in dilute HCl and extracted first with Et_2O and then with EtOAc. The extracts were combined and washed with $NaHCO_3$. The washings were acidified and extracted with EtOAc. The latter extract was evaporated to give 3.67 g of crude acid **8a**, which was immediately treated with acetic anhydride (150 mL) for 3 h. Evaporation of the solvent followed by recrystallization (EtOH) gave 1.53 g of **9a** and chromatography of the filtrate gave an additional 0.27 g (total yield 1.80 g, 24%): mp 124–126 °C; ^1H NMR ($CDCl_3$) δ 1.47 (s, 9 H), 3.50 (s, 2 H), 3.76 (s, 2 H), 6.44 (s, 1 H), 7.34–7.80 (m, 3 H), 8.26 (dd, 1 H, J = 8.1, 0.9 Hz); ^{13}C NMR ($CDCl_3$) δ 27.8, 46.9, 50.1, 82.4, 106.6, 120.4, 125.4, 128.3, 129.5, 134.8, 136.7, 149.9, 162.0, 165.7, 197.1; EI-MS, m/z (relative intensity) 302 ($M^{\cdot+}$, 1), 246 (48), 186 (58), 160 (100), 131 (22), 59 (21), 57 (74), 41 (26); IR (KBr) 2960, 1720, 1660, 1320, 1280, 1150, 1040 cm^{-1}. Anal. Calcd for $C_{17}H_{15}O_5$: C, 67.54; H, 6.00. Found: C, 67.58; H, 5.91.

Anthrone Diester 12. The methyl ester of 3,5-dioxohexanoic acid[29] (0.785 g, 5 mmol) was slowly added to a suspension of NaH (9 mmol) in THF (50 mL) at 0 °C. *sec*-Butyllithium (10 mmol) was slowly added, and the resulting dark red solution of trianion **10** was stirred for 10 min and then treated with isocoumarin **9a** (0.5 g, 1.66 mmol) dissolved in THF (20 mL). After 53 h at 25 °C, the dark red suspension was evaporated in vacuo. The residue was partitioned between Et_2O and cold dilute HCl. The organic solution was evaporated in vacuo. Short-column chromatography of the residual oil (80:19:1 EtOAc/hexane/HOAc) gave a brown oil, which crystallized from CH_2Cl_2/hexane to give 0.188 g (25%) of **12**: mp 164–165 °C; ^1H NMR ($CDCl_3$) δ 1.48 (s, 9 H), 3.73 (s, 5 H), 4.14 (s, 2 H), 4.28 (s, 2 H), 6.80 (s, 1 H), 7.37–7.72 (m, 3 H), 8.25 (d, 1 H, J = 7.2 Hz), 13.87 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 28.03, 32.36, 40.65, 49.91, 51.86, 81.33, 115.63, 121.96, 125.99, 127.17, 127.33, 128.25, 130.63, 133.83, 140.22, 142.06, 144.50, 162.60, 168.12, 169.80, 189.30, 196.35; EI-MS, m/z (relative intensity) 424 ($M^{\cdot+}$, 2), 319 (25), 318 (100), 277 (35), 276 (95), 262 (21), 251 (24), 57 (82), 56 (26), 41 (80), 39 (23); IR (KBr) 2980, 1750, 1725, 1700, 1620, 1600, 1560, 1540, 1515, 1280, 1145, 1010, 985 cm^{-1}; UV (MeOH) λ_{max} nm (ϵ) 399 (13 800), 382 (10 700), 316 (10 700), 304 (12 900), 273 (33 100), 224 (17 400). Anal. Calcd for $C_{24}H_{24}O_7$: C, 67.91; H, 5.70. Found: C, 67.75; H, 5.71.

