Synthesis of Racemic Tenellin

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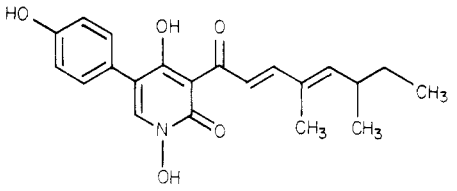
Total synthesis of racemic tenellin, a yellow pigment of the insect pathogenic fungus *Beauveria*, has been accomplished. Preparation of 1,4-dihydroxy-5-(*p*-hydroxyphenyl)-2(1*H*)-pyridinone is achieved in excellent overall yield by utilizing an intramolecular C-acylation of an imidazolide precursor. A facile conjugate reduction of the vinylogous amide **6** is illustrated with sodium cyanoborohydride.

Cultures of the insect pathogenic fungi *Beauveria bassiana* (Bals.) Vuill. and *Beauveria tenella* (Delacroix) Siem. often develop a yellow pigmentation.[1] Two of the fungal biochromes have been isolated from mycelium extracts and identified as tenellin (**1**) and bassianin (**2**).[2]



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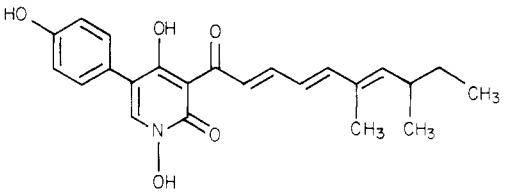

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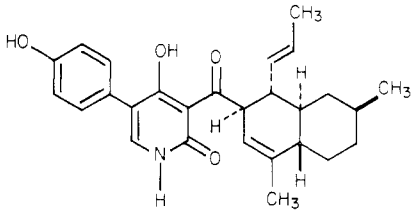

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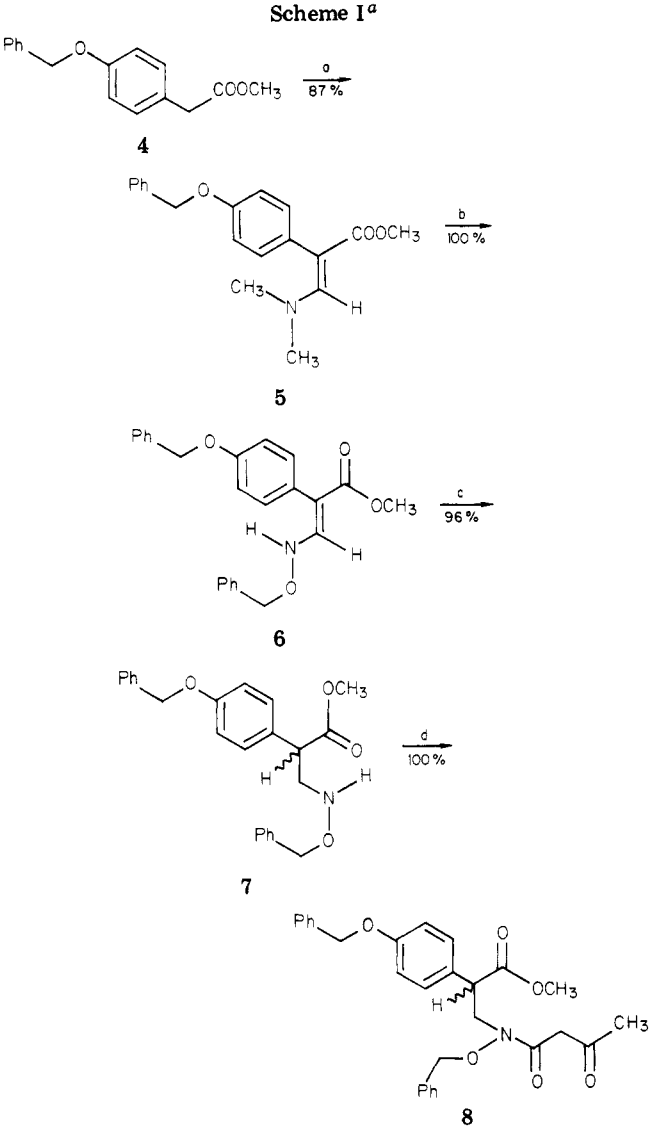
Structural features were established by thorough spectroscopic studies, supported by chemical characterization. Isotopic labeling has shown that phenylalanine is efficiently incorporated into tenellin as an intact biogenetic unit, clearly requiring a structural rearrangement at some stage of the biosynthetic pathway leading to formation of the pyridinone ring.[3] A related antifungal antibiotic, ilicicolin H (**3**), has been isolated from the imperfect fungus *Cylindrocladium ilicicola*.[4] Owing to our general interest in a number of similar naturally occurring heterocycles, we have completed a total synthesis of tenellin (**1**) which provides the heterocyclic moiety in excellent overall yield via a reasonably general scheme.

From the outset, we found it most surprising that few examples of 3-acyl-2,4-pyridinediones had been reported in the literature. These substances were generally assembled with a bimolecular condensation and illustrated substitution of the 6-position (aryl, alkyl, or hydroxy).[5] Unfortunately, numerous attempts to demonstrate a bimolecular condensation for ring construction of the tenellin

Scheme I[a]



[a] (a) *N,N*-Dimethylformamide dimethyl acetal, 200 °C, 12 h; (b) (benzyloxy)amine, benzene, CSA, 80 °C; (c) ethanolic HCl, $NaCNBH_3$, 4.5 h; (d) diketene, THF, Et_3N, -78 °C.

(1) El Basyouni, S. H.; Brewer, D.; Vining, L. C. *Can. J. Bot.* **1968**, *46*, 441.
(2) Wat, C.-K.; McInnes, A. G.; Smith, D. G.; Wright, J. L. C.; Vining, L. C. *Can. J. Chem.* **1977**, *55*, 4090.
(3) McInnes, A. G.; Smith, D. G.; Walter, J. A.; Vining, L. C.; Wright, J. L. C. *J. Chem. Soc., Chem. Commun.* **1974**, 282.
(4) Matsumoto, M.; Minato, H. *Tetrahedron Lett.* **1976**, 3827.
(5) For a review: Tieckelmann, H. In Ed.; "The Chemistry of Heterocyclic Compounds"; Abramovitch, R. A., Ed.; Wiley: New York, 1974; Vol. 14, Suppl. 3. For additional work in this area, see: Kato, T.; Yamamoto, Y.; Kondo, M. *Chem. Pharm. Bull.* **1975**, *23*, 1873. Girora, N. N.; Wendler, N. L. *Heterocycles* **1978**, *11*, 417. Yamamoto, H.; Kawamoto, H.; Morosawa, S.; Yokoo, A. *Ibid.* **1978**, *11*, 267.

