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AN END-GAME STRATEGY FOR CONSTRUCTION OF THE G-H-I RINGS OF PENITREM D, A TREMORGENIC INDOLE ALKALOID

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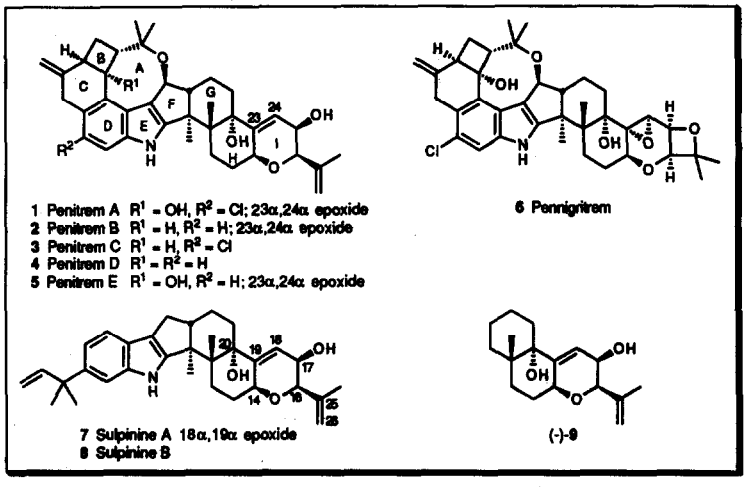
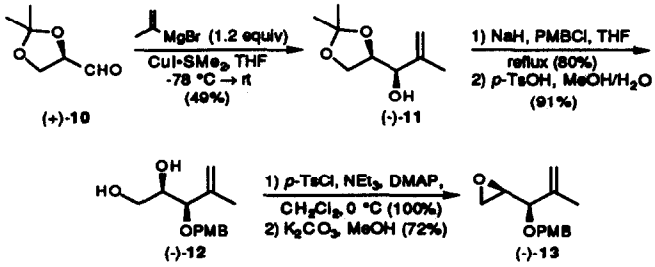
Summary: A synthetic approach to the G-H-I ring system of penitrem D has been developed in a model study. To generate the requisite carbon framework, the Stork protocol was utilized for coupling of a scalemic metalloenamine with an epoxide derived from D-glyceraldehyde. Pyran ring formation was then effected via BF_3•OEt_2-promoted cyclization of a δ-hydroxy allylic acetate.

The tremorgenic indole alkaloids embody unusual, architecturally complex polycyclic skeleta and also present distinctive biological profiles, inducing tremors in animals and possessing significant insecticidal activity.[1,2] Prominent members of the class include the penitrem tremorgenic mycotoxins (1-6), first isolated from *Penicillium crustosum*,[3] which cause severe neurological dysfunction in livestock, not unlike the symptoms observed in human disorders such as Wilson's disease and multiple sclerosis.[3e,4,5] Sulpinine A and B (7 and 8),[6] recently isolated from the sclerotia of *Aspergillus sulphureus*, share the terminal G-H-I ring substructures and 7 exhibits pronounced cytotoxicity toward human lung, breast, and colon carcinomas.[6] Our long-standing interest in the construction of the indole alkaloid tremorgens[7] has led to a penitrem D (4) synthetic venture.[8] Herein we describe an end-game strategy for penitrem D whereby we have prepared (-)-9, a model compound comprising the G-H-I ring system of 4.



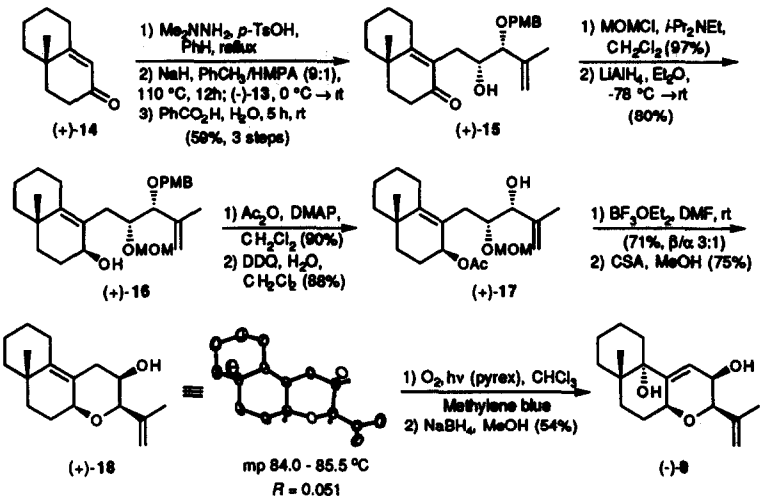
Wishing to exploit and extend an approach developed earlier,[7] we anticipated the use of a metalloenamine[9] as a nucleophilic H-ring synthon. Accordingly, we designed epoxide 13[10] to serve as an electrophilic progenitor of the pyran ring. Addition of the cuprate prepared from isopropenylmagnesium bromide to the acetonide derivative of D-glyceraldehyde [(+)-10][11] gave a 95:5 mixture of diastereomers (Scheme 1). After purification of (-)-11[12,13] by distillation, hydroxyl protection as the PMB ether and deketalization smoothly generated diol (-)-12.[13] The epoxide (-)-13[13] was then formed via tosylation of the primary alcohol and cyclization with potassium carbonate in methanol.

