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Tremorgenic Indole Alkaloids. The Total Synthesis of (−)-Penitrem D

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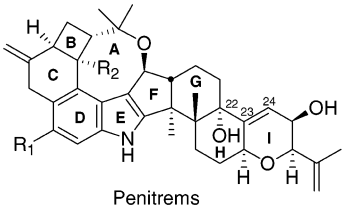
Abstract: A convergent, stereocontrolled total synthesis of the architecturally complex tremorgenic indole alkaloid (−)-penitrem D (**4**) has been achieved. Highlights of the synthesis include an efficient, asymmetric synthesis of the western hemisphere; the stereocontrolled assembly of the **I**-ring; discovery of a novel autoxidation to introduce the C(22) tertiary hydroxyl group, required for tremorgenic activity; union of fully elaborated eastern and western hemispheres, exploiting an indole synthetic protocol developed expressly for this purpose; and a late-stage, stereoselective construction of the **A** and **F** rings exploiting a $Sc(OTf)_3$–promoted reaction cascade. The longest linear sequence leading to (−)-penitrem D (**4**) was 43 steps.

Ergot fungi produce a wide variety of architecturally complex natural products possessing significant bioregulatory properties. Among these, the indole-diterpenes pose significant economic problems for the livestock industry.[1] Members of this family of environmental toxins are responsible for Dallisgrass poisoning (also called "paspalum staggers"),[1a] ryegrass staggers,[1b−d] and other related neurological disorders known to occur sporadically in the Southwest United States, Australia, and New Zealand. Domestic sheep and cattle that graze on ergot-infected grasses suffer from motion-induced tremors, limb weakness, ataxia, convulsions, and eventual death. Fortunately, the symptoms are reversible.[1] From the perspective of human disorders, the symptoms presented by the livestock are similar to those associated with Wilson's disease, multiple sclerosis, Parkinson's disease, and epilepsy and are thereby suggestive of a possible common neurochemical mechanism.[2]

In addition to like biological profiles, the indole-diterpenes share common architectural features, the signature elements being an indole core, biosynthetically derived from tryptophan; a diterpene framework arising from mevalonate; and the *trans* vicinal quaternary methyl substituents.[3] Among the indole tremorgens, the penitrems [A−F (**1**−**6**)] represent the most complex members of the indole-diterpene alkaloid family.



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

Penitrem A was first isolated by Wilson and co-workers in 1968 from the ergot fungus *Penicillium cyclopium*.[4a] Subsequently, Steyne and co-workers reported the complete structures of the penitrems, isolated from the closely related *Penicillium crustosum*.[3b,c,4b,c] The absolute configuration was established by the partial resolution method of Horeau.[5] To date, no X-ray structures have been achieved, although we and others have attempted to obtain suitable crystals. Importantly, all six

(1) (a) Cole, R. J.; Dorner, J. W.; Lansden, J. A.; Cox, R. H.; Pape, C.; Cunfer, B.; Nicholson, S. S.; Bedell, D. M. *J. Agric. Food Chem.* **1977**, *25*, 1197−1201. (b) Mantle, P. G.; Mortimer, P. H.; White, E. P. *Res. Vet. Sci.* **1978**, *24*, 49−56. (c) di Menna, M. E.; Mantle, P. G. *Res. Vet. Sci.* **1978**, *24*, 347−351. (d) Mantle, P. G.; Day, J. B.; Haigh, C. R.; Penny, R. H. *Vet. Rec.* **1978**, *103*, 403. (e) Springer, J. P.; Clardy, J. *Tetrahedron Lett.* **1980**, *21*, 231−234. (f) Gallagher, R. T.; Clardy, J.; Wilson, B. J. *Tetrahedron Lett.* **1980**, *21*, 239−242. (g) Dorner, J. W.; Cole, R. J.; Cox, R. H.; Cunfer, B. M. *J. Agric. Food Chem.* **1984**, *32*, 1069−1071.

(2) Brimblecombe, R. W.; Pinder, R. M. *Tremorgens and Tremorgenic Agents*; Scientechnia; Bristol, U.K., 1972; pp 14−15.

(3) (a) Acklin, W.; Weibel, F.; Arigoni, D. *Chimia* **1977**, *31*, 63. (b) de Jesus, A. E.; Hull, W. E.; Steyn, P. S.; van Heerden, F. R.; Vleggaar, R.; Wessels, P. L. *J. Chem. Soc., Chem. Commun.* **1982**, 837−838. (c) de Jesus, A. E.; Gorst-Allman, C. P.; Steyn, P. S.; van Heerden, F. R.; Vleggaar, R.; Wessels, P. L.; Hull, W. E. *J. Chem. Soc., Perkin Trans. 1* **1983**, 1863−1868.

(4) (a) Wilson, B. J.; Wilson, C. H.; Hayes, A. W. *Nature* **1968**, *220*, 77−78. (b) de Jesus, A. E.; Steyn, P. S.; van Heerden, F. R.; Vleggaar, R.; Wessels, P. L.; Hull, W. E. *J. Chem. Soc., Chem. Commun.* **1981**, 289−291. (c) de Jesus, A. E.; Steyn, P. S.; van Heerden, F. R.; Vleggaar, R.; Wessels, P. L.; Hull, W. E. *J. Chem. Soc., Perkin Trans. 1* **1983**, 1847−1856.

(5) (a) Horeau, A. *Tetrahedron Lett.* **1961**, 506−512. (b) Horeau, A.; Sutherland, J. K. *J. Chem. Soc., Org.* **1966**, 247−248. (c) Herz, W.; Kagan, H. B. *J. Org. Chem.* **1967**, *32*, 216−218.

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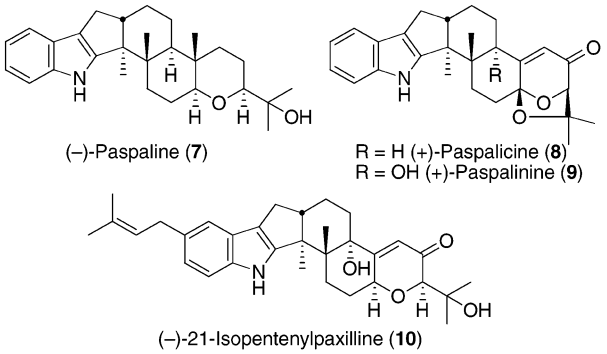
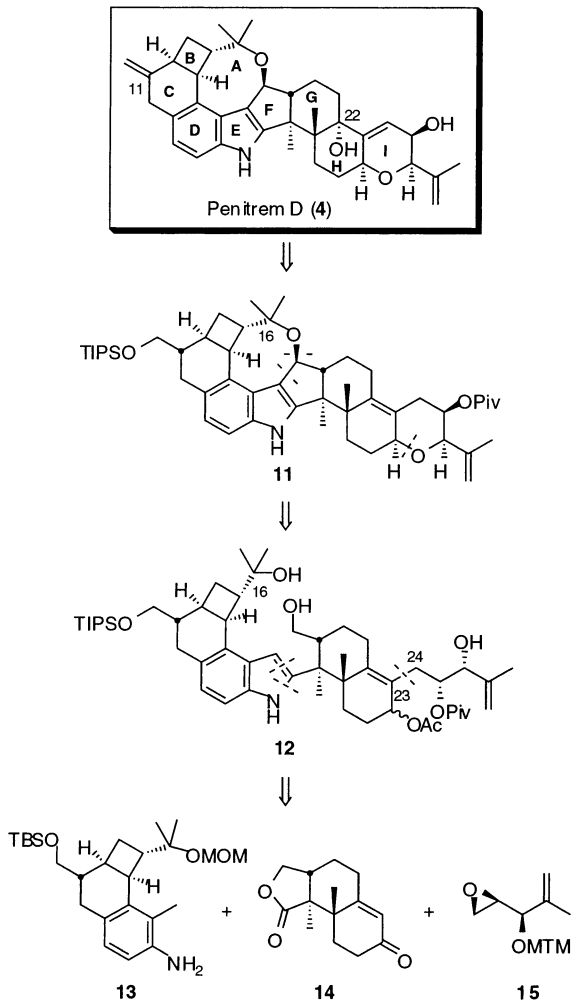
penitrems bear a tertiary hydroxyl at C(22), the requisite structural element required for the neurotoxicity.[1g] Penitrem D (**4**), the simplest member of the penitrem class, also possesses a cyclobutane ring and an eight-membered oxocane cyclic ether, but is devoid of the epoxide and chlorine substituents found in the more complex members of the penitrem family.