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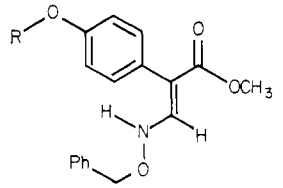
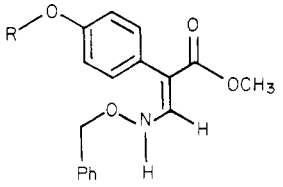
system from readily accessible starting materials resulted in complete failure. Thus, our successful efforts have utilized a strategy for intramolecular acylation with formation of the six-membered ring.

The requisite hydroxamic acid derivative 8 was prepared in excellent overall yield as illustrated in Scheme I. Condensation of methyl 2-[4-(benzyloxy)phenyl]acetate (4) with *N,N*-dimethylformamide dimethyl acetal at 200 °C in a resealable pressure bottle afforded the vinylogous carbamate 5 in 87% yield after crystallization from hot hexane-ethyl acetate. Exchange with *O*-benzylhydroxylamine[6] occurred quantitatively upon heating in benzene solution in the presence of a catalytic amount of camphorsulfonic acid with continuous evolution of gaseous dimethylamine, yielding exclusively the *E* isomer 6. Formation of 6 also proceeds without the presence of acid catalysts but requires much longer reaction times (18–28 h). Assignment of the *E* stereochemistry is based upon the substantial downfield ^{1}H NMR chemical shift of the vinylic hydrogen which agrees with data for analogous *E* and *Z* isomers.[7] However, the NMR spectrum of 6 clearly indicates a 1:1 mixture of conformers **6a** and **6b** as as



6a

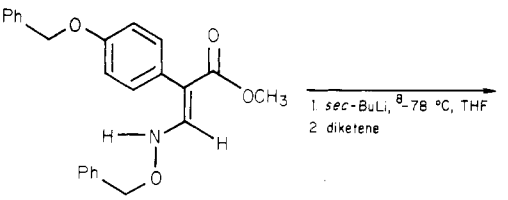


6b

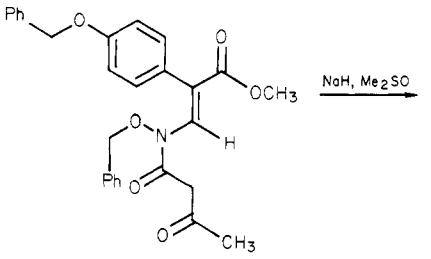
demonstrated by the appearance of two sets of sharp doublets for each of the NH and C=CH moieties. A planar nitrogen allows for maximum overlap with the adjoining α,β-unsaturated carbonyl chromophore and restricted rotation about the C–N linkage as commonly seen in amides. Interestingly, this effect was no longer apparent in the NMR spectra of amides obtained following N-acylation of 6.

Initially our synthetic planning had anticipated the possibility of thermodynamic product control during transformation of 5 to 6 with preferred formation of the *Z* isomer of 6, thus allowing added stability of internal hydrogen bonding. Although this result was not efficiently available, acylation of 6 with diketene gave incomplete conversion to 9 (65%),[8] and after a chromatographic separation from starting material, treatment of this adduct with sodium hydride in Me_2SO (22 °C, 24 h) gave low yields of the desired pyridone 10 (25–35%), requiring inversion of olefin geometry. However, the major component of these attempts was the starting enamino ester 6, which functions as an excellent leaving group for facile elimination from the initial enolate of 9 owing to the high stability of the resulting anion.

To avoid these problems, we treated 6 with sodium cyanoborohydride in ethanolic aqueous HCl which afforded clean reduction of the carbon double bond, pro-



6



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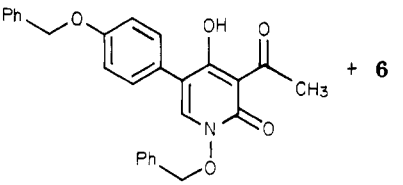
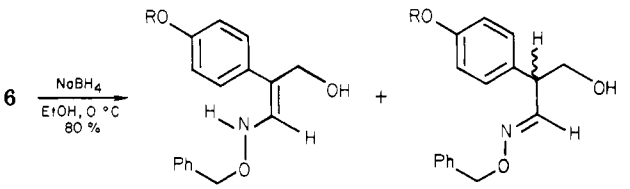


+ 6

10

viding the desired secondary amine 7.[10] On the other hand, reduction with sodium borohydride in ethanol at 0 °C gave 80% yield of the alcohols 11 and 12 in a 1:1 ratio.



11, R = CH_3 12, R = CH_3

Acylation of 7 with diketene was conducted in anhydrous THF containing triethylamine and a small amount of 4-(dimethylamino)pyridine. Thus, the overall yield for the four-step conversion of 4 to the key intermediate 8 was 83.5%.

Intramolecular ring closure with formation of the desired 3-acetyl-2,4-pyridinedione 17 and subsequent transformations to synthetic tenellin are presented in Scheme II. Selective saponification of the methyl ester 8 was achieved in aqueous tetrahydrofuran by addition of lithium hydroxide at 0 °C with warming to room temperature, and the crude carboxylic acid 13 (99%) was treated with 1,1'-carbonyldiimidazole in THF at 0 °C under anhydrous conditions, generating the reactive imidazolide 14 which afforded internal acylation following addition of sodium hydride, thus yielding the 5,6-dihydropyridinone 15 (91%).[11] Addition of phenylselenenyl chloride rapidly

(6) Prepared according to: Chimiak, A.; Kolassa, T. *Bull. Acad. Pol. Sci., Ser. Sci. Chim.* **1974**, *32*, 195.

(7) Abdulla, R. F.; Fuhr, K. H.; Williams, J. C. *J. Org. Chem.* **1979**, *44*, 1349 and references therein.

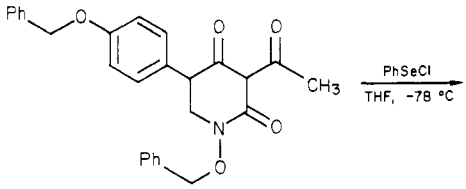
(8) The attempted acylation of 6 with weak bases such as pyridine or triethylamine afforded no reaction. However, deprotonation of 6 with *sec*-butyllithium (−78 °C, THF) followed by addition of diketene conveniently gave N-acylation for small-scale reactions.