Scheme 1



With (-)-**13** in hand, we turned to the metalloenamine coupling with octalone (+)-**14**[14] (Scheme 2). Following the procedure of Stork,[9] the dimethyl hydrazone of (+)-**14** was deprotonated with sodium hydride in toluene/HMPA (9:1) at 110 °C. Addition of the epoxide (-)-**13** at 0 °C and careful hydrolysis[15] of the hydrazone then afforded (+)-**15**[13] in 59% overall yield. Previously we found that stringent deoxygenation of the reaction mixture was essential for successful coupling,[7h] but in this instance such precaution was not necessary. The hydroxyl group in (+)-**15** was next converted to the corresponding MOM ether and 1,2-reduction of the resultant ketone was attempted. Initially we intended to generate the α alcohol, permitting direct conversion to the desired pyran. In the event, however, a variety of reduction protocols [LAH, β/α 9:1; LAH/$AlMe_3$, 2.75:1; DIBAL-H, 1.3:1; DIBAL-H/$AlMe_3$, 3:1] furnished predominantly the β alcohol (+)-**16**.[13]

Scheme 2

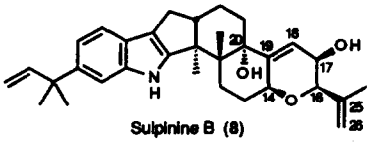
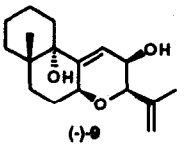


To take advantage of the observed selectivity, we sought to induce cyclization with double inversion [i.e., net retention of configuration at C(14)]; one attractive tactic involved the intermediacy of a π-allyl palladium complex.[16] To this end, acetylation of (+)-**16** and oxidative cleavage of the PMB ether with DDQ provided (+)-**17**[13] in excellent yield [80% for two steps, Scheme 2]. Unfortunately the cyclization required stringent conditions [$(PPh_3)_2PdCl_2$ (0.2 equiv), $(i\text{-}Pr)_2NEt$ (1.0 equiv), DMF, 150 °C, 12 h)] and furnished the desired pyran in low yield with poor stereoselectivity (30-40%, β/α 1.5:1). Upon further investigation, we discovered that Lewis acid-promoted cyclization of the allylic acetate in polar solvents led to significant improvements in both yield and selectivity. For example, exposure of (+)-**17** to $BF_3{\cdot}OEt_2$ (0.5 equiv) in DMF at

room temperature generated the pyran as a 3:1 mixture of β and α epimers in 71% yield; $TiCl_4$ (0.5 equiv) in DMF resulted in higher selectivity (5:1) but a lower yield (42%). Interestingly, this approach afforded similar yields and diastereomer ratios upon cyclization of the α epimer of allylic acetate (+)-17. Detailed studies of these reactions are in progress.

Following the successful elaboration of the pyran ring, completion of the synthesis of 9 entailed introduction of the C(20) hydroxyl substituent with olefin transposition as well as removal of the MOM ether (Scheme 2). The latter was effected with CSA in methanol; at this point the diastereomers were easily separable by flash chromatography, and the stereochemistry of (+)-18[13] was confirmed through the aegis of single-crystal X-ray analysis.[17] Oxidation of (+)-18 with $^1O_2$ (methylene blue sensitizer, $CHCl_3$) followed by $NaBH_4$ reduction of the intermediate hydroperoxide then afforded (-)-9 as the sole product. As shown in Table 1, the stereochemical assignment at C(20) is strongly supported by comparison with the ^1H and ^{13}C NMR data for sulpinine B (8). Our efforts to employ this end-game strategy in the total synthesis of penitrem D will be reported in due course.

Table 1. ^1H and ^{13}C NMR Comparisons of Sulpinine B (8) and (-)-9.[a]

	 Sulpinine B (8)		 (-)-9	
Carbon	^1H	^{13}C	^1H	^{13}C
14	4.61 (br dd, 9.1, 8.8 Hz)	73.7	4.52 (dd, 11.0, 6.9 Hz)	74.1
16	3.86 (br s)	79.1	3.87 (br s)	78.8
17	3.96 (br d, 5.6 Hz)	62.8	3.95 (dd, 5.8, 1.7 Hz)	62.9
18	5.82 (br d, 4.7 Hz)	118.7	5.82 (dd, 5.8, 1.7 Hz)	119.8
19	—	148.1	—	147.6
20	—	77.7	—	75.1
25	—	141.6	—	141.8
26	5.20 (br s) 5.03 (br s)	111.7	5.17 (br s) 5.02 (br s)	111.5

[a]Chemical shifts are reported in ppm. Data reported for sulpinine B[6] were recorded in $CDCl_3$ at 600 and 75.6 MHz. Data for (-)-9 were recorded in $CDCl_3$ at 500 and 125.7 MHz.

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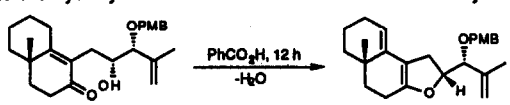
15. Overexposure of (+)-**15** to the hydrolysis conditions resulted in extensive dehydration, furnishing (+)-**I**.



(+)-**15** (+)-**I**

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