The structural complexity of the indole diterpenes, in conjunction with their tremorgenic activity, first captured our attention in the early 1980s and has since led to the first total syntheses of (−)-paspaline (**7**),[6a,b] (+)-paspalicine (**8**),[6c,d] (+)-paspalinine (**9**),[6c,d] and quite recently (−)-21-isopentenylpaxilline (**10**).[6e] Armed with this experience, we embarked on the total synthesis of (−)-penitrem D (**4**). Several strategies were explored.[6f−n] Herein, we describe a full account of this program, which culminated in the first, and to date only, total synthesis of a member of the penitrem family.[6n,7]



Initial Synthetic Plan. From the outset we desired a convergent approach (Scheme 1). Retrosynthetically this entailed removal of the C(22) hydroxyl and refunctionalization of the C(11)-*exo* olefin to afford advanced intermediate **11**, which we envisioned could serve as a common precursor for members of the penitrem family. For this plan to be successful, a viable tactic would be required to introduce the C(22) hydroxyl. Continuing this analysis, opening of the tetrahydropyran, the oxocane, and the **F** rings next led to a 2-substituted indole (**12**), which could be further dissected to reveal three subtargets (**13**, **14**, and **15**). In the synthetic direction, the 2-substituted indole (**12**) was anticipated to arise via union of a benzylic anion generated from **13** with an electrophile such as lactone **14**, followed by ring closure. Rings **A** and **F** would then be constructed via oxidation of the primary hydroxyl to an aldehyde, execution of an intramolecular cyclization to furnish ring **F** and in turn a gramine-like fragmentation and capture by

Scheme 1



the C(16) hydroxyl to complete ring **A**.[8] We reasoned that this cascade of reactions might be possible in one operation. The requisite eastern hemisphere **14**, known as the Nolen-Sprengeler lactone,[6k,l] was readily available in our laboratory, having been designed as a common advanced intermediate for the synthesis of several indole-diterpene tremorgens.[9] To construct the **I** ring, we anticipated attachment of the C(24) side chain via a Stork metalloenamine alkylation[10] of the hydrazone derived from **14** with epoxide **15**. Stereocontrolled cyclization would then generate the tetrahydropyran.[11] At the outset, the precise order of indole construction and elaboration of the **I** ring was unclear. As will be presented, this flexibility of strategic events would prove central to the eventual successful completion of the penitrem D synthesis.

To implement this synthetic plan, we required (1) a viable 2-substituted indole synthesis; (2) methods to construct the **A**, **F**, and **I** rings; and (3) a protocol to insert the C(22) hydroxyl. Although preliminary accounts describing these methods have appeared,[6f−n] their critical importance to the overall development of the penitrem D program demands their brief introduction here.

(6) (a) Smith, A. B., III; Mewshaw, R. *J. Am. Chem. Soc.* **1985**, *107*, 1769−1771. (b) Mewshaw, R. E.; Taylor, M. D.; Smith, A. B., III. *J. Org. Chem.* **1989**, *54*, 3449−3462. (c) Smith, A. B., III; Sunazuka, T.; Leenay, T. L.; Kingery-Wood, J. *J. Am. Chem. Soc.* **1990**, *112*, 8197−8198. (d) Smith, A. B., III; Kingery-Wood, J.; Leenay, T. L.; Nolen, E. G.; Sunazuka, T. *J. Am. Chem. Soc.* **1992**, *114*, 1438−1449. (e) Smith, A. B., III; Cui, H. *Org. Lett.* **2003**, *5*, 587−590. (f) Smith, A. B., III; Visnick, M. *Tetrahedron Lett.* **1985**, *26*, 3757−3760. (g) Smith, A. B., III; Visnick, M.; Haseltine, J. N.; Sprengeler, P. A. *Tetrahedron* **1986**, *42*, 2957−2969. (h) Haseltine, J.; Visnick, M.; Smith, A. B., III. *J. Org. Chem.* **1988**, *53*, 6160−6162. (i) Smith, A. B., III; Haseltine, J. N.; Visnick, M. *Tetrahedron* **1989**, *45*, 2431−2449. (j) Smith, A. B., III; Ohta, M.; Clark, W. M.; Leahy, J. W. *Tetrahedron Lett.* **1993**, *34*, 3033−3036. (k) Smith, A. B., III; Nolen, E. G.; 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*, 7837−7848. (l) Smith, A. B., III; Hartz, R. A.; Spoors, P. G.; Rainier, J. D. *Isr. J. Chem.* **1997**, *37*, 69−80. (m) Smith, A. B., III; Kanoh, N.; Minakawa, N.; Rainier, J. D.; Blase, F. R.; Hartz, R. A. *Org. Lett.* **1999**, *1*, 1263−1266. (n) Smith, A. B., III; Kanoh, N.; Ishiyama, H.; Hartz, R. A. *J. Am. Chem. Soc.* **2000**, *122*, 11254−11255.

(7) Rivkin, A.; Nagashima, T.; Curran, D. P. *Org. Lett.* **2003**, *5*, 419−422.

(8) For examples of gramine-type fragmentations, see: Brewster, J. H.; Eliel, E. L. *Org. React.* **1953**, *VII*, 99−197.

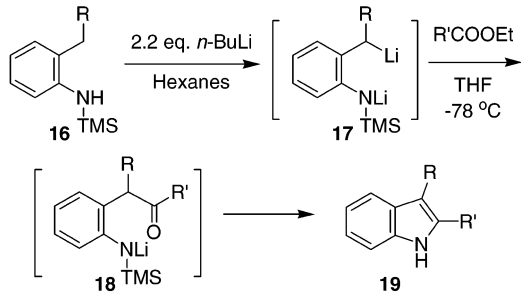
(9) Lactone (+)-**14** can be prepared from commercially available (−)-Wieland−Miescher ketone in 16 steps and 8% overall yield.

(10) (a) Stork, G.; Benaim, J. *J. Am. Chem. Soc.* **1971**, *93*, 5938−5939. (b) Stork, G.; Benaim, J. *Org. Synth.* **1977**, *57*, 69−72.

(11) A similar protocol had also proven effective in our paspalicine and paspalinine synthetic ventures.

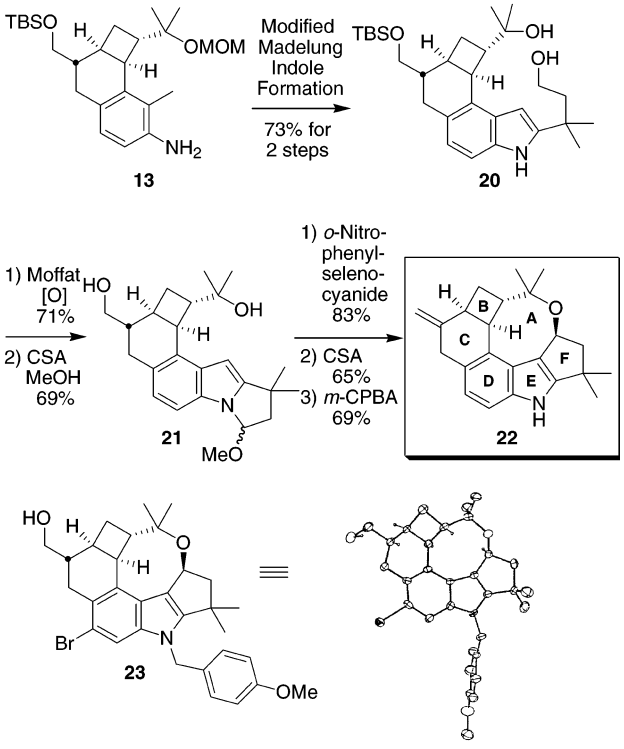
New Indole Synthesis, Model Studies to Construct the A, F, and I Rings, and a Protocol to Introduce the C(22) Hydroxyl. Since the earliest annals of natural products chemistry, bioactive indole alkaloids have evoked enormous interest in the development of new synthetic approaches to the indole ring.[12] In 1985, based on the above penitrem D synthetic scenario, we designed an expedient method for the regiospecific synthesis of mono- and disubstituted indoles (Scheme 2).[6f,g] This protocol involves treatment of *N*-trimethylsilyl-*o*-toluidine or a related derivative with 2.2 equiv of *n*-BuLi to generate the lithium dianion **17**, which upon acylation with either esters or lactones leads to an intermediate (**18**) capable of intramolecular heteroatom Peterson olefination[13] to furnish the desired substituted indole **19**; yields are in general good (50−98%).