(9) Several examples of intramolecular cyclizations which proceed irrespective of initial *E* or *Z* olefin geometry have been reported. See: Lin, Y.; Lang, S., Jr. *J. Heterocycl. Chem.* **1977**, *14*, 345. Bredereck, H.; Effenberger, F.; Botsch, H. *Chem. Ber.* **1964**, *97*, 3397. Bredereck, H.; Sell, R.; Effenberger, F. *Ibid.* **1964**, *97*, 3407. See also ref 7.

(10) Reductions of α,β-unsaturated esters with sodium cyanoborohydride have been previously reported. See: Hutchins, R. O.; Rotstein, D.; Natale, N.; Fanelli, J. *J. Org. Chem.* **1976**, *41*, 3328. However, 1,4-reduction of β-aminoacrylates is especially facile and undoubtedly proceeds via attack on a protonated iminium salt. Harmon, A. D.; Hutchinson, C. R. *J. Org. Chem.* **1975**, *40*, 3474.

(11) Examples of C-acylations with imidazolides include: Hartzell, S. L.; Rathe, M. W. *Tetrahedron Lett.* **1976**, 2757. Brooks, D. W.; Lu, L. D.-L.; Masamune, S. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 72. A similar intramolecular acylation has been performed for synthesis of the tetramic acid malonomicin by utilizing a reactive benztriazolyl ester: Van der Baan, J. L.; Barnick, J. W. F. K.; Bickelhaupt, F. *Tetrahedron* **1978**, *34*, 223.

occurs in the presence of diisopropylethylamine (THF, -78 °C), giving **16**, and standard conditions for oxidative



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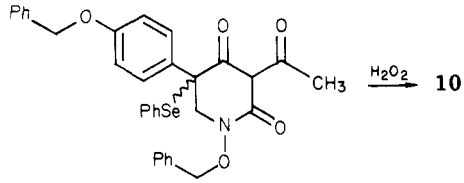


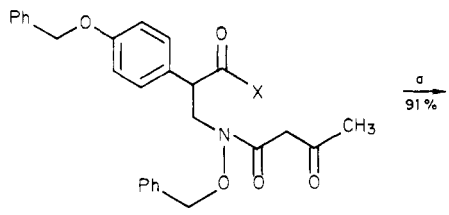
16

elimination provide the pyridone **10**.[12] However, these attempts were decidedly less convenient, and produced lower yields than straightforward oxidation with chloranil in ethylbenzene at reflux, affording 85% of crystalline **10**. Overall, synthesis of the pyridinone ring is achieved in 63% yield from methyl ester **4**. Removal of the benzyl ethers, induced by iodide ion displacements, also resulted in N–O cleavage of the hydroxamic acid moiety, demonstrating the inadequacy of benzylic protection for later stages of the synthesis. Therefore, hydrogenolysis in dioxane was followed by protection with dihydropyran, affording **18** in 94% yield.[13]

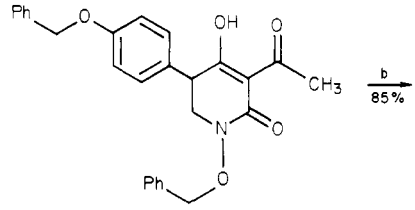
An aldol condensation was planned with the enolate of **18** and 2,4-dimethyl-2-hexenal (**19**).[14] The reaction proved to be deceptively difficult. Initially, we had found the need to use as much as a fivefold excess of lithium diisopropylamide to generate a high conversion to enolate as detected by quenching experiments with D_2O. In part, this observation may have been due to traces of tightly bound, protic solvent in the starting pyridinone. Attempts to trap the dianion of **18** by O-alkylation with trimethylsilyl chloride were unsuccessful apparently because the silyl enol ethers produced are themselves potent silylating agents and are rapidly hydrolyzed in the presence of moisture or cleaved by other available nucleophiles. The desired aldol condensation was accomplished upon treatment of **18** with lithium diisopropylamide (3 equiv) in THF followed by careful addition of a tetrahydrofuran solution of aldehyde **19** (0.9 equiv) and quenching with ammonium chloride at −78 °C. The yield of aldol product **20** was 56% based on recovered starting pyridinone (25–30%). A small amount of elimination product **21** (2–5%) was also obtained. Changes in solvent or inclusion of HMPA gave reduced yields of **20** and production of three additional unidentified products. The addition of Lewis acids such as anhydrous zinc chloride offered no improvement.

Our earlier studies had attempted an alternative construction by reaction of the ethyl ester **22** with excess vinyllithium reagent **23** which was initially prepared by halogen–metal exchange of the corresponding vinyl bromide with *n*-butyllithium (THF, -78 °C). Not surprisingly, reactions gave a 1:1 mixture of the *n*-butyl ester **24**, arising as a result of O-alkylation with *n*-butyl bromide, as well as starting ethyl ester. Metalation with *tert*-butyllithium as described by Seebach,[15] led solely to recovery of **22**.

Scheme II[a]



13, X = OH
14, X = imidazolyl



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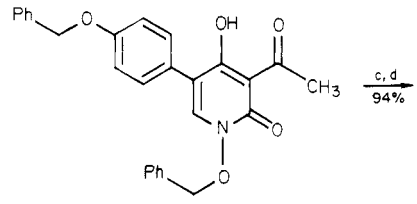

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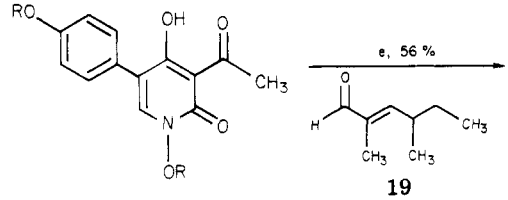

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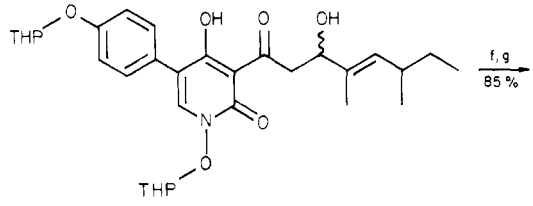
17, R = H
18, R = THP



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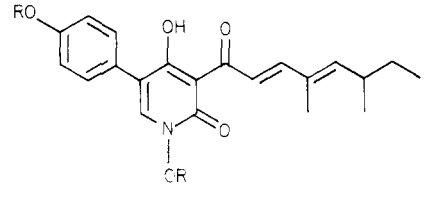


