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Tremorgenic Indole Alkaloids. Studies Directed toward the Assembly of the A, F, and I Rings of Penitrem D: Observation of an Unexpected Stereochemical Outcome

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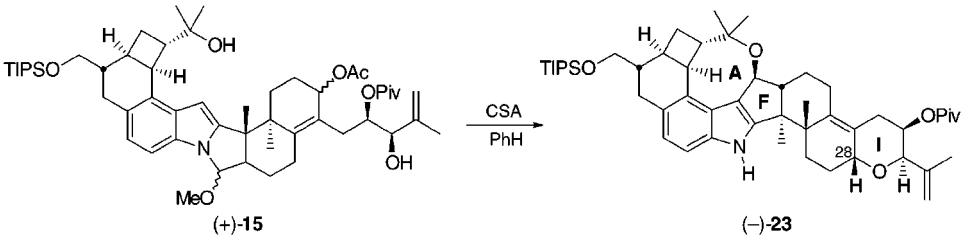
ABSTRACT



(+)-**15** (−)-**23**

In this Letter we demonstrate the viability of a highly stereoselective tandem Mannich cyclization−grammine fragmentation/addition cascade, critical for assembly of the A and F rings of penitrem D. We also explored simultaneous execution of this tactic with concurrent construction of ring I. Reinvestigation of a model system provided an explanation for the unanticipated stereochemical outcome at C(28).

The penitrems A−F (**1**−**6**) comprise a rare class of remarkably complex indole alkaloids produced by ergot fungi that grow on grasses endemic to Australia, New Zealand, and the southwestern United States.[1] Live stock that ingest the infected grasses experience reversible neurological disorders, including sustained tremors upon voluntary movement, hypersensitivity to external stimuli, limb weakness, ataxia, and eventual death, if not removed from the infected pasture. As such these tremorgenic alkaloids represent a significant environmental hazard.

In the early 1980s, we initiated a program directed at the synthesis of the structurally simpler members of this family of tremorgenic alkaloids. This venture, which led to the first total syntheses of paspaline,[2] paspalicine,[3] and paspalinine,[3] set the stage for a synthetic campaign directed toward the penitrems, with penitrem D selected as the initial target.

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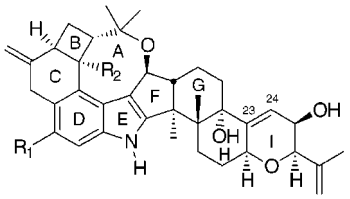
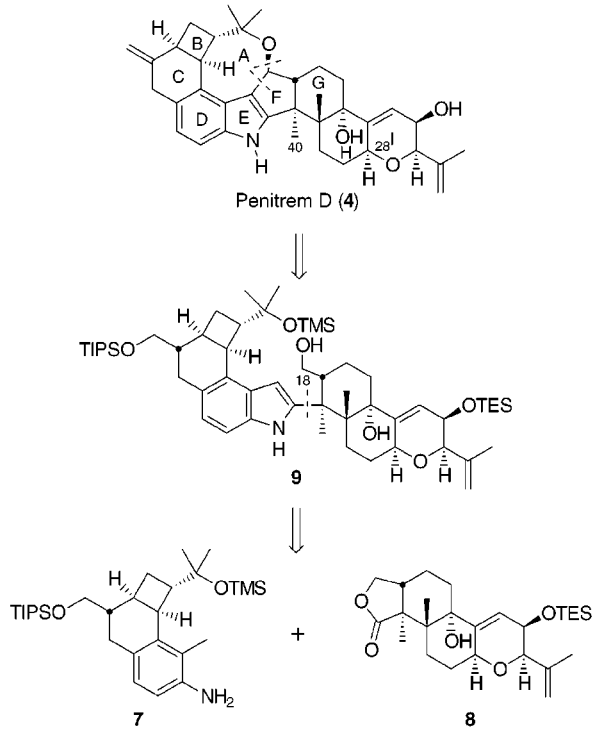


Penitrems

A (**1**) R_1 = Cl, R_2 = OH, 23,24 α-epoxide
B (**2**) R_1 = R_2 = H, 23,24 α-epoxide
C (**3**) R_1 = Cl, R_2 = H
D (**4**) R_1 = R_2 = H
E (**5**) R_1 = H, R_2 = OH, 23,24 α-epoxide
F (**6**) R_1 = Cl, R_2 = H, 23,24 α-epoxide

From the retrosynthetic perspective, we envisioned assembly of the penitrem skeleton via union of the fully elaborated western and eastern hemispheres **7** and **8** (Scheme 1), exploiting an indole ring synthesis[4] devised specifically