Scheme 2



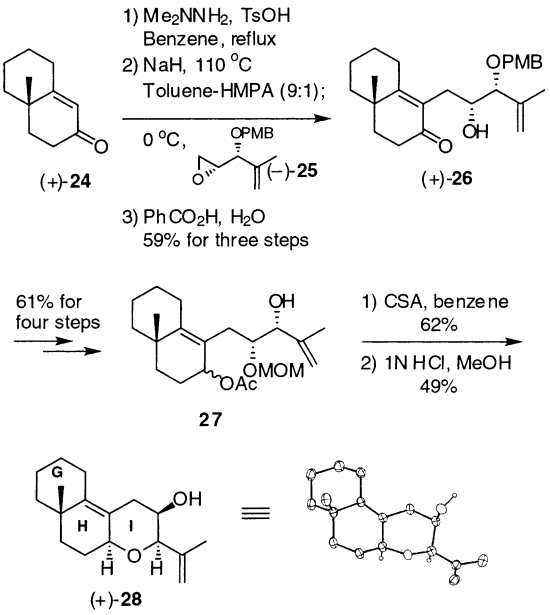
To test the feasibility of constructing the **A** and **F** rings in a single operation via a cyclization-gramine-like fragmentation-cyclization cascade, we selected the **ABCDEF** hexacycle **22** in racemic form as an early target.[6h,i] Indole **20** was therefore prepared from aniline **13**,[6h] oxidized to the corresponding aldehyde, and subjected to camphorsulfonic acid in methanol (Scheme 3). The resultant mixed methyl aminal **21** was next converted to the *o*-nitroselenide,[14] treated with camphorsulfonic acid in benzene, and subjected to oxidative-elimination of the seleno group.[15] Pleasingly, the hexacyclic **ABCDEF** analogue of penitrem D (e.g., **22**), possessing spectroscopic data that correlated well with that of (−)-penitrem D (**4**), was obtained in 38% for the three steps. Structural confirmation of **22** was achieved by single-crystal X-ray analysis of the bromo derivative **23**.

Scheme 3



To model a possible tactic for elaboration of the **I** ring of penitrem D, we prepared acetate **27** (Scheme 4), exploiting the Stork metalloenamine alkylation of the hydrazone[10] derived from (+)-**24** with epoxide (−)-**25**.[6j] Camphorsulfonic acid-promoted cyclization, followed by removal of the MOM group with 1 M HCl in methanol, provided *cis*-tetrahydropyran (+)-**28**, along with what was thought to be the minor *trans* isomer (ca. 3.4:1). The structure of (+)-**28** was again secured by X-ray crystallographic analysis.

Scheme 4



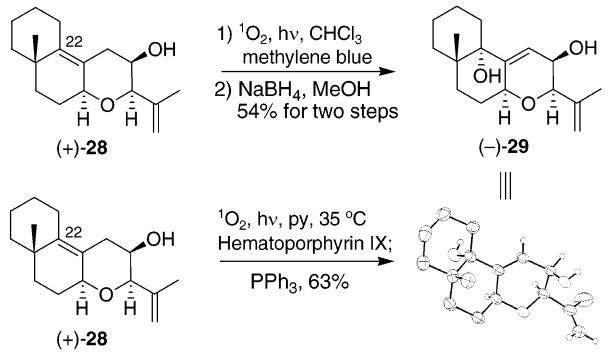
The fact that formation of the **A** and **F** rings in **22** and the **I** ring in (+)-**28** proceeded with good stereoselectivity fortuitously under the identical *mild* acidic conditions (i.e., camphorsulfonic acid/benzene) proved highly seductive, suggesting the intriguing possibility of a combined "one-flask" **A**, **F**, and **I** ring construction.[16] As will become apparent, this prospect markedly influenced the evolution of the penitrem D synthetic program.

The remaining synthetic issue prior to committing to the penitrem D venture concerned installation of the C(22) hydroxyl. A third model study was performed.[6j] Oxidation of (+)-**28** with singlet oxygen employing methylene blue as sensitizer in

(12) For a review on the synthesis of indole derivatives, see: Sundberg, R. J. *Indoles*; Academic Press Inc.: San Diego, 1996.
(13) Krüger, C.; Rochow, E. G.; Wannagat, U. *Chem. Ber.* **1963**, *96*, 2132−2137.
(14) Grieco, P. A.; Gilman, S.; Nishizawa, M. *J. Org. Chem.* **1976**, *41*, 1485−1486.
(15) Sharpless, K. B.; Young, M. W. *J. Org. Chem.* **1975**, *40*, 947−949.
(16) This cascade of reactions is affectionately referred to as the "Shazam" approach, a term to the best of our knowledge first employed by Eaton to describe unsuccessful attempts by several research groups to effect the Lewis acid-promoted isomerization of $C_{20}H_{20}$ and $C_{22}H_{24}$ polycycloalkanes to dodecahedrane and dimethyl dodecahedrane, see: Eaton, P. E. *Tetrahedron* **1979**, *35*, 2189−2223, and references therein.

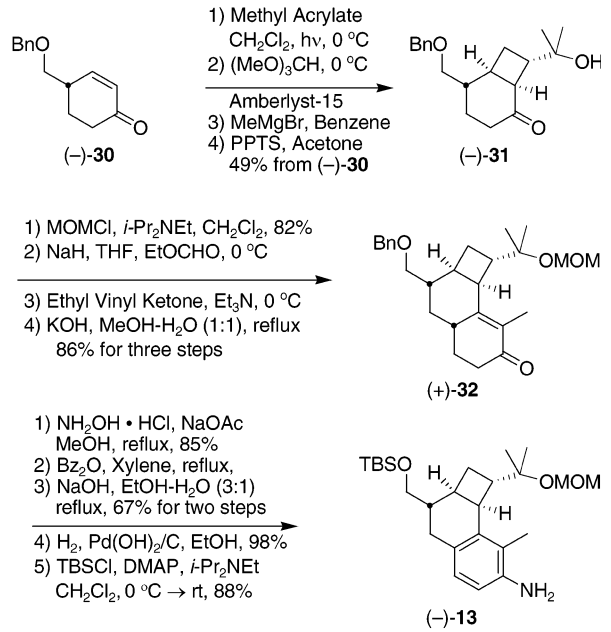
$CHCl_3$, followed by $NaBH_4$ reduction of the resulting hydroperoxide, furnished (−)-**29** (54% yield, two steps), as the sole isolable product (Scheme 5). The yield for this transformation could be improved to 63% using the sensitizer hematoporphyrin IX, in pyridine, followed by reduction with PPh_3 prior to isolation.[17] The stereogenicity of the newly generated hydroxyl was again secured by single-crystal X-ray analysis.

Scheme 5



Initiation of the Penitrem Synthetic Venture: Construction of Western Aniline (−)-13. Having achieved experimental support for the strategic transformations required by our synthetic plan, we initiated work on (−)-penitrem D (**4**) with the synthesis of **13** possessing the requisite absolute stereochemistry (Scheme 6), employing a sequence essentially identical to that of our earlier racemic synthesis of **13**, which was used to access the **ABCDEF** model **22**.[18] Highlights of this sequence include an effective four-step photochemical generation of (−)-**31** from (−)-**30**,[6k] which proceeded in 49% overall yield, a Woodward−Wilds[19] modification of the Robinson annulation to append the carbon skeleton for ring **D**, and a

Scheme 6

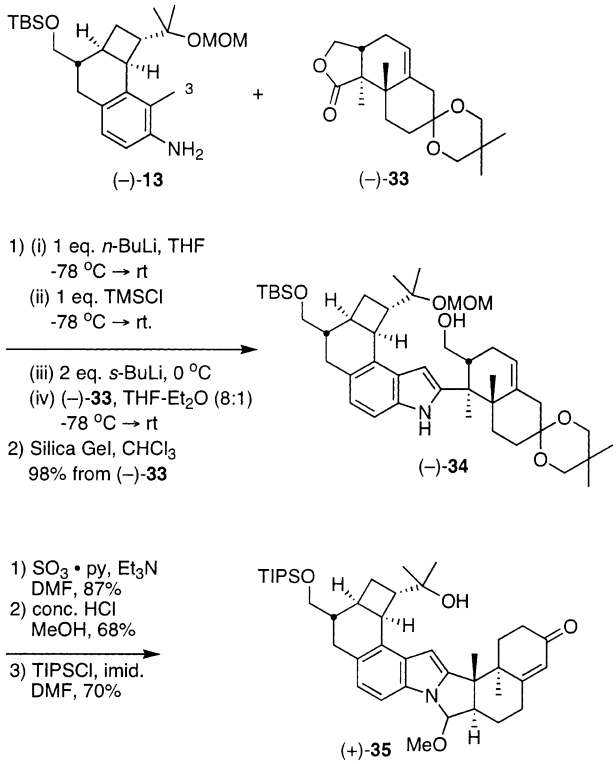


(17) See the Supporting Information for the experimental procedure.
(18) Hartz, R. A. Ph.D. Thesis, University of Pennsylvania, 1996.
(19) (a) Shunk, H.; Wilds, A. L. *J. Am. Chem. Soc.* **1949**, *71*, 3946−3950. (b) Woodward, R. B.; Sondheimer, F.; Taub, D.; Heusler, K.; McLamore, W. M. *J. Am. Chem. Soc.* **1952**, *74*, 4223−4251.