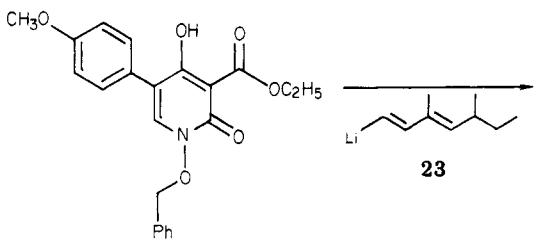
21, R = THP
1, R = H

[a] (a) NaH, THF, 22 °C, 20 min; (b) chloranil, ethylbenzene, 136 °C, 16 h; (c) 10% Pd/C, H_2, dioxane, 22 °C; (d) dihydropyran, CH_2Cl_2, THF, CSA, 0 °C; (e) LDA, THF, −78 °C, then aldehyde **19**; (f) Et_3N_2, $CHCl_3$, CSA, reflux, 45 min; (g) CSA, CH_3OH, benzene, reflux, 1 min.

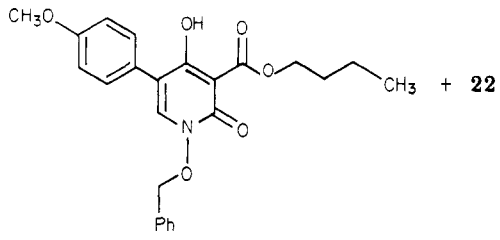
(12) Phenylselenation may initially occur at the 3-position with subsequent enolization and reaction at C-5. Liotta, D.; Saindane, M.; Barnum, C.; Ensley, H.; Balakrishnan, P. *Tetrahedron Lett.* **1981**, *22*, 3043. Liotta, D.; Barnum, C. S.; Saindane, M. *J. Org. Chem.* **1981**, *46*, 4301.

(13) Some examples of catalytic debenzylation of hydroxamates include: Kolasa, T.; Chimak, A. *Tetrahedron* **1977**, *33*, 3285. Herscheid, J. D. M.; Colstee, J. H.; Ottenheijm, H. C. J. *J. Org. Chem.* **1981**, *46*, 3346.

(14) A directed aldol condensation led to preparation of the (*E*)-2,4-dimethyl-2-hexenal via an α-lithio aldimine by adaptation of known methodology: Wittig, G.; Reiff, H. *Angew. Chem., Int. Ed. Engl.* **1968**, *7*, 7. See the experimental section for complete details.



22 23



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Attempts to increase the reactivity of the carbonyl by protection of the enolic (C-21) hydroxy substituent as its (2-methoxyethoxy)methyl (MEM) ether or its corresponding methyl ether with subsequent addition of **23** failed to produce a reaction.[16]

With the aldol product in hand, the necessary deprotection and dehydration to synthetic tenellin could not be conducted in a single step because of considerable decomposition to substances with polarities similar to that of the natural product. Upon examination of the usual acidic and basic techniques which failed to cleanly afford elimination, the selective conversion to **21** was accomplished quantitatively in anhydrous chloroform–triethylamine (4:1 by volume) in the presence of a catalytic amount (0.05 equiv) of camphorsulfonic acid (22 °C, 2.5 h). Removal of the tetrahydropyranyl ethers occurred in high yield upon heating **21** in anhydrous methanolic benzene with camphorsulfonic acid (0.05 equiv) at reflux. The protected hydroxamic acid was cleaved more rapidly than the phenolic THP ether when the reaction mixture was maintained at room temperature. Thus, synthetic tenellin (**1**) was isolated in 82% yield following chromatography through silica gel which had been pretreated (see Experimental Section) to remove various metal cations, particularly iron salts, which invariably formed tightly bound dimeric and polymeric complexes with the hydroxamic acid. Finally, recrystallization from carbon tetrachloride–chloroform (3:1 by volume) afforded racemic tenellin (**1**) as elongated bright yellow platelets (mp 174–176 °C). Comparison with a sample of the natural substance proved it to be identical in all other respects with the exception of optical rotation.

Experimental Section

Melting points were determined on a Thomas-Hoover capillary apparatus and are uncorrected, as are boiling points. Infrared (IR) spectra were recorded on a Perkin-Elmer 298 spectrophotometer, and ultraviolet (UV) spectra were measured on a Perkin-Elmer 552 instrument. Proton magnetic resonance (^{1}H NMR) spectra were obtained at 220 MHz and are given in parts per million (δ) downfield relative to Me_4Si as an internal standard. The spectral descriptors s, d, t, q, and m refer to singlet, doublet, triplet, quartet, and multiplet, respectively, and coupling constants (J) are given in hertz. Carbon magnetic resonance studies (^{13}C NMR) were conducted on a 270-MHz instrument. Mass spectra were determined with Varian-MAT CH-7 and Hewlett-Packard 5992 A GC/MS equipment at 70 eV, and microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, TN.

Anhydrous solvents were routinely distilled from lithium aluminum hydride, calcium hydride, and sodium benzophenone ketyl, and purified nitrogen or argon was used in all reactions requiring an inert atmosphere. The progress of reactions was monitored by thin-layer chromatography (TLC) using precoated glass plates (E.M. Merck silica gel 60 F-254) with visualization by UV light, iodine vapor, and spray reagents containing phosphomolybdic acid or 2,4-dinitrophenylhydrazine. Merck silica gel 60 plates (20 cm × 20 cm × 0.25–2.0 mm thickness) were used for semipreparative separations, and Merck silica (0.063–0.20 mm) was used for column chromatography. Preparative separations were routinely accomplished by using a Waters Prep-500A instrument.

Methyl 2-[4-(Benzyloxy)phenyl]acetate (4). To a solution of freshly distilled boron trifluoride etherate (2.0 mL) in dry methanol (200 mL) was added (*p*-hydroxyphenyl)acetic acid (20.0 g, 0.13 mol, Aldrich) under an inert atmosphere. Esterification was complete after stirring at room temperature for 12 h, and neutralization by addition of an equal volume of saturated aqueous sodium bicarbonate was followed by extractions with ethyl acetate (3 × 70 mL). The combined organic extracts were dried over anhydrous magnesium sulfate, and evaporation of the solvent at reduced pressure gave the methyl ester as a clear oil, which was used immediately without further purification.