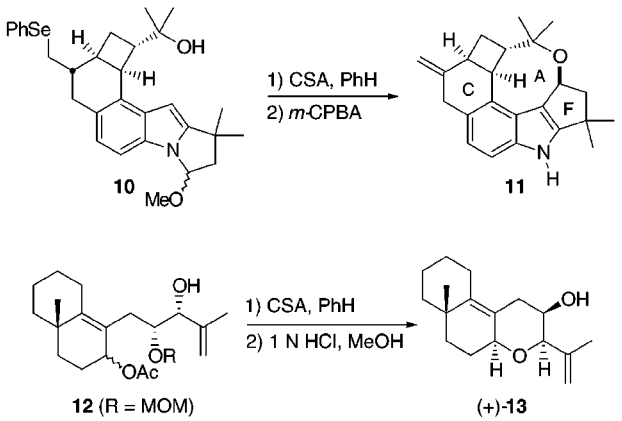
Scheme 1



for this purpose to access 2-substituted indole **9**. Following oxidation of the C(18) primary hydroxyl, a reaction cascade involving a tandem Mannich cyclization−grammine fragmentation/addition process was envisioned to construct the A and F rings in a stereoselective fashion.

To demonstrate the viability of this overall scenario, we carried out the construction of **11**, a diminutive form of

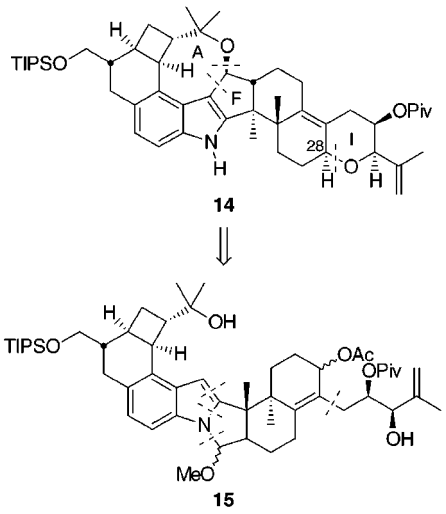
Scheme 2



penitrem D comprising the ABCDEF rings (Scheme 2).[5] Concurrent with this model study, we also developed a strategy for the construction of the I ring, which entailed acid-promoted cyclization of **12** followed by removal of the MOM protecting group (Scheme 2).[6] X-ray crystallographic analysis secured the structures of (±)-**10**[5] and (+)-**13**.[6]

Interestingly, both the tandem assembly of the A and F rings of **11** and closure of ring I in **13** proceeded under precisely the same acid conditions (Scheme 2). This observation suggested the possibility of a dramatic "one-pot" construction of the A, F, and I rings of advanced intermediate **14** from **15** (Scheme 3).

Scheme 3



In this Letter, we describe construction of **15** and the unexpected stereochemical outcome at C(28) upon treatment

(3) (a) Smith, A. B., III; Sunazuka, T.; Leenay, T. L.; Kingery-Wood, J. *J. Am. Chem. Soc.* **1990**, *112*, 8197. (b) Smith, A. B., III; Kingery-Wood, J.; Leenay, T. L.; Nolen, E. G.; Sunazuka, T. *J. Am. Chem. Soc.* **1992**, *114*, 1438.

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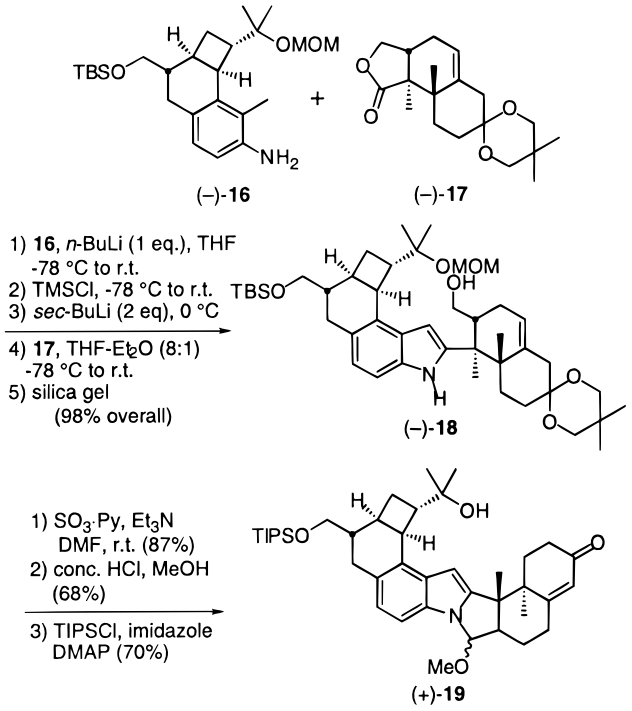
(5) Smith, A. B., III; Haseltine, J. N.; Visnick, M. *Tetrahedron* **1989**, *45*, 2431. For the synthesis of (−)-**16**, see: Hartz, R. A., Ph.D. Thesis, University of Pennsylvania, 1996.