Semmler−Wolff aniline aromatization.[20] The sequence proved highly efficient, requiring 13 steps and furnishing (−)-**13** in 17% overall yield.

Union of the Eastern and Western Hemispheres and Elaboration of an ABCDEFGH Octacyclic Model. With both aniline (−)-**13** and the protected Nolen−Sprengeler lactone (−)-**33**[6k,l] in hand, we explored their union via the aforementioned indole synthesis (Scheme 7).[6m] Treatment of the *N*-silylated derivative of (−)-**13** with 2 equiv of *s*-BuLi, followed by addition of lactone (−)-**33** and work up involving exposure of the intermediate product to silica gel, provided indole (−)-**34** in near quantitative yield.[21] Parikh−Doering oxidation[22] of the primary hydroxyl, and in turn treatment with methanolic HCl to remove simultaneously the hydroxyl protecting groups and ketal, and then selective reinstallation of the TIPS silyl group furnished (+)-**35** as a single isomer (stereochemistry undefined) in 41% yield for three steps.

Scheme 7

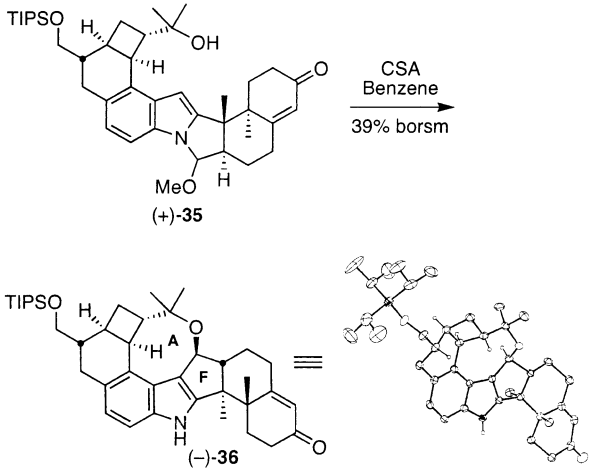


At this juncture, we decided to evaluate the tandem **AF** ring construction tactic with the more complex substrate (+)-**35**. An alternative would have been to introduce the **I** ring first (vide infra). As in the earlier model study, treatment with camphorsulfonic acid in benzene furnished the octacyclic enone (−)-**36** in 39% yield based on recovered (+)-**35** (Scheme 8). The structure of (−)-**36** was confirmed by X-ray crystallography.

"One-Pot" Formation of the A, F, and I Rings. Having achieved access to the advanced **ABCDEFGH** model system [(−)-**36**], we turned to the possibility of the "one-pot" construc-

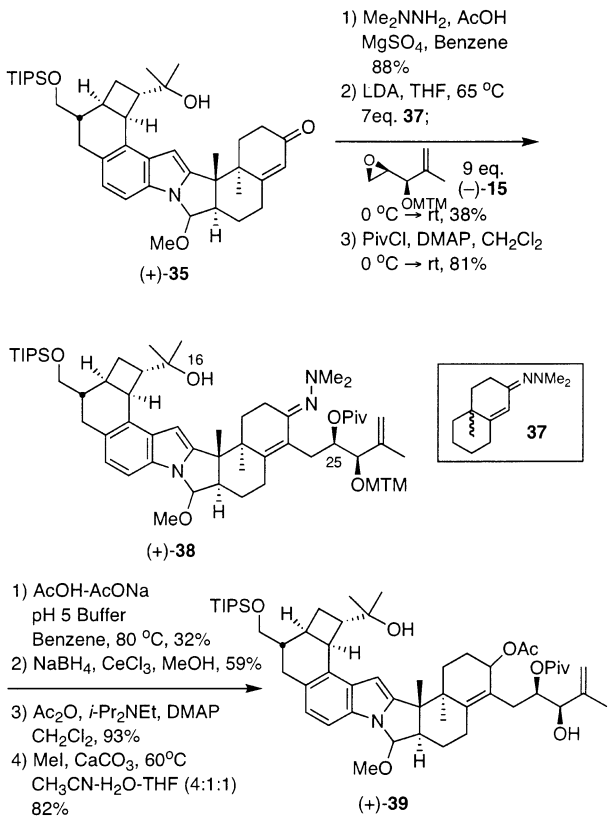
(20) (a) Semmler, W. *Chem. Ber*. **1892**, *25*, 3352−3354. (b) Wolff, L. *Annalen* **1902**, *322*, 351−391. (c) For a review of the transformation, see: Conley, R. T.; Chosh, S. In *Mechanism of Molecular Migrations*; Thyagarajin, B. S., Ed.; Interscience: New York, 1971; Vol. 4, pp 251−308.
(21) With the fully elaborated coupling partners, the heteroatom Peterson olefination did not go to completion without external promoters such as silica gel or heating; see also ref 6e.
(22) Parikh, J. R.; Doering, W. E. *J. Am. Chem. Soc.* **1967**, *89*, 5505−5507.

Scheme 8



tion of the **A**, **F**, and **I** rings. Stork metalloenamine alkylation[10] of the dimethylhydrazone derived from (+)-**35** with epoxide (−)-**15** as the electrophile (Scheme 9), followed by protection of the newly generated hydroxyl (PivCl, DMAP), furnished (+)-**38**, albeit in 27% yield for the three steps.[23] In our hands, a particularly troubling (and recurring) aspect of the Stork protocol is the necessity to carry out the reaction on a reasonable scale

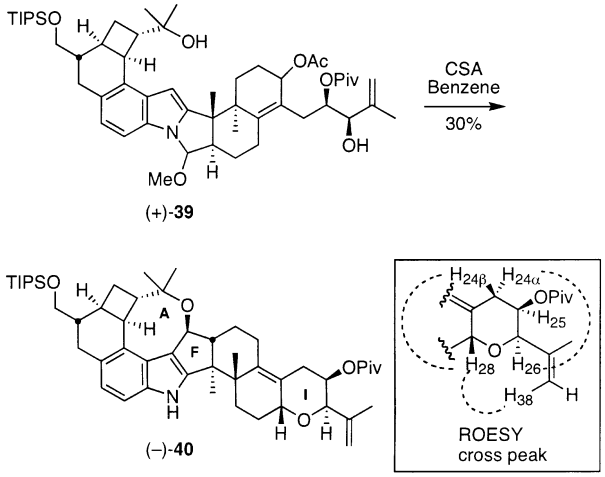
Scheme 9



when advanced (+)-**35** was in limited supply. To circumvent this problem, we added the readily available auxiliary hydrazone **37**.[6j] We surmised that the auxiliary hydrazone would also facilitate anion equilibration, required for successful Stork metalloenamine alkylation. The use of **37** did improve the yield of (+)-**38** to 38%.[24] Hydrolysis of the hydrazone, followed in turn by reduction of the enone, acetylation of the resultant alcohol, and removal of the MTM group, then furnished (+)-**39**, embodying the complete carbon skeleton and functionality required to attempt the proposed **A**, **F**, and **I** ring construction in a single operation.[25]

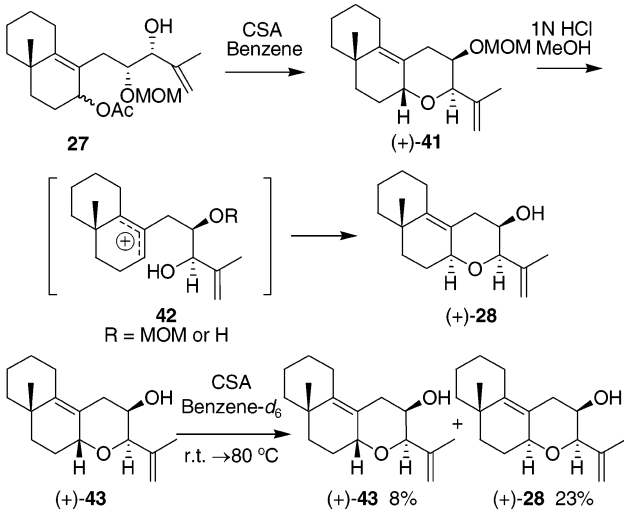
Initial observations were encouraging. Treatment of (+)-**39** with camphorsulfonic acid in benzene did indeed result in the required reaction cascade, furnishing the **A** and **F** rings, *and* in the formation of the tetrahydropyran **I** ring (Scheme 10). The stereochemical outcome was, of course, the question. After extensive NMR analysis, we were forced to conclude that, although formation of rings **A** and **F** had proceeded correctly, as predicted by model (−)-**36**, the stereogenicity at C(28) in the **I** ring was incorrect vis-à-vis the penitrem skeleton. This result was clearly unexpected given the earlier successful **I** ring model study (see Scheme 4).[6m]

