Total Synthesis of (−)-Penitrem D

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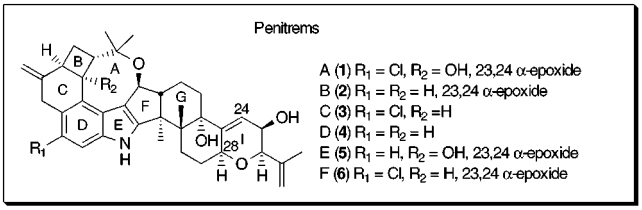
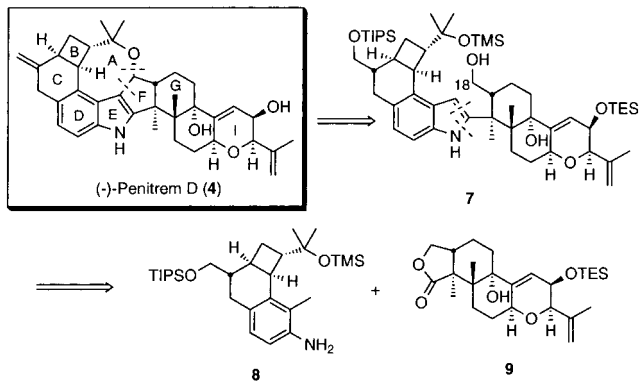
The indole-diterpene tremogens comprise an important family of environmental toxins, produced by ergot fungi that grow on a variety of grasses endemic to South Africa, New Zealand and the United States. Among the indole tremogens, penitrems A−F (**1**−**6**)[1] constitute a rare class of remarkably complex synthetic targets. Our long standing interest in this area, having led to the first total syntheses of (−)-paspaline,[2a,b] (+)-paspalicine,[2c,d] and (+)-paspalinine,[2c,d] set the stage for a synthetic venture directed toward the penitrems, with penitrem D selected as the initial target. In a recent letter,[2e] we reported studies on the assembly of the A, F, and I rings of penitrem D. Although the A and F rings were elaborated in a highly stereoselective fashion, considerable difficulty was encountered in the construction of ring I possessing the correct stereogenicity at C(28). In this contribution, we disclose a solution to this problem, culminating in the first total synthesis of (−)-penitrem D (**4**).



Penitrem D possesses a number of intriguing structural elements, including a highly substituted indole core, a cyclobutane moiety, an eight-membered cyclic ether (oxocane), nine fused rings, eleven stereogenetic carbons, and two allylic hydroxyl groups. To assemble the complex penitrem skeleton with complete control of stereochemistry, we envisioned union of the fully elaborated western and eastern hemispheres **8**[2h,3a,b] and **9** (Scheme 1). Toward this end, we developed an efficient synthesis of 2-substituted indoles exploiting the reaction of *o*-toluidine derivatives with esters and lactones.[2f,i] Oxidation of the C(18) primary hydroxyl in **7**, followed by an acid-promoted cyclization−gramine fragmentation/addition cascade, demonstrated in model systems

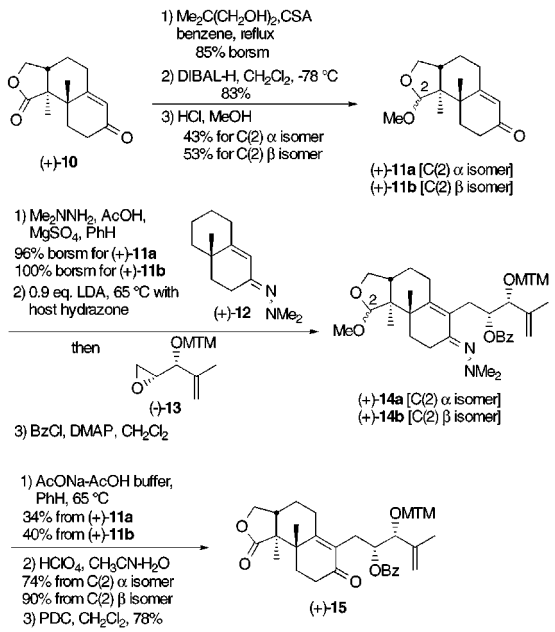
Scheme 1



to be highly successful,[2e,3a] would then complete the construction of rings A and F.