The methyl ester was dissolved in methyl ethyl ketone (200 mL), and addition of anhydrous potassium carbonate (19 g) was followed by treatment with benzyl chloride (17 g, Aldrich). The resulting mixture was heated to reflux under argon for 24 h. After addition of water to dissolve inorganic salts and extraction with ethyl acetate (3 × 80 mL), the combined organic layers were dried over anhydrous magnesium sulfate. Removal of solvent at reduced pressure and distillation afforded 32.0 g (95%) of the benzyl ether **4** as a pale yellow oil which solidified on standing: bp 160–165 °C (0.1 mmHg), 54–55 °C (in a sealed capillary); IR (Nujol) 1720, 1600, 1580, 1500, 1295, 1260, 1230, 1173, 1162, 1007, 853, 840, 750, 730, 700 cm^{-1}; NMR ($CDCl_3$) δ 3.61 (s, 2) 3.72 (s, 3), 5.09 (s, 2), 7.00 (d, 2, J = 8.5 Hz), 7.27 (d, 2, J = 8.5 Hz), 7.5 (m, 5); mass spectrum, m/e (relative intensity) 256.1 (M^+, 33), 257.1 (5.2), 93.7 (20.1), 92.8 (100). Anal. Calcd for $C_{16}H_{16}O_3$: C, 74.98; H, 6.29; O, 18.73. Found: C, 74.89; H, 6.38; O, 18.41.

Methyl (*E*)-3-(Dimethylamino)-2-[*p*-(benzyloxy)-phenyl]propenoate (5). A neat solution of methyl 2-[4-(benzyloxy)phenyl]acetate (**4**); 30 g, 0.12 mol) in *N,N*-dimethylformamide dimethyl acetal (28 g, 0.24 mol, Aldrich) and *N,N,N',N'*-tetramethylethylenediamine (1 mL) was heated in a pressure bottle at 200 °C for 12 h. After cooling, the homogeneous brown solution was poured into saturated aqueous ammonium chloride (150 mL) and extracted with ethyl acetate (3 × 100 mL). The combined organic layers were dried over anhydrous magnesium sulfate, and the solvent was removed under reduced pressure, leaving a yellowish semisolid which was crystallized from hot hexane–ethyl acetate to afford 29.5 g of pale yellow, rhombic crystals, mp 88–89 °C. Further concentration of the mother liquor provided an additional 3.7 g (89% yield) of product: IR (Nujol) 1680, 1590, 1605, 1510, 1460, 1375, 1285, 1235, 1220, 1100, 1040, 1015 cm^{-1}; NMR ($CDCl_3$) δ 2.66 (s, 3), 3.62 (s, 3), 5.45 (s, 2), 6.91 (d, 2, J = 8 Hz), 7.14 (d, 2, J = 8 Hz), 7.55 (m, 5), 7.57 (s, 1); mass spectrum, m/e (relative intensity) 311.1 (M^+ 4.1), 256.1 (24.2), 220.1 (17.9), 93.7 (100). Anal. Calcd for $C_{19}H_{21}NO_3$: C, 73.29; H, 6.80; N, 4.50. Found: C, 73.12; H, 6.90; N, 4.43.

Methyl (*E*)-3-[(Benzyloxy)amino]-2-[(*p*-benzyloxy)-phenyl]propenoate (6). A solution of enamino ester **5** (5.0 g, 16.06 mmol) and (benzyloxy)amine[6] (1.98 g, 16.06 mmol) in 50 mL of anhydrous benzene containing a catalytic amount of camphorsulfonic acid (0.1 g) was heated to reflux with evolution of dimethylamine gas as detected by moist red litmus at the top of the condenser. The reaction was complete after 12 h and the solvent removed in vacuo, leaving a thick yellow oil, which was purified by filtration through a silica gel column (25 g of silica) with 30% ethyl acetate in hexane, yielding 6.2 g (100%) of the (benzyloxy)amine **6** as a very pale yellow oil: R_f 0.53 (ethyl

(15) Neumann, H.; Seebach, D. *Chem. Ber.* **1978**, *111*, 2785.

(16) Our enol ethers derived from this β-diketone are cleaved under mild circumstances, and varying amounts of deprotected ester **22** were often obtained from these reactions. However, even in more resistant molecules, the (β-methoxyethoxy)methyl ether is cleaved upon treatment with *n*-butyllithium. Anderson, R. J.; Adams, K. G.; Chinn, H. R.; Hendrick, C. A. *J. Org. Chem.* **1980**, *45*, 2229. Ireland, R. E.; Wuts, P. G. M.; Ernst, B. *J. Am. Chem. Soc.* **1981**, *103*, 3205.

acetate–hexane, 3:7); IR (neat) 1732, 1607, 1507, 1500, 1240, 1020, 730, 695 cm^{-1}; NMR ($CDCl_3$) δ 3.63 (m, 3), 4.45 (d, 0.5 H, J = 9 Hz, NH, 4.99 (s, 2), 5.05 (m, 2.5 H), 6.92 (d, 2, J = 8.5 Hz), 7.19 (d, 2, J = 8.5 Hz), 7.36 (m, 9.5 H), 7.77 (d, 0.5 H, J = 9 Hz, vinyl proton); mass spectrum, m/e (relative intensity) 389 (M^+, 0.4), 256 (100), 197 (14.2), 93 (100). Anal. Calcd for $C_{24}H_{23}NO_4$: C, 74.02; H, 5.95; N, 3.60. Found: C, 73.95; H, 6.09; N, 3.89.

Methyl 3-[(Benzyloxy)amino]-2-[(*p*-benzyloxy)phenyl]-propionate (7). A solution of the enamino ester **6** (4.4 g, 11.3 mmol) in ethanol (40 mL) containing bromothymol blue indicator was made acidic by dropwise addition of aqueous (1.0 N) hydrochloric acid until the yellow color persisted. Sodium cyanoborohydride (0.9 g, 1.2 equiv) was added in three equal portions. The reduction was complete after vigorous stirring for 4.5 h. Following dilution with water (60 mL) and extraction with ethyl acetate (3 × 15 mL), the combined organic layers were dried over anhydrous magnesium sulfate and concentrated under reduced pressure. Silica gel chromatography (30 g of silica) with 30% ethyl acetate in hexane afforded 4.2 g (96%) of **7** as colorless oil: R_f 0.45 (ethyl acetate–hexane, 3:7); IR (neat) 1730, 1610, 1510, 1450, 1240, 1175, 1160, 1020, 830, 735, 690 cm^{-1}; NMR ($CDCl_3$) δ 3.15 (dd, 1, J = 6.6, 13.8 Hz), 3.54 (dd, 1, J = 8.6, 13.8 Hz), 3.61 (s, 2), 4.00 (s, 2), 5.01 (s, 2), 6.93 (d, 2, J = 9 Hz), 7.22 (d, 2, J = 9 Hz), 7.41 (m, 10); mass spectrum, m/e (relative intensity) 392.4 (M^+, 45.2), 256.2 (100), 180.2 (78.2), 92.1 (45.1). Anal. Calcd for $C_{24}H_{25}NO_4$: C, 73.64; H, 6.44; N, 3.58. Found: C, 73.51; H, 6.58; N, 3.51.