(6) Smith, A. B., III; Ohta, M.; Clark, W. M.; Leahy, J. W. *Tetrahedron Lett.* **1993**, *34*, 3033.

with CSA in benzene, conditions that proved successful with both **10** and **12**. Reinvestigation of model system **12** provided an explanation for the observed stereochemical outcome.

Our point of departure involved union of (−)-**16**[5] and (−)-**17**[7] via our previously disclosed indole ring synthesis (Scheme 4).[4] To this end, treatment of the TMS derivative

Scheme 4

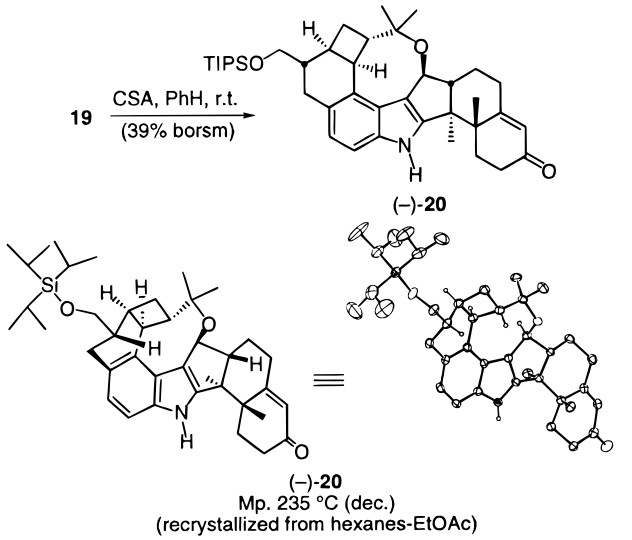


of (−)-**16** with *s*-BuLi, followed in turn by addition of (−)-**17** to effect acylation at the lactone carbonyl and in situ hetero-Peterson olefination furnished (−)-**18**[8] in near quantitative yield. Oxidation of the resultant primary hydroxyl (SO_3·pyr), treatment with methanolic HCl, and reinstallation of a silyl protecting group (TIPSCl) furnished (+)-**19**[8] in 41% yield for the three steps.

To demonstrate further the feasibility of the required tandem Mannich cyclization−grammine fragmentation/addition cascade to construct rings A and F in an advanced system, we subjected (+)-**19** to the previously developed CSA/benzene conditions; octacyclic ketone (−)-**20**[8] was isolated in 39% yield (Scheme 5). The structure of (−)-**20** was secured by single-crystal X-ray analysis.

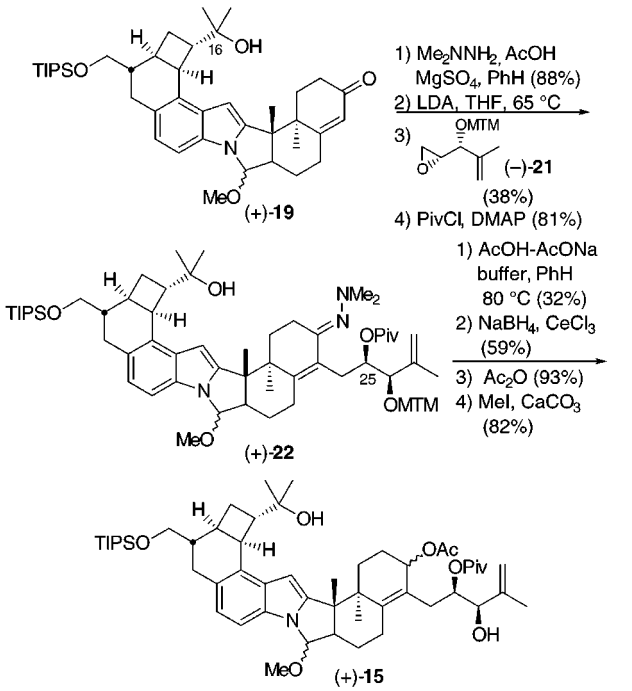
Encouraged by this result, we continued with the elaboration of (+)-**19** (Scheme 6). Conversion of ketone (+)-**19** to the corresponding dimethyl hydrazone and coupling with epoxide (−)-**21**[8] via the Stork metalloenamine protocol[9] furnished the coupled adduct in 38% yield. Protection of the