The synthesis of the eastern hemisphere (**9**) began with lactone (+)-**10**,[2g,h] available from (−)-Wieland-Miesher ketone[4] (15 steps, 8.3% yield; Scheme 2). A three-step sequence furnished the individual acetals (+)-**11a** and **b**, substrates for Stork metalloenamine alkylation.[5] Toward that end, conversion of (+)-**11a** and **b** individually to the corresponding dimethyl hydrazones followed, in turn, by metalloenamine coupling with epoxide (−)-**13**[6] in the presence of (+)-**12** (1.2 equiv) and protection of the hydroxyls as the benzoates, furnished (+)-**14a** and **b**, respectively. Presumably, the host hydrazone (+)-**12** is required to promote anion equilibrium.[7] Hydrolytic removal of the hydrazone and acetal (2 steps), followed by PDC oxidation reinstalled the lactone carbonyl

Scheme 2



to yield (+)-**15**. For preparative purposes acetals (+)-**11a** and (+)-**11b** were carried forward without separation.

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(3) A closely related derivative of (+)-**8** has been prepared; see: (a) Smith, A. B., III; Haseltine, J. N.; Visnick, M. *Tetrahedron* **1989**, *45*, 2431. (b) Hartz, R. A.; Ph.D. Thesis, University of Pennsylvania, 1996; also see Supporting Material.

(4) Gutzwiller, J.; Buchshacher, P.; Fürst, A. *Synthesis* **1977**, 167.

(5) (a) Stork, G.; Benaim, J. *J. Am. Chem. Soc.* **1971**, *93*, 5938. (b) Stork, G.; Benaim, J. *Org. Synth.* **1977**, *57*, 69.

(6) Epoxide (−)-**13** was prepared in four steps; Smith, A. B., III; Ohta, M.; Clark, W. M.; Leahy, J. W. *Tetrahedron Lett.* **1993**, *34*, 3033; also see Supporting Material.

(7) Our initial attempt at Stork metalloenamine alkylation of the hydrazones derived from (+)-**11a** and **b** with (−)-**13** resulted in low yield. Considerable experimentation led to the observation that a host dimethyl hydrazone was required; see Supporting Material.

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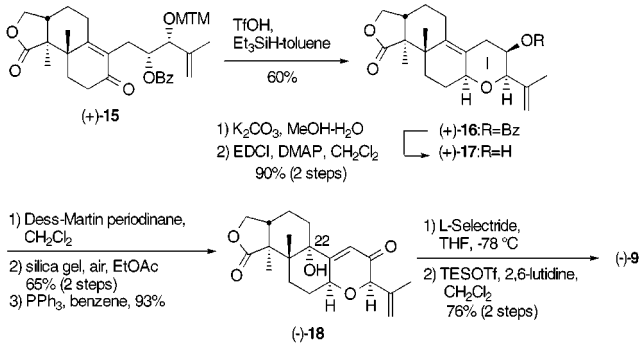
Assembly of the I ring entailed a reaction cascade initiated by treatment of (+)-**15** with TfOH in Et_3SiH-toluene (1:1) (Scheme 3). A similar reaction sequence was described by Nicolaou for the elegant construction of oxepanes.[8] In our case the sequence involved removal of the MTM moiety, cyclization, and silane reduction of the resulting hemiacetal to furnish exclusively *cis*-pyran (+)-**16**. Removal of the benzoyl group (K_2CO_3/MeOH−H_2O) also resulted in partial hydrolysis of the lactone; the lactone functionality was restored with EDCI. Introduction of the C(22) hydroxyl was next achieved via Dess−Martin oxidation of (+)-**17** to the corresponding β,γ unsaturated ketone, followed by autoxidation (i.e., air) in the presence of silica gel to furnish the tertiary hydroperoxide. Reduction with PPh_3 provided alcohol (−)-**18**. Stereoselective reduction (L-selectride) of the C(25) ketone followed by protection of the secondary hydroxyl completed the synthesis of the eastern hemisphere (−)-**9**. The structure of (−)-**9** was confirmed by X-ray analysis.[9]