5-(2′-Oxopropyl)isoxazole (17). The ethylene ketal (9.76 g, 61 mmol) of methyl acetoacetate was added to a suspension of acetaldoxime dianion [112 mmol, formed by addition of acetaldoxime (11.8 g, 200 mmol, syn:anti 61:39) to 350 mmol of LDA in 300 mL of THF at −10 °C];[23] the mixture was stirred for 1.5 h at 0 °C. The resulting bright orange suspension was evaporated in vacuo; the residue was partitioned between Et_2O and H_2O at 0 °C. The aqueous layer was acidified with dilute HCl, refluxed for 15 min, cooled, and extracted with Et_2O. The extract was evaporated. The residue was purified by Kugelrohr distillation (40–80 °C, 0.05 mm), flash chromatography, and redistillation (70–75 °C, 0.05 mm) to give 0.87 g (11%) of **17** as a colorless liquid, which was stable at 4 °C: ^1H NMR ($CDCl_3$) δ 2.24 (s, 3 H), 3.96 (s, 2 H), 6.26 (s, 1 H), 8.23 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 29.16, 40.49, 102.41, 150.03, 164.65, 200.79; EI-MS, m/z (relative intensity) 125 ($M^{\cdot+}$, 2), 83 (49), 43 (100); IR (neat) 3130, 2900, 1720, 1600, 1470 cm^{-1}. Anal. Calcd for $C_6H_7NO_2$: C, 57.59; H, 5.64. Found: C, 57.51; H, 5.74.

Trianion **18** was prepared from isoxazole **17** (0.5 g, 4 mmol) by addition to 1.32 mmol of LDA in 100 mL of THF at 0 °C. The mixture was allowed to warm to room temperature during 0.5 h to give the lithium salt of **18**.

3,5-Dioxohexanenitrile (16). *N*-methoxy-*N*-methylacetamide (8.26 g, 80.2 mmol) was added slowly to the lithium salt of 3-oxobutanenitrile (80.0 mmol) prepared by reaction of 5-methylisoxazole (6.65 g, 80 mmol) with 2.1 equiv of LDA in THF at −10 °C by the method of Vinick et al.[22] The resulting yellow suspension was held at 0 °C for 1.25 h and evaporated to dryness in vacuo. The residue was partitioned between Et_2O and cold dilute HCl. The organic extract was washed with brine, dried, and evaporated; the residue was distilled (80–90 °C, 0.1 mm, Kugelrohr) to give 7.18 g (73%) of diketo nitrile **16**, slightly (7%) contaminated with 3-oxobutanenitrile. Treatment with $Cu(OAc)_2$ gave the crystalline copper chelate, which was washed with EtOAc and Et_2O and then decomposed with 6 M HCl. Nitrile **16** was recovered by extraction into Et_2O. The solution was dried, concentrated, and redistilled to give 4.61 g (46%) of pure **16** as a colorless liquid, which solidified near room temperature: mp 22–24 °C; ^1H NMR ($CDCl_3$) enol form δ 2.12 (s, 3 H), 3.44 (s, 2 H), 5.75 (s, 1 H), 14.62 (br s, 1 H); keto form δ 2.29 (s, 3 H), 3.67 (s, 2 H) 3.78 (s, 2 H) enol:keto ratio 90:10; ^{13}C NMR ($CDCl_3$) enol form δ 23.53, 28.14, 98.56, 114.06, 184.81, 188.92; EI-MS, m/z (relative intensity) 125 ($M^{\cdot+}$, 9), 85 (37), 43 (100); IR (neat) 2945, 2910, 2250, 1740, 1710, 1600 cm^{-1}. Anal. Calcd for $C_6H_7NO_2$: C, 57.59; H, 5.64. Found: C, 57.43; H, 5.75.

Dimerization of Diketo Nitrile 16. A solution of **16** (0.117 g) in pH 5.0 acetate buffer was allowed to stand for 16 h; 0.056 g of dimer **19a** or **19b** precipitated as pale green crystals. Extraction of the filtrate with Et_2O and CH_2Cl_2 gave an additional 0.016 g of dimer (76% total yield). Recrystallization (EtOH) gave pale green crystals: mp 140–142 °C; ^1H NMR ($CDCl_3$) δ 2.74 (s, 6 H), 3.94 (s, 2 H) 7.03 (s, 1 H), 13.05 (br s, 1 H); ^{13}C NMR (acetone-d_6) δ 22.86, 22.91, 32.02, 100.79, 114.31, 116.93, 124.30, 125.93, 139.66, 146.22, 162.58, 205.70; EI-MS, m/z (relative intensity) 214 ($M^{\cdot+}$, 22), 199 (100), 43 (33); IR (KBr) 2210, 1600, 1400 cm^{-1}. Anal. Calcd for $C_{12}H_{10}N_2O_2$: C, 67.28; H, 4.71; N, 13.08. Found: C, 67.08; H, 4.68; N, 12.99.