Acylation of Amine 7 with Diketene. To a solution of the amine **7** (3.83 g, 9.8 mmol) in dry tetrahydrofuran (30 mL) were added 5 mg of 4-(dimethylamino)pyridine and 1.4 mL (1 equiv) of anhydrous triethylamine at room temperature under argon. The solution was cooled to -78 °C, and freshly distilled diketene (0.9 mL, 1.2 equiv) was added via syringe in small portions over a period of 30 min. After stirring at -78 °C for 30 min, the reaction mixture was warmed to 0 °C for an additional 30 min, and the resulting orange solution was diluted with saturated aqueous ammonium chloride followed by ethyl acetate extraction (3 × 10 mL). The organic extracts were combined and dried ($MgSO_4$), and evaporation of the solvent at reduced pressure gave a crude oil which was purified by filtration through a silica gel column (25 g silica/1 g of crude product) with 40% ethyl acetate in hexane to afford 4.7 g (100%) of the desired amide **8** as a thick, gummy oil: IR (neat) 3400, 1730, 1660, 1610, 1510, 1450, 1240, 1180, 1160, 1030, 830, 730 cm^{-1}; NMR ($CDCl_3$) δ 1.93 (s, enolic CH_3), 2.05 (s, keto CH_3), 3.36 (s, keto tautomer, 1.5 H), 3.59 (s, 3), 3.98 (m, 1), 4.20 (m, 2), 4.73 (m, 2), 5.02 (s, 2), 5.32 (s, enolic 0.5), 6.93 (d, 2, J = 8.5 Hz), 7.27 (d, 2, J = 8.5 Hz), 7.39 (m, 10), 14.0 (s, enolic OH); mass spectrum (20 eV), m/e (relative intensity) 358.2 (16.1), 268.1 (99.6), 256.1 (100), 192.2 (26.6), 180.0 (25.2), 92.0 (31.7). Anal. Calcd for $C_{28}H_{29}NO_6$: C, 70.7; H, 6.15; N, 2.95. Found: C, 69.39; H, 7.02; N, 2.85.

3-Acetyl-1-(benzyloxy)-4-hydroxy-5-[(*p*-benzyloxy)-phenyl]-5,6-dihydro-2(1*H*)-pyridinone (15). A solution of the methyl ester **8** (4.27 g, 9.1 mmol) in a mixture of 40 mL tetrahydrofuran and 50 mL of water was cooled to 0 °C, and solid lithium hydroxide (1.10 g, 5 equiv) was added all at once. The heterogeneous suspension was stirred at 0 °C for 5 min, becoming homogeneous, and the ice bath was removed, allowing the reaction mixture to warm to room temperature. The reaction was complete after stirring at 22 °C for 2.25 h, and dilution with cold ethyl acetate (30 mL) was followed by repeated aqueous extraction (3 × 20 mL). The combined aqueous portions were acidified to pH 1 with cold aqueous sulfuric acid and shaken with ethyl acetate (3 × 20 mL). The combined organic layers were dried over magnesium sulfate, and the solvent was removed in vacuo, leaving 4.14 g (99%) of the carboxylic acid **13** as a viscous amber oil: IR (neat) 3400, 3200–2500, 1712, 1683, 1505 cm^{-1}; NMR ($CDCl_3$) δ 9.50 (br s, 1, COOH). This material was rigorously dried under high vacuum at 56 °C for 10 h before proceeding further.

A solution of 1,1'-carbonyldiimidazole (1.7 g, 1.2 equiv, Aldrich) in 10 mL of tetrahydrofuran was added dropwise with stirring to the carboxylic acid **13** (4.14 g, 8.97 mmol) in dry tetrahydrofuran (20 mL) under argon. The resulting pale yellow solution was maintained at 0 °C for 15 min and then at room temperature for 12 h. Sodium hydride dispersion (7.0 g, 2.6 equiv, Alfa) was added to the reaction mixture in three equal portions, and the development of product could be visualized as a violet coloration on TLC chromatography upon application of aqueous ferric chloride solution. After being stirred at room temperature for 20 min, the dark blue reaction mixture was diluted in water (50 mL), made acidic to pH 1 by dropwise addition of concentrated hydrochloric acid, and extracted with ethyl acetate (4 × 15 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure, leaving a reddish oil, which was purified by column chromatography (25 g of silica gel/1 g of product) with 40% ethyl acetate in hexane, providing 3.62 g (91%) of the dihydropyridone **15** as a gummy semisolid: UV max (absolute EtOH) 224 nm (ϵ 16 500), 275 (15 200); IR (neat) 3350, 1660, 1600, 1550, 1505, 1370, 1310, 1237, 1172, 1015, 910, 855, 827, 745, 725 cm^{-1}; NMR ($CDCl_3$) δ 2.52 (s, 1.5), 2.72 (s, 1.5), 3.64 (m, 2), 3.75 (m, 1), 4.98 (m, 0.5), 5.06 (s, 3.5), 6.98 (m, 4), 7.40 (m, 10), 17.45 (s, 0.5) (indicates a mixture of keto and enol tautomers); mass spectrum (20 eV), m/e (relative intensity) 443.3 (M^+, 57.1), 426.3 (12.8), 398.3 (21.6), 337.4 (100), 308 (41.1), 300 (22.1), 210.5 (21.0), 92.1 (51.8). Anal. Calcd for $C_{27}H_{25}NO_5$: C, 73.12; H, 5.68; N, 3.16. Found: C, 72.95; H, 5.77; N, 3.14.

