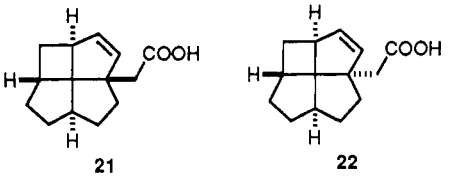

21 22

The origin of the rate accelerations recorded above might be attributed to stabilization of a polar transition state by water, but it should be recognized that the rate response of **1** to polar solvents is far less than what might be anticipated for an S_N1 reaction.[2] Another factor, particularly the effect of solvent pressure on a reaction with a negative activation volume, appears to be important.

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Enantiospecific Synthesis of D-*myo*-Inositol 1,4,5-Trisphosphate from (−)-Quinic Acid

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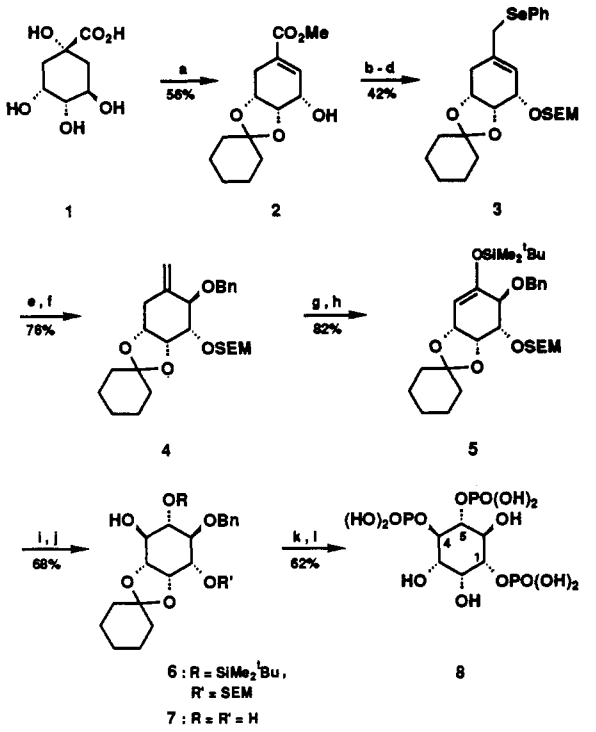
Summary: A versatile, enantiospecific approach to functionalized cyclitols from (−)-quinic acid is illustrated by a synthesis of D-*myo*-inositol 1,4,5-trisphosphate, the calcium-mobilizing intracellular second messenger of the phosphatidylinositol cycle.

Sir: In recognition of the physiologic role of the phosphatidylinositol cycle in receptor-mediated signal transduction[1] and the limited availability of its metabolites from natural sources, there has been a resurgence of interest in the chemical synthesis of inositol (poly)phosphates and analogues.[2] To date, the majority of preparative studies have exploited readily available *myo*-inositol as the initial precursor and relied upon protection/deprotection sequences to differentiate amongst this cyclitol's six hydroxyls.[3] Furthermore, since *myo*-inositol is meso, a resolution is required to obtain optically active products. Herein, we described an enantiospecific approach to functionalized cyclitols from commercial (−)-quinic acid and illustrate its versatility by a synthesis of the calcium mobilizing intracellular second messenger D-*myo*-inositol 1,4,5-trisphosphate (**8**).

(−)-Quinic acid (**1**) was converted to ester **2** (mp 75 °C) in four steps according to literature procedure[4,6] (Scheme I). Sequential protection of the C(1)-alcohol (inositol numbering) as its β-(trimethylsilyl)ethoxymethyl (SEM) ether,[7] diisobutylaluminum hydride (DIBAL-H) reduction of the ester, and selenylation[8] of the resultant primary alcohol furnished **3**. Rearrangement of the allylic selenoxide[9] derived from **3** and benzylation generated a single stereoisomer[10] identified as **4** by ^{1}H NMR analysis (250

Scheme I[a]