Scheme 10



The I Ring Model Study Revisited. After considerable analysis, we recognized that the major product obtained by initial treatment of model **27** (ca. 3.4:1 mixture) with camphorsulfonic acid was not the desired *cis*-tetrahydropyran (Scheme 11), but instead the *trans* isomer (+)-**41**, the result of a kinetically

Scheme 11

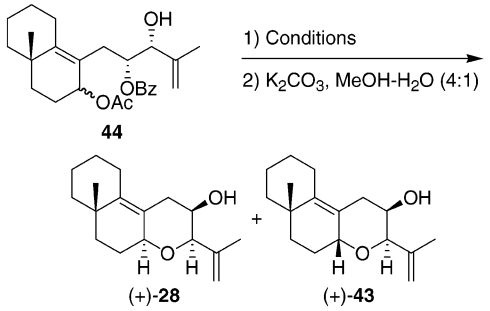


(23) Attempts to use a MOM protecting group at C(25) as in the earlier model study failed due to our inability to differentiate the secondary and tertiary hydroxyls at C(25) and C(16), respectively.

controlled cyclization, and that (+)-**28**, the thermodynamically more stable isomer, for which we had structural confirmation by X-ray analysis, had arisen during the 1 N HCl treatment to remove the MOM protecting group. This scenario was easily confirmed both by conversion of (+)-**43** to the corresponding MOM ether (+)-**41** and by isomerization of (+)-**43** to (+)-**28** monitored by NMR.[26] Unfortunately, all attempts to effect a similar isomerization of the advanced penitrem D **ABCDEF-GHI** nonacycle [(−)-**40**] to access the correct penitrem core (**11**), via HCl treatment, proved unsuccessful due to the inherent acid lability of the **A** ring oxocane.

Given the critical nature of the required isomerization, we thought it prudent to explore other solvent and acid systems. Again, initial studies proved encouraging. Treatment of **44** with a catalytic amount of several acids including the Grieco solvent system[27] (Table 1), followed by removal of the benzoyl moiety,

Table 1. Tetrahydropyran Formation

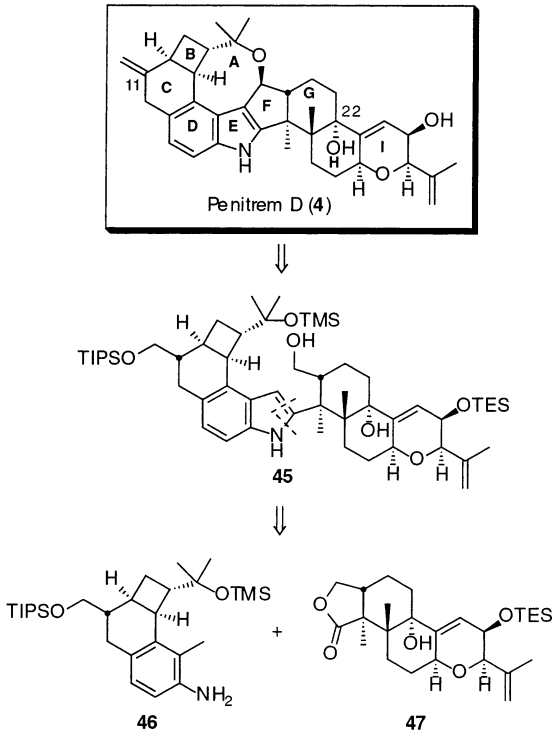


entry	conditions	yield for two steps
1	0.25 equiv CSA, benzene, 4 h	52% (1:1)
2	3 M $LiClO_4$−Et_2O, 5 °C → rt, 23 h	no reaction
3	0.01 equiv AcOH, 3 M $LiClO_4$−Et_2O, 5 °C → rt, 18 h	85% (1:1)
4	0.01 equiv CSA, 3 M $LiClO_4$−Et_2O, 5 °C → rt, 16 h	88% (8:1)
5	0.01 equiv $HClO_4$, 3 M $LiClO_4$−Et_2O, 0 °C → rt, 1.5 h	84% (13:1)

furnished (+)-**28**. The highest level of selectivity for the desired *cis*-tetrahydropyran (+)-**28** (ca. 13:1) was obtained with 0.01 equiv of $HClO_4$. These conditions however failed to generate the requisite **A** and **F** rings with (+)-**35**. Taken together these results forced the conclusion that construction of the **A**, **F**, and **I** rings, employing a single set of reaction conditions, would not be feasible and that independent approaches to the **A**, **F**, and **I** ring systems would have to be achieved. The successful construction of the three rings in (−)-**40** nonetheless was taken as a milestone in our penitrem D venture.

Penitrem D: A Revised Synthetic Plan. To preserve the convergent strategy, we chose to move the **AF** ring construction tactic that had proven so successful in the early model studies[6h,i,m] to late in the synthetic sequence. This strategic reorganization suggested **45** (Scheme 12), possessing a prein-

Scheme 12

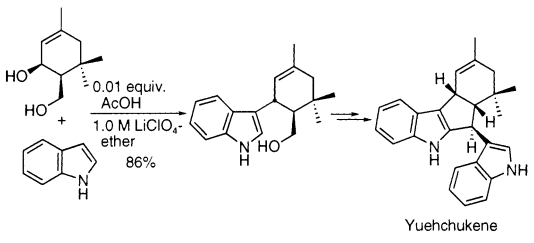


stalled tetrahydropyran **I** ring, to be a more viable advanced intermediate. A similar 2-substituted indole synthesis employing western hemisphere aniline **46**, with a fully elaborated eastern hemisphere **47**, would then be required.

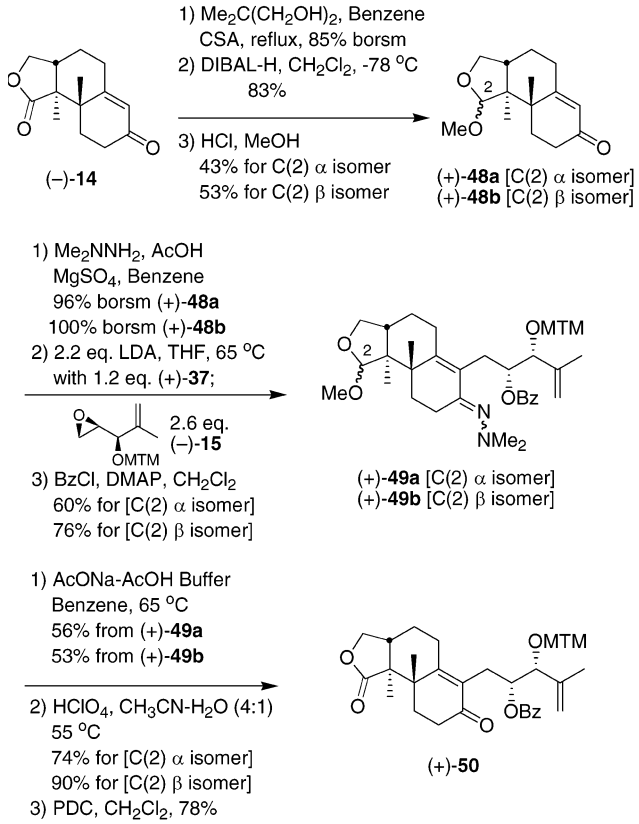
A Second-Generation Eastern Hemisphere (47). To generate **47**, we first explored installation of the C(23) side chain onto the now familiar Nolen−Sprengeler lactone (−)-**14**,[6k,l] again via a Stork metalloenamine alkylation.[10] The lactone moiety however precluded direct Stork alkylation with epoxide (−)-**15**. Lactone (−)-**14** was therefore converted to a mixture of acetals (+)-**48a** and (+)-**48b** via a three-step sequence (Scheme 13). The acetals, after separation, were individually converted to the corresponding dimethyl hydrazones. Stork metalloenamine alkylation with epoxide (−)-**15**, employing again the auxiliary hydrazone (+)-**37**,[6j] followed by benzoylation of the derived hydroxyls led to (+)-**49a** and -**b**. In this case the yields were somewhat improved to 58% and 76% respectively, compared to (+)-**38** (see Scheme 9). Hydrolysis of both the hydrazones and methyl acetals in turn, followed by PDC oxidation, furnished lactone (+)-**50**. For the purposes of material advancement, the overall sequence could, of course, be carried forward with the mixture of **48a** and **48b**.