3-Acetyl-1-(benzyloxy)-4-hydroxy-5-[(*p*-benzyloxy)-phenyl]-2(1*H*)-pyridinone (10). To a solution of the dihydropyridinone **15** (368 mg, 8.30 mol) in 4.0 mL of freshly distilled ethylbenzene was added 1,2,4,5-tetrachlorobenzoquinone (chloranil, recrystallized from hot toluene; 210 mg, 1.03 equiv). The mixture was heated to reflux for 16 h. The progress of the reaction was followed by TLC with 20% ethyl acetate in hexanes and four elutions. The product and starting material have very similar R_f values but differ in appearance under long-wavelength (366 nm) UV light. The solvent was removed in vacuo and replaced by hot 20% ethyl acetate in hexane, and the product separated out as fine off-white crystals (310 mg, 84.6%) upon cooling of the mixture to room temperature. Recrystallization from hot ethyl acetate–hexane (1:4) afforded the pyridinone **10** as very pale yellow platelets: mp 155–156 °C (sealed capillary); UV max (absolute EtOH) 205 nm (ϵ 27 650), 250 (15 200), 346 (5890); IR (KBr) 3450, 1660, 1600, 1520, 1505, 1445, 1405, 1240, 1215, 1175, 1105, 1017, 935, 910, 820, 740, 700, 690 cm^{-1}; NMR ($CDCl_3$) δ 2.84 (s, 3), 5.05 (s, 2), 5.26 (s, 2), 6.95 (d, 2, J = 8.5 Hz), 7.09 (d, 2, J = 8.5 Hz), 7.23 (s, 1), 7.5 (m, 10); mass spectrum, m/e (relative intensity) 441.2 (M^+, 100), 350.3 (21.4), 335.3 (27.8), 92.0 (35.5). Anal. Calcd for $C_{27}H_{23}NO_5$: C, 73.46; H, 5.25; N, 3.17. Found: C, 73.33; H, 5.25; N, 3.04.

Preparation of Bis(tetrahydropyranyl) Ether 18. A flask containing the pyridinone **10** (120 mg, 0.27 mmol) in 4 mL of dioxane and 10% palladium on carbon (120 mg) was placed under hydrogen (1 atm) and stirred at room temperature for 45 min. After filtration through a Celite pad with the aid of ethyl acetate, the filtrate was concentrated in vacuo, providing **17** as a thick oil which solidified as a white powder upon being allowed to stand under high vacuum. This residue was used directly by dissolution in 4 mL of methylene chloride–tetrahydrofuran (1:1) followed by addition of dihydropyran (150 mg, 7 equiv) and a catalytic amount of camphorsulfonic acid (5 mg) at 0 °C under argon. The protection was complete upon stirring 5 h at 0 °C. After dilution with aqueous sodium carbonate (5 mL) and extraction with ethyl acetate (3 × 3 mL), the combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. Purification by preparative thick-layer chromatography on silica gel with 20% ethyl acetate in hexane (two elutions, recovery with ethyl acetate) provided 110 mg (94%) of the bis(tetrahydropyranyl) ether **18**: IR ($CHCl_3$) 3500, 1672, 1615, 1517, 1458, 1230, 1120, 1080, 1040, 975, 925, 915, 880 cm^{-1}; NMR ($CDCl_3$) δ 1.5–2.1 (m, 12), 2.77 (s, 3), 3.6 (m, 2), 3.9 (m, 2), 5.36 (br s, l), 5.45 (br s, 1), 7.11 (d, 2, J = 9 Hz), 7.39 (d, 2, J = 9 Hz), 7.66 (s, 1), 16.59 (s, 1); mass spectrum (20 eV), m/e (relative intensity) 429.3 (M^+, 2.0), 345.3 (100), 261.1 (100), 245.3 (77.9), 86.0 (39.5), 85.0 (29.6). Anal. calcd for $C_{23}H_{27}NO_7$: C, 64.32; H, 6.34; N, 3.26. Found: C, 63.97; H, 6.27; N, 2.78.

(*E*)-2,4-Dimethyl-2-hexenal (19). To a solution of freshly distilled (1,1-dimethyl-*N*-propylidene)ethylamine[17] [bp 101–103 °C (760 mmHg); 20 g (0.177 mol)] in anhydrous tetrahydrofuran (50 mL) was added slowly over 30 min a solution of 1.5 M *n*-

(17) The imine was prepared according to the general procedure of: Campbell, K. N.; Sommers, A. H.; Campbell, B. K. *J. Am. Chem. Soc.* **1944**, *66*, 82.

butyllithium in hexane (120 mL, 0.18 mol) at −78 °C under argon. When the addition was complete, the solution was allowed to warm to −20 °C and maintained there for 20 min followed by cooling to −78 °C and introduction of distilled 2-methylbutyraldehyde (19 mL, 0.177 mol, Aldrich) via syringe over 15 min. After the mixture, was warmed and stirred at −20 °C for 4 h, the reaction was quenched with an aqueous solution of oxalic acid (150 g in 550 mL of H_2O), and the resulting mixture was vigorously stirred overnight at room temperature. Following ethereal extraction (3 × 100 mL) of the product, the organic portions were combined, dried ($MgSO_4$), and concentrated under reduced pressure. Purification by chromatography on silica gel (220 g) with 10% ethyl ether in hexane provided 19.2 g (86%) of aldehyde **19** as a nearly colorless liquid: IR (neat) 2920, 1675, 1633, 1450, 1375, 1213, 1145, 1000, 826, 774 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.88 (t, 3, J = 7.5 Hz), 1.06 (d, 2, J = 8 Hz), 1.44 (m, 2), 1.75 (s, 3), 2.63 (m, 1), 6.28 (d, 1, J = 10 Hz), 9.44 (s, 1); ^{13}C NMR ($CDCl_3$) δ 11.8, 19.5, 29.5, 30.8, 35.2, 138.0, 160.1, 195.3. None of the corresponding Z isomer could be detected in the NMR spectra. careful distillation of **19** was attemped [lit.[18] bp 63–65 °C (17 mmHg)], but the yield and quality of the product were adversely affected. Aldehyde **19** did not store well at −20 °C and was routinely chromatographed prior to use.