[a] (a) Four steps, ref 4; (b) SEM-Cl, *i*-Pr_2NEt, THF, 45 °C, 12 h; (c) DIBAL-H, $PhCH_3$, −78 °C, 3 h; (d) *N*-(phenylseleno)phthalimide, Bu_3P, THF, 0 °C, 45 min; (e) $NaIO_4$, pH 7 buffer, 1,4-dioxane/H_2O (1:1.6), 0 °C, 6 h; (f) KH, $PhCH_2Br$, THF, 12 h; (g) O_3, CH_2Cl_2/MeOH (4:1), −78 °C; Me_2S, −78 → 25 °C, 4 h; (h) *t*-$BuMe_2SiOTf$, Et_3N, CH_2Cl_2, 2 h; (i) BH_3, THF, 25 °C, 3 h; alk H_2O_2, 1 h; (j) *n*-Bu_4NF, HMPA, 4-Å MS, 100 °C, 1 h; (k) KH, $[(BnO)_2PO]_2O$, THF, 60 °C; (l) H_2, 10% Pd/C, 50 psig, 95% EtOH; AcOH/H_2O.

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(3) For recent significant exceptions using chiral precursors, see: (a) Ballou, C. E.; Tegge, W. *Proc. Natl. Acad. Sci. U.S.A.* **1989**, *86*, 94–98. (b) Watanabe, Y.; Mitani, M.; Ozaki, S. *Chem. Lett.* **1987**, 123–126. (c) Kazikowski, A. P.; Fauq, A. H.; Rusnak, J. M. *Tetrahedron Lett.* **1989**, *30*, 3365–3368.

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(6) Satisfactory spectral data and elemental analyses were obtained for all stable intermediates.

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(9) Alternatively, the phenyl sulfide analogue of **3** could be prepared in good yield from the corresponding alcohol using tributylphosphine and phenyl disulfide. Oxidation with 3-chloroperoxybenzoic acid gave a ca. 1:1 mixture of sulfoxides which rearranged (45 °C, $(MeO)_3P$, MeOH) to **4** only. The rearrangement of diastereomeric allylic sulfoxides to the same stereoisomeric alcohol in biased polycyclic systems has precedent: Evans, D. A.; Andrews, G. C. *Acc. Chem. Res.* **1974**, *7*, 147–155.

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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.

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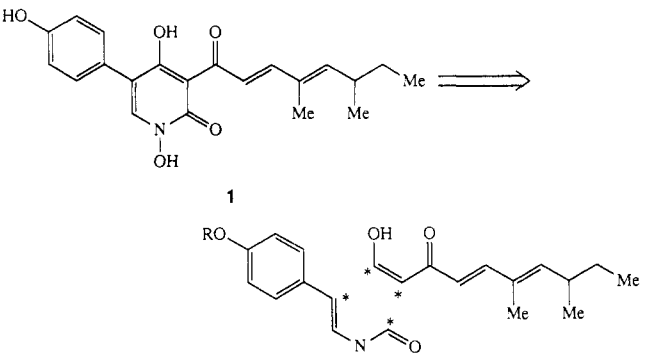
Summary: A convergent total synthesis of the fungal biochrome tenellin is reported. The synthesis features an efficient cyclocondensation of a cinnamate derived isocyanate with a fully elaborated diene β-keto ester enolate reaction partner.

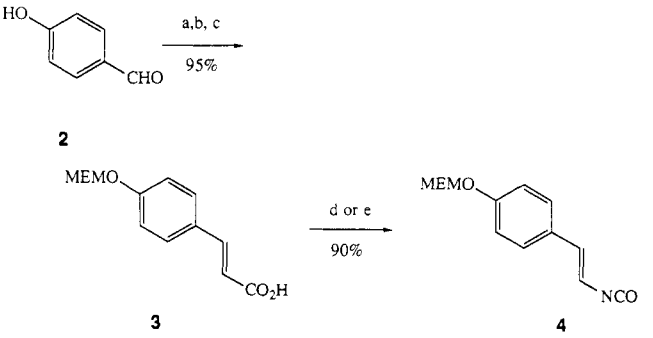
Sir: Tenellin (1) and several closely related substances that exhibit the characteristic 3-acyl-4-hydroxy-2-pyridone unit as a prominent structural feature have been recently isolated by Vining and co-workers from mycelium extracts of *Beauveria basiana* and *Beauveria tenella*.[1] To date, only one 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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