MHz: COSY, J-resolved). The critical transformation of 4 to silyl enol ether 5 by low-temperature ozonolysis and treatment with excess *tert*-butyldimethylsilyl (TBDMS) triflate as described by Corey[11] proceeded smoothly and with nearly complete regiospecificity. Hydroboration[12] of the enol ether from the less hindered β-face followed by alkaline peroxide oxidation afforded differentially protected cyclitol 6, which upon desilylation gave the known triol 7 (mmp 136–137 °C; lit.[13] mp 137–139 °C), identical in all respects with an authentic sample. Phosphorylation of 7 using tetrabenzyl pyrophosphate[14] and removal of the protecting groups as previously described[13] provided D-*myo*-inositol 1,4,5-trisphosphate (8), isolated as its hexasodium salt.

Extensions of this strategy to the preparation of other inositol (poly)phosphates as well as the C(5)-phosphonomethyl analogue of 8 are in progress.

Acknowledgment. Supported by a Grant-in-Aid from the American Heart Association and the Robert A. Welch Foundation. We express our gratitude to Dr. Joseph P. Vacca (Merck Sharp & Dohme) for his advice and for providing an authentic sample and spectral data of 7. Preliminary experiments were conducted by Dr. Stephen Douglas. Additional assistance was provided by Drs. Steven J. Wittenberger and Abdelkrim Abdali.

Supplementary Material Available: ^{1}H NMR data for compounds 2, 3, 4, 5, and 6 (2 pages). Ordering information is given on any current masthead page.

(10) As judged by ^{1}H NMR analysis (250 MHz) under conditions in which ≥5% of the C(6)-epimer of 4, prepared independently, could be detected.

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Convergent Total Synthesis of (±)-Tenellin

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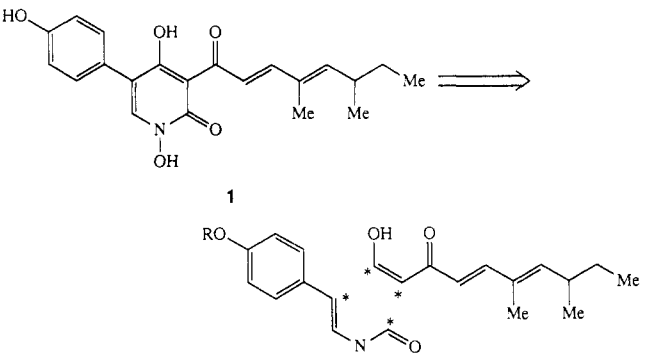
Summary: A convergent total synthesis of the fungal biochrome tenellin is reported. The synthesis features an efficient cyclocondensation of a cinnamate derived isocyanate with a fully elaborated diene β-keto ester enolate reaction partner.

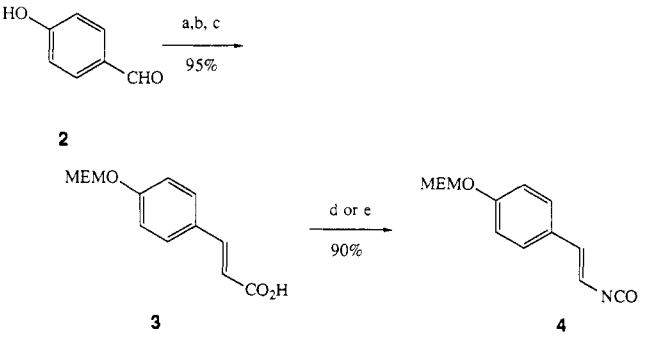
Sir: Tenellin (1) and several closely related substances that exhibit the characteristic 3-acyl-4-hydroxy-2-pyridone unit as a prominent structural feature have been recently isolated by Vining and co-workers from mycelium extracts of *Beauveria basiana* and *Beauveria tenella*.[1] To date, only one synthesis of this unusual natural product has been reported.[2] Our interest in this species stems from our ongoing program to develop and exploit the efficient cyclocondensation chemistry of vinyl isocyanates for the rapid construction of highly substituted pyridone systems.[3] The basic strategy envisioned for the assembly of tenellin is depicted in Scheme I and relies on the "riveting" of two preformed segments of the target molecule at the 2-pyridone moiety in a highly convergent fashion. A useful tactic for implementing this conceptual approach to tenellin would employ a cinnamate derived vinyl isocyanate as a convenient 2-azadiene equivalent in combination with an appropriately substituted β-keto ester enolate species as the nucleophilic "dienophile" reaction partner.