Scheme 5



C(25) secondary hydroxyl was now required. Initially, we explored the use of a MOM group as in model system **12**; however, we were unable to differentiate between the secondary and tertiary hydroxyls at C(25) and C(16). Selective protection of the secondary alcohol was however achieved with PivCl (DMAP), to provide (+)-**22**[8] in 81% yield. Hydrolysis of the dimethyl hydrazone of (+)-**22**, reduction of the ketone under Luche conditions, acetylation of the resultant mixture of epimeric alcohols, and removal of the MTM group (MeI/$CaCO_3$) then completed the synthesis of (+)-**15**.[8]

Scheme 6

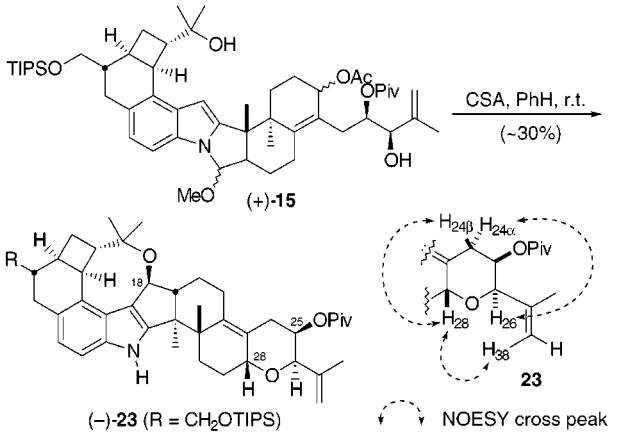


(7) (a) Smith, A. B., III; Nolen, E. G., Jr.; Shirai, R.; Blase, F. R.; Ohta, M.; Chida, N.; Hartz, R. A.; Fitch, D. M.; Clark, W. M.; Sprengeler, P. A. *J. Org. Chem.* **1995**, *60*, 7837. (b) Smith, A. B., III; Hartz, R. A.; Spoors, P. G.; Rainier, J. D. *Israel J. Chem.* **1997**, *37*, 69.

(8) The structural assignment to each new pure compound is in accord with its IR, ^{1}H and ^{13}C NMR, and high-resolution mass spectra.

To our delight exposure of (+)-**15** to CSA in benzene effected both the tandem Mannich cyclization−grammine fragmentation/addition cascade and tetrahydropyran ring formation to furnish what we initially assumed to be the desired nonacycle **14** (Scheme 7). Careful 2D-NOE analysis of the product, however, revealed that we had instead obtained (−)-**23**,[8] possessing the undesired stereochemistry at C(28).

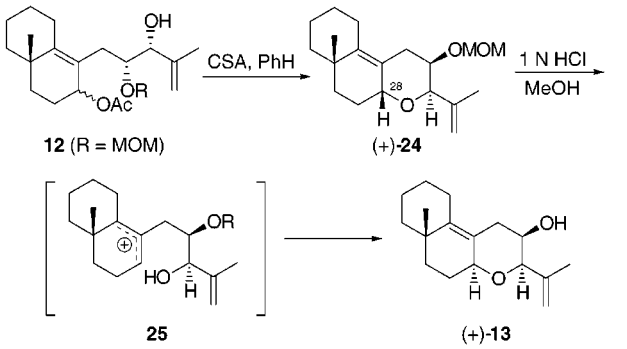
Scheme 7



The unexpected stereochemical outcome prompted us to reinvestigate model system **12**.[6] Although the structure of (+)-**13** had been established via X-ray crystallography, we discovered that the initial product of the acid-catalyzed cyclization of **12** was in fact the *trans*-pyran (+)-**24**[8] (Scheme 8). That is, the conditions employed to remove the MOM protecting group in (+)-**24** had led via isomerization to the *cis*-tetrahydropyran (+)-**13** presumably via cationic intermediate **25**. Unfortunately, all attempts to effect a similar isomerization of (−)-**23** to **14** employing 1 N HCl in MeOH proved unsuccessful due to the acid instability of the oxocane ring.

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

Scheme 8



In summary, we have demonstrated the viability of the tandem Mannich cyclization-grammine fragmentation/addition tactic, critical for our penitrem synthetic venture, with two advanced intermediates [(+)-**19** and (+)-**15**]. In both cases the A and F rings of the penitrem skeleton were elaborated in a highly stereoselective fashion. Although execution of this reaction cascade with concurrent construction of ring I afforded the undesired stereochemical outcome at C(28), the construction of three rings in one operation represents a milestone in our penitrem synthetic program. Studies directed toward the completion of the penitrem D program continue in our laboratory.

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Supporting Information Available: Spectroscopic and analytical data for compounds **13**, **15**, and **18**−**24** and selected experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

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