For the preparation of trianion **18**, diketo nitrile **16** (0.313 g, 2.5 mmol) was added slowly to LDA (9 mmol) in 100 mL of THF at −10 °C. The cold bath was removed, and the solution was allowed to warm to room temperature during 1 h to provide an orange solution of trianion **18** to which electrophiles were then added.

2,4-Dihydroxy-6-phenylbenzonitrile (21). Ethyl benzoate (0.3 g, 2 mmol) was added to 4 mmol of trianion **18** (prepared from **17**) in THF at room temperature. After 2 h, the mixture was evaporated to dryness the residue was partitioned between Et_2O and cold dilute HCl. The organic extract was evaporated, and the residue was purified by flash chromatography (50% EtOAc/hexane) to give **21** (0.085 g, 20% yield) as a solid after trituration with CH_2Cl_2: mp 217–218 °C; ^1H NMR (acetone-d_6) δ 3.33 (br s, 2 H), 6.51 (d, 1 H, J = 1.8 Hz), 6.57 (d, 1 H,

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J = 1.8 Hz), 7.50 (m, 5 H); ^{13}C NMR (acetone-d_6) δ 91.61, 102.23, 109.92, 117.08, 129.21, 129.32, 139.72, 148.77, 162.74, 163.29; EI-MS, m/z (relative intensity) 211 ($M^{\cdot+}$, 100), 183 (22), 43 (32); IR (KBr) 3250 (br), 2210, 1600 cm^{-1}. Anal. Calcd for $C_{13}H_9NO_2$: C, 73.92; H, 4.29. Found: C, 73.73; H, 4.40.

7-Phenyl-3,5,7-trioxoheptanenitrile (20). *N*-Methoxy-*N*-methylbenzamide (0.428 g, 2.59 mmol) was added to 2.67 mmol of trianion **18** (from **17**) at −10 °C. After 3 h at room temperature the reaction mixture was worked up as above; the product was purified by flash chromatography (deactivated silica gal, 45% EtOAc/hexane) followed by crystallization (Et_2O/hexane) to give **20** (0.172 g, 29%): mp 71–73 °C; ^{1}H NMR ($CDCl_3$) a mixture of enol–keto tautomers δ 3.38 (s), 3.39 (s), 3.44 (s), 3.72 (s), 3.75 (s), 4.01 (s), 5.66 (s), 5.67 (s), 5.68 (s), 5.92 (s), 5.95 (s) 6.23 (s), 7.50 (m), 7.86 (m), 14.57 (br s), 15.63 (br s), area of signals at 7.50 and 7.86 was 5 H relative to all others being 6 H; EI-MS, m/z (relative intensity) 229 ($M^{\cdot+}$, 6), 147 (26), 105 (100), 77 (59), 69 (56), 51 (30); IR (KBr) 3500–2600 (br), 2250 (w), 1610, 1570, 1490, 1390 cm^{-1}. Anal. Calcd for $C_{13}H_{11}NO_3$: C, 68.12; H, 4.84. Found: C, 67.91; H, 4.90.

The trilithium salt of **18** (2.5 mmol) prepared from **16** was treated with *N*-methoxy-*N*-methylbenzamide (0.447 g, 2.7 mmol) for 30 min at −10 °C followed by 3.5 h at room temperature. The red solution was evaporated, and the residue was partitioned between Et_2O and dilute HCl. The ether layer was evaporated, and the residue was washed with Et_2O (5 × 2 mL) to give 0.213 g of **20**. Flash chromatography of the washings gave an additional 0.138 g of **20** (57% total yield). The spectra and melting point were indistinguishable from those for material obtained above from **17**.