A straightforward and efficient sequence for the construction of the left-hand "2-azadiene" fragment starts from commercial 4-hydroxybenzaldehyde (2) and is displayed in Scheme II. The requisite vinyl isocyanate 4 was routinely produced in overall yields in excess of 80%. The final conversion of carboxylic acid 3 into the vinyl isocyanate could be conveniently effected in one of two ways.

Scheme I



Scheme II



[a] (a) MEMCl, i-Pr_2EtN, room temperature; (b) $(EtO)_2POCH_2CO_2Et$, NaH, THF, room temperature; (c) LiOH, H_2O, room temperature; (d) $(PhO)_2PON_3$, Et_3N, toluene 110 °C; (e) EtOCOCl, Et_3N, NaN_3, toluene, 110 °C.

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(3) (a) Rigby, J. H.; Holsworth, D. D.; James, K. *J. Org. Chem.* **1989**, *54*, 4019. (b) Rigby, J. H.; Balasubramanian, N. *Ibid.* **1989**, *54*, 224. (c) Rigby, J. H.; Burkhardt, F. J. *Ibid.* **1986**, *51*, 1374. (d) Rigby, J. H.; Balasubramanian, N. *Ibid.* **1984**, *49*, 4569.

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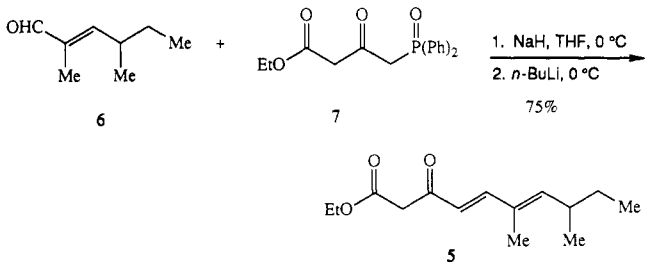
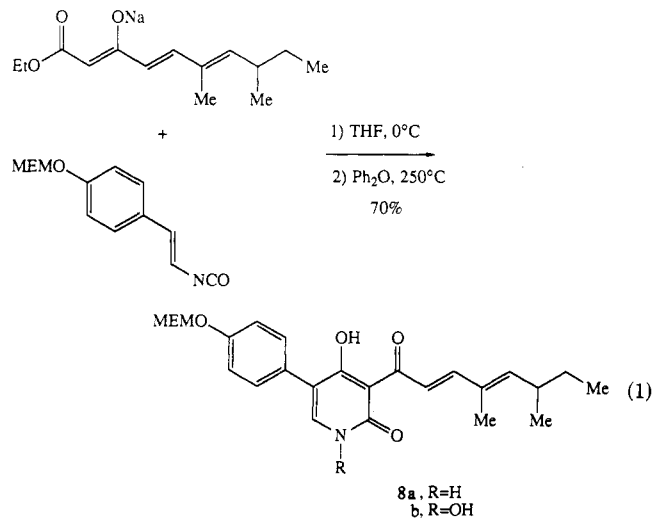
Scheme III



Exposure of **3** to diphenyl phosphorazidate (DPPA)[4] in toluene followed by refluxing of the resultant acyl azide for several hours produced the isocyanate in 90% yield. Alternatively, the isocyanate could be accessed with equal efficiency by using the Weinstock mixed anhydride protocol.[5] In practice, the isocyanate was prepared just prior to the addition of the elements of the right-hand fragment as described below.