To elaborate the **I** ring, we explored the conditions that had proven successful with model system **44** (vide supra). Lactone **51** was prepared from (+)-**50** by 1,2-reduction of the enone,

(24) Without the auxiliary hydrazone **37**, we were unable to detect the desired coupling product between (+)-**35** and (−)-**15**.
(25) Intermediates (+)-**38** and (+)-**39** were both single isomers; the stereochemistry was not determined.
(26) Heating (e.g., 80 °C) was required for isomerization in benzene due to the lower polarity of the solvent compared to that of methanol. Due to the overlap of signals from residual MeOH, water, and compounds (+)-**43** and (+)-**28**, we decided to utilize benzene-d_6 instead of CD_3OD.
(27) Grieco and co-workers exploited these conditions in an elegant synthesis of yuehchukene, see: (a) Grieco, P. A.; Clark, J. D.; Jagoe, C. T. *J. Am. Chem. Soc.* **1991**, *113*, 5488−5489. (b) Henry, K. J., Jr.; Grieco, P. A. *J. Chem. Soc., Chem. Commun.* **1993**, 510−512.

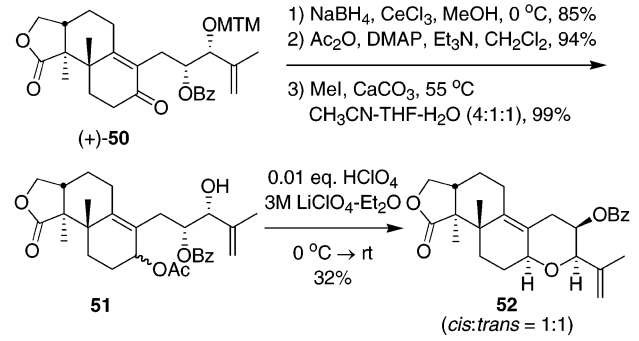


Scheme 13



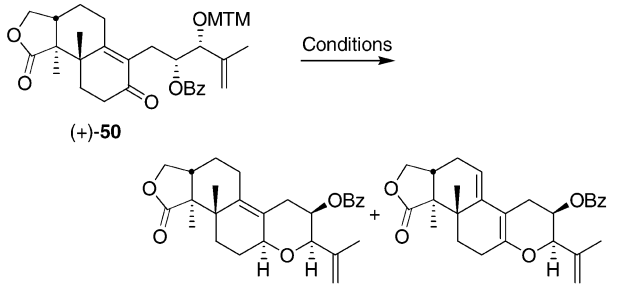
acetylation of the resultant hydroxyl, and removal of the MTM protecting group (Scheme 14). Treatment of **51** with $HClO_4$ (0.01 equiv) in 3 M $LiClO_4$−ether furnished a mixture of *cis*- and *trans*-tetrahydropyrans **52**. Unfortunately, the yield (32%) and stereoselectivity (*cis*:*trans* = 1:1) of the ring closure proved incommensurate with material advancement.[28] Clearly, an alternate approach to the **I** ring was required.

Scheme 14



In 1989 Nicolaou reported an elegant synthesis of oxepanes via reductive cyclization of simple hydroxy ketones through the intermediacy of an oxonium ion.[29] The conditions of choice were Et_3SiH and TMSOTf. That complete *syn* diastereoselectivity was observed was of considerable significance. To implement this tactic, we first removed the MTM protecting group in (+)-**50** (Table 2; entry 1) and then subjected the resultant alcohol to the conditions of TMSOTf and Et_3SiH; surprisingly diene (−)-**53**, the product of elimination, as opposed to silane reduction was the exclusive product. Replacement of TMSOTf with TfOH led to the desired *cis*-tetrahydropyran (+)-**52** in 38% yield for the two steps, albeit still accompanied by the diene in 45% yield (entry 2). Importantly, none of the *trans*-isomer was observed. A one-pot procedure comprising MTM removal, cyclization, and silane reduction proved feasible with Et_3SiH−TfOH, to furnish a mixture (1:1.8) of (+)-**52** and (−)-**53**, respectively (entry 3). Although we could transform (−)-**53** to (+)-**52** in 35% yield [82% yield based on recovered (−)-**53**],[30] employing the same Et_3SiH−TfOH conditions, we sought further optimization. Eventually, use of toluene as solvent in place of CH_2Cl_2, with careful control of reaction temperature, proved effective, furnishing the *cis*-tetrahydropyran (+)-**52** in 60% yield.

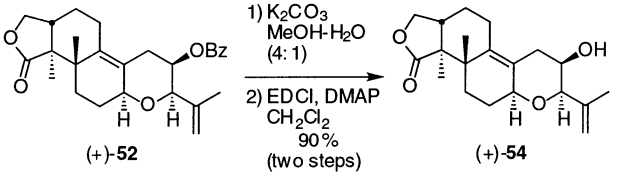
Table 2. Reductive Cyclization Leading to (+)-**52**



entry	conditions	yield (%) (+)-**52**	yield (%) (–)-**53**
1	(1) MeI, $CaCO_3$, CH_3CN−THF−H_2O (4:1:1), 55 °C (2) 1.2 equiv TMSOTf, 9.7 equiv Et_3SiH, CH_2Cl_2, 0 °C	0	82
2	(1) MeI, $CaCO_3$, CH_3CN−THF−H_2O (4:1:1), 55 °C (2) 4.8 equiv TfOH, Et_3SiH−CH_2Cl_2 (1:1), 0 °C	38	45
3	4.9 equiv TfOH, Et_3SiH−CH_2Cl_2 (1:1), −78 °C → −20 °C	35	63
4	8.4 equiv TfOH, Et_3SiH−toluene (1:1), −40 °C → rt	60	0

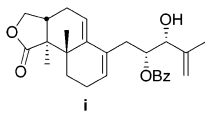
To complete construction of the advanced lactone (+)-**54**, the benzoyl group was removed (methanolic K_2CO_3), followed by regeneration of the partially hydrolyzed lactone with 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI);[31] the overall yield for the two steps was 90% (Scheme 15).

Scheme 15



Introduction of the C(22) Hydroxyl. Having arrived at the complete carbon skeleton of the eastern hemisphere, we turned to introduce the C(22) hydroxyl employing the photo-oxidation

(28) The major byproduct was a diene **i** (32% yield).

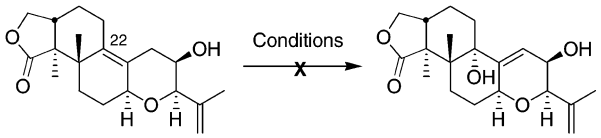


i

(29) Nicolaou, K. C.; Hwang, C.-K.; Nugiel, D. A. *J. Am. Chem. Soc.* **1989**, *111*, 4136−4137.

conditions developed with model (+)-**28** (see Scheme 5). Unfortunately, all attempts to achieve this transformation with the advanced system (+)-**54** proved totally unrewarding (Table 3). We speculate, as illustrated, that the vicinal quaternary

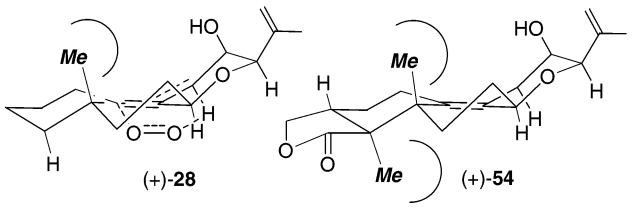
Table 3. Photo-Oxidation of (+)-**54**



(+)-**54** **55**

entry	conditions
1	$^1O_2$, *hν*, py, 35 °C, hematoporphyrin IX; PPh_3
2	$^1O_2$, *hν*, benzene, reflux, hematoporphyrin IX, TPP; PPh_3
3	$^1O_2$, *hν*, $CHCl_3$, 35 °C, methylene blue; $NaBH_4$, MeOH
4	$^1O_2$, *hν*, MeOH−benzene (1:1), 35 °C, methylene blue; $NaBH_4$, MeOH
5	$^1O_2$, *hν*, MeOH−benzene (1:1), 35 °C, methylene blue; PPh_3 (TPP = 5,10,15,20-tetraphenyl-21*H*,23*H*-porphyrin)

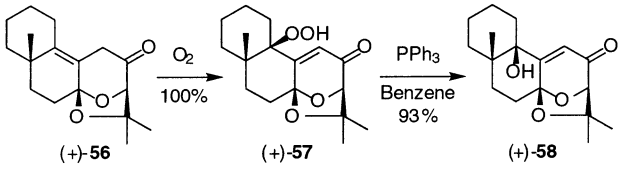
methyl groups block the appropriate trajectory of singlet oxygen, possible with (+)-**28**, to both faces of the tetrasubstituted olefin.