Preparation of Bis(tetrahydropyranyl) Ether 21 via Aldol Condensation. A flame-dried flask was charged with anhydrous diisopropylamine (130 μL, 0.93 mmol) followed by addition of 560 μL (0.84 mmol) of 1.5 M n-butyllithium in hexane at 0 °C under argon. Dry tetrahydrofuran (0.2 mL) was introduced, and the mixture cooled to −78 °C with subsequent dropwise addition of a solution of pyridinone **18** (164 mg, 0.382 mmol) in tetrahydrofuran (0.8 mL). After stirring the deep yellow enolate solution for 15 min, the aldehyde **19** (48 μL, 0.34 mmol) was added via syringe, and the resulting mixture was maintained a −78 °C for 30 min followed by warming to 0 °C for 1 h. A few drops of saturated aqueous ammonium chloride were used to quench the reaction, and addition of anhydrous magnesium sulfate, filtration, and evaporation gave a reddish oil containing four components as indicated by TLC in 30% ethyl acetate–hexanes: (a) the dehydrated aldol product **21** (4.7 mg, 2.5%; R_f 0.49), (b) an uncharacterized substance (6.0 mg; R_f 0.44), (c) unreacted starting pyridinone **18** (40 mg, 27%; R_f 0.38), and (d) aldol product **20** (64.2 mg, 35%; R_f 0.32). The components were successfully separated by preparative TLC after two elutions with 20% ethyl acetate in hexanes.

Selective dehydration was performed upon treatment of a solution of the aldol diastereoisomers **20** in 2 mL of triethylamine–chloroform (4:1) with a catalytic amount of dry camphorsulfonic acid (5 mg) at reflux under argon for 45 min. Concentration under reduced pressure gave a paste, and addition of chloroform resulted in separation of the ammonium salt. Preparative TLC of the decanted chloroform solution with 20% ethyl acetate in hexanes afforded 62 mg (100%) of the bis(tetrahydropyranyl) ether **21** as yellow oil: IR ($CHCl_3$) 1660, 1630, 1615, 1515, 1465, 1245, 1130, 1115, 1040, 970; NMR ($CDCl_3$) δ 0.84 (t, 3, J = 7 Hz), 1.02 (d, 3, J = 6 Hz), 1.36 (m, 3), 1.66 (m, 6), 1.93 (m, 6), 1.91 (s, 3), 2.50 (m, 1), 3.64 (m, 2), 3.98 (m, 2), 5.36 (br s, 1), 5.45 (br s, 1), 5.84 (d, 1, J = 10 Hz), 7.5 (d, 2, J = 8 Hz), 7.4 (d, 2, J = 8 Hz), 7.64 (s, 1), 7.65 (d, 1, J = 15 Hz) 8.00 (d, 1, J= 15 Hz); mass spectrum (19 eV), m/e (relative intensity) 453.5 (6.0), 370.5 (11.2), 312.4 (62.2), 296.5 (15.1), 85.2 (100). Anal. Calcd for $C_{23}H_{27}NO_7$: C, 69.25; H, 7.31; N, 2.61. Found: C, 69.13; H, 7.58; N, 2.88.

Synthetic Tenellin (1). A solution of anhydrous methanolic benzenes (2.0 mL; 2:3 by volume) containing the bis(tetrahydropyranyl) ether **21** (154 mg, 0.286 mmol) and a catalytic amount of dry camphorsulfonic acid (0.5 mg) was heated at reflux for 20 min under argon. After concentration of the reaction mixture, the yellow oil was purified by column chromatography on silica gel (10 g) with chloroform elution. This silica gel had been prewashed by being allowed to stand as a slurry in 50% aqueous nitric acid for 24 h followed by rinsing with doubly distilled water until the aqueous filtrates were neutral. Subsequent trituration with reagent-grade acetone was followed by drying in a crystallizing dish at room temperature and finally under high vacuum at room temperature. Synthetic tenellin (1) immediately crystallized upon evaporation of the chloroform from the column fractions (82% yield). Two successive recrystallizations from carbon tetrachloride–chloroform (3:1 by volume) gave 60.7 mg (58%) of **1** as elongated bright yellow platelets: mp 174–176 °C; UV max (absolute EtOH) 340 nm (log ϵ 4.56), 259 (4.41), 242 (sh, 4.40); IR (KBr) 3300, 3110, 1630, 1610, 1600, 1500, 1425, 1350, 1250, 1210, 1165, 1110, 975, 824 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 0.82 (t, 3, J = 7 Hz), 1.07, (d, 3, J = 8 Hz), 1.36 (m, 2), 1.85 (s, 3), 2.52 (m, 1), 5.99 (d, 1, J = 10 Hz), 6.81 (d, 2, J = 7.5 Hz), 7.33 (d, 2, J = 7.5 Hz), 7.57 (d, 1, J = 15 Hz), 8.06 (d, 1, J = 15 Hz), 8.20 (s, 1), 9.61 (br s, 1), 11.91 (br s, 1), 17.18 (s, 1); ^{13}C NMR (Me_2SO-d_6) δ 11.7, 12.3, 19.8, 29.4, 34.6, 105.8, 110.9, 115.0, 122.9, 123.1, 130.2, 132.6, 140.0, 149.7, 150.8, 156.9, 157.6, 173.0, 193.8; mass spectrum, m/e (relative intensity) 369.1 (M^+, 15.0), 353.1 (2.5), 313.1 (19.5), 312.1 (100), 246.0 (24.0), 230 (11.9). Anal. Calcd for $C_{21}H_{23}NO_5$: C, 68.28; H, 6.28; N, 3.79. Found (synthetic tenellin): C, 66.85; H, 6.20; N, 3.68. Found (authentic tenellin): C, 65.82; H, 6.44; N, 3.71.

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Registry No. (±)-**1**, 81844-67-9; **4**, 68641-16-7; (*E*)-**5**, 81790-25-2; (*E*)-**6**, 81790-26-3; (±)-**7**, 81790-27-4; (±)-**8**, 81790-28-5; (1,1-dimethyl-*N*-propylidene)ethanamine, 7020-81-7;, 81790-29-6; **10**, 81790-30-9; (*E*)-**11**, 81790-31-0; (±)-**12**, 81790-32-1; (±)-**13**, 81790-33-2; (±)-**14**, 81790-34-3; (±)-**15**, 81790-35-4; **16**, 81790-36-5; **17**, 81790-37-6; **18**, 81790-38-7; (±)-(*E*)-**19**, 34696-39-4; **20**, 81802-25-7; **21**, 81790-39-8; (*p*-hydroxyphenyl)acetic acid, 156-38-7; methyl (*p*-hydroxyphenyl)acetate, 14199-15-6; *N*,*N*-dimethylformamide dimethyl acetal, 4637-24-5; diketene, 674-82-8; 1,1′-carbonyldiimidazole, 530-62-1; (1,1-dimethyl-*N*-propylidene)ethanamine, 7020-81-7; (benzyloxy)amine, 622-33-3; 2-methylbutyraldehyde, 96-17-3.

(18) Chong, R.; King, R. R.; Whalley, W. B. *J. Chem. Soc. C* **1971**, 3566.