The right-hand portion of tenellin, in the form of diene keto ester **5**, was prepared by the condensation of the known (*E*)-2,4-dimethyl-2-hexenal (**6**)[2] with the dianion of β-keto ester phosphine oxide **7**.[6] This process proceeded in good yield and provided **5** in isomerically homogeneous form (Scheme III). None of the corresponding *Z* geometrical isomer could be detected by ^{1}H NMR analysis. With both fragments now in hand, the final assembly of the tenellin skeleton was achieved by generation of the sodium salt of **5** (NaH, THF, 0 °C) followed by the addition of freshly prepared isocyanate **4**. The solvent was then removed in vacuo from the resultant enamide adduct and replaced with dry Ph_2O. This bright yellow solution was immediately plunged into a silicone oil bath preheated to 250 °C and heated at this temperature for 3 min. The intensely yellow pyridone **8a** (mp 149–50 °C) crystallized out of solution in 70% yield from **5** upon cooling. Shorter

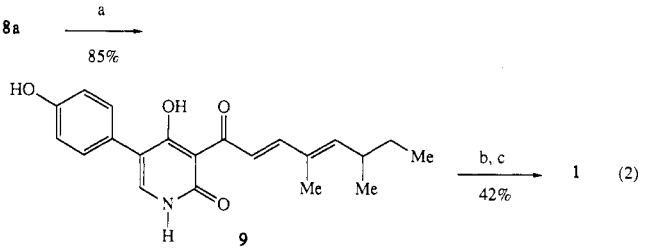


(1)

reaction times or lower temperatures gave incomplete conversions and longer residence times resulted in substantial product decomposition. Furthermore, the enamide produced during the enolate addition to isocyanate **4** could be isolated and purified prior to final thermal cyclization; however, this additional handling did not have a substantive impact on the efficiency of the overall process.

Our attention now turned to the introduction of the hydroxamate *N*-OH functionality onto the pyridone ring. Efforts to bring about direct oxidation of the pyridone nitrogen in **8a** with a variety of peracids and related oxidizing agents proved to be totally unproductive. 2-Pyridones and, in particular, 3-acyl-2-pyridones were found to be exceptionally recalcitrant participants in any oxidation schemes that were employed. At this juncture, it was deemed advantageous to explore potential avenues for oxidation that would proceed via a pyridine derivative of **8a** since pyridines tend to be more easily N-oxidized than the corresponding 2-pyridones. Toward this end a process originally described by Sammes and co-workers for converting amides into hydroxamic acids appeared particularly attractive.[7]

Exposure of **8a** to excess refluxing hexamethyldisilazane containing a catalytic quantity of chlorotrimethylsilane provided the extremely moisture sensitive 2,4-bis(silyloxy)pyridine derivative, which was neither isolated nor characterized but was immediately treated with oxodiperoxymolybdenum(pyridine)(HMPA) complex[8] in CH_2Cl_2 at room temperature. This transformation provided the corresponding N-hydroxylated pyridone **8b** in 25% yield. Unfortunately, efforts to remove the MEMO protection from **8b** (TMSCl, NaI, −20 °C)[9] resulted in considerable cleavage of the newly created N–OH bond. In response to this event, the deprotection and oxidation operations were performed in reverse order. This sequence modification proved to be quite effective and provided the desired tenellin target in 35% overall yield from **8a** via the readily accessible phenol pyridone **9** as outlined in eq 2.[10] The synthetic tenellin produced in this manner was shown to be identical with the natural product in all respects but optical rotation by comparison of spectral data kindly provided by Prof. D. R. Williams.



(2)

(a) TMSCl, NaI, MeCN, −20 °C; (b) TMS_2NH, cat. TMSCl, reflux; (c) MoO_5·py·HMPA, CH_2Cl_2, room temperature.

Acknowledgment. We wish to thank the National Science Foundation (Grant CHE-8719185) for their generous support of this work and Prof. D. R. Williams (Indiana University) for providing spectra of authentic tenellin.

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(10) All new compounds described in this paper display spectral (^{1}H NMR, ^{13}C NMR, IR) and HRMS or analytical data consistent with the assigned structures.