(+)-**28** (+)-**54**

At this juncture, we recalled that during our earlier syntheses of (+)-paspalicine and (+)-paspalinine, a model β,γ-unsaturated ketone (+)-**56** had proven highly susceptible to autoxidation, quantitatively affording the corresponding hydroperoxide (+)-**57** (Scheme 16).[6d] Similar autoxidation of steroids has been

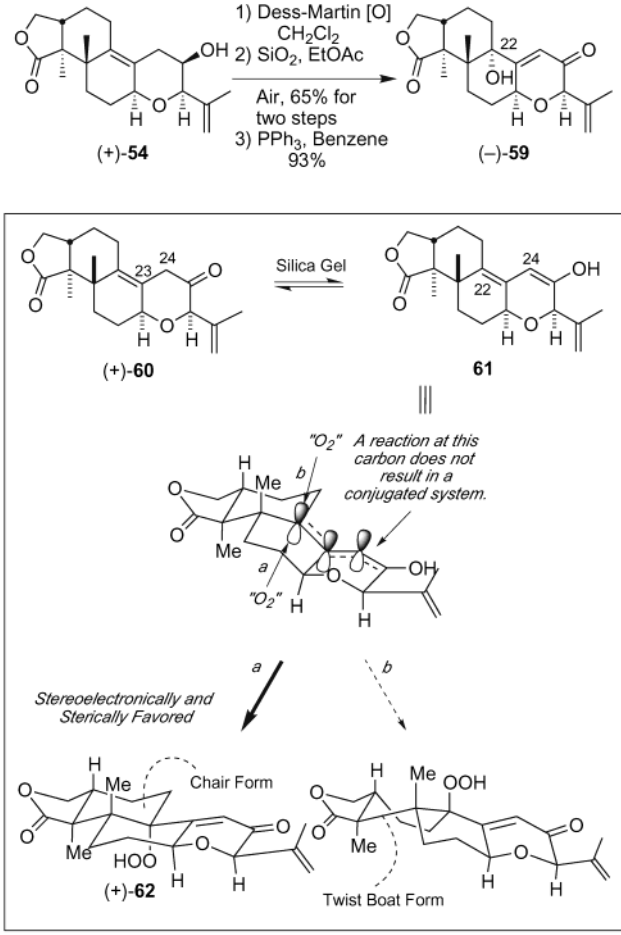
Scheme 16



(+)-**56** (+)-**57** (+)-**58**

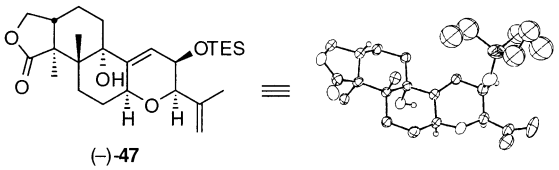
attributed to hydrogen atom abstraction, followed by the addition of oxygen to the resultant radical.[32] To explore this possibility, (+)-**54** was oxidized to the corresponding β,γ-unsaturated ketone (+)-**60** with the Dess−Martin periodinane.[33] During the purification of (+)-**60**, we observed a minor amount of hydroperoxide formation. This observation led us to develop a three-step oxidation/autoxidation/reduction protocol employing in turn the Dess−Martin periodinane, air/silica gel oxidation, and PPh_3 reduction to furnish (−)-**59** in 60% yield for the three steps (Scheme 17). In an effort to accelerate the oxidation, the radical initiator AIBN was added. No improvement in the reaction rate occurred, suggesting that hydrogen atom abstraction

Scheme 17



is not the rate-limiting step. Instead, we suggest that silica gel-promoted keto−enol tautomerization, to generate the C(22−24) dienol, may be the rate-limiting step.[34] The alpha stereoselectivity of the autoxidation process presumably derives from stereoelectronic factors, namely, a "product-like" transition state wherein direct chair formation (pathway *a*) is favored as opposed to a twist boat (pathway *b*) as illustrated in Scheme 17.[35]

To arrive at the fully elaborated eastern hemisphere, all that remained was stereoselective reduction of the C(25) carbonyl and protection of the secondary hydroxyl as the TES ether. Several reducing agents were screened; L-selectride produced the highest level of stereoselectivity (Table 4). Protection of the hydroxyl completed the synthesis of the eastern hemisphere(−)-**47**, the structure being confirmed by single-crystal X-ray analysis.

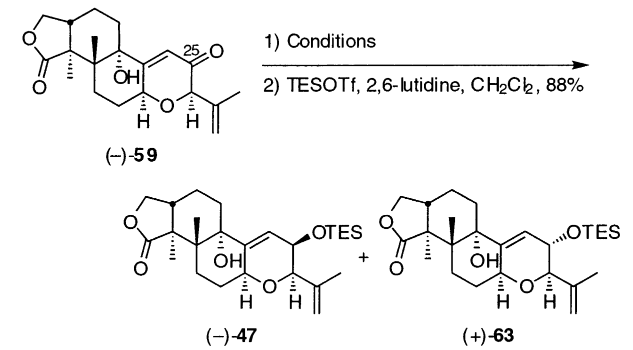


(−)-**47**

Fragment Union. Recognizing the potential acid sensitivity of the intermediates anticipated to arise post 2-substituted indole construction, we chose to replace the MOM protecting group in (−)-**13** with the more easily removable TMS group. Not surprisingly, the harsh conditions required to remove the MOM group also led to loss of the TBS group. Reprotection was

(30) Higher reaction temperature and/or longer reaction time resulted in over-reduction of the olefin in the side chain.
(31) Dhaon, M. K.; Olsen, R. K.; Ramasamy, K. *J. Org. Chem.* **1982**, *47*, 1962−1965.
(32) Nickon, A.; Mendelson, W. L. *J. Org. Chem.* **1965**, *30*, 2087−2089.
(33) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277−7287.

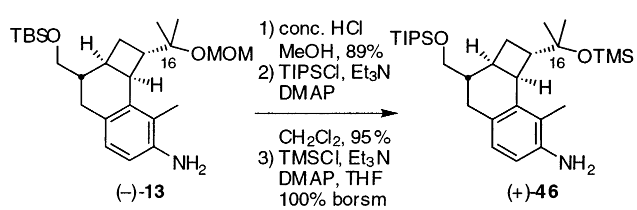
Table 4. Reduction of (−)-**59**



entry	conditions	yield (%) (47:63)
1	$NaBH_4$, $CeCl_3$, MeOH, 0 °C	96 (1:8)
2	Li(O *t*-Bu)$_3$AlH, THF, 0 °C → rt	94 (1:2)
3	NaBH(OAc)$_3$, AcOH, 80 °C → 100 °C	no reaction
4	L-Selectride, THF, −78 °C	86 (19:1)

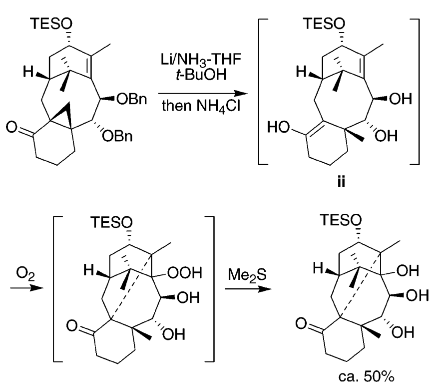
achieved with a TIPS group at the primary hydroxyl[36] and a TMS at the C(16) hydroxyl to furnish (+)-**46** [48% yield, 100% yield based on recovered starting material (Scheme 18)].

Scheme 18



Following our 2-substituted indole protocol, *o*-toluidine (+)-**46** was converted to the *N*-trimethylsilyl-*o*-toluidine derivative and, in turn, treated with 2.1 equiv of *s*-BuLi. Addition of lactone (−)-**47** furnished the coupled product, which upon exposure to silica gel underwent the requisite heteroatom Peterson olefination to provide indole (−)-**45** (Scheme 19).[6n] The excellent yield (e.g., 81% yield) was quite gratifying.