3,5,7-Trioxooctanenitrile (22) and 2,4-Dihydroxy-6-methylbenzonitrile (23). *N*-Methoxy-*N*-methylacetamide (0.257 g, 2.5 mmol) was added slowly to 2.5 mmol of trianion **18** at −10 °C. The mixture was stirred for 1 h and then warmed to room temperature and stirred for an additional 1 h. The resulting yellow suspension was evaporated to dryness. The customary workup gave an oil (0.38 g), which was shown by NMR to contain triketo nitrile **22**. Short-column chromatography (deactivated silica gel, 25% EtOAc/hexane) caused cyclization to occur, yielding 0.168 g (44% overall yield) of benzonitrile **23**, which was recrystallized from EtOH to give colorless crystals: mp 217–218 °C; ^{1}H NMR (acetone-d_6) δ 2.35 (s, 3 H), 3.32 (br s, >2 H), 6.36 (m, 2 H); ^{13}C NMR (acetone-d_6) δ 20.48, 92.97, 100.93, 109.98, 116.86, 145.08, 162.63, 162.80; EI-MS, m/z (relative intensity) 149 ($M^{\cdot+}$, 100), 122 (25), 121 (27), 120 (33), 94 (23), 66 (29), 65 (21); IR (KBr) 3350, 3120, 2230, 1610, 1480, 1350, 1150 cm^{-1}. Anal. Calcd for $C_8H_7NO_2$: C, 64.42; H, 4.73. Found: C, 64.34; H, 4.86.

In a separate experiment, 1.7 mmol of *N*-methoxy-*N*-methylacetamide was added to 1.05 mmol of trianion **18** at −10 °C followed by standard workup after 1.5 h. Isolation of triketo nitrile **22** was accomplished by flash chromatography (deactivated silica gel, 55% EtOAc/hexane) to give 0.0856 g (49%) of nitrile **22** as a light orange oil. The nitrile was purified further by formation of the copper chelate (mp 210–235 °C dec) followed by reversal of the chelate by treatment with acid, extraction of nitrile **22** into Et_2O, and flash chromatography: ^{1}H NMR ($CDCl_3$) complex mixture of tautomers δ 2.04 (s), 2.10 (s), 2.28 (s), 3.38 (s), 3.48 (s), 3.50 (s), 3.58 (s), 3.75 (s), 5.29 (s), 5.48 (s), 5.49 (s), 5.59 (s), 5.84 (s), 14.11 (s); EI-MS, m/z (relative intensity) 167 ($M^{\cdot+}$, 5), 127 (20), 85 (34), 43 (100); IR (neat) 3300 (br), 2240 (w), 1720, 1600 cm^{-1}; HRMS calcd for $C_8H_9NO_3$ m/z 167.0582, found m/z 167.0580.

7,7-Diphenyl-3,5-dioxo-7-hydroxyheptanenitrile (24). A solution of benzophenone (0.457 g, 2.5 mmol) in THF (20 mL) was added to 2.5 mmol of trianion **18** at −10 °C, and the mixture was stirred for 1 h. Standard workup gave 0.89 g of an oil, the NMR of which indicated that **24** was the major component. Short-column chromatography (deactivated silica gel, 25% EtOAc/hexane) gave partial purification of **24**. The compound was converted to the copper chelate (0.156 g, 18% yield, mp 196–199 °C) by treatment with excess $Cu(OAc)_2$ followed by washing of the solid with Et_2O. Treatment of the chelate with dilute HCl freed nitrile **24**, which was extracted into CH_2Cl_2; the nitrile was obtained as a solid and recrystallized from Et_2O: mp 97–99 °C; ^{1}H NMR of enol form ($CDCl_3$, keto–enol mixture ~1:9) δ 3.33 (s, 2 H), 3.38 (s, 2 H) 4.32 (br s, 1 H) 5.78 (s, 1 H), 7.35 (m, 10 H) 14.17 (br s, 1 H); EI-MS, m/z (relative intensity) 307 ($M^{\cdot+}$, not observed), 183 (30), 182 (35), 105 (100), 77 (61), 51 (23), 43 (37); IR (KBr) 3400, 2240 (w), 1630, 1560, 1440, 1390 cm^{-1}. Anal. Calcd for $C_{19}H_{17}NO_3$: C, 74.25; H, 5.58. Found: C, 74.21; H, 5.70.