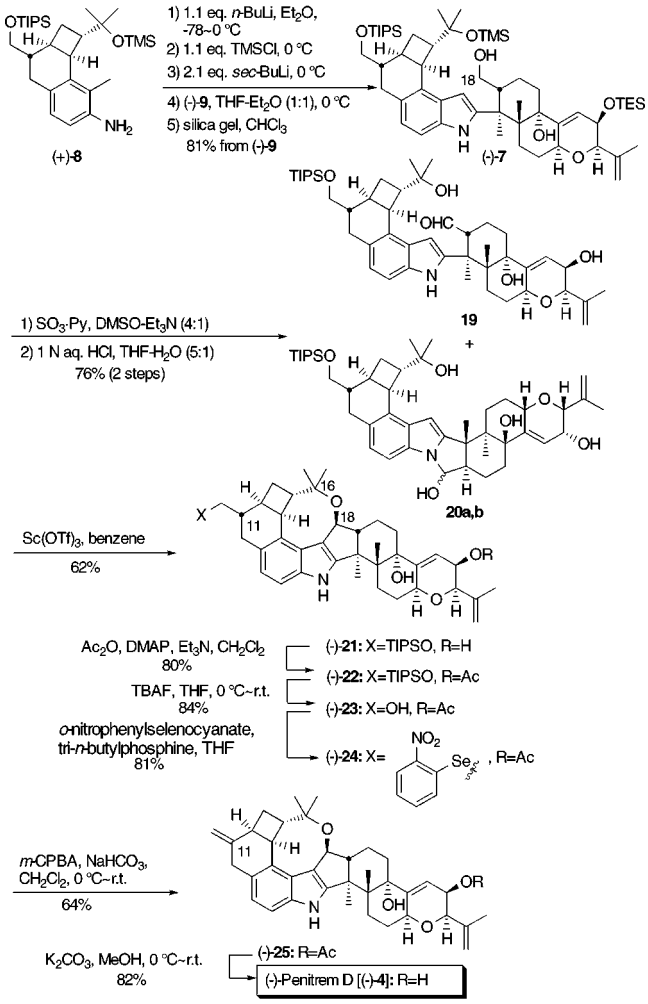
Scheme 3



With both the western and eastern hemispheres (+)-**8**[2h,3a,b] and (−)-**9** in hand, we turned to the 2-substituted indole synthetic protocol[2f,i] (Scheme 4). Treatment of the TMS derivative of (+)-**8** with *s*-BuLi, followed by addition of (−)-**9** resulted in acylation at the highly hindered lactone carbonyl; subsequent in situ hetero-Peterson olefination[10] furnished (−)-**7**. The efficiency of the 2-substituted indole protocol is clearly demonstrated by the 81% overall yield. Parikh-Doering[11] oxidation followed by selective removal of the TMS and TES groups then afforded an equilibrium mixture of **19**, **20a** and **20b** (3:1:3).

Tandem assembly of the AF ring system was next achieved by treatment of the mixture with $Sc(OTf)_3$[12] (1.2 equiv) in benzene to provide indole (−)-**21** in 62% yield, possessing the complete penitrem D carbon skeleton.[13] As anticipated, $Sc(OTf)_3$ promoted a reaction cascade involving an aldehyde cyclization-gramine fragmentation, followed by capture of the intermediate carbocation by the tertiary C(16) hydroxy to construct rings A and F in a highly stereoselective fashion (>95:5). The required β-stereochemistry at C(18) was anticipated, given earlier model studies.[3a,b] Acetylation followed by removal of the TIPS group then furnished alcohol (−)-**23**, which upon selenation a lá Grieco[14a] and oxidative-elimination[14b] of the selenide installed the C(11) exo olefin in (−)-**25**. Hydrolytic removal of the acetate completed the synthesis of (−)-penitrem D, which proved identical in all respects to the natural material (i.e., 500 MHz ^{1}H and 125 MHz ^{13}C NMR, IR, HRMS, and chiroptic properties).[15]

Scheme 4



In summary, the first total synthesis of (−)-penitrem D has been achieved. Key elements of the synthesis include the stereocontrolled elaboration of the advanced eastern hemisphere (−)-**9**, a highly efficient union of the hemispheres (+)-**8** and (−)-**9** exploiting a 2-substituted indole synthesis, and the efficient construction of rings A and F via a $Sc(OTf)_3$ promoted cation cascade.

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Supporting Information Available: Specrotoscopic and analytical data for **4**, **7**−**25**, as well as representative experimental procedures (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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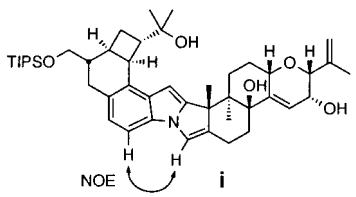
(11) Parikh, J. R.; Doering, W. E. *J. Am. Chem. Soc.* **1967**, *89*, 5505.

(12) $Sc(OTf)_3$ is known as water-tolerant Lewis acid; See: Kobayashi, S.; Hachiya, I.; Araki, M.; Ishitani, H. *Tetrahedron Lett.* **1993**, *34*, 3755.

(13) In some experiments, as much as 25% of an elimination product **i** was observed; the structure of **i** was assigned via a NOESY NMR experiment.



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(15) We thank Professor Ken-ichi Kawai (Hoshi University) for a generous sample of (−)-penitrem D.