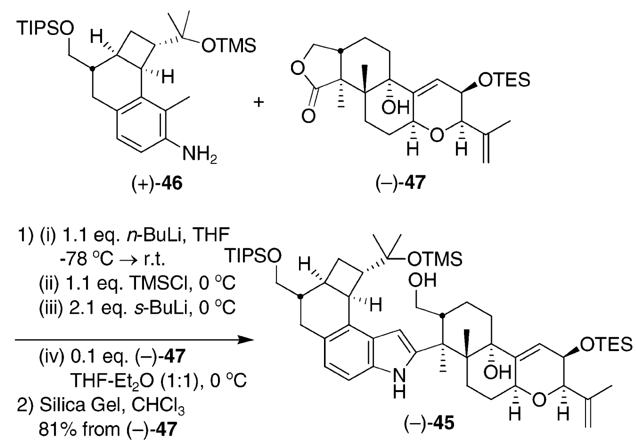
(34) A similar autoxidation of an enol (**ii**) was observed by Kuwajima and coworkers during the synthesis of (+)-taxusin, see: Hara, R.; Furukawa, T.; Kashima, H.; Kusama, H.; Horiguchi, Y.; Kuwajima, I. *J. Am. Chem. Soc.* **1999**, *121*, 3072−3082.



(35) (a) House, H. O.; Tefertiller, B. A.; Olmstead, H. D. *J. Org. Chem.* **1968**, *33*, 935−942. (b) Paquette, L. A.; Belmont, D. T.; Hsu, Y.-L. *J. Org. Chem.* **1985**, *50*, 4667−4672. (c) Stereoselective Alkylation Reactions of Chiral Metal Enolates. Evans, D. A. *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1983; Vol. 3, Chapter 1, pp 1−110.

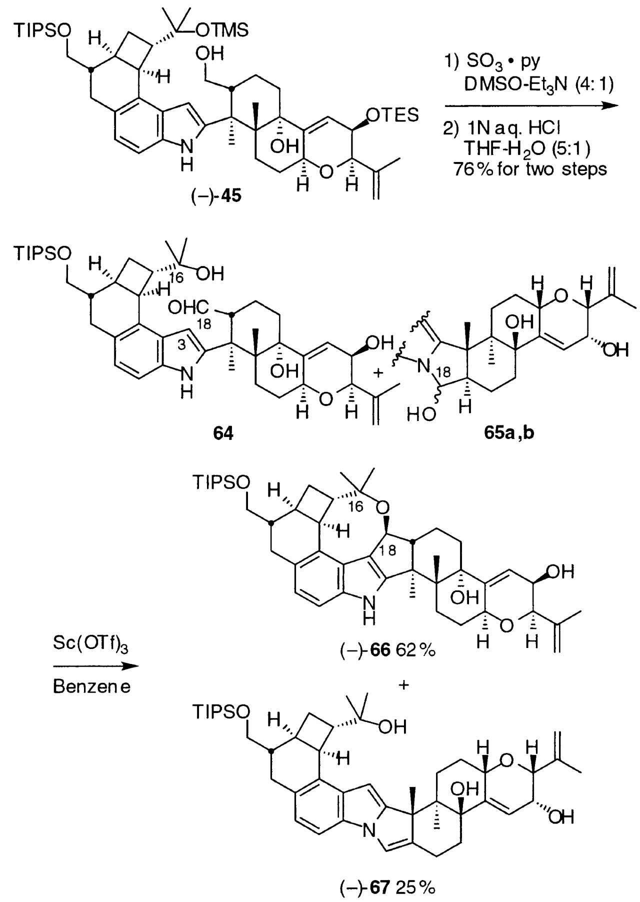
(36) The lability of the TBS protecting group suggested that the use of the more robust TIPS ether would prove advantageous.

Scheme 19



End Game. The last major hurdle to overcome was generation of the **A** and **F** rings (Scheme 20). Parikh−Doering oxidation[22] of the primary hydroxyl followed by selective removal of the TMS and TES groups afforded a serviceable equilibrium mixture of **64**, **65a**, and **65b** (3:1:3). Initial attempts to construct the **A** and **F** rings with CSA in benzene provided the desired oxocane (−)-**66**, albeit in low yield (ca. 19%), along with a considerable amount of the elimination product (−)-**67** (56%). The structure of (−)-**67** was deduced via 2D NMR experiments. In an attempt to improve the ratio of (−)-**66** and (−)-**67**, a series of Lewis acids was screened; best results were obtained with 1.2 equiv of Sc(OTf)$_3$ in benzene.[37] These conditions furnished (−)-**66** in 62% yield. The requisite β-ster-

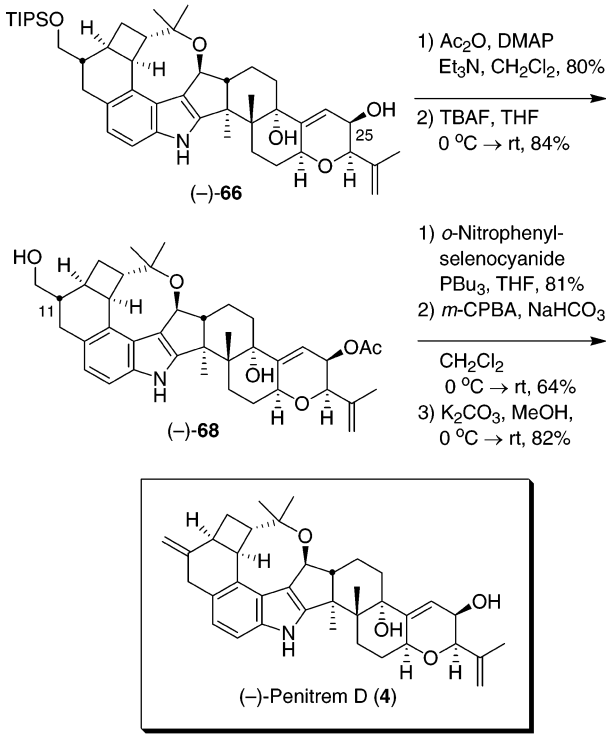
Scheme 20



eochemistry at C(18) of (−)-**66**, as in the earlier model studies, was again obtained with excellent selectivity (>95:5 by ^{1}H NMR).

With the critical **A** and **F** rings secure, final conversion to penitrem D (**4**) proved straightforward. Acetylation of the C(25) hydroxyl (Scheme 21), followed by removal of the TIPS group, furnished alcohol (−)-**68**, which in turn was subjected to Grieco selenation[14] of the primary hydroxyl followed by oxidative elimination to install the C(11) *exo* olefin.[15] Saponification then provided (−)-penitrem D (**4**), identical in all respects to a sample of the natural product (e.g., ^{1}H and ^{13}C NMR, IR, HRMS, and chiroptic properties).

Scheme 21



Summary. The first total synthesis of (−)-penitrem D has been achieved in a highly convergent and stereocontrolled manner. The initial approach afforded nonacycle (−)-**40**, possessing the undesired stereogenicity at C(28) via a dramatic one-pot construction of the **A**, **F**, and **I** rings. The second-generation strategy called for the construction of the fully elaborated eastern hemisphere (−)-**47**, possessing a preinstalled **I** ring; highlights of the **I** ring construction included a Stork metalloenamine alkylation, an acid-promoted reductive cyclization, and autoxidation at C(22). Union of the fully elaborated eastern and western hemispheres was then achieved employing the 2-substituted indole synthesis, developed expressly for the (−)-penitrem D synthetic venture. The excellent efficiency of this union (81%) stands as a testimony for the application of this method in complex molecule synthesis. Finally, a $Sc(OTf)_3$-promoted cationic cascade completed construction of the **A**−**I** nonacyclic system. The longest linear sequence to (−)-penitrem D (**4**) required 43 steps from (−)-Wieland−Miescher ketone.

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Supporting Information Available: Experimental procedures and analytical data for compounds (−)-**13**, (+)-**28**−(−)-**36**, (+)-**38**−(+)-**41**, (+)-**43**, (−)-**45**−(+)-**50**, (+)-**52**−(+)-**54**, (−)-**59**, (+)-**60**, (+)-**62**, (+)-**63**, (−)-**66**−(−)-**68**. This material is available free of charge via the Internet at http://pubs.acs.org.

JA034842K

(37) (a) Kobayashi, S.; Hachiya, I.; Araki, M.; Ishitani, H. *Tetrahedron Lett.* **1993**, *34*, 3755−3758. (b) Kobayashi, S.; Hachiya, I.; Ishitani, H.; Araki, M. *Synlett* **1993**, 472−474.