From the chromatographic separation a dimeric product was also obtained, which is assigned as **25a** or **25b**. More of the dimer also arose during manipulation of **24**: mp 235–236 °C; ^{1}H NMR ($CDCl_3$) δ 3.61 (s, 2 H), 3.82 (s, 2 H), 5.68 (s, 1 H), 6.99 (s, 1 H), 7.28 (m, 20 H); ^{13}C NMR ($CDCl_3$) δ 22.56, 38.75, 82.42, 87.29, 98.24, 106.85, 113.51, 115.30, 115.84, 119.58, 126.40, 126.67, 127.73, 127.84, 128.22, 128.46, 133.99, 136.10, 142.98, 144.07, 155.61; EI-MS, m/z (relative intensity) 542 ($M^{\cdot+}$, 1), 91 (32), 78 (100), 77 (25), 52 (22); IR (KBr) 3040, 2240 (w), 2210, 1655, 1600, 1490, 1445, 1430 cm^{-1}. Anal. Calcd for $C_{32}H_{26}N_2O_2$: C, 84.11; H, 4.83; N, 5.16. Found: C, 83.98; H, 4.92; N, 4.97.

7-Phenyl-3,5-dioxoheptanenitrile (26). Benzyl chloride (0.317 g, 2.5 mmol) was added slowly to a solution of trianion **18** (2.5 mmol) at room temperature. After 0.5 h, standard workup gave an oil, which was fractionated by flash chromatography (deactivated silica gel, 20% EtOAc/hexane) to give 0.27 g (48%) of **26**. The material was further purified via the copper chelate (mp 175–179 °C dec) to give pure **26** as a thick colorless oil: ^{1}H NMR of the enol form ($CDCl_3$, enol–keto mixture, 3:1) δ 2.54–3.06 (AA'BB' m, 4 H), 3.37 (s, 2 H), 5.73 (s, 1 H), 7.25 (m, 5 H), 14.86 (br s, 1 H); EI-MS, m/z (relative intensity) 215 ($M^{\cdot+}$, 17), 105 (22), 104 (26), 91 (100); IR (neat) 3030, 2925, 2255, 1740, 1710, 1600 cm^{-1}. Anal. Calcd for $C_{13}H_{13}NO_2$: C, 72.54; H, 6.09. Found: C, 72.40; H, 6.21.

9-Phenyl-3,5,7,9-tetraoxononanenitrile (27). Methyl benzoylacetate (0.445 g, 2.5 mmol) was added slowly to 5.8 mmol of NaH (prepared from 0.28 g of a 50% oil dispersion by washing with pentane) in 30 mL of THF at room temperature, and the mixture was stirred until evolution of H_2 had ceased (15 min). The clear yellow solution of the enolate anion was added dropwise to 2.5 mmol of trianion **18** in 100 mL of THF at −10 °C, and the mixture was stirred for 12.5 h at room temperature. Standard workup followed by flash chromatography (deactivated silica gel, 60% EtOAc/hexane) gave 0.61 g (90%) of **27**, which was triturated with Et_2O/hexane to give a poor recovery of crystalline material (0.179 g, 23%): mp 85–88 °C; ^{1}H NMR ($CDCl_3$, a complex mixture of enol–keto tautomers) δ 3.46 (s), 3.47 (s), 3.71 (s), 5.46 (s), 5.90 (s), 5.95 (s), 6.27 (s), 7.51 (m), 7.87 (m), 14.63 (s), 15.75 (br s); EI-MS, m/z (relative intensity) 271 ($M^{\cdot+}$, 97), 254 (46), 147 (40), 105 (100), 77 (50), 69 (53), 51 (23), 45 (36); IR (KBr) 2900, 2230 (w), 1735, 1645, 1600 cm^{-1}. Anal. Calcd for $C_{15}H_{13}NO_4$: C, 66.41; H, 4.83. Found: C, 66.26; H, 5.00.

Anthrone Ester–Nitrile 29. The monosodium salt of isocoumarin **9a** was generated by addition of **9a** (0.785 g, 2.6 mmol) to NaH (4 mmol) in 30 mL of THF at 25 °C. The anion was added slowly to trianion **18** (10.4 mmol) at −78 °C. The resulting dark green solution was kept at −78 °C for 2.5 h and then at 25 °C for 9.5 h, during which time a brick red suspension formed. The mixture was evaporated in vacuo, and the residue was partitioned between Et_2O and cold dilute HCl. The organic extract was concentrated. Flash chromatography of the residue (50% EtOAc/hexane) gave a mixture of diketo nitrile **16** and anthrone **29** as a light orange oil; crystallization (EtOH/H_2O) gave 0.133 g (13%) of anthrone **29** as a yellow solid, which was further recrystallized from EtOH/H_2O: mp 217–219 °C dec; ^{1}H NMR ($CDCl_3$) mixture of tautomers, keto form δ 1.47 (s, 9 H), 3.83 (s, 2 H), 4.27 (s, 2 H), 4.35 (s, 2 H), 6.81 (s, 1 H), 7.42–7.69 (m, 3 H), 8.34 (d, 1 H, J = 7.2 Hz), 14.03 (s, 1 H); ^{13}C NMR was not obtained due to poor solubility of **29** in DMSO-d_6 and other NMR solvents; EI-MS, m/z (relative intensity) 391 ($M^{\cdot+}$, 10), 335 (3), 251 (32), 57 (45), 56 (45), 41 (100), 39 (34); IR (KBr) 3550, 3350, 2975, 2250 (w), 1700, 1630, 1590, 1560, 1440, 1390, 1150, 1100 cm^{-1}; UV (MeOH) λ_{max} nm (ϵ) 455 (2600), 430 (3200), 398 (6600), 374 (7100), 355 (3700), 303 (14 800), 292 (15 800), 253 (42 700), 224 (17 400). Anal. Calcd for $C_{23}H_{21}NO_5$: C, 70.58; H, 5.41; N, 3.58. Found: C, 70.64; H, 5.34; N, 3.65.

1,3,11,12-Tetrahydroxynaphthacene-2-carboxamide (10-Dehydroxypretetramide, 30). Anthrone **29** (20.7 mg, 0.053 mmol) was refluxed with HI/H_2O (47%, 2 mL) in phenol (4 mL) for 12 h. The solution was stored at 20 °C for 12 h, during which time a crystalline solid precipitated. The solid was collected by filtration and washed with H_2O, MeOH, and CH_2Cl_2 to give 3.8 mg (21%) of **30** as a bright yellow solid: mp (vac) 291–300 °C dec; NMR spectra could not be obtained due to poor solubility; EI-MS, m/z (relative intensity) 335 ($M^{\cdot+}$, 50), 319 (22), 318 (100); IR (KBr) 3460, 3200 (br), 2700 (br), 1640, 1620, 1600, 1460, 1370, 1310 cm^{-1}; UV [H_2SO_4/0.1% (w/w) H_3BO_3] λ_{max} nm (ϵ) 575 (12 900), 530 (9800), 500, (8500), 395 (13 800), 326 (28 200), 302 (31 600), 275 (20 900), 223 (18 600); HRMS calcd for $C_{19}H_{13}NO_5$ m/z 335.0794, found m/z 335.0766.

Methyl 2-Carboxy-3-methoxyphenylacetate (7b). 3-Methoxyhomophthalic acid (3.74 g, 17.8 mmol) was treated with methanolic HCl for 6 h at 25 °C and then evaporated to dryness in vacuo. The residue was partitioned between CH_2Cl_2 and H_2O. The organic layer was extracted with aqueous $NaHCO_3$. The extract was acidified (dilute HCl) and extracted with CH_2Cl_2. The organic extract was evaporated in vacuo to give 3.27 g (82%) of monoester **7b** as an oil, which crystallized: mp 40–41.5 °C; ^{1}H NMR ($CDCl_3$) δ 3.67 (s, 3 H), 3.85 (s, 2 H), 3.87 (s, 3 H), 6.92 (d, 2 H, J = 7.2 Hz), 7.38 (t, 1 H, J = 7.2 Hz), 10.24 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 39.57, 51.81, 56.25, 110.80, 121.10, 124.02, 131.77, 135.35, 157.61, 169.48, 171.59; EI-MS, m/z (relative intensity)

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.

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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]

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